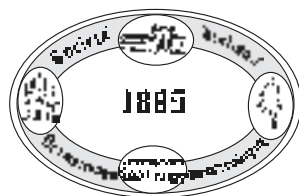


GIORNALE ITALIANO DI DERMATOLOGIA E VENEREOLOGIA

Vol. 150

February 2015

No. 1



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Cosmetics for acne: indications and recommendations for an evidence-based approach

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Aim. The aim of this review was to evaluate, by a thorough revision of the literature, the true efficacy of currently available topical and systemic cosmetic acne agents.

Methods. The efficacy of currently available cosmetic acne agents has been retrospectively evaluated via thorough revision of the literature on matched electronic databases (PubMed). All retrieved studies, either randomized clinical trials or clinical trials, controlled or uncontrolled were considered.

Results. Scientific evidence suggests that most cosmetic products for acne may enhance the clinical outcome. Cleansers should be indicated to all acne patients; those containing benzoyl peroxide or azelaic/salicylic acid/triclosan show the best efficacy profile. Sebum-controlling agents containing nicotinamide or zinc acetate may minimize excessive sebum production. Cosmetics with antimicrobial and anti-inflammatory substances such as, respectively, ethyl lactate or phytosphingosine and nicotinamide or resveratrol, may speed acne recovery. Topical corneolytics, including retinaldehyde/glycolic acid or lactic acid, induce a comedolytic effect and may also facilitate skin absorption of topical drugs. Finally, the use of specific moisturizers should be strongly recommended in all acne patients.

Conclusion. Cosmetics, if correctly prescribed, may improve the performance of the therapy, whereas wrong procedures and/or inadequate cosmetics may worsen acne. Cosmetological recommendations may allow clinicians to make informed decisions about the role of various cosmetics and to identify the appropriate indications and precautions. The choice of the most effective product should take into consideration the ongoing pharmacological therapy and acne type/severity as well.

KEY WORDS: Acne vulgaris - Cosmetics - Therapeutics.

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The mainstay of acne treatment is pharmacological therapy. However, cosmetics if correctly prescribed may improve the therapeutic outcome, whereas wrong practices and/or inadequate cosmetic use may worsen acne.¹ It is therefore important to provide dermatologists with the essential notions that are useful for a correct cosmetic prescription, taking into consideration the ongoing pharmacological therapy and acne type/severity as well.^{2, 3}

The cosmetic products indicated for acne patients, alongside cleansers that are necessary in daily hygienic routine, include sebum controlling, antimicrobial, anti-inflammatory, corneolytic, and moisturizing agents. The majority of these products contain a mixture of active ingredients that are supposed to act synergistically.⁴ However, few *in vitro* studies and/

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or *in vivo* randomized clinical trials (RCTs) on acne patients have demonstrated a real advantage *versus* placebo of each single active substance. The aim of this article is to revise scientific knowledge on currently available cosmetic agents whose efficacy is supported by substantial clinical studies, in order to provide indications and recommendations useful for daily clinical practice.

Materials and methods

The efficacy of currently available cosmetic acne agents has been retrospectively evaluated by a thorough revision of the literature on matched electronic databases (PubMed) from 1975 to 2012 using the following matched key words: “cosmetic and acne” or “cleanser” or “sebum” or “antimicrobial” or “anti-inflammatory” or “corneolytic” or “moisturizers” and “placebo”, “comparative”, “double blind”, “single-blind”, and “*in vivo*”. All controlled or uncontrolled clinical trials (CTs) or RCTs, were considered. In addition, references cited in the retrieved papers were checked for further quotations.

Results

Fifty-eight trials, 30 RCTs, 14 controlled CTs and 14 uncontrolled CTs were found. Details are provided in the discussion sections, and the appropriate indications and precautions are shown in Tables I-VII.

Discussion

Cleansers

Skin cleansing is an essential part of skin care. It consists in removing different types of dirt: liposoluble, hydrosoluble, and insoluble.^{1, 5} Several types of cleansers with different mechanisms of action are available, including surfactants, make-up removers, astringent cleansers, and abrasive cleansers. Table I describes the various available cleansers and their mechanisms of action. Surfactants, which act by decreasing surface tension, represent the most important group⁶ and are classified as anionic, cationic, ampholytic, and non-ionic. Surfactants for acne are generally synthetic (syndets), and are commercially available as soaps, dermatologic bars or cakes, liquid or gel or foam cleansers, surfatted soaps and lipid-free cleansers. They may be enhanced with active substances such as sebum controlling, antimicrobial, anti-inflammatory, corneolytic, and soothing agents.⁷ The ideal cleanser should be non-comedogenic, non-acnegenic, non-irritating and non-allergenic. Among the different cleansers available, the use of aggressive and strong surfactants, such as the so-called “natural soaps”, should be avoided because of their strongly alkaline pH. Excessively aggressive care in an attempt to reduce skin oiliness should also be discouraged, as it can cause erythema and irritations, as well as acne worsening (“acne detergicans”).⁸⁻¹¹ Finally, some cleansers containing ground fruit pits or other granular materials may prove to be too aggressive.³ The use of mild syndet cleansers with a pH closer to normal skin should be preferred.^{12, 13}

Of note, the daily regular use of facial cleansers designed for normal to oily skin has demonstrated a

TABLE I.—Common cleansers for acne, formulations and type of cleansing.

Cleansers	Formulations	Type of cleansing
Surfactants (natural soaps or syndets; may be enhanced with active substances)	Soaps, dermatological bars or cakes, liquid, foam cleansers, surfatted soaps, lipid-free cleansers	Mild; may or may not require rinsing with water
Make-up removers (may be enhanced with anti-microbial and sebum-controlling agents)	Cleansing milks, toners/liquids, water solutions	Mild; may or may not require rinsing with water; can cause dryness or irritation (alcohol-based leave-on toners/liquids)
Astringent cleansers (may contain alcohol, absorbent products such as clay, bentonite, kaolin)	Toners/liquids pastes, earth-based masks	Absorbent; require rinsing with water; can cause dryness or irritation (alcohol-based leave-on toners liquids)
Abrasive cleansers (may contain natural, synthetic or organic granules)	Vinyl masks, scrubs	Microabrasion; require rinsing with water; may be excessively abrasive

to improve seborrhea without impairing skin barrier function or causing rebound sebum overproduction after treatment discontinuation.^{5, 14} Active ingredients contained in acne cleansers are available in the literature include: azelaic acid 1% + salicylic acid 1% + triclosan 0.04%,¹⁵ benzoyl peroxide at concentrations ranging from 4 to 9.81%,¹⁶⁻¹⁸ chlorhexidine gluconate 4%,¹⁹ clay,²⁰ and salicylic acid 2%.²¹

In a double-blind, placebo RCT, a cleanser containing a mix of azelaic acid 1% + salicylic acid 1% + triclosan 0.04% has shown 46% reduction of inflammatory lesions (IF) (evaluated by facial photographs and skin biopsy), and downsizing of the expected rebound effect after treatment.¹⁵

In inflammatory acne concurrently treated with topical antibiotics, a cleanser enhanced with BPO 9.8% has shown to induce 98.3% reduction of *P. acnes* colony forming units (CFUs) compared to baseline on trunk acne skin, even when used in short contact therapy.¹⁸

Two studies have shown promising results that have not been further confirmed: a RCT on a 4% chlorhexidine gluconate cleanser that showed favorable outcome on non-inflammatory (NIF) lesions compared to placebo,¹⁸ and a crossover uncontrolled CT study using a 2% salicylic acid cleanser that has demonstrated improvement of NIF lesion count (16.6 to 10.9) compared to baseline.²⁰ Finally, a recent uncontrolled CT on a cleanser containing clay and jojoba has shown a reduction in the total lesions count (TLC) of 54%.¹⁹

RECOMMENDATIONS FOR USE

Always discuss with patients their cleansing habits. Most patients do not use any specific cleanser, use average cleansers or do not use any at all. A cleanser

designed for acne prone skin should be recommended to all acne patients in association or not with the ongoing therapy (Table II). Its use should also be recommended after drug discontinuation and during summer months. BPO cleansers are best indicated for mild to moderate inflammatory acne, in patients undergoing systemic and/or topical antibiotic treatments,²² and in those who do not tolerate irritation from BPO products. Patients undergoing treatment with products containing BPO should be advised of the potential cumulative effect and to avoid concomitant sun exposure. The use of cleansers containing salicylic acid should be recommended in comedonal acne, whereas those containing clay should be encouraged in mild/moderate acne with hyperseborrhea. In the case of undesired xerosis due to retinoid treatments, switching to a cleanser containing soothing agents is advisable.

Sebum controlling agents

Sebum is the result of androgen-driven secretion by sebaceous glands and an overproduction of sebum is frequently seen in acne patients. Topical sebum-controlling agents are cosmetic products used to reduce skin oiliness, which are available in different formulations such as emulsions, gels and/or lotions. Their action seems mostly due to the presence of the so-called "matifying" agents, like methacrylate copolymers, mycospheres, able to absorb sebum from the skin surface.² For many of them, a role on 5 α -reductase or on sebaceous glands activity has been claimed, but this issue still needs to be confirmed.^{23, 24}

Sebum controlling agents trials include: nicotinamide 2% + panthenol 1%,²⁵ retinaldehyde 0.1% + glycolic acid 6%,²⁶ *Serenoa repens* 2%,^{24, 27} silicic acid,²⁸ triethyl citrate + ethyl linoleate + salicylic

TABLE II.—*Cleansers for acne: recommendations.*

Indications

- A cleanser should be prescribed to all acne patients associated with or not with undergoing therapy; it may also be considered after treatment discontinuation and during summer months
- Benzoyl peroxide cleansers are better suited in mild to moderate inflammatory acne, in patients undergoing systemic and/or topical antibiotic treatments, and in those who do not tolerate other BPO topical products
- Use of sebum controlling cleansers (containing clay) is useful in intensely seborrheic acne patients
- Salicylic acid cleansers are recommended in comedonal acne

To be considered

- Always discuss cleansing habits with the patients
- Check for aggressive care by patients
- Discourage the use of natural soaps as well as of cleansers containing ground fruit pits or other granular materials
- In case of concomitant use of BPO cream or gel, patients should be advised of a possible irritant and cumulative effect and to avoid sun exposure
- In case of xerosis from retinoid treatments switch to a mild soap containing soothing agents

acid 0.5%,²⁹ and zinc pyrrolidone 0.1% + *Laminaria digitata*.³⁰

Poor evidence supports the efficacy of sebum controlling agents as the sebostatic activities proven *in vitro* are seldom supported *in vivo*. In addition, a possible placebo effect should be considered, since it is well known that sebum excretion rate (SER) may change according to psychological influences.^{31, 32} Among the various sebum controlling agents, 2% nicotinamide + 1% panthenol gel has shown good evidence of efficacy, according to one placebo controlled RCT on 126 patients, in reducing the SER of facial acne skin after 4 weeks of treatment (mean value: 21.85% vs. 10.7% in placebo group).²⁵ Its mechanism of action is still unclear, but probably consists in a reduction of sebocyte secretion and in a reduction of sebum retention in the sebaceous ducts obtained by promoting a faster ductal epithelial turnover. The latter, along with increased stratum corneum hydration, could prevent duct closure facilitating sebum flow to the skin. A multicentre, double-blind, placebo RCT on 128 patients treated with 0.1% retinaldehyde (RAL) + 6% glycolic acid (GA) (RALGA) emulsion showed a statistically significant reduction of SER.²⁶ In a small uncontrolled CT, 2% *Serenoa repens* cream-gel showed a sebum-controlling effect (22% reduction of casual sebum level/cm² and 42% reduction of infundibular reservoir sebum level/cm² by a photometric device) after 4 weeks of treatment.²⁷ A double-blind, placebo RCT demonstrated SER reduction from 93 to 42 induced by a lotion containing triethyl citrate + ethyl linoleate + 0.5% salicylic acid (TES) compared to placebo group in which SER increased (from 93 to 42 for TES vs. 86 to 107 for placebo).²⁹ Limited evidence supports the sebosuppressive activity of zinc; one study on zinc acetate 1.2% has shown that this agent is able to decrease significantly SER and casual sebum (CS) level when associated with topical erythromycin compared to

topical erythromycin alone that did not cause any change.^{33, 34} Finally, silicic acid is a natural molecule that has shown in a placebo RCT, using biophysical measurement of SER (by gravimetric technique), to be effective in decreasing sebum production (from 193 to 88 vs. unchanged to placebo).²⁸

RECOMMENDATIONS FOR USE

Standard therapy for mild/moderate acne does not affect sebum production, therefore, hyperseborrhea may often be a major complaint (Table III). Among the different products available, those containing *Serenoa repens* extract or TES may be suggested to manage oily skin when the use of anti-androgens (such as birth control pill) or isotretinoin, is not justified or contraindicated or in those cases in which they are temporarily discontinued (during wash out for hormonal screening, or because of side effects/intolerances). Nicotinamide use is best encouraged in hyperseborrhea associated with mild to moderate inflammatory acne, due to its additional anti-inflammatory properties.³⁵ All sebum controlling products may be associated with standard pharmacologic treatments with no specific precautions needed.

Antimicrobial agents

Topical antibiotics are commonly used for the management of moderate to severe acne vulgaris. In order to optimize efficacy and to reduce the emergence of *P. acnes* resistance, they are commonly used in combination with antimicrobial agents such as BPO. Substances with antimicrobials properties are contained in several cosmetic for acne and those substantiated by scientific evidence, include: ethyl lactate 10%,³⁶ phytosphingosine 0.2%,³⁷ retinaldehyde 0.1% + glycolic acid 6%,^{26, 38} tea tree oil 5%,^{39, 40} and triclosan 0.1%.⁴¹⁻⁴³

TABLE III.—*Sebum controlling topical agents for acne: recommendations.*

Indications

- Sebum controlling agents are indicated in acne patients with hyperseborrhea
- Nicotinamide use is best encouraged in hyperseborrhea associated with mild to moderate inflammatory acne due to its additional anti-inflammatory properties
- *Serenoa repens* extract or triethyl citrate/ethyl linoleate/salicylic acid agents may be suggested in intensely oily skin when the use of anti-androgen (such as birth control pill), or isotretinoin, are temporarily discontinued or contraindicated (during wash out for hormonal screening or because of side effects/intolerances)

To be considered

- In general, standard therapy for mild/moderate acne does not influence sebum production, therefore, hyperseborrhea may often be a major complaint
- No specific precautions are needed with the use of such agents

Ethyl lactate and phytosphingosine (PS) have been proven to effectively reduce *P. acnes* growth both *in vitro* and *in vivo*.^{36, 37} In particular, the efficacy of 10% ethyl lactate lotion has been supported by *in vivo* measurement of inhibitory effect on lipase/esterase activity on sebum hydrolysis.³⁶ However, no data on clinical efficacy on acne lesions were provided. Conversely, the antimicrobial action of 0.2% phytosphingosine emulsion, previously assessed *in vitro*, was firstly evaluated *in vivo* on unwashed hands, calculating the total microbial count before and after treatment, and then in a placebo RCT on 30 patients with moderate facial acne, showing 68% reduction of *P. acnes* colony forming units (CFUs).³⁷ A multicentre, double blind, placebo RCT on 0.1% retinaldehyde (RAL) + 6% glycolic acid (GA) (RALGA) emulsion showed its capability to reduce the proliferation of *P. acnes* by histological evaluation.²⁶ A 6-week double-blind placebo RCT aimed at evaluating the efficacy of 5% tea tree oil gel in reducing TLC and Acne Severity Index (ASI) has shown 43.64% (tea tree oil) vs. 12% (placebo) TLC reduction and 40.49% (tea tree oil) vs 7.04% (placebo) ASI reduction.⁴⁰ An old double-blind placebo CT using 0.1% triclosan cream has shown efficacy in reducing IF lesions count (from 2.4 to 1.3) on a 4 point severity scale.⁴³

RECOMMENDATIONS FOR USE

Cosmetics containing antimicrobial agents, such as phytosphingosine, retinaldehyde/glycolic acid or tea tree oil, may be an option in patients affected by mild inflammatory acne that get easily irritated by BPO or retinoids (Table IV). They may also be considered during maintenance treatment as well as following antibiotic discontinuation. As they are non photosensitizing, they may be used during summertime. Finally, their use may also be suggested in moderate acne as an adjunct to standard pharmacological treatments with no specific precautions needed.

Antinflammatory agents

Recent understanding in the pathogenesis of acne has suggest a pivotal role of inflammatory events in the development of acne lesions. As efficacy of most topical or systemic pharmacological agents for acne relies on their antinflammatory action, the use of cosmetics with such properties may seem reasonable. Antinflammatory agents for acne found in clinical trials include: lactic acid 5%,^{44, 45} myrtacine + nicotinamide 4%,^{46, 47} nicotinamide 4%,⁴⁸⁻⁵⁰ nicotinamide + linoleic acid-rich phosphatidylcholine 4%,⁵¹ nicotinamide 4% + retinol 1% + dehydrocholesterol 0.5%,³⁵ phytosphingosine 0.2%,³⁷ resveratrol 0.01%,⁵²⁻⁵⁴ salicylic acid 0.5%,^{49, 55} tea 2%,⁵⁶⁻⁶⁰ tea tree oil 5%,^{40, 61} triethyl citrate + ethyl linoleate + salicylic acid 0.5%,²⁹ zinc pyrrolidone 0.1% + *Laminaria digitata*,³⁰ and zinc sulphate 2%.^{59, 62, 63}

Among the various agents, nicotinamide 4% has shown a considerable amount of *in vitro* and *in vivo* clinical evidence. A recent study, evaluating by PCR the expression of interleukins, transforming growth factor-beta (TGF- β), macrophage migration inhibitory factor (MIF), monocyte chemoattractant protein-1, monocyte chemoattractant protein-1 (MCP-1), at the beginning and at the end of treatment, has shown the efficacy of nicotinamide in reducing inflammation.³⁵ These results were consistent with a previous *in vitro* study demonstrating that nicotinamide inhibited keratinocyte IL-8 production induced by *P. acnes* through the nuclear transcription factor-kappaB (NF-kB) and the mitogen-activated protein kinase (MAPK) pathways.⁴⁸ Clinical studies have shown that 4% nicotinamide gel enhances therapeutic efficacy when used in combination with 0.2% myrtacine⁴⁷ or linoleic acid-rich phosphatidylcholine⁵¹ or topical antibiotics such as clindamycin.^{64, 65} The efficacy of 0.5% salicylic acid formulated in alcohol solution has shown poor or no advantage over placebo in reducing open (39% vs. 28%) and closed

TABLE IV.—Antimicrobial topical agents for acne: recommendations.

Indications

- Antimicrobial topical agents may be an option in patients affected by mild acne with few inflammatory lesions
- They may be considered in cases of irritation from BPO or retinoids
- They may be used following antibiotic discontinuation as maintenance treatment
- Phytosphingosine and retinaldehyde/glycolic acid have shown the best clinical evidence of efficacy
- Tea tree oil is preferable in mild/moderate inflammatory acne

To be considered

- They are not photosensitizing and may be used safely during summertime
- They may be used in association with standard pharmacological treatment with no specific precautions needed

(21% vs. 21%) comedones, whereas better efficacy in reduction of inflammatory lesions (54% vs. 29%) has been found.⁵⁵ An innovative lotion containing a combination of triethyl citrate + ethyl linoleate + 0.5% salicylic acid (TES) has demonstrated, by clinical assessment in a double-blind placebo RCT, to effectively reduce IF lesion compared to placebo (from 31 to 15 TES vs. 27 to 44 placebo).^{29, 62} Among natural derivatives, 2% tea and 5% tea tree oil have demonstrated, in a placebo RCT study, to be capable of reducing total lesions count (65% for tea and 45% for tea tree oil).^{40, 58} A placebo RCT on 0.2% phytoshingosine (PS) emulsion showed a resolution of 89% of IF lesions vs. 43% increase with placebo.³⁷ Resveratrol is another promising agent that has shown histologically proven anti-inflammatory action in a placebo RCT (66.7% reduction of microcomedones density for resveratrol vs. 9.7% for placebo).^{29, 62} Pooled data do not allow the evaluation of the real efficacy of 5% lactic acid solution,⁴⁵ and no significant differences were observed between 2% zinc sulphate solution and placebo in TLC and acne grading.^{59, 63} A recent double-blind, placebo RCT on 0.1% zinc pyrrolidone + *Laminaria digitata* cream has suggested that it may be a reasonable option to consider in acne patients as it has shown to significantly decrease IF lesions count.³⁰

RECOMMENDATIONS FOR USE

Antiinflammatory agents, such as nicotinamide, which have the best clinical evidence of efficacy, or new natural derivatives, such as resveratrol, tea or tea tree oil, may be used in mild inflammatory acne in patients that do not tolerate BPO or topical retinoids and in those cases in which additional antiinflammatory action is required (Table V). Another possible use is after post-superficial chemical peels, or in association with standard pharmacological treatments with no specific precautions needed.

Corneolytic agents

Corneolytics are products that cause intercorneocyte cell detachment so as to induce a comedolytic effect. This group of cosmetics is particularly indicated for comedonal acne, making comedones more superficial and at the same time smoothing the skin. Some of them may cause skin irritation. Available trials on corneolytics in acne include: glycolic acid 10%,^{66, 67} gluconolactone 14%,⁶⁸ lactic acid 2%,⁶⁹ malic acid 2%,⁷⁰ retinaldehyde 0.1% + glycolic acid 6%,^{26, 71-74} and salicylic acid 0.5%.⁵⁵

The role of corneolytics in acne treatment has been widely confirmed. Current research is aimed at identifying new corneolytic ingredients that are active at low concentrations and thus better tolerated. The efficacy of 10% glycolic acid oil-water emulsion was evaluated in a double-blind, placebo RCT on 115 patients affected by mild acne. At 3 months, a statistically significant improvement vs placebo was demonstrated.⁶⁷ The tolerance and acceptability of a 0.1% retinaldehyde (RAL) + 6% glycolic acid (GA) topical emulsion was tested in a multicentre CT on 1709 acne women.⁷² After 12 weeks of treatment, a marked decrease (59%) in both retentional and inflammatory lesions was recorded by clinical assessment. One placebo RCT on 46 adult subjects with mild acne or oily skin using a 2% lactic acid cream-gel demonstrated by skin biopsy that follicular penetration of this agent occurred, but a poor clinical efficacy on acne lesions was found.⁶⁹ A recent multicentre, comparative CT on 2% malic acid cream has shown similar efficacy, when used as a single agent compared to its use in association with topical antibiotics (64.8% vs. 63.3%) or vs. retinoid or BPO (69.2% vs. 66.7% vs. 58%).⁷⁰ In a double-blind, placebo RCT on 49 patients a reduction in retentional (39% vs. 28%) and inflammatory lesions (54% vs. 29%) was demonstrated following use, for 12 weeks, of a 0.5% salicylic acid alcohol-solution.⁵⁵ Finally,

TABLE V.—*Antiinflammatory topical agents for acne: recommendations.*

Indications

- Antiinflammatory topical agents may be used in mild inflammatory acne
- *Nicotinamide* and some new natural derivatives, such as resveratrol, tea and tea tree oil are the ones with the best clinical evidences of efficacy
- They may be considered in cases of irritation from standard treatments, after superficial chemical peels or in those cases in which additional antiinflammatory action is required

To be considered

- They are not photosensitizing and they may be used safely during summertime
- They can be associated with any undergoing topical and/or systemic pharmacological therapy with no specific precautions needed

a lotion containing 14% gluconolactone, was tested in a double-blind placebo RCT by evaluating NIF and IF lesions, showing a significant improvement of both types of acne lesions.⁶⁸

RECOMMENDATIONS FOR USE

Corneolytics are indicated for comedonal acne, as they make retentional lesions more superficial and at the same time smooth the skin (Table VI). They represent a valid and useful option for patients who do not tolerate topical retinoids and during maintenance therapy.³ Some of these agents also have a mild blanching effect that may be useful for the management of postinflammatory hyperpigmentation, but that may be detrimental in dark-skinned subjects.⁷⁵⁻⁷⁷ Retinaldehyde/glycolic acid, have also shown to be effective in preventing and treating post-acne scarring.⁷⁸ In case of undergoing treatment with systemic or topical retinoids or with other topic exfoliating agents, their use should be carefully evaluated as additional xerosis may ensue.

Moisturizers

Moisturizers are products designed to hydrate the stratum corneum and to make the skin softer and smooth. Adequate moisturization is a key issue in acne patients, considering that many treatments, such as topical and systemic retinoids or BPO, may cause skin xerosis. Moisturizers for acne patients are mostly humectants and emollients.¹ Specific lines of moisturizers indicated for patients receiving oral isotretinoin, are commercially available. Some of them include cheilitis, dry eyes or nose-bleeding among their indications. Trials on moisturizers indicated for acne patients include: glycerine,^{79, 80} witch hazel + glycerine,⁸¹ urea 10%⁸² and ceramide.⁸³

These studies confirm that they can be used with no

risk of comedogenic effect. A single-blind RCT on 50 patients has demonstrated by biophysical measurement that glicerine water/oil based cream is an excellent moisturizing/hydrating agent.^{79, 80} Another study showed an average 39.7% increase in moisture following twice daily application for 60 days of a with hazel extract + glycerine oil/water based emulsion.⁸¹ A CT on 947 patients using 10% urea combined with 4.5% BPO has demonstrated in addition to a moisturizing effect an enhanced antimicrobial action.⁸² An open study on the moisturizing effects of a ceramide lotion demonstrated its ability to reduce dryness, discomfort and skin irritation resulting from concomitant tretinoin or BPO use.⁸³

RECOMMENDATIONS FOR USE

Moisturizers designed for acne are by definition non comedogenic and should be considered in patients under oral isotretinoin, as they may improve adherence to therapy by alleviating the discomfort and feeling of skin dryness and cheilitis (Table VII). Specific moisturizers designed to alleviate dry eyes or nose-bleeding are also available. The use of moisturizers should also be considered in case of xerosis following topical treatment with exfoliating agents. Among the various available products, the ones containing urea have the advantage of an antimicrobial effect.

Nutriceuticals and acne

Several nutriceuticals, with possible different roles, have been suggested as complementary therapy in acne. Different types of zinc salts have been used, and several mechanisms have been suggested for zinc efficacy in acne management. Due to its role as a cofactor of cytosolic superoxide dismutase, zinc shows antioxidant properties⁸⁴ and can effec-

TABLE VI.—*Corneolytics topical agents for acne: recommendations.*

Indications

- Corneolytics are indicated for comedonal acne and in patients that do not tolerate prescription topical retinoids
- They may be also considered as maintenance after topical retinoids therapy
- Retinaldehyde/glycolic acid have shown the best efficacy profile; they may also be effective in the management of postinflammatory hyperpigmentation, and in the prevention and treatment of post-acne scarring

To be considered

- In case of undergoing systemic or topical retinoid therapy or other topic exfoliating agents application, their use should be carefully considered as additional xerosis may ensue
- They have a mild blanching effect that may be useful for the management of postinflammatory hyperpigmentation, but that may be sometimes detrimental in dark-skin subjects

TABLE VII.—*Moisturizers agents for acne: recommendations.*

Indications
– Moisturizers agents for acne are useful in cases of xerosis resulting from topical BPO or topical/systemic retinoid
– Glycerin, witch hazel extract + glycerine and urea may be considered as in combination or added to standard treatment formulations
– Those containing urea may be considered in inflammatory forms due to its antimicrobial effects
To be considered
– Discourage the use of moisturizers not specifically designed for acne patients that might potentially worsen acne (occlusive effect, comedogenesis)

tively contribute to the reduction of oxidative stress in acne.⁸⁵ Several *in vitro* studies have shown that zinc is able to inhibit granulocyte chemotaxis. Oral supplementation with 30 mg of zinc gluconate for three months reduced the number of inflammatory lesions in acne patients by 57%. Oral zinc administration also induced a significant decrease of sebum secretion⁸⁶ possibly through the ability to inhibit 5- α -reductase activity.⁸⁷ Zinc also has an antimicrobial effect, since it has been shown to inhibit *P. acnes* growth and to act *in vitro* against antibiotic resistant *P. acnes* strains when used in combination with clindamycin or erythromycin. A combination of zinc, nicotinamide, azelaic acid, pyridoxine, copper, and folic acid as a dietary supplement administered in a multicenter, open-label, 8-week, prospective study on 235 patients with inflammatory acne has determined a significant ($P < 0.0001$) clinical improvement when added to the preexisting treatment regimen.⁸⁸

Because omega-3 fatty acids inhibit synthesis of the proinflammatory agent leukotriene B4, and blockage of leukotriene B4 release leads to reduced inflammatory acne lesions,⁸⁹ it has been postulated that increased relative consumption of omega-3 polyunsaturated fatty acids may suppress inflammatory cytokine production and reduce insulin-like growth factor-1 (IGF-1)⁹⁰ levels, thereby exerting a therapeutic effect on acne.⁹¹ However, *in vivo* studies focused on the clinical effectiveness of omega-3 fatty acids in acne patients are still few and on a small number of patients.

Lactoferrin, a non-heme iron binding glycoprotein produced by epithelial cells at mucosal surfaces, is a prominent component of the first line of mammalian host defense and its expression is upregulated in response to inflammatory stimuli. Lactoferrin has long been recognized for its antimicrobial properties and plays a key role in the innate immune system.⁹² Moreover lactoferrin suppresses the adipogenic differentiation reducing accumulation of lipids in the

sebaceous gland and sebum production.⁹³ A few studies report a clinical improvement in acne patients on a lactoferrin-rich diet. Double blind clinical trials demonstrated that oral supplementation significantly improved mild to moderate lesions, reduced sebum secretion, and altered sebum composition by decreasing the amount of free fatty acids and triglycerides.^{94, 95}

Probiotics

A gut-brain-skin connection has been proposed in acne because of the possible correlation between intestinal microflora, skin microflora and inflammatory skin conditions.⁹⁶ Probiotics, such as *L. acidophilus* and *L. acidophilus*-fermented milk products, have been suggested as a complementary treatment for acne. Although oral probiotics seem to theoretically have value as adjuvant care in acne vulgaris, clinical studies able to clearly demonstrate their efficacy are scant and performed in small groups of acne patients. Their oral administration reduces the production of systemic and local inflammatory markers^{97, 98} such as IL-1.⁹⁹

RECOMMENDATIONS FOR USE

Even if the oral administration of nutraceuticals or probiotics have some theoretical and conceptually interesting reasons, the clinical trials performed are not sufficient to support a clear beneficial effect.

Conclusions

Considering the wide range of available cosmetics for acne sometimes showing multiple functional effects as well as the increased demand for specific counseling, the dermatologist's advice for cosmetological recommendations appears essential. If pre-

cise indications about cosmetics use are not provided by the consulted physician, and patients are left free to choose the ones they prefer, the risk of compromising the ongoing prescription treatment is high, either due to acne worsening likely from the use of inadequate comedogenic products, or to the onset of xerosis, irritant/allergic contact dermatitis or photo-dermatitis resulting from overtreatment. On the contrary, as demonstrated by several studies, a correct cosmetic approach may significantly enhance the therapeutic outcome and improve patients' compliance. Cosmetics specifically designed for acne are usually safe, and unlike drugs they may be used all year with few exceptions. In conclusion, the correct use of these products may play an important role in the management of acne. Global guidelines for treatment of acne do not provide specific suggestions/indications for cosmetics, and their use mostly relies on the physician's personal experience.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on August 21, 2014.

Accepted for publication on September 24, 2014.

Epub ahead of print on October 15, 2014.

Symmetric bilateral transposition flap: a very versatile option in facial dermatological surgery

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Aim. Repair following excision of large tumours of the face can be problematic; primary closure may not be achievable and grafting or secondary intention healing carry the risk of necrosis and lengthy healing times. Flaps are usually associated with earlier healing and better cosmetic results, as the skin used for closure is similar to the tissue requiring repair. However, large wound sizes and difficulty in finding a suitable donor area means flaps can be complicated to perform. The aim of this paper was to identify a comparatively quick and simple alternative to standard repair techniques for the closure of large wound defects in critical anatomical areas, when the only realistic alternative would be grafting, offering both good cosmetic results and minimal risk of complications.

Results. We have developed a flap, modified from the classic, single lobe transposition flap. Two similar lobes placed symmetrically and perpendicularly to two opposite sides of the surgical wound are incised with fulcra centred on two opposite corners. The flaps are then rotated by approximately 80-90° into position side by side, sutured to the borders of the surgical wound and finally together with a longitudinal suture. The principle behind this flap is the split of the covering surface into 2 small units, rather than using a large single lobe, which, for large wounds, would make closure of the single donor area by first intention impossible. The split of the donor area in 2 smaller subunits makes it easier to close the two donor areas and allows a larger amount of tissue to be harvested.

Conclusion. We have developed a twinned symmetric transposition flap to close large wounds on the face when the only realistic alternative would have been the use of grafting. It offers minimal distortion, and is both quick and simple to perform. The use of tissue similar to the original defect ensures good cosmetic results. Healing times were usually very rapid and complications limited to a very few cases of end flap

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necrosis. This technique is not applicable where donor areas fall in anatomic spots where harvesting of the lobes is impossible, e.g. when the wound is too close to the hair line and transposition of the lobes would cause the transfer of hairy skin to an area where the presence of hair is not desirable.

KEY WORDS: Surgical flaps - Carcinoma, basal cell - Dermatologic surgical procedures.

In facial surgery, repair following excision of large tumours can be challenging. Depending on the site and diameter of the surgical wound, direct closure may not be feasible.

Over the years, a number of flap techniques have been proposed, recruiting tissue from adjacent anatomic subunits which can redistribute tension and overcome lack of tissue.¹⁻³ However, due to the size or location of the defect requiring closure, traditional techniques such as advancement flaps,^{4,5} rotation or transposition flaps, including rhomboid flaps with their variants⁶ and the bilobed flap⁷ are not always possible.

Consequently, grafting can be the most viable option. This procedure however, requires a second operation to harvest the graft and carries the risk of lengthy healing times and possible tissue necrosis. Furthermore, the donor skin is inevitably different

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in texture, colour and thickness leading to suboptimal cosmetic results, often with depressed contours. Alternatively, secondary intention healing usually leaves depressed scars and over certain wound diameters, healing times can be unacceptable.

We describe a new symmetric bilateral transposition flap, which represents an alternative mainly to closure by grafting. It involves transposing two individual lobes obtained from each side of the wound, harvested from areas where tissue is most abundant. The two flaps are then moved into position side by side, sutured firstly to the borders of the primary wound, and finally together with a longitudinal suture. Given the mechanics of this flap, with movement of the two lobes towards a major longitudinal axis, mimicking the closing of an umbrella, the provisional name for this technique was the “Tongs (or Pincers) flap”.

In designing this flap, the same principles used in the Bilateral Asymmetric Transposition flap (BAT flap),⁸ which we implemented specifically for use on the limbs were applied. Both these techniques have

an advantage over the traditional single transposition flap, as the donor area consists of two distant individual subunits, which results in a more balanced and widespread redistribution of tension. The Peng flap, which is again a bilateral flap, is completely different in terms of its mechanics, with the flaps advanced rather than transposed, as in our technique.

In the symmetric bilateral transposition flap the lobes are obtained from relatively distant areas, overcoming difficulties relating to lesion size and position. It is relatively quick to perform and both the short and long term cosmetic results have been good. This technique also reduces risks of damage to underlying structures such as blood vessels or nerves, as only very minimal undermining is required.

Materials and methods

We treated 35 patients using this flap for repairs of the tip of the nose (Figure 1), forehead (Figure

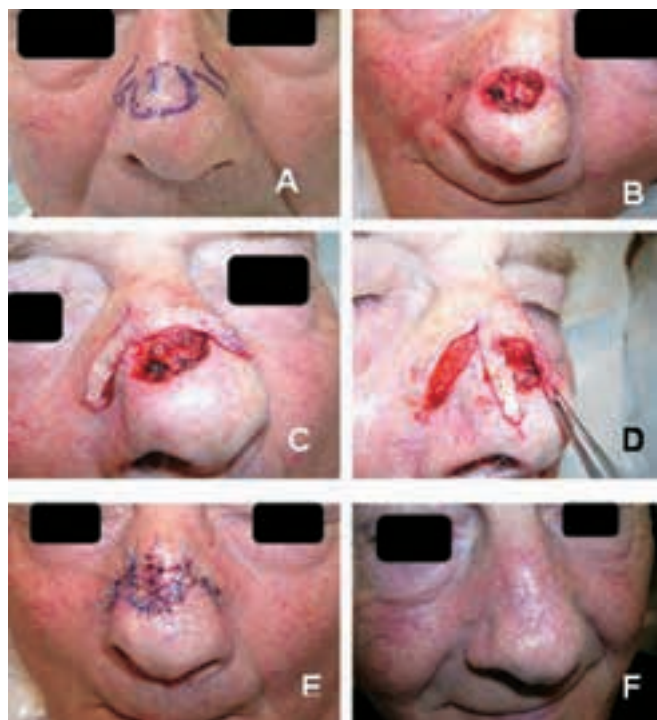


Figure 1.—A-F) Infiltrating basal cell carcinoma of the nose: Sequence of the operation. After harvesting, the two flaps are trimmed to the correct length. The peduncles’ width to length ratio is 1:2.5. After five weeks (F) the scar is satisfactory.



Figure 2 A-F) Nodular BCC of the forehead: Sequence of the operation: The patient was shaved before the operation. The shape of the hair line was different when the hair grew back, but the final result was satisfactory (F).



Figure 3.—A-E) Infiltrating BCC of the upper lip: Sequence of the operation. A well consolidated scar represents the final result after nine weeks, with only minimal deformity of the lip outline (E), which was however already present before the operation (A). Dog ears or trapdoor deformity never represented a real problem when using this technique.

2), temple, lips (Figure 3), scalp, postauricular area (Figure 4), and legs.

No restriction was made based on age, or pre-existing conditions such as vasculopathy, renal failure or smoking. Six patients were transplant recipients.

Twenty-three patients were treated for full excision of basal cell carcinoma of the head, two for atypical fibroxanthoma of the scalp, one lentigo maligna of the scalp and nine for excision of squamous cell carcinomas *i.e.* eight of the head and one of the lower leg (Table I).

The average diameter of the wounds was 1.7 cm for the nose, 3.5 cm for the temple, 3.7 cm for the postauricular areas, 4.2 cm for the forehead, 3.9 cm on the scalp and 2.2 and 4.5 cm for single cases on the upper lip and lower limb, respectively (Table I).

Polyamide interrupted sutures were used to close the wounds, and patients were allowed home after their surgery. Sutures were removed between 9 days to 2 weeks later. Complications and outcome were recorded.



Figure 4.—A-D) BCC of the right postauricular area. It is possible to appreciate the broad size of the peduncle (B). Even in this difficult area, with part of the flap folded to cover the posterior aspect of the pinna, the healing process was limited to 4 weeks and no complications were recorded.

Surgical technique

The procedure is performed under local anaesthesia. The defect is measured and the two opposite flaps marked. The location of the two donor areas are chosen to take advantage of natural tension lines of the skin and are delineated by an imaginary line, representing the ideal continuation of one of the sides of the wound, usually the upper one.

The length of each flap equates approximately to the longitudinal diameter of the wound, into which it will be rotated. The width of the flaps corresponds approximately to the radius of the defect with width to length ratio of approximately 1:2 to 1:2.5 (Figure 5). The flaps are cut through the dermis, undermined and elevated and any excess fat that may be present is removed. They are then rotated through an angle of approximately 80-90° into the recipient area. The donor areas are sutured first and the two flaps should then fall into place spontaneously, with no need for pulling or stretching. The two flaps are subsequently sutured to the lateral borders of the wound and together, using percutaneous sutures. If properly measured and shaped, this final suture develops a minimal tension, ideal for making the two flaps adhere to the sub cutis and to gently pull down the tissue around the pivotal area, preventing the formation of tricones/dog ears, which represent a possible risk when moving two flaps centrally.^{9, 10} In all the cases we treated, the longitudinal tension applied when su-

TABLE I.—Summary of the operations, including diagnosis, location and size of the wounds and recorded complications.

Case N°	Sex	Age	Diagnosis	Size	Location	Complications
1	M	74	Bcc	1.4	Nose	-
2	M	56	Bcc	1.7	Nose	-
3	F	83	Bcc	3.9	Temple	-
4	F	82	Bcc	1.5	Nose	-
5	M	66	Bcc	3.1	Postauricular area	Persistent pain
6	F	87	Bcc	2.0	Nose	-
7	F	58	Bcc	3.6	Temple	-
8	F	61	Sc	2.6	Temple	-
9	M	54	Bcc	1.5	Nose	End flap necrosis
10	M	67	Bcc	3.3	Forehead	-
11	M	70	Bcc	3.4	Scalp	End flap necrosis
12	M	73	Bcc	3.0	Scalp	-
13	M	83	Atypical fibroxanthoma	3.8	Forehead	-
14	F	77	Bcc	2.2	Upper lip	-
15	M	80	Sc	3.8	Postauricular area	-
16	F	61	Bcc	3.2	Temple	-
17	M	58	Sc	1.8	Nose	-
18	M	56	Sc	3.6	Forehead	-
19	F	84	Bcc	4.3	Forehead	-
20	F	69	Bcc	1.3	Nose	Partial necrosis
21	F	77	Bcc	2.9	Temple	-
22	M	69	Sc	4.0	Right lower leg	End flap necrosis
23	M	54	Bcc	5.6	Forehead	-
24	F	61	Bcc	4.8	Scalp	-
25	M	78	Sc	4.0	Scalp	-
26	M	59	Bcc	5.0	Forehead	-
27	F	87	Sc	4.3	Temple	-
28	M	77	Atypical fibroxanthoma	4.0	Scalp	-
29	M	78	Lentigo maligna	4.1	Scalp	-
30	F	69	Bcc	3.8	Temple	-
31	M	68	Bcc	3.7	Temple	-
32	F	78	Bcc	4.0	Forehead	-
33	M	64	Sc	4.2	Postauricular area	-
34	M	76	Sc	2.3	Nose	-
35	F	71	Bcc	3.6	Temple	-

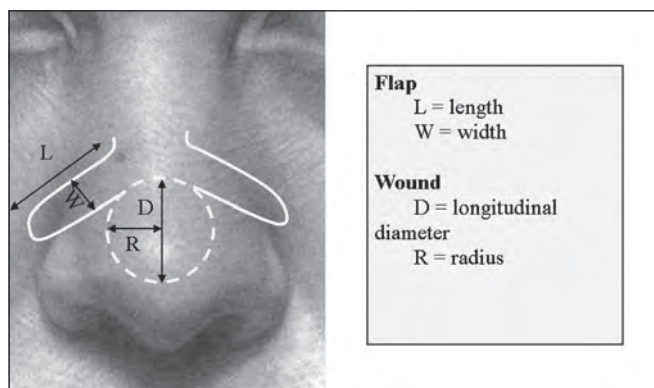


Figure 5.—Scheme of the incision. The length measurement of the flap (L) matches the cranial-caudal diameter (D). The width measurement (W) is the same as the radius (R) of the wound. The width to length ratio is usually 1:2 and never exceeds 1:3. The angle of rotation is usually between 75 to 90 degrees.

turing the edges of flaps to the area opposite to the pivots, seemed in fact to be able alone to minimise the development of this undesired effect. Trapdoor deformity, which represents another possible risk when moving flaps in general, was also negligible (Figures 1-F, 2E, 3E). This might be because we routinely keep the donor flaps relatively thin and also due to the small amount of tension we allow across the flaps after suturing.¹¹ In all 35 cases we treated, repair of tricones/dog ears^{12, 13} or a trapdoor deformity was never required.

Discussion

Five of the 35 patients developed some minor complication, such as small areas of end flap necrosis

(Table I). Complications were however never particularly serious, and in the cases of end flap necrosis, they were left to heal by second intention. All other patients reported an excellent outcome, with healing times usually between 3 to 4 weeks post operation.

One case, where the patient had a tumour of the lower leg removed, resulting in a 4.5 cm diameter wound, healed within 6 weeks, despite vasculopathy and severe stasis dermatitis.

The main limitation with this procedure relates to the position of the defect to be repaired and therefore to the areas from which the flaps can be harvested. For example, if the area needing repair is too close to the hairline, there is a risk of moving hairy skin to a non hairy area, with the obvious cosmetic implications. This is illustrated in Figure 2F where alteration of the hairline become obvious after the hair, previously shaved for the operation, grew back.

Another possible limitation is the fact that, when compared with a traditional transposition flap, the bilateral transposition flap is designed to cover the wound from two different sides, and whereas the length of the flaps is maintained, the width is necessarily split in two. This means that the width to length ratio automatically doubles in favour of the length, which maybe explains the presence, in a number of cases, of end flap necrosis.

Conclusions

Despite these limitations, this technique proved to be very successful in our hands, and we believe that

it might represent a further useful tool in the dermato-surgical armamentarium, broadening the spectrum of flaps currently available.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on December 29, 2013.

Accepted for publication on March 3, 2014.

Treatment adherence and real-life effectiveness of topical therapy in patients with mild or moderate psoriasis: uptake of scientific evidence in clinical practice and dermatologists' preferences for alternative treatment options

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Aim. Topical corticosteroids and the vitamin D analogue calcipotriol are the cornerstone of therapy for patients with mild-to-moderate plaque psoriasis. Lack of patients' adherence leads to suboptimal effectiveness of topical therapy in real-life practice. The fixed combination betamethasone/calcipotriol gel is more effective and safe than the administration of single components and may enhance patients' adherence. We aimed at evaluating the pattern of care and dermatologists' expert opinion toward the available topical treatments for the management of mild-to-moderate psoriasis in Italy.

Methods. We enrolled 242 Italian dermatologists and collected information related to their practice pattern and opinion toward available topical treatments with a face-to-face structured interview. We evaluated dermatologists' ratings of therapy with 16 items tapping their opinion toward the relevance and satisfaction toward 8 therapy attributes in clinical practices which tapped aspects of real-life effectiveness, adherence promotion, toxicity, convenience of use. Ratings occurred along a 10-point scale. We compared single-attribute and weighted overall therapy ratings across alternative treatment options with random-intercept linear models to account for ratings clustering within dermatologists.

Results. There was a wide variation in practice patterns: 1/3 of dermatologist had seen more than 30 patients with psoriasis while around 1/4 had seen less than 10 patients. The fixed combination betamethasone/calcipotriol gel was considered superior to monotherapies in all the eight attributes considered which tapped aspects of real-life effectiveness, adherence promotion, toxicity, convenience of use.

Conclusion. Participant dermatologists' strongly preferred the fixed betamethasone/calcipotriol combination gel over both the fixed combination ointment formulation and corticosteroid or vitamin D analogues monotherapies. Such find-

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ings are in line with evidence from randomized controlled trials and few observational studies demonstrating superior clinical outcomes, quality of life, tolerability and lower risk of side effect in patients treated with the fixed combination of betamethasone/calcipotriol gel.

KEY WORDS: Psoriasis - Adrenal cortex hormones - Administration, topical.

Psoriasis is a common dermatological condition affecting over 1,500,000 people in Italy and exerts a significant impact on patients' quality of life and every day functioning.¹ The most common clinical subtype is the chronic plaque form, an immune-mediated condition affecting about 80-90% of patients.²

The evaluation of clinical severity is a key step in disease management, since treatment options are different for patients with mild/moderate vs. severe psoriasis. The Psoriasis Area and Severity Index (PASI) is widely adopted in clinical setting and research to assess cutaneous involvement and combines the severity (erythema, induration and desquamation) and percentage of the affected area.³ Given that the PASI has several well documented weaknesses, it has been suggested that a through clinical severity assessment

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should include an evaluation of the body surface area (BSA) affected and evaluations of disease-related interference with daily life. The latter dimension is assessed with the Dermatology Life Quality Index (DLQI), a self-report instrument.⁴⁻⁶

Ideally, treatment of mild/moderate forms should provide fast relief from symptoms (*e.g.*, erythema, edema, pruritus, etc.) and contextually reduce the hyperproliferation of keratinocytes.⁷ Approximately 4 in 5 patients with psoriasis presents with mild/moderate severity and can be effectively treated with topical formulations.^{4, 7} However, in a minority of patients presenting with severe lesions the administration of traditional systemic therapies, biotechnological drugs or PUVA therapy is indicated.⁴

There is a wide international consensus on the application of both topical corticosteroids and the vitamin D analogue calcipotriol for the management of mild-to-moderate plaque psoriasis.^{4, 7, 8} The mechanism of action involve corticosteroid-driven inhibition of the inflammatory response and calcipotriol-related inhibition of keratinocytes proliferation (Figure 1). However, despite the combination of corticosteroids and calcipotriol has demonstrated excellent efficacy in several randomized clinical trials, suboptimal effectiveness has been noted in real-life clinical practice.

Meta-analytic results based on 26 studies involving over 19,000 patients show that adherence to medical prescription contributes with 26% increased

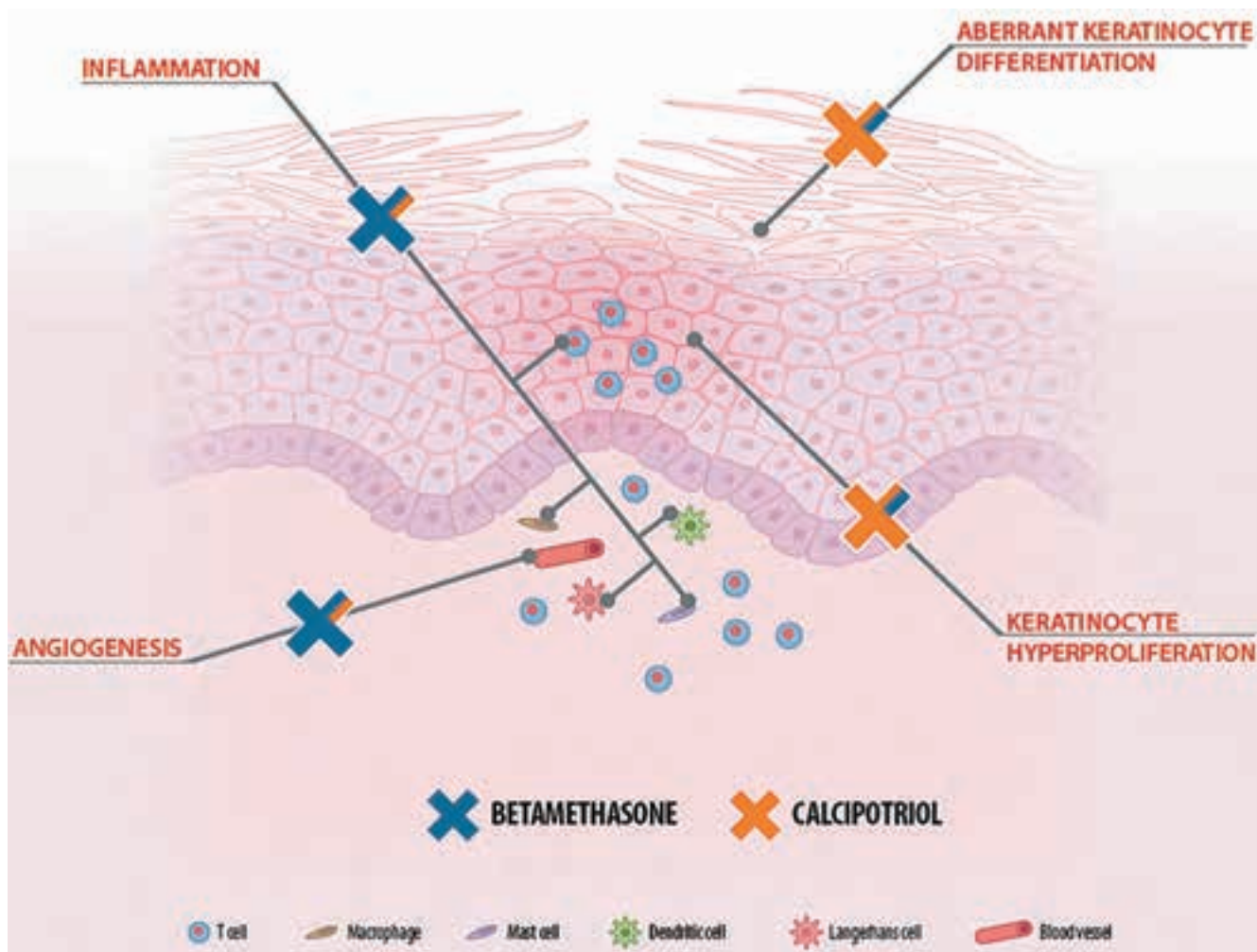


Figure 1.—Mechanism of action of the calcipotriol/betamethasone combination.

likelihood of reaching therapeutic end-points, an effect size comparable to many pharmacological interventions.⁹ Adherence to dermatological treatment is unsatisfactory in 34-45% of patients, leads to poor clinical outcomes and increases health care costs, a problem shared with several chronic medical conditions.¹⁰ Adherence estimated in patients with psoriasis is similar to those reported for other chronic dermatological conditions, according to meta-analyses of scientific evidence.^{11, 12}

Most researches on the antecedents of adherence in different therapeutic areas have shown that medical, psychological and socio-demographic barriers may hamper patients willingness or ability to comply with medical prescriptions and persist with their therapeutic regimen for the entire duration of treatment. It has been shown that simplified treatment regimens, easy-to-use and “clean” products, enhanced provider-patient communication and patients’ evaluation of effectiveness and side effects might affect adherence to topical regimens in patients with dermatological conditions.^{10, 13}

Therefore, new products meeting patients’ preferences might increase adherence and effectiveness in clinical practice. The combined formulations of steroids and vitamin D analogs which allow a single daily self-administration has been designed to reduce therapy burden.¹⁴ This meta-analysis has shown that the fixed combination of calcipotriol and betamethasone dipropionate is the most effective treatment applied once daily with a 70.90% *vs.* 67.90% difference compared to very potent steroids. Before the introduction of the fixed betamethasone/calcipotriol combination, indeed, the individual drugs had to be applied separately since calcipotriol is active at alkaline pH, an environment which inactivate betamethasone.⁷ Additionally, patients with psoriasis rated gels and foams more convenient and easy-to-use than ointments in several respects.^{15, 16} For this reason a gel formulation of the fixed betamethasone/calcipotriol combination was recently marketed to substitute the ointment formulation in clinical practice.

Despite there is strong evidence from clinical trials that the fixed betamethasone/calcipotriol combination is superior to both the individual products alone in terms of efficacy, short-term and long-term safety,^{8, 13} concerns about the side effects of corticosteroids¹⁷ may limit the translation in clinical practice of recent experimental evidence from clinical trials. Hence it is possible that many dermatologists still prescribe

single products to enhance their ability to manipulate corticosteroids administration along the course of therapy. However, this strategy may backfire if adherence is decreased due to increased regimen complexity and “messy” formulations. From the data available in the literature^{13, 18} a superior tolerability profile with the combination of betamethasone/calcipotriol compared to very potent steroids is evident.

In order to understand the uptake in real life setting of recent scientific evidence and evaluate whether clinicians consensus toward topical therapies can be achieved, we conducted a nation-wide survey on a sample of Italian dermatologists.

The aim of the study was to assess the pattern of care and dermatologists’ expert opinion toward the available topical treatments for the management of mild-to-moderate psoriasis in Italy.

Materials and methods

Dermatologists were invited to join a face-to-face structured interview with an independent contractor interviewer. The interaction occurred at each dermatologists’ office in 2012 and 2013. The survey included items concerning the volume of patients seen at the clinic, the share of patients with psoriasis seen during the month preceding the interview, the therapy prescribed, therapy switches, knowledge about specific topical products, share of patients to whom the dermatologist has prescribed specific topical treatments, and physicians’ opinions toward a set of therapy attributes. We asked dermatologists to rate their agreement toward 8 statements concerning topical therapies. Statements included, “patients’ adherence affects effectiveness in real-life settings”, “gel formulations are more convenient to apply”, “fixed combinations are more effective than single products in real-life settings”, “higher patients’ adherence is associated with better quality of life outcomes”, “gel formulations are associated with increased adherence in real-life settings”, “patients adherence is a key issue in topical therapies”, “formulation is a key factors in ensuring adherence to topical therapies”, “adherence is negatively affected by poor convenience of use (*i.e.*, “messy” formulations, difficult to apply, unpleasant smell, etc.). Ratings occurred along a 10-point scale anchored at 0=totally disagree and 10=totally agree. Additionally, the survey prompted each dermatologist to assign a priority score to 8

therapy attributes, namely: effectiveness, tolerability (local), tolerability (systemic), adherence enhancing, time needed to exert clinical effect, convenience of application, skin adsorbtion, cost-benefit ratio. Ratings occurred on a 10-point scale. Finally, dermatologist were asked to provide satisfaction ratings about different topical therapies (*i.e.*, fixed combination of betamethasone/calcipotriol gel, fixed combination of betamethasone/calcipotriol ointment, clobetasol, tacalcitol) concerning the above mentioned attributes based on their own clinical experience. Again, ratings occurred along a 10-point scale anchored at 0=extremely unsatisfied and 10=extremely satisfied.

Statistical analysis

We computed single-attribute therapy ratings as the product of priority scores by the corresponding satisfaction ratings for each topical treatment. We then computed an overall therapy rating score by averaging single-attribute therapy ratings. The overall therapy rating was the primary outcome for the analysis. We tested differences in physicians' single-attributes and overall therapy ratings with random-intercept linear models to account for the clustering of ratings for different pharmaceutical products within clinicians. Finally, we tested the robustness of the associations observed after adjustment for confounding by patients' volume, share of patients with psoriasis seen in the past month, geographical region, knowledge of specific product with random-intercept linear models. All analysis have been performed with SAS 9.2®.

Results

Sample characteristics

Characteristics of study sample are summarized in Table I; 242 dermatologists participated in the survey. About 15% had seen more than 400 patients while around half had seen less than 200 patients in the month prior to the interview. In the same time frame, outpatients with psoriasis represented 13% of all patients seen at the surveyed dermatological clinics. However, there was a wide variation in practice patterns: 1/3 of dermatologist had seen more than 30 patients with psoriasis while around ¼ had seen less than 10 patients.

TABLE I.—*Sample characteristics.*

Characteristics	N. (%) or mean (SD)
Region	
North	95 (39)
Center	80 (33)
South	67 (28)
Overall patients' volume (1 month)	257 (201)
Share of patients with psoriasis (1 month)	18.3% (16.9%)
Share of with any topical therapy (past month)	80.2% (17.9%)
Share of patients with:	
Betamethasone/calcipotriol gel	70.2% (19.2%)
Betamethasone/calcipotriol ointment	20.8% (13.9%)
Tacalcitol	14.1% (8.9%)
Clobetasol	16.7% (11.9%)

Among patients with psoriasis, 80% have been treated with topical therapy. Therapy switch, a phenomenon associated with product wastage, was reported in 51% of patients treated with topical therapy, either changing active agents (67%) or formulations (33%). In the month prior to the interview, about 95% of dermatologists reported to have prescribed a calcipotriol/betamethasone dipropionate two-compound (50 µg/g; 0.5 mg/g) product gel, 70% clobetasol, 60% calcipotriol/betamethasone dipropionate two-compound (50 µg/g; 0.5 mg/g) product ointment, and 50% tacalcitol.

Dermatologists' expert opinions toward topical therapies

There was a strong agreement toward each statement concerning topical therapies. The average scores are reported in Figure 2. Most dermatologists (86.4-98.4%) reported strong or very strong agreement (score≥8) toward each statements whereas only 0.0-0.8% reported poor agreement (score≤3) toward each statements.

Dermatologists' therapy ratings

We observed statistically significant differences in dermatologists' overall and single-attribute therapy ratings across different therapeutic options (Table II). The associations observed was robust to adjustment for possible confounders (*i.e.*, patients' volume, share of patients with psoriasis seen in the past month, geographical region, knowledge of specific product). Adjusted ratings are reported in Table III.

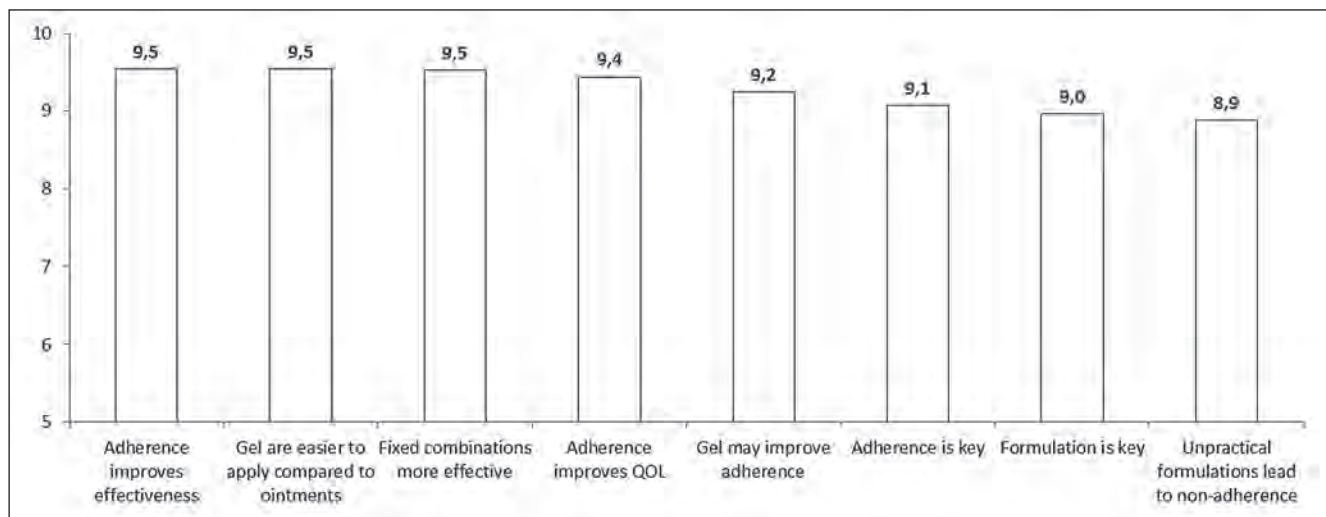


Figure 2.—Dermatologists’ agreement on 8 statements concerning topical therapy for plaque psoriasis. Physicians’ rated their agreement on a 10 point scale. Statements were: “patients’ adherence affects effectiveness in real-life settings”, “gel formulations are more convenient to apply”, “fixed combinations are more effective than single products in real-life settings”, “higher patients’ adherence is associated with better quality of life outcomes”, “gel formulations are associated with increased adherence in real-life settings”, “patients adherence is a key issue in topical therapies”, “formulation is a key factor in ensuring adherence to topical therapies”, “adherence is negatively affected by poor convenience of use (i.e. “messy” formulations, difficult to apply, unpleasant smell, etc).

TABLE II.—Single-attribute and overall therapy ratings across different topical treatments for plaque psoriasis.

	Betamethasone/ Calcipotriol Gel	Betamethasone/ Calcipotriol Ointment	Clobetasol	Tacalcitol	P*
	Mean (SD)				
Effectiveness	8.27 (1.37)	7.66 (1.72)	6.43 (1.89)	6.02 (1.70)	<0.05
Adherence enhancing	8.26 (1.42)	6.66 (1.68)	6.53 (2.09)	6.26 (1.57)	<0.05
Local tolerability	8.16 (1.46)	7.30 (1.77)	7.36 (1.81)	6.81 (1.80)	<0.05
Easy of administration	7.97 (1.43)	6.22 (1.70)	6.48 (2.53)	5.97 (1.68)	<0.05
Time-to-clinical efficacy	7.42 (1.54)	6.82 (1.75)	6.16 (2.00)	5.48 (1.71)	<0.05
Systemic tolerability	8.22 (1.72)	7.81 (1.92)	7.35 (2.15)	7.40 (2.05)	<0.05
Skin adsorbtion	7.77 (1.54)	6.06 (1.94)	6.51 (2.23)	5.90 (1.82)	<0.05
Cost-benefit ratio	7.55 (1.73)	7.20 (1.81)	5.08 (1.97)	6.68 (1.76)	<0.05
Overall therapy rating	7.95 (1.73)	6.98 (1.22)	6.58 (1.46)	6.30 (1.27)	<0.05

TABLE III.—Adjusted single-attribute and overall therapy ratings across different topical treatments for plaque psoriasis.

	Betamethasone/ Calcipotriol gel	Betamethasone/ Calcipotriol ointment	Clobetasol	Tacalcitol	P*
	Mean				
Effectiveness	8.21	7.59	6.36	5.99	<0.05
Adherence enhancing	8.19	6.62	6.50	6.22	<0.05
Local tolerability	8.14	7.28	7.36	6.85	<0.05
Easy of administration	7.95	6.23	6.48	5.97	<0.05
Time-to-clinical efficacy	7.34	6.76	6.06	5.44	<0.05
Systemic tolerability	8.19	7.79	7.32	7.42	<0.05
Skin adsorbtion	7.80	6.09	6.55	5.94	<0.05
Cost-benefit ratio	7.51	7.13	5.75	6.66	<0.05
Overall therapy rating	7.92	6.94	6.56	6.30	<0.05

Discussion

In this large, nation-wide survey of Italian dermatologists' practices, there was a strong agreement among physicians on the importance of achieving optimal adherence to topical therapies in order to translate evidence from clinical trials into real-life settings. In line with previous evidence from observational and randomized clinical trials as well,^{8, 10, 16} most dermatologists strongly agreed that gel formulations over ointments and fixed combination over single products administered in free associations are more convenient for their patients, may enhance adherence and may result in increased real-life effectiveness.

Such results are confirmed by the analysis of therapy ratings provided by the physicians interviewed in our survey. Dermatologists reported higher overall therapy ratings for the fixed combination of betamethasone/calcipotriol gel compared to single products (*i.e.*, tacalcitol and clobetasol) and betamethasone/calcipotriol ointment. Of note, this difference was robust to adjustment for proxies of clinical experience in the field of psoriasis (*i.e.*, number of patients seen in the month prior to the interview, knowledge of specific topical therapies) and geographical region. In a secondary analysis, we evaluated single-attribute drivers of the difference observed in the overall score. Again, betamethasone/calcipotriol gel was considered by dermatologists' superior to single products in all 8 attributes and superior to the ointment formulation in respect to adherence promotion, local tolerability, ease of administration and skin adsorption. The latter observation is consistent with recent results from an interim analysis of an ongoing observational study showing that betamethasone/calcipotriol gel was more convenient, easier to use and faster to apply than the ointment formulation.¹⁹ Hence, it is not surprising that the fixed combination betamethasone/calcipotriol gel was prescribed to most patients seen in the month prior to the interview, suggesting that the uptake of current evidence from RCTs into clinical practice was very high among the participant dermatologists.

In the lack of conclusive real-life evidence^{10, 20} showing a link between the fixed combination of betamethasone/calcipotriol gel, increased adherence and better real-life effectiveness, expert opinion may provide useful directions for clinical decision making. It is important to highlight that the opinions col-

lected in our survey are consistent with the evidence from existing literature. A systematic review,⁸ and an integrated safety analysis of RCTs of RCTs combining results of 3767 patients receiving the treatment¹⁸ have demonstrated that the fixed combination betamethasone/calcipotriol gel has superior efficacy and safety over the individual active components administered as monotherapies in the gel vehicle and is well tolerated in patients with mild-to-moderate psoriasis. Additionally one study show greater efficacy of the fixed combination betamethasone/calcipotriol gel in patients with scalp psoriasis.²¹ Further, a systematic review of long-term studies has shown that the fixed combination betamethasone/calcipotriol gel consistently shows significantly lower side-effects and drug-related adverse events compared to monotherapy over a 52 week observation period, results discounting concerns of corticosteroids toxicity in the maintenance phase of therapy when associated to a vitamin analog.¹³

The improved efficacy and safety of the fixed combination is partly explained by the synergistic effect of corticosteroids and calcipotriol in down-regulating the skin inflammatory response and skin cell proliferation in fast-growing keratinocytes and by the antagonist effect of calcipotriol on the skin atrophy produced by corticosteroids via stimulation of collagen synthesis and keratinocyte proliferation in slowly proliferating layers.²²

However, other factors may contribute to the superior efficacy and safety of the fixed combination betamethasone/calcipotriol gel. A recent phase IV RCT has shown that patients switching from previous therapy to an 8-week treatment course plus a 56-week maintenance phase with the fixed combination betamethasone/calcipotriol gel reported strong preference for this therapy compared with previous treatments and achieved excellent effectiveness. In particular patients were more satisfied about treatment effectiveness, ease of application, side effect burden, tolerability,²³ all conditions possibly associated with improved adherence.^{10, 13} These results are confirmed by two observational open-label studies showing better tolerability and greater treatment satisfaction in patients treated with the fixed combination betamethasone/calcipotriol gel over competing alternatives.^{24, 25} It is also evident from the literature a greater adherence of the fixed combination betamethasone/calcipotriol once daily in gel formulation *vs.* ointment formulation, reported up to 19% or

higher, due to the better patient satisfaction mostly in terms of application timings.

Additionally, it has been shown that patients treated with betamethasone/calcipotriol gel applied significantly less product compared to those treated with single products, a finding possibly explained by drug over-use.²⁶ From the data available in the literature,^{25, 27} it has been estimated an average consumption of 17,35 g per week with the fixed combination betamethasone/calcipotriol gel in patients with mild to moderate psoriasis (BSA >4% or an average PASI score of 7.7). Despite most studies on adherence focus on drug underuse and its detrimental effects on effectiveness, over-use might be a relevant issue with topical therapies and may cause significant side effects and health-care costs.

Finally, indirect evidence of better real-life effectiveness and safety of the fixed combination betamethasone/calcipotriol gel over monotherapies or multiple monotherapies in the treatment of plaque psoriasis can be obtained from micro-level pharmacoeconomic studies. In clinical practice topical treatments with more than one product may jeopardize the real-life efficacy due to poor patient compliance. An analysis of US insurance claims data showed that patients who only used the fixed combination gel (N.=367/1923) to treat both their body and scalp psoriasis had significantly lower overall health-care costs, needed fewer outpatient visits and used less systemic agents compared with patients who used multiple scalp and body psoriasis medications (N.=1556/1923), during a 6-month observation period.²⁸

Limitations of the study

Our analysis of dermatologist opinion have some limitations. First, the sample of Italian dermatologists enrolled was non-random and there is some risk that results may not be generalizable to all dermatologists in Italy. Conversely, data suggest that participating physicians had clinical experience on the treatment of psoriasis and excellent knowledge of available topical therapies for the disease, thus lending credibility to the expert opinion provided. However, expert opinion can never substitute empirical evidence and further, real-life observational open-label studies should corroborate recommendations emerging from physicians' consensus. Finally, the questionnaire adopted to collect participants' ratings

of current topical therapy has never been validated. Despite the instrument tap important attributes of topical therapies, we cannot exclude that further key element have been overlooked.

Conclusions

In conclusion, our data show that the fixed combination of betamethasone/calcipotriol gel is strongly preferred as topical therapy by most dermatologists with experience in the treatment of plaque psoriasis. The fixed combination was considered superior to monotherapies in all the eight attributes considered which tapped aspects of real-life effectiveness, adherence promotion, toxicity, convenience of use. Of note the fixed combination of betamethasone/calcipotriol gel was considered superior to the ointment formulation concerning adherence promotion and convenience of use. Such findings are in line with evidence from randomized controlled trials and few observational studies demonstrating superior clinical outcomes, quality of life, tolerability and lower risk of side effect in patients treated with the fixed combination of betamethasone/calcipotriol gel. Further long-term open label observational research should corroborate dermatologists' opinions collected in this survey.

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Funding.—This study was funded by an unrestricted grant by LEO Pharma Inc. to Luca Neri.

Conflicts of interest.—Both authors work as consultants for LEO Pharma, Rome, Italy.

Received on November 21, 2014.

Accepted for publication on December 18, 2014.

CUTANEOUS VASCULITIDES: A CLINICAL AND PATHOLOGICAL PERSPECTIVE

Guest Editors: G. Borroni, C. Tomasini, E. Berti

G ITAL DERMATOL VENEREOL 2015;150:27-8

To classify or to discern? That's the problem

G. BORRONI ¹, C. TOMASINI ², E. BERTI ³

An issue on histopathological changes of cutaneous vasculitides gives rise to a main problem, whether to give room to a systematic classification of the different types of vasculitides, or to analyse vasculitides and their histopathological features from the point of view of their most important histopathological simulators.

Since a widely accepted classification of cutaneous vasculitides has been traditionally based on the anatomical type of vessel involved (veins and arteries) of small, medium and large size, and on the type of inflammatory infiltrate, *i.e.* non-granulomatous (neutrophilic, lymphocytic) and granulomatous, a traditionally-based monographic approach may seem, to some extent, effete. For that reason, the invited papers have been selected on the base of their original approach to the problem. Thus, the fascinating paper by Angelo Cassisa ¹ analyses minutely the role of all the players of the complex pathogenetic pathway of the cutaneous and systemic vasculitides, rather than proposing a mere classification of vasculitides.

Angelo Valerio Marzano *et al.*² describe peculiar types of small vessel vasculitides, but from the specific point of view of urticarial vasculitis and urticarial autoinflammatory syndromes. Giovanni Borroni *et al.*³ consider the wide spectrum of the vasculitides of the small, medium and large size, and of granulomatous and non-granulomatous types, but from the pediatric viewpoint.

The exhaustive paper by Carlo Tomasini ⁴ consid-

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ers the histopathological differential diagnosis of vasculitis and vasculopathy, but in the complex context of the infectious emergencies.

A changing view on granuloma faciale vasculitis is proposed by Camilla Vassallo *et al.*⁵

The serious problem of misdiagnosing intravascular large cell lymphoma or lymphomatoid granulomatosis as inflammatory or vasculitic processes is approached by the masterly done paper by Dario Tomasini and Emilio Berti.⁶

In the same way, the paper by Caterina Ferrelli *et al.*⁷ analyses acutely the histopathological changes in four cases of diffuse dermal angiomatosis, in differential diagnosis with vasculitis and vasculopathy.

In the vast majority of the papers, histopathological findings have been supported by the constant presence of a specific clinical correlation.

For all these reasons, this issue on histopathological changes of vasculitides is mostly dedicated to the pleasure and consideration of dermatopathology thinkers, rather than to dermatopathology classifiers.

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Cutaneous and systemic vasculitis: cellular players and pathogenetic aspects

A. CASSISA

Vascular wall damage, inflammatory cell recruitment and subsequent structural remodelling define a vasculitic process. Histopathological classification of vasculitis is based on the caliber of the vessel involved and on the prevalent type of inflammatory cells (neutrophils in acute forms, lymphocytic for chronic, histiocytic for granulomatous). A large amount of information is emerging from the literature on the complex pathophysiology of the cellular components of vessel wall. For instance, endothelial cells not only have the task to cover the inner surface of the vascular system but they also play an active role in tuning the immunological response in a very sophisticated way. Neutrophils are not only terminally differentiated cells sacrificed for a valuable cause. Cellular types of the perivascular microenvironment play roles one time not expected. The spread of the inflammatory process into the vascular wall is not necessarily inside-out. These and other selected concepts will be discussed in this paper.

KEY WORDS: Vasculitis - Endothelial cells.

The dermal microvasculature consist of two parallel networks of paired arterioles and venules a deep one and a superficial one coursing parallel to the epidermal surface. The deep arteriolar plexus derive from arterioles and arteries crossing subcutaneous septa.¹ Venules of the deep vascular plexus drain in larger veins in subcutaneous layer. At this junction valves are present to regulate unidirectionally the blood flow. Vertical oriented vessel interconnect superficial and deep plexus, they run in part along sweat gland excretory ducts. Capillaries of the deep vascular plexus form collaterals nets around pilose-

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baceous unit and erector muscle (vasa musculorum). Anastomotic vessels connect arterioles and venules of the deep vascular plexus and are under the direct control of autonomic nervous system. Their regulation is relevant in regulating body temperature. They are particularly abundant at the fingertip.² Papillary dermis is served by arcade like capillaries arising from arterioles of the superficial vascular plexus. At the end of their descending branch, at the level of the tip of rete ridges anastomose with venules. The venular part of papillary capillaries is more permeable to inflammatory cells. Changes of papillary vessels are very prominent in various type of dermatitis, psoriasis over all, but are not ordinarily included in the vasculitis chapter. Cutaneous vascular system is more complex than other organs because it combines various sophisticated functions only partially carried out by other organs of the body.

Dermal microvascular unit

The dermal microvascular unit is composed of different cellular elements that express common antigens, are spatially related, perform integrated functions, are involved in inflammatory and neoplastic processes, may, in particular situations, transdifferentiate from one to another.³⁻⁹ A neural plexus is anatomically and functionally integrated with vascular structures and neighbouring immunologic cells.¹⁰

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Endothelial cells, pericytes, dermal dendrocytes, mast cells, T cells belong to microvascular unit and will be discussed below.

Endothelial cells

ECs functions and interaction with immune cells

Endothelial cells (ECs) are flat cells layering the vascular lumen. Their major functions are to provide a smooth surface for an efficient blood flow, regulate the passage of macromolecules and oxygen supply to organs and tissues, and block fibrin formation. Endothelial cells are not a homogeneous population of cells, there are inter-organ and intra-organ specific differences that render them more or less susceptible to activation in response to a specific stimulus or otherwise susceptible to damaging factors. ECs from different organs present a variegated response profile to inflammatory cytokines and effector immune cells. Actually, there is no recognised diagnostic marker that can distinguish different subsets of microvascular endothelial cells (MECs) but it is likely that immune effectors cells can. For example, we know that ECs and NK cells modulate each other through cytokine release. In an experimental study the response of renal MECs to inflammatory cytokines and to proteinase 3 (PR3) was stronger than lung and dermal MECs in activation and degranulation of NK cells.¹¹ Other evidences have shown that renal and lung activated ECs express more intensely than cutaneous ECs cognate receptors for NK cells in granulomatosis with polyangiitis (GPA).^{11, 12} Experimental studies demonstrate that shear stress, IL2 activation, Mg2 dependent adhesion, TNF, perforin/granzyme pathway are all variables in regulating NK killing of endothelial cells.¹³ This may explain why a vascular district may be more heavily involved than another in a vasculitis process.

Intercellular junctions

Adherents, tight and gap junctions dynamically connect endothelial cells and provide a sophisticated communication system. In general the density of tight junctions is inversely proportional with a dynamic trafficking of circulating cells.^{14, 15} Cell to cell junction may be influenced structurally by inflammatory molecules. This interaction results in

new dyapedesis sites in the course of different inflammatory scenarios. Vascular endothelial (VE)-cadherin, an endothelial cell-specific adhesion molecule, which plays a critical role in angiogenesis and endothelial integrity, rise in the serum in the course of HSP¹⁶ suggesting an active remodelling of intercellular junctions in the course of vasculitis. VE-cadherin may also act as a transducer of shear stress signals acting in concert with VEGFR2.¹⁷ Autoantibodies against vascular cadherins have been demonstrated in rheumatoid arthritis and other autoimmune diseases and are responsible of structural endothelial changes such as endothelial cell retraction, redistribution of VE-cadherin, and the formation of numerous intercellular gaps.¹⁸ Heterotypic cell-cell contacts are also present and are being investigated as a relevant mechanism in vasculitis processes. β 2 integrin mediates the formation of close neutrophilic-EC cell synapse-like structures through which active MPO is transferred into the cytoplasm of the endothelial cells directly contributing to the vascular damage.¹⁹ Damage of membrane junctions produce also detachment of endothelial cell in the blood flow. These cells, identified as inflammatory endothelial cells, express vascular-adhesion protein-1 (VAP-1) and MHC class I-related chain A (MICA). They represent a disease activity marker in vasculitis. In a study on GPA it has been suggested that circulating IEC may contribute to the pathogenesis/progression of the disease because they can interfere with endothelial progenitor cells in their reparative role.²⁰

The extracellular portion of the numerous membrane-bound macromolecules on the apical surface of endothelial cells constitute the glycocalyx (GCX). GCX is mainly formed from molecules with receptor and adhesion functions actively regulating cell traffic across the vascular wall. Recent studies have also investigated a new role for the GCX. This molecular layer can in fact sense the shear stress of flowing blood and transmits the force through the cytoskeleton so generating a biochemical response (mechanotransduction). The shear stress response system consists of numerous genes, proteins, and biochemical molecules. Hemodynamic force exerts anti-inflammatory effects on cytokine-activated endothelium by attenuation of cytokine expression and neutrophil firm arrest.²¹ Shear-dependent inflammation is, for example, a key feature of atherosclerosis. Although in experimental in vitro studies venular shear stress reduce neutrophils transmigration across the endothe-

lium²² no data are available about its effective role in vasculitis and on the correlation between shear stress and the predisposition of a particular anatomic district to develop a vasculitis process.

VEGF

One of the major factors to which ECs are sensitive is VEGF (vascular endothelial growth factor) a potent angiogenic cytokine. VEGF increases also vascular permeability to fluids and plasma proteins. It is estimated that VEGFR activity is 50,000 times higher than that of histamine in enhancing the vascular endothelium permeability. It also stimulates mitotic activity, regulates chemotaxis, endothelial cell migration, interstitial collagenase production, releases von Willebrand factor and enhances procoagulant activity.²³ It also plays an important role in remodelling the extracellular matrix. Various cell types can produce VEGF: activated T lymphocytes²⁴ activated platelets,²⁵ activated neutrophils,²⁶ epidermal cells,²⁷ and monocytes. Even dermal fibroblasts constitutively produce VEGF. Impairment of VEGF signalling with age is associated with a reduction of dermal blood vessels and the number of dermal fibroblasts.²⁸ VEGF through the increase of vascular permeability influences the persistence of the inflammatory conditions. Moreover, it regulates in various ways the immunological response, and plays a role in autoaggressive phenomena as well as immediate- and delayed-type hypersensitivity. VEGF genetic polymorphism may predispose ethnic groups to develop vasculitis.²⁹ Specific VEGF alleles are frequently demonstrated in patient with giant cell arteritis (GCA).³⁰

In leukocytoclastic (hypersensitivity) vasculitis VEGF is overexpressed suggesting a relevant role in different phases of the disease.³¹ In EPA infiltrating eosinophils express VEGF in cytoplasmic granules and VEGF blood levels are correlated with disease activity.³² Serum levels of VEGF are markedly elevated also in patients with GPA.^{33, 34} All these data suggest that high blood levels of VEGF are not specific for a subtype of vasculitis but instead correlate generically with a vascular damage.

Another fundamental mechanism regulating the pathophysiology of endothelial cells is represented by High-mobility group box-1 (HMGB1). HMGB1 is a nonhistone nuclear protein that binds DNA, regulate transcription and determine chromosomal architecture. Outside the cell, HMGB1 activates the

innate system and mediates a wide range of physiological and pathological responses. HMGB1 activation may represent a common inflammatory pathway in many form of vasculitis. Its role has indeed been studied in Henoch-Schönlein purpura (HSP),³⁵ AAV (antineutrophil cytoplasmic antibodies [ANCA] associated vasculitis),³⁶ SLE associated vasculitis.³⁷

Endothelial progenitor cells

ECs are presumed to derive from a common precursor for hematopoietic and endothelial cell line, the hemangioblast.^{38, 39} A few endothelial progenitor cells circulate in peripheral blood providing angiogenic functions. Endothelial to mesenchymal cell transition is a phenomenon according to which endothelial cells loose CD31 and vascular endothelial cadherin (VE-cadherin) and express mesenchymal markers including procollagen 1, fibroblast-specific protein-1, and α -SMA.^{40, 41} Endothelial-to-mesenchymal transition is regulated by inflammatory cytokines such as FGF and TGF β .⁴² Glomerulosclerosis, the renal end stage of many vasculitic processes, is sustained by TGF- β mediated endothelial-mesenchymal transition.^{43, 44} The same mechanism is implicated in the pathogenesis systemic sclerosis.⁴⁵

ECs and neurotransmitters

Norepinephrine (NE) and the cotransmitter adenosine-5'-triphosphate (ATP) regulate the expression and release of inflammatory factors from ECs. Among these IL-6 is implicated in the induction of Th17 cells. Th17 lymphocytes augment in stress-induced exacerbation of psoriasis, and perhaps, other skin disorders involving Th17-type immunity.⁴⁶ Th17/Treg ratio is altered in many forms of vasculitis. It resulted abnormal for example in Chinese children with HSP.⁴⁷ Administration of norepinephrine promoted, in experimental conditions, pulmonary angiitis in mice together with reduction of Tregs cells.⁴⁸ These observations support the theories about the importance of a still little known neural-immunological network.

Microvesicles

Microvesicles (MVs) include microparticles (MPs) and exosomes, are membrane vesicles released upon activation or apoptosis from various cell types includ-

ing neutrophils, platelets, endothelial cells. These phospholipid vesicles are generated in activated cells by the loss of phospholipid asymmetry a process that involves degradation of cytoskeletal proteins.⁴⁹ Microvesicles transport inflammatory molecules in the vascular system propagating endothelial damage.^{50, 51} CD18 antigen expressed on endothelial cells is the molecular target of microparticles detached from primed neutrophils. In AAV this molecular interaction results in release of inflammatory cytokines (IL6, IL-8), expression of intercellular adhesion molecule-1 and production of endothelial reactive oxygen species by endothelial cells that sustain the inflammatory process.⁵² Microparticles are augmented in children with AAV. MPO and PR3 contained in microvesicles exert direct proteolytic activity on the endothelial barrier. Further damage results from complement activation and thrombin generation.⁵²

Pericytes

Pericytes are stromal cells disposed around endothelial cells. They are characterized by long cytoplasmic processes extending from their body toward endothelial surface. Pericytes to endothelial cells contacts are provided by gap junction, adherent junctions and thigh junctions. Actin filaments are responsible for gap formation in the vessel wall in response to various inflammatory stimuli. Common ultrastructural changes have been documented in pericytes and endothelial cells in allergic vasculitis^{53, 54} and in erythema elevatum diutinum.⁵⁵ The glomerular podocytes in the kidney are the cell equivalent of pericytes in the skin. Cross-talk between pericytes and endothelial cells influence immunologic response can contribute to the persistence and spreading of a vasculitic process.^{56, 57} Pericyte lamination around vessel wall is considered a sign of chronic damage and a diagnostic clue for lymphocytic vasculitis.⁵⁸ Electron microscopic studies have demonstrated the presence of viral inclusion in both pericytes and endothelial cells in various vasculitic processes: leukocytoclastic vasculitis associated with herpesvirus infection,⁵⁹ equine arteritis virus (EAV) arthritis,⁶⁰ hepatitis C.⁶¹

Veil cells/dendritic cells

Veil cells cover the vessel circumferentially. They are mesenchymal cells separating the capillary wall

from dermal connective. Their ultrastructure resembles a fibroblast.⁶² Their function is not yet completely known. Abnormal collagen production by veil cells seems responsible of perivascular fibrosis in collagenous vasculopathy.^{63, 64} According a 3D reconstruction of human skin veil cell coincide with dermal dendritic cells.⁶

DCs

Dermal dendritic cells

Dermal DCs origin from bone marrow precursors, exhibit immunohistochemical features in common with cells of the mononuclear-macrophage lineage and display phagocytic functions. Dermal dendrocytes are spatially related to mast cells, monocyte/macrophages, microvessels, and nerves. In a 3D reconstruction of human dermis it was elegantly demonstrated with the use of electron microscopy that dermal dendritic cells are actually non-dendritic. DCs are equipped with lamina cytoplasmic extension called membranous flaps that wrap around, more or less extensively, neighbouring cells and other structures.⁶⁵ It is likely that these cells actively participate in vasculitic processes as members of dermal microvascular unit. DCs are critical for the induction of primary immune responses. In erythema elevatum diutinum, a leukocytoclastic vasculitis followed by a fibrotic process, an increased number of FXI-IIa+ dermal dendritic cells has been documented.⁶⁶ Dendrocytosis of perivascular dendrocytes has been described in HSP.⁶⁷ So DCs add to neutrophils in the production of nuclear fragments. Perivascular dendrocytes are distinct from CD1a+ Langerhans type dendritic cells. This last type of dendritic cell may however accumulate in the perivascular dendritic meshwork in pathologic conditions like in the late phase of leukocytoclastic vasculitis and in lymphocytic vasculitis.⁶⁸ Moreover, they may play a role in presenting neutrophil cytoplasmic antigens to T cells thus perpetuating the vasculitic process.

Adventitial DCs

An adventitial DC network is present into arterial branches of 3 to 5 mm diameter, such as temporal arteries. DCs located in adventitial-media border and are responsible in initiating the inflammatory process

in GCA⁶⁹ and Kawasaki disease (KD).⁷⁰ Activated DCs in the adventitia recruit CD4⁺ T lymphocytes, cause local clonal expansion, polarize CD161⁺ T cells lymphocytes into Th1 and Th17 cells⁷¹ that produce IFN- γ ⁷² and IL-17, in turn these cytokines activate macrophages, giant cells and smooth muscle cells inducing vascular remodelling leading to ischemic manifestations of GCA. DCs participate also in granuloma formation. Macrophages infiltrating the adventitia produce also IL-1 β and IL-6 that are responsible for general symptoms encountered in GCA.⁷¹ The initial activation of DCs in GCA depend from innate immunological mechanisms. Toll-like receptor 4 (TLR4) on the membrane of DCs is activated by lipopolysaccharide derived from enterobacteria.⁷³ A switch from innate to adaptive immune response depend on migration of DCs to lymphatic organs in which they present a not yet recognized antigen to lymphocytes. The occasional presence of plasma cells in GCA⁷⁴ may indicate also pleiotropic effect eliciting alternative modalities of immune response. For all practical purpose, two main sets of cytokines may be activated in GCA: the IL-6-IL-17 axis that is highly responsive to standard corticosteroid therapy, and the IL-12-IFN- γ axis that is not responsive to corticosteroid therapy.⁷⁵ Understanding these mechanisms helps to choose the right therapy.

DCs in other tissues

In ANCA associated glomerulonephritis DCs accumulate in kidney in association with T cells. It is not yet established whether the inflammatory response is dampened or facilitated by this DC-T-cell interaction.⁷⁶

DCs play an important role in induction of immunological tolerance and orchestrate the quality of T-cell-mediated immune response. In eosinophilic granulomatosis with polyangiitis (EGPA) the rate of CD83⁺ DCs maturation from monocytes is related to disease activity and to the number of T regulator cells (Treg). CD83⁺ DCs increase during the remitting phase of the disease suggesting an active role in modulating Treg phenotype.⁷⁷

Mast cells (MCs)

MCs are bone marrow derived cells that are dispersed throughout the body, are the repository of histamine, contribute to the development and preserva-

tion of the endothelium and small blood vessels, and influence the pathophysiology of inflammatory conditions.^{78, 79} Their concentration is high at mucosal surfaces, where they respond to external stimuli. MCs contribute to the constitution of vascular unit.^{80, 81} They are partially wrapped by membrane flaps of DCs in a ball and socket way.⁶⁵ MCs plasticity determine their different role pro- or anti-inflammatory according to the signals that they receive from the microenvironment. In immune complex related vasculitis, such as leukocytoclastic vasculitis, activated mast cells contribute to increase vascular permeability and leukocytes migration. Interestingly this mechanism is independent of integrins or selectin-mediated rolling. A vicious mechanism involving CX3CL1-CX3CR1-axis and TNF-alpha recruit activated mast cell in leukocytoclastic vasculitis.⁸² Other cellular types are involved in this mechanism and therapeutic strategies are being developing to block them.⁸³ In an experimental model of rheumatoid factor mediated vasculitis IC bind to Fc γ RIII of activated MCs that in turn produced TNF responsible for the vascular damage.⁸⁴ Perivascular accumulation of MCs has been demonstrated in the skin lesion of cutaneous allergic vasculitis⁸⁵ and in urticarial vasculitis associated with systemic sclerosis.⁸⁶ In drug induced vasculitis MCs may be activated directly by the drug and act as effectors cells together with neutrophils, lymphocytes, macrophages.⁸⁷ In experimental AAV activated MCs reduced inflammatory reaction and prevented glomerular damage. IL10 dependent recruitment of Tregs orchestrate by MCs was the key mechanism in this model.⁸⁸ In GCA activated MCs associate with CD3⁺ T cells and CD31/CD34⁺ neointimal microvessels suggesting their active involvement in promoting neovascularization and neointimal thickening in this form of vasculitis.⁸⁹

Macrophages

Macrophages differentiate from blood monocytes that are recruited from blood in the inflamed tissue where the process of differentiation takes place. This step is characterised by loss of MPO and PR3 on the cell membrane rendering macrophages insensitive to activation by ANCA. Macrophages main task is in clearing apoptotic neutrophils and NETS accumulated around vessels in vasculitis. This process is called efferocytosis (from effero, "to carry to the grave",

“to bury”).^{90, 91} Macrophages express Fc γ RIII and Fc γ RI that recognise immune complexes so they play a role in hypersensitivity vasculitis.⁹² In mice with inactivated mast cells inverse Arthus reaction can take place equally with the only contribution of macrophages.⁹³ A favorable microenvironment favour the aggregation of macrophages in granulomas in several forms of vasculitis. Granulomas are highly organized structures favouring T cell-macrophages interaction with reciprocal activation. Aberrant Th1 and Th17 cells may be formed in these niches and seed into the circulation sustaining systemic inflammation and chronicity of the process.⁹⁴

Neutrophils

Neutrophils derive from bone marrow precursors and are the most abundant white cell circulating in the blood. Their main and best-known function is phagocytosis. Nevertheless in the last years other features have been defined. They have a unique way of dying called NETosis which stands for neutrophils extracellular traps (NETs) formation. As a matter of fact stimulated neutrophils extrude intracellular organelles together with nuclear proteins, mainly histones, to form a net that entraps extracellular microbes. They represent a fundamental mechanism of innate immune response.^{95, 96} Whilst in infections NETs are induced by microorganisms and are rapidly removed from the tissue in autoimmune or autoinflammatory disorders spontaneous production on NETs may occur and their clearance is impaired so favouring formation of autoantigens against the intracellular molecules exposed on NETs.⁹⁷ In vasculitis and other inflammatory processes, activated endothelial cells induce NETs formation.⁹⁸ Due to their antigenic content NETs are implicated in the pathogenesis of AAV.⁹⁹ In glomerulonephritis developing in the course of AAV the presence of intraglomerular NETs has been directly documented by differential interference contrast microscopy.¹⁰⁰ Inability to degrade NETs or the presence of subsets of neutrophils with a NETosis propensity may favour autoimmune diseases like systemic Lupus erythematosus.^{101, 102} NETs can damage directly endothelial layer acting as a glutinous web that stick and on endothelial membrane.⁹⁹ PR3 and MPO are present in NETS and can activate plasmacytoid DCs and autoreactive B cells in a Toll-like receptor 9-dependent manner.¹⁰³

NETs formation induced by bacterial infections such as *Staphylococcus aureus*, a potent NETs inducer, may explain the link between bacterial infections and autoimmune vasculitis relapses.¹⁰⁰ Aberrant generation of extracellular traps has recently been implicated in a number of cutaneous pathologies including small vessel vasculitis.^{98, 104} NETs have in addition procoagulant and prothrombotic activity further aggravating vascular damage. Histones are the largest molecular component of nets. They exert a potent inflammatory stimulus^{105, 106} and prevent extracellular DNA degradation favouring the formation of anti-DNA autoantibodies. A vicious cycle involving MPO-ANCA and the regulation of NETs could be critically involved in the pathogenesis of MPO-ANCA-associated microscopic polyangiitis.¹⁰⁷ Pathogenic ANCAs can originate from precursor natural autoantibodies.¹⁰⁸ These natural autoantibodies are normally present in small quantities in healthy individuals so the shift to a pathologic state requests triggers or an imbalance in regulatory activity of T-cell and B-cell.

Neutrophils can modulate inflammatory mechanism in other ways. Neutrophil to dendritic hybrid conversion has been demonstrated in living animals.¹⁰⁹ Neutrophil-B-helper cells (NBH) seem to be involved in T-independent B cell response *via* TRAP-like structures.¹¹⁰ This hypothesis has been however recently challenged.¹¹¹ In GCA a dysregulated neutrophil subpopulation cross talking with T lymphocytes may influence the progression of the disease despite immunosuppressive therapy.¹¹²

Eosinophils

Eosinophils are bone-marrow derived cells characterized by cytoplasmic granules containing a protein pool with toxic activity. Eosinophils homeostasis is very important in our body. Major basic protein and eosinophilic cationic protein can directly kill metazoan parasites but can also cause tissue damage. Eosinophils protein granules induce histamine release from basophils. Secretion of mediators by eosinophils is regulated by complex and partially understood mechanisms. IL5 is the principal regulator of eosinophilic pool and differentiation. Interestingly a basic IL5 production is regulated by Type2 innate lymphoid cells (ILC2) disposed in close association with blood vessels. They are also involved in

the circadian eosinophilic cycling.^{113, 114} Eosinophils recruitment is also mediated by GM-CSF, leukotriene B4, platelet activation factor, platelet activation factor, complement fraction 5. In EGPA IL5 overproduction by Th2 lymphocytes recruit and activate eosinophils.^{115, 116} Another molecule, eotaxin-3 (CCL26), play a major role in recruiting eosinophils in EGPA.¹¹⁷ Eotaxin-3 concentration in blood seems to be a more reliable marker of disease activity than the number of circulating eosinophils.¹¹⁸ Phenotypical changes in membrane receptor CCR3 modify eosinophils sensibility. CCR3R genetic variants are associated with KD occurrence.¹¹⁹ Mutation of the platelet derived growth factor receptor gene (PDGFRA) may be useful in some cases to discriminate between eosinophilia associated with systemic vasculitis with clonal hypereosinophilia.¹²⁰

Eosinophils primed by IL-5 or IFN- γ rapidly expel ETs (extracellular traps) in response to stimulation with LPS, eotaxin, complement factor 5a (C5a) or infection with Gram-negative bacteria. Eosinophils ETs are different from neutrophils ETs because are formed by both nuclear and mitochondrial DNA and are produced in a ROS-dependent manner. They contain also cytoplasmic granules but lack cytosolic proteins.¹²¹

Eosinophils are present in various proportion in many cutaneous vasculitis patterns: drug related leukocytoclastic vasculitis, eosinophilic vasculitis, urticarial vasculitis, granuloma faciale, erythema elevatum diutinum (rare), EGPA, GPA. Eosinophils rather than monocytes/macrophages are the main source of the plasma cell survival factors APRIL and IL-6. In the murine bone marrow APRIL produced by eosinophils contribute to the formation of plasma cell niches.¹²²

Eosinophils together with plasma cells are a common finding in granuloma faciale, and GPA.

Lymphocytes

Dermal T cells are predominantly disposed in close proximity of dermal vessel in superficial dermis¹²³ and take part in the microvascular unit (see above). CD4⁺ lymphocytes with effector memory phenotype (CD45RA⁻; CD45RO CCR7⁻) constitute the main cellular subtype. They express the skin addressins CLA, CCR6, and CCR4. Relationship between lymphocytes and the endothelial barrier are

regulated by sophisticated and still not completely unveiled mechanisms. Recently the term “tenertaxis” has been coined to describe a transcellular role of endothelial crossing by witch lymphocytes extend invadosome-like protrusions (ILP) into endothelial cell surface corresponding to the point of endothelial least cytoskeleton resistance. ILP deform the nuclear lamina, distort actin filaments and ultimately breach the barrier.¹²⁴ Interestingly lymphocyte transendothelial migration is promoted by endothelial chemokines stored in vesicles docked on actin fibres beneath the plasma membrane.¹²⁵ According to this mechanism, the establishment of a chemokine gradient outside ECs is not strictly necessary to sustain the transmigration of lymphocytes into inflammatory tissues and through the vessel.

T cell-mediated immunity is implicated in a number of vasculitis.¹²⁶

Tregs dysfunction or an altered Th17/Treg ratio is a constant finding in many form of vasculitis. It has been documented in GPA,^{127, 128} KD,¹²⁹ GCA,¹³⁰ Churg-Strauss syndrome (CSS),¹³¹ AAV.¹³² A defective CD4⁺ T cell population resistant to Treg cell suppression has also been described.¹³² Fc-specific Tregs, a subset of Tregs recognizing the heavy chain constant region of immunoglobulin G (Fc), are activated by intravenous immunoglobulin therapy secrete IL-10 downsizing vascular inflammation in KD¹³³ (Franco A). Tregs can be increased for therapeutic purposes by the infusion of autologous mesenchymal stromal cells. Promising results have been obtained in the treatment of AAV.¹³⁴

Natural killer cells are innate effector cells. They play a critical role in the early defence against viral infection and malignant transformation and in non-bone marrow allograft rejection. NK lymphocytes seems to be able in recognising different organ specific endothelial cells at least in experimental studies.¹³ In AAV increased expression of TLR in NK has been documented.¹³⁵ B lymphocytes are classically identified with the process of plasma-cell differentiation. A novel population of B cells with long dendrites and uninvolved in follicular structure formation has recently been described in GPA.¹³⁶ These B lymphocyte subtype has been previously described in the context of orofacial granulomatosis.¹³⁷ Their persistence in tissue and proliferative fraction seems to be APRIL and BAFF dependent. Immunohistochemistry demonstrated positivity for these two B survival factors in granulomas. B den-

drific lymphocytes were also spatially related to PR3 positive cells the main target of autoantibodies produced in GPA.¹³⁶ Another aspect of GPA is the role of innate-like CD4⁺ T cells subpopulation expressing NK receptor NKG2G that exert MHC-independent cytotoxicity toward selected microvascular endothelial cells expressing the cognate ligands of NK cell receptors. IL15 seems to drive further expansion of this subpopulation in the generalized form of the disease.¹²

Plasma cells

Plasma cells are a heterogeneous population of antibody secreting cells. Different subclasses of B-lymphocytes may generate plasma cells. Natural antibodies and some secretory IgA in the gut are secreted by B1 precursors derived from bone marrow. Marginal zone B cells may differentiate in short living IgM secreting plasma cells after encounter with foreign antigens. Steroids may easily deplete short living plasma cells. Long living plasma cells, produced in germinal centres, are instead refractory to immunosuppressive drugs and their persistence depends from the presence of survival niches provided by stromal cells.¹³⁸ In inflamed tissue, survival niches for plasma cells may take place. Plasma cells are prominent in small-vessel neutrophilic vasculitis with patterned fibrosis (chronic localized fibrosing leukocytoclastic vasculitis), *i.e.*, granuloma faciale and erythema elevatum diutinum or in a minority of patients with GPA patients⁵⁸ and with GCA.⁷⁴ In GPA elevated levels of B stimulatory factors such as B cell activation factor (BAFF) and raised number of T follicular helper cells (TFH) determine an elevated production of self-reactive B lymphocytes that in turn may mature into long-lived plasma cells which secrete ANCA.¹³⁹

IgA production by plasma cells is the typical feature of HSP however the presence of plasma cell infiltrate is not common finding. It was documented in only one case in a review of 68 cases.¹⁴⁰ Were these plasma cells develop and how survive is the challenge in this and other forms of vasculitides. Understanding the mechanism will help to choose the right therapy. In this regard, recent studies have tested the use of proteasome inhibitor in mouse models. This treatment was successful in depleting MPO-specific plasma cells and preventing glomerulonephritis in AAV.¹⁴¹

Conclusions

At present how a vasculitis starts and evolves is still an unresolved question. Its cellular players constitute a complex microenvironment and interact each other in a very complex way. It is not easy to figure out who is the aggressor and who the victim in the fight between the players. A large amount of information is now available an old concepts are going to be overtaken. Many of them have pleiotropic activity that dynamically change according to microenvironment. At this stage it is important to focus on the mechanisms that we are able to manipulate effectively. This review, far from complete, contain some selected points of interest.

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This paper was presented at the 89th SIDEMAST Congress, held on May 14-17, 2014 in Parma, Italy.

Conflicts of interest.—The author certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Epub ahead of print on December 12, 2014.

Urticarial vasculitis and urticarial autoinflammatory syndromes

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Urticaria is a frequent disorder classified as acute and chronic forms, which presents with wheals that can be associated with angioedema. Several entities may manifest with urticarial skin lesions, encompassing a heterogeneous group of conditions that have to be differentiated from ordinary urticaria. This review is focused on two of these urticarial syndromes: urticarial vasculitis (UV), which represents the most important differential diagnosis with common urticaria, and autoinflammatory diseases such as cryopyrin-associated periodic syndromes (CAPS) and Schnitzler's Syndrome, both rare multisystem forms that may masquerade as common urticaria. UV is a small-vessel vasculitis with predominant skin involvement, characterized by wheals persisting for more than 24 hours, burning rather than itching and resolving with hyperpigmentation as well as by other cutaneous manifestations including purpura, papules, vesicles, bullae and necrotic-ulcerative lesions. Histology shows a classic pattern of leukocytoclastic vasculitis, with possible presence of upper dermal edema. CAPS are classified as three distinct entities: familial cold autoinflammatory syndrome, Muckle-Wells Syndrome and chronic infantile neurological cutaneous and articular syndrome, which represent a spectrum of disorders caused by different mutations in a single gene, NLRP3 (NOD-like receptor 3). This gene encodes for cryopyrin, an inflammatory protein that activates interleukin-1 β , leading to an overproduction of this pivotal proinflammatory cytokine. Histologically, urticarial lesions are generally characterized by a perivascular neutrophilic infiltrate. Unlike urticaria, neither UV nor urticarial autoinflammatory syndromes do respond to antihistamines: thus, it is important not to misdiagnose such conditions in order to give the patients specific treatments, potentially preventing serious systemic complications.

KEY WORDS: Urticaria - Hereditary autoinflammatory diseases - Cryopyrin-associated periodic syndromes.

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Urticaria is a common disease that is classically distinguished into acute and chronic forms; the two forms are similar clinically, both presenting with wheals sometimes associated with angioedema, but differ in etiologic factors, pathophysiological aspects, epidemiology, prognosis and treatment.¹ There is a number of conditions that may present with urticaria-like skin lesions, encompassing the heterogeneous group of the so-called urticarial syndromes, which have to be distinguished from ordinary urticaria.^{2, 3} Some of these urticarial syndromes are purely cutaneous diseases, such as exanthematous drug eruption and bullous pemphigoid, while others are forms with predominant skin involvement but potentially affecting also internal organs, like urticaria pigmentosa and urticarial vasculitis (UV); finally, there are conditions in which the cutaneous manifestations occur in the context of a multisystem disorder, as in autoinflammatory diseases (Table I). The present review is focused on UV and autoinflam-

matory diseases like cryopyrin-associated periodic syndromes (CAPS) and Schnitzler's Syndrome: the first is a small-vessel vasculitis manifesting mainly with urticarial skin lesions and representing the most important differential diagnosis with common urticaria,⁴ the latter are both rare and disabling conditions mediated by interleukin (IL)-1 overproduction whose differential diagnosis with common urticaria may be not straightforward.⁵

Urticarial vasculitis

Definition

UV is a small-vessel vasculitis with predominant skin involvement, characterized clinically by urticarial lesions and histologically by leukocytoclastic vasculitis.⁴ It is a chronic-relapsing disease, which presents with long lasting (>24 hours) and painful wheals, and generally resolve with bruising or hyperpigmentation.⁶ Two main forms of UV are well recognized: UV associated with hypocomplementemia, called hypocomplementemic UV (HUV), which may occur with or without systemic manifestations, and UV without associated hypocomplementemia or normocomplementemic UV (NUV), usually manifesting without systemic involvement; a very rare, syndromic variant of HUV is also known.⁷⁻⁹ UV was initially reported as a continuum of disease progressing from NUV to HUV; more recently, Wisnieski, based on his retrospective study,⁷ suggested that there is no transition between these UV subtypes and that they are distinct clinical entities with similar clinicopathological aspects.

Epidemiology

Concerning the gender distribution, NUV has a slight female predominance, whereas HUV is seen almost exclusively in female patients, with a peak of incidence in the fourth decade of life for both forms.^{7, 10} Although UV is more common in adults, few pediatric cases have been reported, which are characterized by more severe renal disease than in adults.¹¹⁻¹⁵ The disease follows a chronic-relapsing but quite short-term course, the average time of duration being three years; however, as reported in the literature and according also to our experience, there are UV cases lasting several years, up to 23.¹⁶

Etiology and pathogenesis

Although most cases of UV are idiopathic, there are a variety of conditions associated with it such as chronic infections (hepatitis viruses B and C, Epstein-Barr virus or *Borrelia burgdorferi*), hematologic diseases (lymphoma, monoclonal gammopathy), malignancies, drugs (cimetidine, fluoxetine, procainamide, atenolol, sulfamethoxazole, paroxetine, sodium valproate, ciprofloxacin), physical exercise, exposure to physical stimuli (ultraviolet light, cold) and connective tissue diseases; these last represent the most commonly associated disorders, particularly systemic lupus erythematosus and Sjögren's Syndrome.^{17, 18} The pathogenesis of UV is thought to be mediated by a type III hypersensitivity reaction, with the formation of immune complexes which deposit at the vessel walls and lead to complement activation.^{10, 19} The immune complex can be endogenous, resulting from the production of immunoglobulin (Ig) G autoantibodies, or exogenous, whose formation is induced by drugs or viral infections. Circulating immune complexes may be demonstrated in 30-75% of patients with UV.²⁰ In HUV, there are Ig G serum autoantibodies directed against the collagen-like region of complement (C) 1q, which form immune complexes and activate the complement pathway, resulting in a reduction of C 1q in the patients' serum.^{21, 22} After the classical pathway of complement has been activated, C3a and C5a are generated. These complement split products induce mast cell degranulation and the generation of proinflammatory cytokines and chemokines, which are responsible for the increased vessel permeability and recruitment of neutrophils into the site of inflammatory process; neutrophils release proteolytic enzymes like collagenases and elastases that exacerbate tissue damage and edema.²⁰ However, circulating anti-C1q antibodies are not specific to UV and are also found in patients with systemic lupus erythematosus, even when there is no associated vasculitis.²³ Positive autologous serum skin test has often been reported in patients with UV, most likely due to circulating IgG with high affinity to IgE receptors or IgE, resulting in histamine release from mast cells and basophils.²⁴ A possible role of blood coagulation factors as mediators in the pathogenesis of UV has first been suggested by Mark *et al.*:²⁵ they showed that intradermal injection of platelet-activating factor causes endothelial swelling and vessel disruption.

TABLE I.—Main diseases that can manifest with urticarial lesions.

Cutaneous
– Exanthematous drug eruptions
– Arthropod bite reactions
– Atopic dermatitis
– Contact dermatitis (irritant or allergic)
– Pruritic urticarial papules and plaques of pregnancy (PUPPP)
– Bullous pemphigoid (and other rarer autoimmune bullous diseases)
– Eosinophilic cellulitis (Wells syndrome)
Mainly cutaneous
– Urticaria pigmentosa (mastocytosis)
– Urticarial vasculitis
– Cutaneous small-vessels vasculitis
Multisystem
– Cryopyrin-associated periodic syndromes (CAPS)
– Schnitzler's syndrome
– Urticarial lesions associated with:
– Connective tissue diseases
– Systemic vasculitis
– Hematologic disorders

tion, along with an inflammatory infiltrate mainly consisting of neutrophils and mononuclear cells.²⁵ The pathogenic role of coagulation in UV has been further demonstrated by Criado *et al*:²⁶ these investigators found elevated serum levels of the coagulation/fibrinolysis marker D-dimer in patients with active UV. These findings are in agreement with those reported by some of us on the involvement of

coagulation activation in chronic urticaria^{27, 28} and in bullous pemphigoid, which is the most frequent autoimmune blistering disorder presenting with urticarial lesions^{29, 30} (Table I). In both diseases, the activation of coagulation is due to tissue factor, a molecule expressed by eosinophils present in the inflammatory infiltrate of skin lesions; the tissue factor pathway of coagulation results in the generation of thrombin, which induces oedema by means of release of inflammatory mediators increasing vascular permeability.²⁷⁻³⁰ Further studies are needed to confirm whether this cross-talk between inflammation and coagulation acts in UV as in chronic urticaria and bullous pemphigoid.^{31, 32}

Clinical features

UV is a chronic-relapsing disease, which presents with wheals most often occurring on the proximal limbs and trunk (Figure 1A). The individual lesions last for over 24 hours, are more commonly painful or accompanied by burning sensation than pruritic, and often leave bruising (Figure 1B) or post-inflammatory pigmentation after resolution, in contrast to the wheals of ordinary urticaria; the latter are pruritic, not painful and resolve within 24 hours, leaving no trace.⁶ Cutaneous lesions of both the hypocomple-



Figure 1.—A) Multiple urticarial vasculitis lesions on the dorsum; B) resolution of the wheals with bruising.

mentemic and normocomplementemic forms of UV are erythematous wheals that may contain purpuric foci and may be associated with angioedema. The lesions are recurrent and usually persist more than 4 to 6 weeks. Livedo reticularis as well as the other cutaneous manifestations of the so-called cutaneous small-vessel vasculitis, the most common type of vasculitis with predominant skin involvement, may be observed;³³ they include papules, nodules, bullae and necrotic-ulcerative lesions. Hypocomplementemic UV syndrome (HUVS), regarded as the idiopathic form of HUV, occurs in less than 5% of patients with HUV.^{7, 9} For HUVS, first reported in 1973 by McDuffie *et al.*,³⁴ diagnosis can be established if two major criteria and at least two out of six minor criteria are fulfilled.⁹ The major criteria for HUVS are urticaria persisting for more than 6 months and hypocomplementemia; the minor criteria include: leukocytoclastic vasculitis, arthritis and arthralgia, eye disease (uveitis, episcleritis or conjunctivitis), glomerulonephritis, abdominal pain, positive circulating anti-C1q antibodies. UV patients with hypocomplementemia, notably those suffering from HUVS, may have constitutional symptoms such as fever, malaise and myalgia, arthralgia and arthritis; arthralgia/arthritis are the most commonly encountered systemic symptoms with roughly 50% of patients complaining of arthralgias, that tend to be migratory and transient, mostly affecting the pe-

ripheral joints.^{35, 36} Renal involvement, manifesting as glomerulonephritis, interstitial nephritis or necrotizing vasculitis, has been found to occur in 20-30% of patients with hypocomplementemia.^{35, 37} Chronic obstructive pulmonary disease and asthma can be present in around 20% of hypocomplementemic patients; other respiratory symptoms are dyspnea, hemoptysis and laryngeal edema.^{36, 38} Gastrointestinal symptoms comprise abdominal pain, nausea, vomiting and diarrhea and are noted between 15% and 30% of patients with UV, particularly those having the hypocomplementemic form.³⁵ Ophthalmologic complications, including episcleritis, uveitis and conjunctivitis, may occur in up to 10% of UV patients.⁶ Cardiac abnormalities (pericarditis, cardiac tamponade, cardiac valve involvement and pericardial effusion)³⁹ and central nervous system complications (pseudotumor cerebri, aseptic meningitis and cranial nerve palsy)^{40, 41} have rarely been reported, notably in HUVS. Finally, UV patients may have lymphadenopathy and/or hepatosplenomegaly.

Histopathologic and direct immunofluorescence aspects

Lesions of UV typically show a histologic pattern of leukocytoclastic vasculitis³⁸ characterized by a perivascular inflammatory infiltrate mainly consisting of neutrophils, with variable numbers of

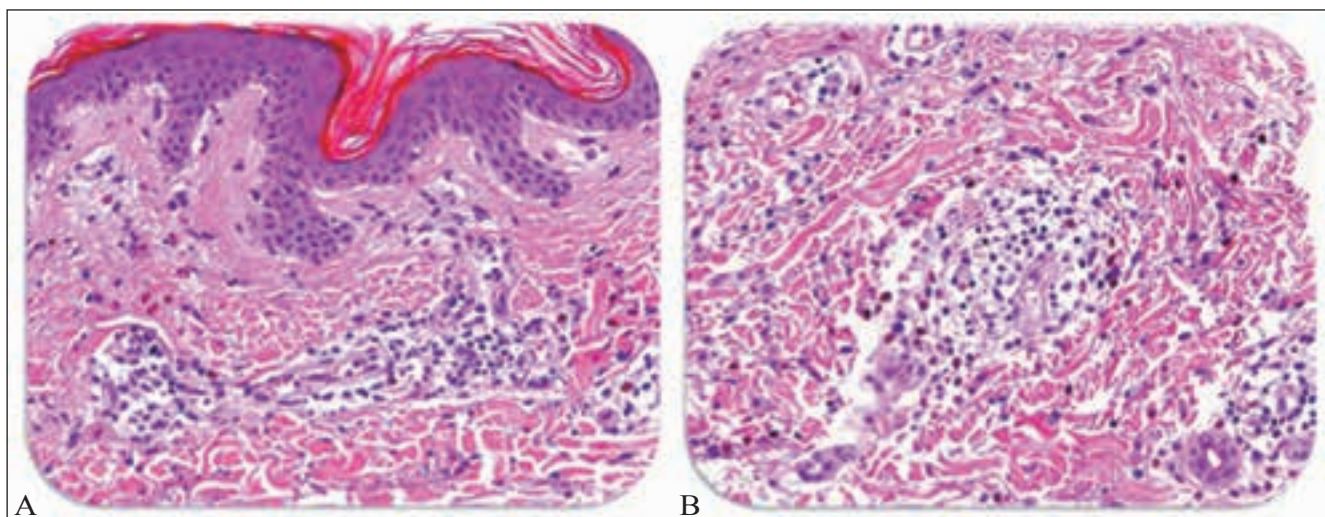


Figure 2.—A) Skin biopsy specimen taken from an urticarial vasculitis wheal showing a perivascular inflammatory infiltrate mainly consisting of lymphocytes and eosinophils, with neutrophil fragmentation; upper dermal oedema is also evident (haematoxylin-eosin stain; original magnification, x200). B) Close-up view showing fibrinoid necrosis of a dermal small vessel with a perivascular infiltrate of lymphocytes, eosinophils and some neutrophils (haematoxylin-eosin stain; original magnification, x400).

lymphocytes and eosinophils, and fibrinoid necrosis of the wall of dermal small vessels; endothelial cell swelling, neutrophil fragmentation, nuclear dust and red blood cell extravasation are also seen. Aspects of common urticaria, namely upper dermal oedema with a minimal diffuse infiltrate consisting of lymphocytes and eosinophils, may be associated (Figures 2A, B).⁷ On the other hand, some UV cases have a lymphocyte-predominant perivascular infiltrate with scattered or numerous eosinophils,³² which represents also the histopathological pattern usually seen in biopsy specimens taken from late-onset UV lesions.⁴² Direct immunofluorescence examination of early UV lesions reveals IgM, IgG, C3 and/or fibrinogen perivascular deposits in the upper dermis. Also, granular deposits of immunoglobulins and complement at the dermoepidermal junction are sometimes observed.¹⁰

Laboratory changes and instrumental investigations

Patients with hypocomplementemic form demonstrate an elevated erythrocyte sedimentation rate, positive cryoglobulins, hypocomplementemia with low C1q, C3 and C4 plasma levels and presence of circulating C1q autoantibodies; these last are present in all HUVS patients. Low-titer positive antinuclear antibodies are also detectable in NUV. Anti-Ro/SSA, anti-La/SSB, anti-Sm, antiphospholipid and anti-endothelial cell antibodies may be present in HUV associated to connective tissue diseases and also in HUVS. Pulmonary function tests and echocardiogram should be done suspecting pulmonary and cardiac involvements, respectively, in patients with hypocomplementemia.⁴³

Prognosis and treatment

The prognosis is variable and the course is chronic-relapsing. Hypocomplementemic forms are associated with worse clinical outcomes; causes of death may be laryngeal edema, cardiac tamponade or respiratory failure in advanced chronic obstructive pulmonary disease. The majority of patients with UV respond to systemic corticosteroids, namely methylprednisolone at an initial dosage of 0.5-1 mg/kg/day and then at progressively tapering doses until discontinuation after 8-12 weeks;⁴ in contrast, urticaria-like lesions as well as angioedema are typically resistant to oral antihistamines. Immunomodulating agents,

including dapsone, hydroxychloroquine, colchicine and thalidomide may be useful in long-lasting cases lacking systemic involvement;^{4, 43} cinnarizine has also been used with some success.⁴⁴ If necrotic-ulcerative skin lesions occur and/or in recalcitrant cases, steroid-sparing immunosuppressive drugs such as cyclosporine, azathioprine, methotrexate, cyclophosphamide and mycophenolate mofetil have to be considered; the same immunosuppressants have been successfully used to control pulmonary and/or renal disease.⁴⁵⁻⁴⁷ A few case reports demonstrated efficacy and safety of the anti-CD20 monoclonal antibody rituximab, intravenous immunoglobulins, plasmapheresis and IL-1 antagonists.⁴⁸⁻⁵¹

Urticarial autoinflammatory syndromes

Urticarial lesions may be the skin hallmark of different monogenic autoinflammatory syndromes, which clinically present also with systemic symptoms and signs, particularly periodic fever, arthralgia or arthritis and fatigue, as well as the involvement of a number of internal organs.⁵²⁻⁵⁶ Autoinflammatory syndromes are due to mutations of various genes regulating the innate immune response and occur in the absence of high titers of circulating autoantibodies and autoreactive T cells.⁵⁷⁻⁶⁰ From the etiopathogenetic point of view, in all these forms, there is an aberrant activation of the inflammasome, which is an intracytoplasmatic multiprotein platform responsible for the activation of caspase 1, a protease cleaving the pro-IL-1 β to the biologically active IL-1 β .⁶¹ IL-1 β is the leading actor in the autoinflammation, since its overproduction triggers the release of several other proinflammatory cytokines and chemokines, leading to a disproportionate overwhelming inflammatory response that is mainly mediated by the recruitment and activation of neutrophils.^{62, 63} The main autoinflammatory disorders that typically present with urticarial lesions are the so-called CAPS⁶⁴⁻⁶⁶ and Schnitzler's Syndrome,^{67, 68} both rare and disabling conditions in which the characteristic urticarial rash is associated with a number of other clinical manifestations. Urticarial lesions occur, albeit less frequently, also in other rare autoinflammatory diseases, such as tumour necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS), in which the urticarial rash is associated with a characteristic and almost pathognomonic periorbital edema, and NLRP12-associated

TABLE II.—*Clinical spectrum of cryopyrin-associated periodic syndromes.*

	Gene	Protein	Inheritance	Clinical picture
FCAS	<i>NLRP3</i>	Cryopyrin	AD	Urticarial rash, fever and arthralgia after cold exposure. Dramatic response to IL-1 blockade
MWS	<i>NLRP3</i>	Cryopyrin	AD	Recurrent or sub-chronic urticarial lesions, sensorineural hearing loss, amyloidosis. Dramatic response to IL-1 blockade
CINCA/NOMID	<i>NLRP3</i>	Cryopyrin	De novo-mutations/ mosaicisms	As above + mental retardation, chronic aseptic meningitis and bone deformities. Dramatic response to IL-1 blockade

FCAS: familial cold autoinflammatory syndrome; MWS: Muckle-Wells syndrome; CINCA/NOMID: chronic infantile neurological cutaneous and articular syndrome/neonatal-onset multisystem inflammatory disease; NLRP3: NOD-like receptor 3; AD: autosomal dominant.

cold-induced autoinflammatory syndrome (FCAS2), which is regarded as a mild form of CAPS.⁵ Based on the frequency and relevance of the urticarial lesions, only CAPS and Schnitzler's Syndrome are described in detail below.

CAPS

CAPS, also called cryopyrinopathies, are classified as three distinct entities, namely familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA), also known as NOMID (neonatal-onset multisystem inflammatory disease) (Table II).^{5, 52-56, 64-66} The three entities of CAPS group represent a clinical spectrum of autosomal dominant disorders caused by different mutations in a single gene, *NLRP3* (NOD-like receptor 3, also known as cold-induced autoinflammatory syndrome 1, *CIAS1*); this gene encodes for cryopyrin, a crucial inflammasome protein that directly activates IL-1 β . To date, more than 90 *NLRP3* gene mutations have been found, most of which in exon 3.⁵⁴ Concerning the seriousness of the three forms, FCAS is the least severe, MWS is the clinical phenotype of medium severity and CINCA shows the most severe overall clinical picture.

CLINICAL PICTURE

The urticarial rash occurs in almost all patients with CAPS and shows the same features in all three forms of CAPS; namely, it consists of rose or red macules (Figure 3) or slightly elevated plaques. Unlike chronic spontaneous urticaria, typical wheals with surrounding flare and raised edematous plaques are usually absent. These lesions last hours, but



Figure 3.—Widespread urticarial lesions in a young patient with chronic infantile neurological cutaneous and articular syndrome (CINCA).

generally vanished within 24 hours; however, more solid and persistent lesions resembling the wheals of UV can be observed. Contrary to chronic spontaneous urticaria, the lesions have rather symmetrical distribution and, as in UV, are accompanied by burning or pain rather than pruritus.^{5, 69} The histopathological pattern of these urticarial lesions is that of neutrophilic dermatosis and not that of urticaria; in fact, as expected according to the pathophysiology of these entities, it is characterized by a dense neutrophil-rich perivascular and interstitial inflammatory infiltrate, without dermal edema, which is the typical finding of urticaria histopathology.^{5, 69, 70} Interestingly, the Lipsker's research team coined the designation of neutrophilic urticarial dermatosis for this clinicopathological setting observed not only in the context of autoinflammatory syndromes like CAPS and Schnitzler's syndrome but also in association with lupus erythematosus and adult-onset Still disease.⁶⁸⁻⁷⁰ On the other hand, nonspecific histopathological features can be seen when the cutaneous picture consists only of flat wheals or slight erythematous lesions. In FCAS, which generally appears during the first few months of life, the urticarial rash is typically triggered by cold exposure and accompanied by fever spikes of short duration (usually less than 24 hours); arthralgia/arthritides, conjunctivitis, headache and fatigue are also common. In FCAS, an increase in acute-phase phlogistic indicators is seen during acute episodes and inflammatory attacks decrease spontaneously.⁷¹ MWS also develops in the first months of life and is characterized, in addition to the symptoms of FCAS, by neurosensory deafness, episcleritis and, in the late stage of the disease, amyloid A amyloidosis (in up to 25% of cases).^{65, 72, 73} As in FCAS, acute phase reactants are elevated during fever episodes. Finally, patients with CINCA, the most severe form of CAPS that appears in the first weeks of life, present a typical *facies* characterized by frontal bossing, saddle back nose and midface hypoplasia, leading to a sibling-like appearance (Figure 4). Bone involvement is another hallmark of the disease, the most typical finding being represented by bony overgrowth mainly affecting the knees and distal extremities of hands and feet.^{74, 75} Central nervous system manifestations include chronic aseptic meningitis, ventriculomegaly, increased intracranial pressure, cerebral atrophy, sensorineural hearing loss and papilloedema with associated optic-nerve



Figure 4.—Typical *facies* of CINCA associated with urticarial rash in a pediatric patient.

atrophy leading to blindness; mental retardation and seizures have also been reported. Also in CINCA, amyloidosis is a complication of the late stage of the disease and patients show persistent elevation of acute phase reactants.^{66, 76-78}

TREATMENT

IL-1 antagonists represent the treatment of choice for cryopyrinopathies. The recombinant IL-1 receptor antagonist, anakinra, given at a starting dosage of 1 mg/kg/day subcutaneously, is effective in controlling the urticarial picture and constitutional symptoms of all forms of CAPS; the anakinra safety profile proved to be excellent.^{79, 80} Other IL-1 blockers such as IL-1 TRAP (riloncept) and the anti-IL-1 monoclonal antibody canakinumab are also effective and safe in the management of CAPS.⁸¹⁻⁸³

Schnitzler's Syndrome

Schnitzler's syndrome is a rare, chronic-relapsing disorder characterized by urticarial lesions with clinicopathological features very similar to those of CAPS and a Ig M monoclonal gammopathy in combination with symptoms and signs of systemic inflammation, including recurrent fevers, arthritis or arthralgia, myalgia, lymphadenopathy and hepatomegaly; bone pain due to hyperostosis or osteosclerosis can also occur.^{67, 68, 84-86} Severe anaemia and life-threatening thrombophilia have rarely been reported.^{87, 88} Around 15% of patients develop a lymphoproliferative disorder, particularly Waldenström's macroglobulinemia.⁸⁵ Concerning laboratory findings, investigations reveal increase in erythrocyte sedimentation rate and C-reactive protein. No genetic basis for Schnitzler's syndrome has been found, so that it is regarded as an acquired disorder whose pathogenesis is, however, inflammasome- and IL-1 β -mediated, similar to that of CAPS.⁸⁹ IL-1 antagonists represent thus the choice treatment for this disease, as for CAPS.^{90, 91} Other agents that have been used with variable results include systemic corticosteroids, colchicine, thalidomide, TNF- α inhibitors, and, based on the elevated serum levels of IL-6 found in patients with Schnitzler's syndrome, the IL-6 blocker tocilizumab.⁵³

Differential diagnosis of UV and urticarial autoinflammatory syndromes

The differential diagnosis of both UV and urticarial autoinflammatory syndromes includes, in addition to all the other urticarial syndromes listed in Table I, Sweet's syndrome, a rare inflammatory skin disease classified within the spectrum of neutrophilic dermatoses, which may follow upper respiratory tract infections or be associated with haematologic or solid neoplasia or inflammatory bowel diseases.⁶² However, in Sweet's syndrome there is a febrile acute onset of the skin lesions, which may be typical as tender erythematous plaques and nodules or atypical as bullae and targetoid lesions; in contrast, urticarial lesions are usually lacking in this condition. Moreover, the histology of Sweet's syndrome is characterized by a dermal neutrophil infiltration without leukocytoclastic vasculitis. Finally, the clinical manifestations of Sweet's Syndrome are dramatically responsive to systemic corticosteroid.

Conclusions

UV is a small-vessel vasculitis with predominant cutaneous involvement that represents the main differential diagnosis with chronic spontaneous urticaria, the most frequent form of chronic urticaria.^{1, 5} In UV, the long duration of individual wheals, their resolution with hyperpigmentation, their unresponsiveness to antihistamines, the development of skin lesions other than hives and the presence of associated systemic symptoms are helpful diagnostic clues for distinguishing this condition from chronic spontaneous urticaria; however, a skin biopsy for histology and direct immunofluorescence examination is recommended to confirm the diagnosis. In autoinflammatory disorders like CAPS and Schnitzler's Syndrome, the urticaria-like skin lesions are only a part of a more complex inflammatory process that involves other organs and systems. These forms do not respond to conventional treatments of urticaria and are often misdiagnosed for many years. Thus, it is important not to miss autoinflammatory diseases masquerading as common urticaria and to treat the patients with the IL-1 blockers targeting selectively the main effector cytokine, in order to prevent long-term complications such as amyloidosis or those involving eye, bone and central nervous system.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Epub ahead of print on January 14, 2015.

Vasculitides with cutaneous expression in children: clinico-pathological correlations

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The most recent pediatric vasculitis classifications (EULAR/PRINTO/PRES) have proposed the use of an integration of clinical signs and symptoms, laboratory data, imaging and pathologic data. Pediatric vasculitis represent a peculiar clinical-diagnostic model, compared to the corresponding adult pathology chapter, and in particular, dermatopathologic aspects of these diseases identify more specific issues, made contingent by crucial variables such as duration of vasculitis lesion, site of the biopsy, proper biopsy depth, and possibility to correlate histopathological findings with immunopathological results. Possible additional diagnostic difficulties may arise from the fact that, in children, the same systemic disease, such as lupus erythematosus, may present with different clinical manifestations, with histopathological features of a precise type of vasculitis specific for that type of clinical manifestation. Examples are provided by hypocomplementemic urticarial vasculitis, cryoglobulinemic purpura, lymphocytic vasculitis of livedoid lesions. This paper describes the cutaneous histopathological findings of some vasculitis related pediatric diseases, be they pertaining to a systemic vasculitis with corresponding cutaneous vasculitis, to a systemic vasculitis with sporadic cutaneous vasculitic involvement, and to a systemic vasculitis without cutaneous vasculitic involvement. Type and level of histopathological vasculitic involvement, caliber of the vessel, type of vasculitis associated infiltrate, are likewise reliable integration in the complex diagnostic path of vasculitis in childhood. On the basis of these criteria dermatopathologists should be confident in identifying the type of the vasculitis and relate them to a specific pediatric disease.

KEY WORDS: Cutaneous disease - Vasculitis - Pediatrics.

This paper describes the cutaneous histopathological findings of some vasculitis related pediatric

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diseases, be they pertaining to a systemic vasculitis with corresponding cutaneous vasculitis, to a systemic vasculitis with sporadic cutaneous vasculitic involvement, and to a systemic vasculitis without cutaneous vasculitic involvement.

Vasculitis in pediatric age

Problems in classifying cutaneous vasculitides in children

The term "vasculitis" is histologically defined by the inflammatory involvement of endothelial cells of blood vessel walls, by the presence of fibrin within and around the vessel walls, and by the presence of the above mentioned changes with a variable intraluminal presence of fibrin or thrombi. The likely destruction of the vessel structure is the endpoint of the vasculitic process. The early changes involve the endothelial cells. The inflammatory infiltrate may be predominantly neutrophilic, yet eosinophils, lymphocytes, plasma cells, and mononuclear cells may be found. Vasculopathy is morphologically characterized by a less prominent, if any, inflammatory component with degeneration and proliferation of intima, and the presence of intraluminal fibrin thrombi.

Since the classification of vasculitides has been

the object of different approaches in adulthood cases, in children the classification has been regarded as even more problematic.¹ Despite the fact that the Chapel Hill Consensus Conference modified in 1994 the American College of Rheumatology (ACR) classification, both the approaches failed to specifically consider the chapter of pediatric vasculitides. More recently, in 2008, a more productive approach to vasculitis classification in pediatrics has been proposed by EULAR (European League Against Rheumatism), by PRINTO (Pediatric Rheumatology International Trials Organization), and PRES (Pediatric Rheumatology European Society).^{2,3}

On the basis of those major contributions by Ozen *et al.*² and Ruperto *et al.*,³ the classification is based on 1) size of the vessels; 2) presence of granulomatous involvement or not; 3) vasculitides found in different diseases.

As a conclusion of EULAR/PRINTO/PRES criteria traced in that paper,³ a classification of at least four types of vasculitic diseases, such as Henoch-Schönlein purpura (HSP), childhood polyarteritis nodosa (PAN), childhood Wegener granulomatosis (c-WG), and childhood Takayasu arteritis (c-TA), became reliable, using combinations of clinical signs, symptoms, laboratory, histopathology, and imaging data. However, despite the possibility of the critical discrimination, based on the method, between patients with a specific type of vasculitis (sensitivity), and patients with different diseases (specificity), several pediatric vasculitides are in tremendous need for a better nosological placement. Numerous clinical variables may, in fact, greatly influence in modifying or modulating one or more of the major diagnostic criteria, for example in the field of the dermatological contribution, the type and the site of biopsy, its depth, the timing, the histopathological recognition of the type and the depth of vessel involvement. Furthermore, histopathologic evidence of leukocytoclastic vasculitis of small vessels may be found in different and unrelated disorders, such as hypocomplementemic urticarial vasculitis, purpuric vasculitic lesions in systemic lupus erythematosus (SLE), purpuric vasculitic lesions in PAN, in HSP and in acute hemorrhagic edema of infancy.

Frequency of the most common vasculitides in children, and rarer vasculitic forms

Frequency of vasculitis may be defined more easily in adulthood than in children, despite the fact that

the idiopathic forms account for about 50% of the cases. The postinfectious cases reach about 30%, the autoimmune disease related vasculitis about 20%, the drug-induced cases about 10%, and malignancy-related about 5%.⁴ In childhood, the most frequent cutaneous vasculitides are HSP and Kawasaki disease (KD), even if some differences among different geographic areas have been observed. In fact, KD and TA are mostly prevalent in Japan, while HSP and WG have a major diffusion in Europe and North America. PAN is more common in Japan and Turkey. The United States annually reported incidence of HSP is 1 in 5.000 children,⁵ while other Authors report a frequency ranging from 10 to 30 per 100 000 children.⁶

KD is reported as the second more frequent vasculitis, however this is obviously to be intended as a systemic vasculitis, because as we will see later, vasculitis is not a feature of its polymorphous cutaneous involvement.

Aim of this paper is to propose the histopathologic features of different pediatric vasculitides in order to infer repeatable criteria for a specific diagnosis, on histopathological grounds, after an integration of the clinical and laboratory findings of that patient. For this purpose, it will be here considered for each pediatric vasculitis the following features: 1) the size of vessels involved; 2) the depth of vessel involvement (superficial; superficial and med; superficial, med and deep dermis; and sometimes subcutaneous vessels involvement); 3) cutaneous and extracutaneous signs and symptoms; 4) laboratory findings.

HSP: diagnostic criteria, etiology, clinical features, and immunopathology.

HSP, also known as anaphylactoid purpura, is an IgA small-vessel leukocytoclastic vasculitis. Although the first description is probably attributable to Heberden in 1801, the disease is eponimically known from Johann Schönlein, who in 1837 reported the association of purpuric rash, arthritis, and urinary abnormalities, and from Eduard Henoch, who described in 1874 a purpuric rash, abdominal pain with bloody diarrhea, and proteinuria.

The diagnostic criteria for HSP have been modified several times over the years; recently, in 2010, EULAR/PRINTO/PRES elaborated a revision of diagnostic criteria, according to which purpura or petechiae is a mandatory criterion, and when it lacks

the lower limbs predominant distribution, the demonstration of vascular deposits IgA. In addition to this criterion, at least one of the four following criteria should be present: 1) abdominal pain; 2) histopathology; 3) arthritis or arthralgia; 4) renal involvement.³

HSP is the most common vasculitis in childhood, and occurs mainly in children aged from 5 to 15 years; adults may also be affected with a worse prognosis. A slightly male prevalence has been reported (males/females ratio=1.5/1), and seasonal outbreaks in late winter are common. Etiology remains unknown; yet, upper respiratory tract infections frequently (in about 30-50% of cases) precede the onset of the disease, and several infectious agents has been identified as triggers, such as group A β -haemolytic streptococci (in about 30% of cases), *Bartonella henselae*, *Haemophilus parainfluenzae*, *parvovirus B19*, *Staphylococcus aureus*, *coxsackie viruses*, *adenovirus*, *hepatitis A and B viruses*.⁷ However, in about half of the cases, trigger agents remain unidentified. IgA, which are mainly secreted in upper respiratory tract, have a key role in HSP pathogenesis. In fact, increasing of serum level of IgA may be found in about 50% of cases in acute phase, IgA vascular deposits may be observed both in skin and in renal mesangium, and circulating immunocomplexes containing IgA may be detected in patients affected by HSP. Genetic predisposition may be also play a role, in particular human leukocyte antigen (HLA) polymorphisms. Recently, Peru et al. reported that HLA A2, A11, and B35 antigens are associated with a higher risk for the disease, while HLA A1, B49, and B50 with a lower risk.⁸ Furthermore, HLA B35 is associated with an increased risk of developing renal involvement. Mutations in the familial Mediterranean fever gene were found frequently in patients affected by HSP.

In most cases, the onset of HSP is characterized by purpura, arthralgia and abdominal pain. In about two thirds of pediatric cases, gastrointestinal involvement with vasculitis of blood vessels of bowel walls, causing edema and submucosal and intramural hemorrhage. Abdominal pain is the most frequent gastrointestinal symptom, and it generally occurs 7-30 days after the appearance of skin rash. Vomiting is frequent (more than 50% of cases), and melena and hematemesis may also occur. Renal involvement is common, with a reported frequency varying from 30% to 50%. It may develop until 4-6 weeks after the onset of the disease. The spectrum of renal findings

is wide. Microscopic hematuria and mild proteinuria, to nephritic syndrome and nephrotic syndrome, to end-stage renal disease may be observed. Glomerulonephritis is the most frequent finding, and mesangial deposits of IgA are observed. Arthritis with periarticular swelling and tenderness are frequent findings, and affect generally large joints (knees, ankles), and is transient, resolving within a week.

Other less common manifestations of HSP include neurological manifestations (such as isolated central nervous system vasculitis, seizures, coma, and hemorrhage, Guillain-Barré Syndrome), orchitis, pancreatitis, hepatobiliary involvement, uveitis, carditis and pulmonary involvement.

Cutaneous features

Skin involvement typically occurs 5 to 7 days after upper respiratory tract infection or other trigger factors, whenever identified. Erythematous or urticarial papules are typical cutaneous finding, and they turn into palpable, purpuric papules and patches within 24 hours. Skin lesions have a symmetrical distribution, and are more frequently localized on lower limbs and buttocks (Figure 1A); extensor aspects of upper limbs too, and rarely, trunk and face, may be involved. More unusual presentation of HSP includes vesicles, hemorrhagic bullae (Figure 1B), necrotic lesions (Figure 1C).

Cutaneous findings have a self-limiting course with a resolution within 5-7 days, but they may recur from a few weeks to several months.

Histopathology

HSP leukocytoclastic vasculitis of capillary vessels and of postcapillary venules, immediately beneath the papillary dermis, is characterized by presence of neutrophils within and around the vessel walls, by presence of fibrin deposition within the vessel walls, occasional endoluminal thrombi with remarkable endothelial damage, and by different degrees of leukocytoclasia. Sometimes prominent spongiosis and blistering formation is associated with extravasation of erythrocytes, and in later stages, by the presence of siderophages (Figure 1D).

The clue to the histopathological diagnosis of HSP vasculitis is the superficial involvement of both capillaries and postcapillary venules. Positive direct immunofluorescence, characterized by IgA (mainly

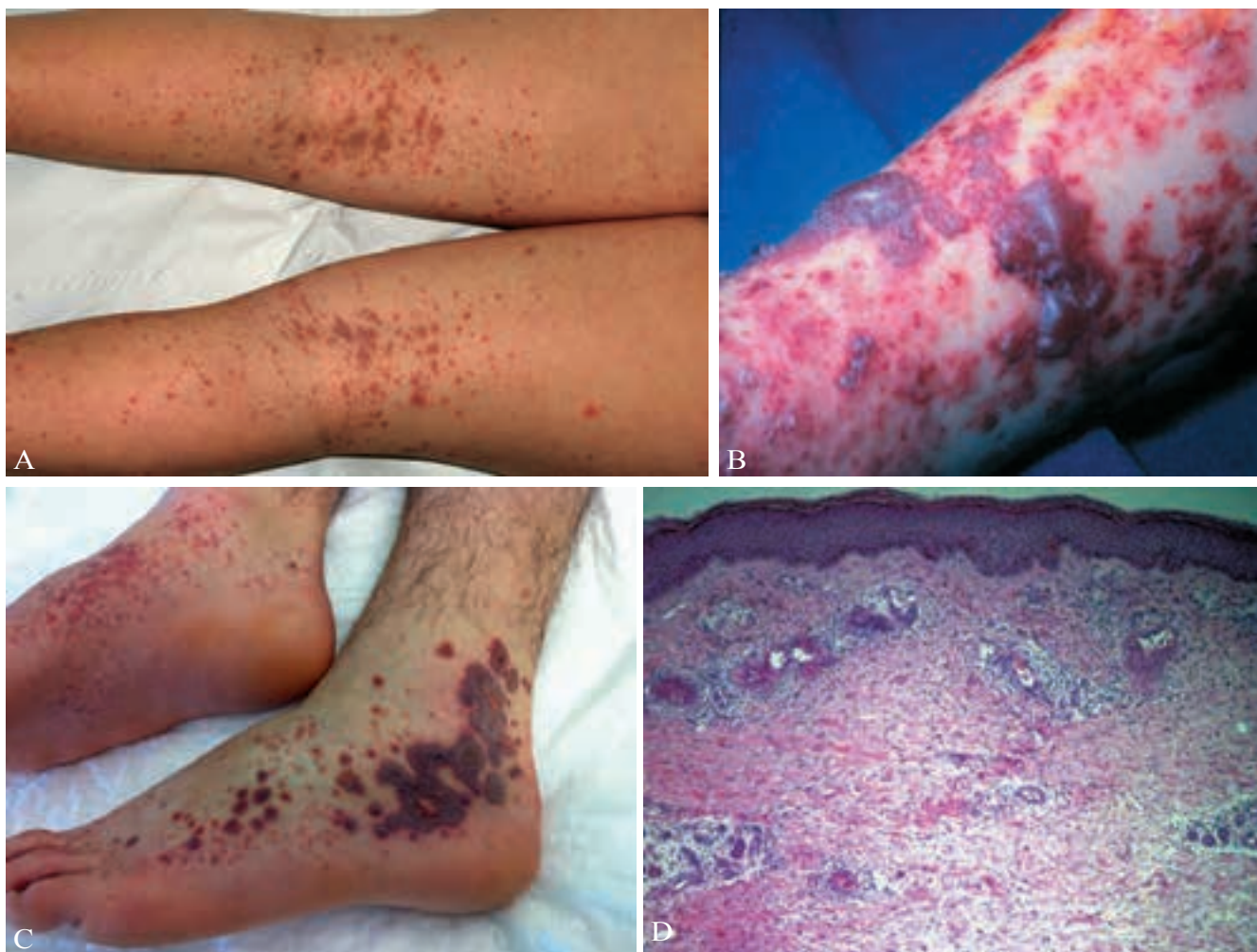


Figure 1.—A) Symmetrical distribution on lower limbs of vasculitic purpuric patches in a case of HSP; B) purpuric lesions and unusual tense hemorrhagic blisters in a case of HSP; C) purpuric tiny palpable lesions associated with hemorrhagic necrotic tense blisters in a 16-year-old boy affected by HSP; D) leukocytoclastic vasculitis of HSP, typically involving predominantly the capillary vessels, and post-capillary venules, characterized by the stereotypical histopathological expressions, namely neutrophilic infiltrate with karyorrhexis around and within the vessel walls, fibrin deposition, degeneration of vessel walls, and endoluminal thrombi (hematoxylin and eosin, X 100).

IgA₁) deposition, is diagnostic, provided that the biopsy is taken early in the course of the disease and not in the centre of the purpuric lesions, where the presence of proteolytic enzymes that may cause negative staining for IgA.⁹

Furthermore, direct immunofluorescence may reveal additional deposition of IgM and C₃.

Leukocytoclasia is not *per se* synonymous with leukocytoclastic vasculitis, that is, indeed, a feature found in several neutrophilic dermatosis, such as Sweet Syndrome, and Behçet disease, less frequently characterized by true vasculitis. A simula-

tor of a postcapillary venule vasculitis, is given by the following clinico-pathological correlation, in a 13-year-old boy affected by aplastic anemia, and by asymmetrical purpuric lesion on his left leg (Figure 2A). Histopathology was characterized by superficial perivascular inflammatory infiltrate without vasculitic involvement in the papillary dermis, and by a deeper venulitis with neutrophilic perivascular and interstitial infiltrate, with evident leukocytoclasia, without evidence of fibrin deposition in and around vessel walls (Figure 2B). Direct immunofluorescence proved negative.

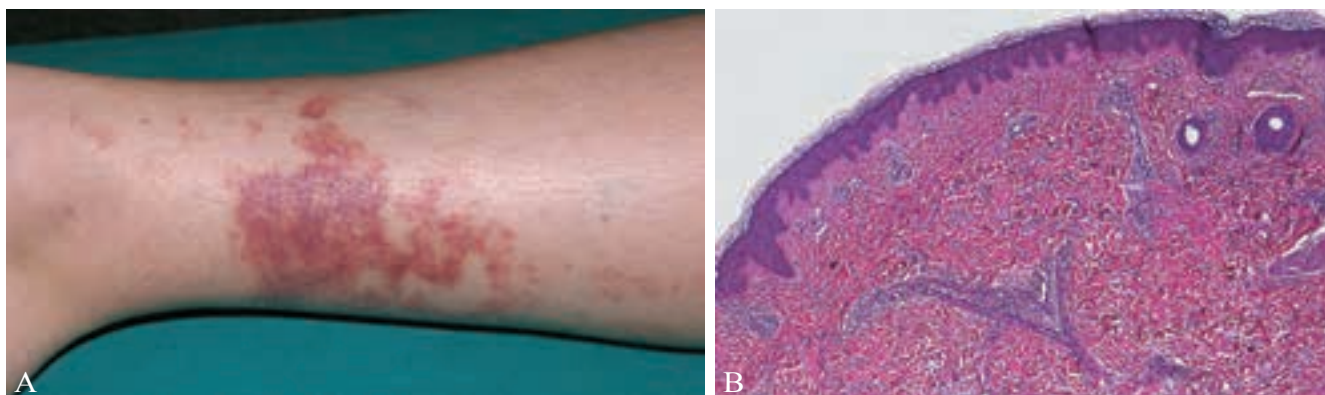


Figure 2.—A) Asymmetrical purpuric lesions on the right leg in a 13-year-old boy affected by aplastic anemia. The purpuric patch is irregularly shaped; B) histopathology of the purpuric lesion of the 13-year-old boy, characterized by intense venulitis with perivascular and interstitial neutrophilic infiltrate and evident karyorrhexis without signs of fibrin deposition or thrombi. Direct immunofluorescence proved negative (hematoxylin and eosin, X 50)

Acute hemorrhagic edema of infancy: etiology, clinical features, immunopathology

Acute hemorrhagic edema of infancy (AHEI), also known as Finkelstein disease, is a rare leukocytoclastic small-vessel vasculitis described first by Snow in 1913, and then by Finkelstein in 1938. It occurs predominantly in children less than 2-year-old, and has generally a benign course with a mean duration of about 2 weeks. The etiology unknown. Frequently, the onset of the disease is preceded by infections, mainly upper respiratory and urinary tract infection (*i.e.* Streptococci, Staphylococci, *Mycoplasma pneumoniae*, cytomegalovirus, adenovirus, coxsackie virus, rotavirus or *Escherichia coli*). Drugs, and vaccines, too, may play a role in eliciting AHEC. The disease is most frequently seen in cold seasons.

AHEI is characterized by a triad of symptoms: fever, edema and skin rash. No relapses are seen, and usually the disease is self-limiting. Overlap forms of AHEI and HSP with systemic involvement may be observed.

Cutaneous features

Urticarial plaques or small papulo-macular rash are observed at the onset of the disease, and later they turn into erythematous, purpuric cockade lesions. A 10-month-old newborn cockade erythematous and edematous lesions characterized symmetrically lower limbs and buttocks of the patient (Figure 3A). A purpuric component was unevenly distributed in several of the edematous lesions. The same type of

lesions were localized on cheeks, chin, and upper arms with puffy iuxta articular edema without true joint involvement. Kidney involvement is extremely rare.

Histopathology

The presence of a true leukocytoclastic vasculitis is controversial, however some authors in a review of 150 children¹⁰ collect a high frequency of leukocytoclastic vasculitis (77%) with positivity of IgA vascular deposits in 24% of the cases. According to Alain Taïeb and Valérie Legrain,¹¹ AHEI is an immune complex mediated vasculitis not necessarily linked to IgA deposits.

Histopathology is characterized mainly by a postcapillary venules vasculitis (Figure 3B) with a more tiny involvement of capillary vessels, edema of the papillary dermis, and frequent lymphangiectases. The venule of superficial dermis, as in the present case, is characterized by fibrin deposition within and around the vessel walls, by a neutrophilic infiltrate within and around the vessel walls, and karyorrhexis. Histopathology clues of AHEI are: 1) postcapillary venules leukocytoclastic vasculitis; 2) edema of papillary dermis; 3) tiny lymphangiectases. Histopathology of AHEI vasculitis can hardly be distinguished by that of HSP. However, in the latter, a more typical involvement of capillary vessels, rather than pure postcapillary venules vasculitic involvement, is seen.

Differently from HSP, immunopathology shows perivascular C1q deposits, with a predominance of IgM deposits (80% of cases).¹⁰

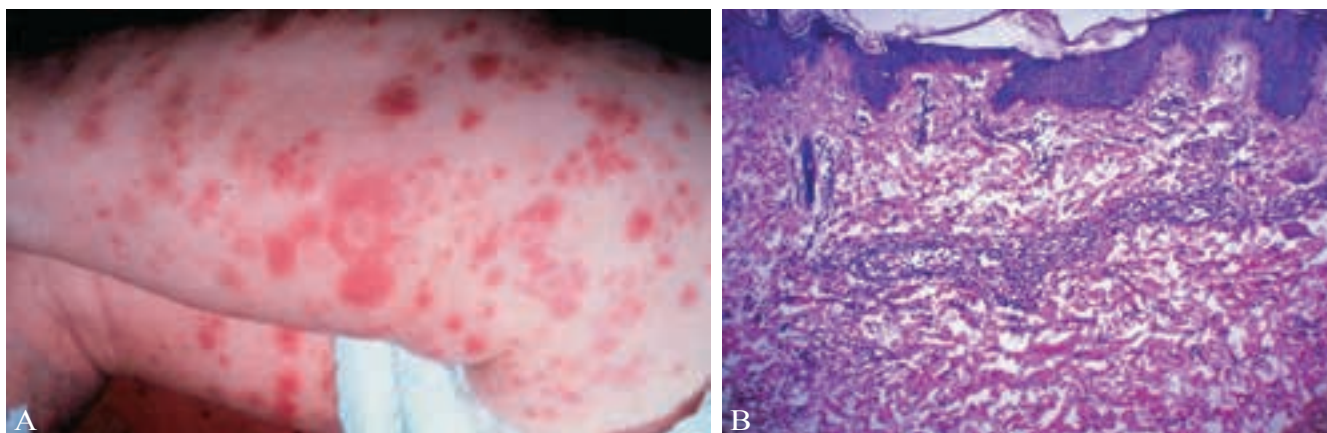


Figure 3.—A) Symmetrical cockade purpuric and edematous lesions fully involving lower limbs and buttocks in a patient affected by AHEI; B) leukocytoclastic vasculitis involving mostly subpapillary venules with slight edema and lymphangectases in the papillary dermis (hematoxylin and eosin, X 100).

Vasculitis in SLE: protean clinical presentation, pathogenesis, immunopathology

Two main groups of cutaneous changes in SLE should be considered: the first one including LE specific changes, pertaining to major diagnostic criteria, and the second one encompassing non specific LE changes *i.e.* that may be seen also in other collagen vascular diseases. Cutaneous vasculitis in SLE is included in the second group of skin manifestations, and it may be seen more commonly in children than in adults.¹² In a series of 540 cases of SLE reported by Drenkard C *et al.*,¹³ at least one episode suggesting vasculitis, of both cutaneous and visceral significance, may be recorded in 36% of patients, with a biopsy or angiography confirmation reported in 10% of the cases. In 540 cases of SLE, cutaneous vasculitis was present in 160 patients (30%). According to Vitali C *et al.*,¹⁴ 19-28% of patients with SLE may present with cutaneous vasculitis. Despite the fact that major diagnostic criteria for SLE (malar rash, photosensitivity, discoid lesions, mucous membrane involvement, and ulcers) do not include cutaneous vasculitis, a variety of clinical features of SLE are expression of different types of vasculitides, clinically indistinguishable from vasculitic lesions of other connective tissue disorders, including palpable purpura, petechiae, *livedo reticularis* (LV), ulcers, and cutaneous necrosis. As the important paper by Calamia K and Balabanova M stresses,¹⁵ the diversity of cutaneous vasculitic lesions in SLE depends on the different type of vessel involvement (capillary,

venules, arterioles), the depth of their involvement, and their size, in conjunction with the severity of the systemic disease. Different simultaneous types of clinical lesions of SLE may occur in conjunction with cutaneous vasculitis.

Vasculitis associated to SLE is a small vessels vasculitis (capillary, postcapillary venules, arterioles) and usually of the leukocytoclastic type. However, lymphocytic vasculitis may be the histopathologic counterpart of cutaneous SLE livedoid lesions or long lasting lesions.

Four types of clinico-pathological correlations in pediatric SLE may be considered: 1) urticarial vasculitis (UV); 2) cryoglobulinemia; 3) livedo vasculitis/vasculopathy (LV); 4) Chilblain LE (CHLE perniosis-like LE).

UV

UV is a extremely rare finding in children with SLE (Figure 4A, B) and is characterized clinically by urticarial persistent wheal-like lesions lasting for more than 24 hours and fading in days with a postinflammatory grayish pigmentation. In particular, hypocomplementemic UV (HUV) is more frequently seen in young patients, usually girls, with SLE, with a more severe course than in normocomplementemic form.^{16, 17} Clinically they are characterized by recurrent episodes of wheal-like lesions, variably associated, albeit not always with pruritus and burning sensation. Systemic signs and symptoms include fever, vomit, abdominal pain, arthralgia, and

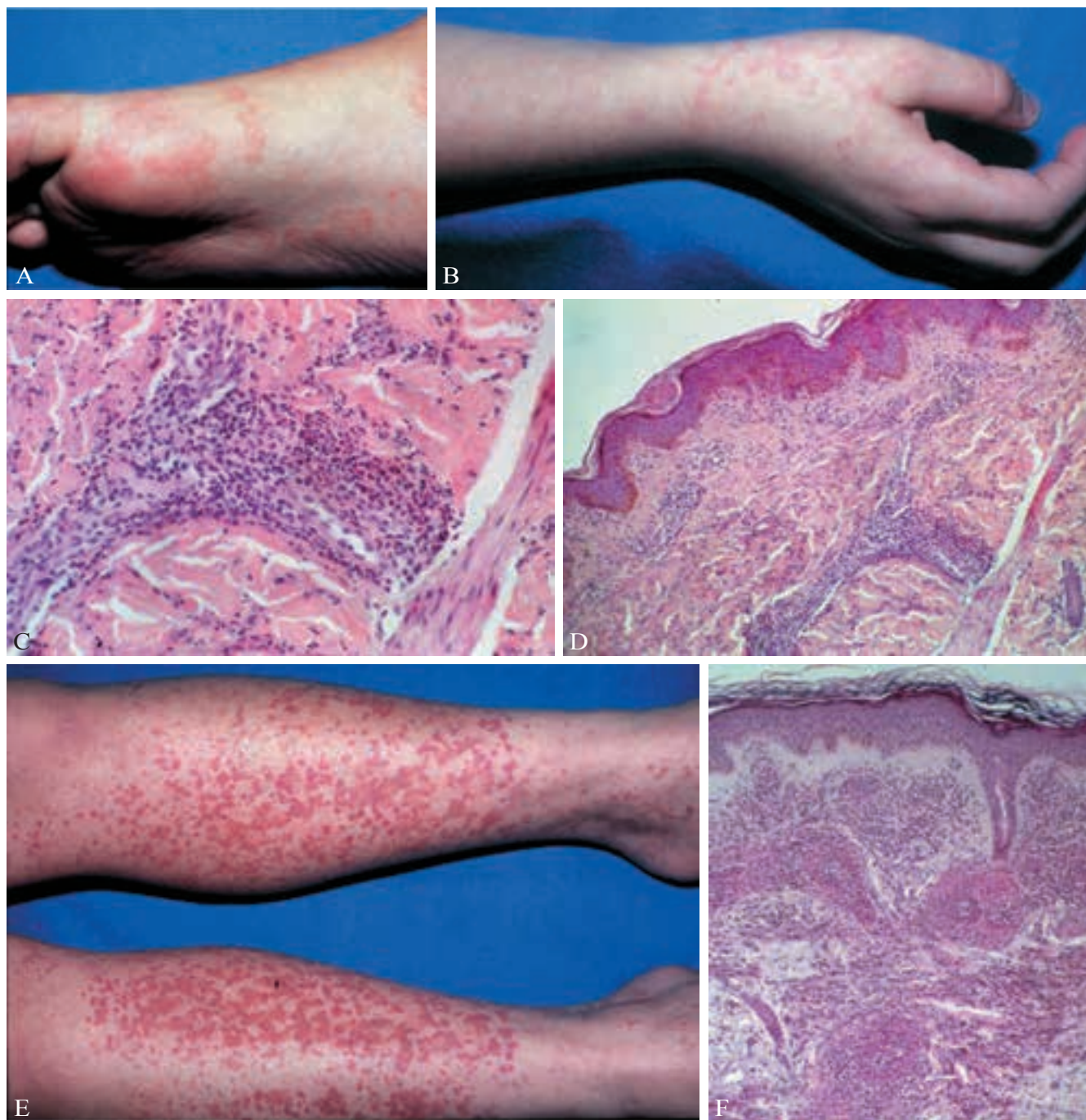


Figure 4.—A) Persistent urticarial lesions involving feet sites of a girl affected by hypocomplementemic urticarial vasculitis in SLE; B) the same patient with urticarial vasculitis involving forearms and fingers; C) vasculitis of postcapillary venules (hematoxylin and eosin, X 200), and D) of capillaries are characteristic of hypocomplementemic urticarial vasculitis in SLE (hematoxylin and eosin, X 100); E) clinical presentation of a case of pediatric SLE with small symmetrical confluent purpuric patches of leukocytoclastic vasculitis on lower legs; F) pandermal leukocytoclastic vasculitic involvement of small postcapillaries venules and arterioles (hematoxylin and eosin, X 100), in the patient showed in Figure 4E. Without clinic-laboratory correlation these histopathologic features are virtually indistinguishable from those of cryoglobulinemia. They are strongly suggestive for a systemic involvement.

conjunctivitis. Progressive glomerulonephritis may ensue. An immunocomplex mechanism, with classic complement pathway activation, and consequent hypocomplementemia, parallels reactivation of systemic disease.

HISTOPATHOLOGY

Histopathology of HUV is characterized by leukocytoclastic vasculitis of small vessels, with particular involvement of post-capillary venules in sub-papillary dermis (Figure 4C). Major histopathological evidence of HUV is given by fibrin deposition within and around the venule wall, with neutrophilic infiltration and karyorrhexis. However, small capillary vessels may be involved by vasculitis too, as shown in Figure 4D. Direct immunofluorescence in the case of the patient showed in Figure 4A, demonstrated IgG and C3 depositions within and around the superficial blood vessels and along the dermo-epidermal junction.

Cryoglobulinemia

Mixed cryoglobulinemia (type II, characterized by a monoclonal component, usually of IgM class, and type III, characterized by a polyclonal component) is rarely described in children, yet it may be found in association with SLE.

In cryoglobulinemia, cutaneous involvement is relatively frequent in children, with symmetrical distribution of purpuric lesions and ulcerations on lower limbs (Figure 4E), with a frequency of the involvement ranging from about 30% and 80% of the cases.¹⁸ This type of cutaneous expression is less frequently seen in children than in adults. It is precipitated by exposure to cold. Cutaneous vasculitis is often associated with kidney (membrano-proliferative glomerulonephritis), musculoskeletal, joints and pulmonary involvement.

Serological diagnosis is based on the demonstration of IgG and IgM cryoglobulins, and by low levels of C4.

HISTOPATHOLOGY

Histopathology of mixed cryoglobulinemia is characterized by full thickness dermal vessels involvement, with leukocytoclastic vasculitis and fibrin deposits in and around the vessels walls (Figure

4F). Immunocomplex deposits may be found in capillaries, venules and arterioles of the skin.

LV

LV is rarely found in children affected by SLE (Figure 5A), and on clinical grounds alone it may be difficult to distinguish it from livedo vasculitis found in PAN and in other collagen vascular disease.

HISTOPATHOLOGY

Histologically, LV is characterized by a predominantly lymphocytic vasculitis in reticular dermis with endoluminal thrombi, thus summing up the features of a true vasculitis with those of a vasculopathy (Figure 5B).

CHLE, perniosis-like LE

Sporadic CHLE is rarely observed in childhood.¹⁹ Major diagnostic criteria of CHLE, as proposed by Su *et al.*²⁰ in a clinical review of adult patients, include acral clinical manifestation of CHLE, precipitated by cold, and histopathology of LE, *i.e.* variable atrophy of epidermis, vacuolar changes at the dermo-epidermal junction, superficial and deep perivascular and periadnexial lymphocytic infiltrate, and typical direct immunofluorescence features of LE, such as granular IgM, IgG, and/or C3 deposits at dermo-epidermal junction.

A rare, single case of CHLE, recently reported in a child by Hedrich *et al.*¹⁹, is not conclusive about this association, since the chilblain presentation was not characterized by the serologic changes of SLE, and only a transitory positivity of anti-ds-DNA antibodies was reported. CHLE may persist even after the cold season, and during systemic therapy, with the features of well demarcated chronic erythematous non edematous patches of the forefoot, heels, and distal phalanges (Figure 5C-D). Somewhat surprisingly, the histopathologic perivascular infiltrate was lacking, as well as the interface changes, while a remarkable superficial and mid dermis vasodilatation persisted (Figure 5E). Yet, mucin deposits were detectable between collagen fibers.

HISTOPATHOLOGY

Histopathologically, CHLE is not characterized by vasculitis, and its histopathology changes may dis-



Figure 5.—A) Persistent acral livedoid changes in a patient affected by SLE; B) Histopathology from a livedoid lesion of the same patient of Figure A) showing a lymphocytic vasculitis characteristic of late or chronic vasculitic cutaneous manifestations in collagen-vascular disease patient (hematoxylin and eosin, X 200). C) Chronic features of Chilblain LE characterized by well demarcated patches of erythema in a young patient with SLE involving toes, forefoot, and heel. D) In reality, the diffuse erythema is pitted with superficial, irregularly shaped ulcers (arrows). Those findings were persistent also in mild, non-winter seasons. E) Histopathology of the same case (Figure 5C) failed to demonstrate any superficial or deep infiltrate, showing only striking superficial and mid dermal vasodilation with scant lymphocytic infiltrate (hematoxylin and eosin, X 100) and interstitial mucin deposits.

tinguished from those of the erythematous and edematous acral lesions of PAN. However, thrombosis of superficial dermal vessels have been reported in two adult cases of CHLE.²¹

Juvenile dermatomyositis: etiopathogenesis, clinical features and the burden of the systemic vasculitis

Recent hypotheses on pathogenesis of juvenile dermatomyositis (JDM) define that, in genetically susceptible patients, the simultaneous presence of environmental factors (drugs, infections) and immune system dysfunctions play a major role. In particular, type I Interferons are released in the skin by plasmacytoid dendritic cells activated by viruses, UV, mechanical stimuli²² and in muscles *via* a previous damage to endothelial cells. Moreover, plasmacytoid dendritic cells chemokines may stimulate a T-cell response, paralleled by the formation of immunocomplexes, leading to chemoattraction of other different cells, thus amplifying in turn the overexpression of type I interferons.²³ The complex pathogenetic role of auto-antibodies recognizes two categories of JDM patients: 1) myositis specific antibodies (MSA auto-antibodies) directed to nuclear and cytoplasmic targets; 2) myositis associated antibodies (MAA) that may also be found in several autoimmune disorders.

Contrarily to dermatomyositis-polymyositis (DM) of adulthood, characterized by the association of a neoplasm in more than one third of the patients, JDM

is an idiopathic autoimmune chronic multisystem disease, affecting primarily skin and muscles. Yet, a case of JDM of paraneoplastic significance has been recently reported.²⁴ Further differences characterize the two forms.

Adulthood DM is characterized clinically by erythematous-edematous changes on eyelids, cheeks, neck, décolleté, back, with a clear predilection for photoexposed sites, and in later stages by chronic papules and plaques on iuxta articular extensor surfaces of the hands with the features of the so called Gottron's papules. In both cases, histopathology changes of DM are those of an interface dermatitis with vacuolar changes of the dermo-epidermal junction, variable atrophy of the epidermis, and by a variable degree of superficial lymphocytic infiltrate around the vessels of the superficial plexus. Vasodilation is a constant feature. No evidence of true vasculitis or vasculopathy may be found in cutaneous changes of adult DM.

On the contrary, JDM is regarded today as a rare systemic autoimmune vasculopathic disease. Cutaneous features include periorbital and eyelids edema with tiny telangiectases (the so called heliotropic rash) (Figure 6A), Gottron's papules, and widespread photosensitive erythema (Figure 6B).

Visceral vasculopathic/vasculitic involvement in JDM is rare, and mostly affects gastrointestinal tract, leading in some cases to infarction and perforation. However, muscle degeneration in some cases of JDM has been demonstrated to be secondary to a polyarteritis-like involvement of middle sized arteries.²⁵

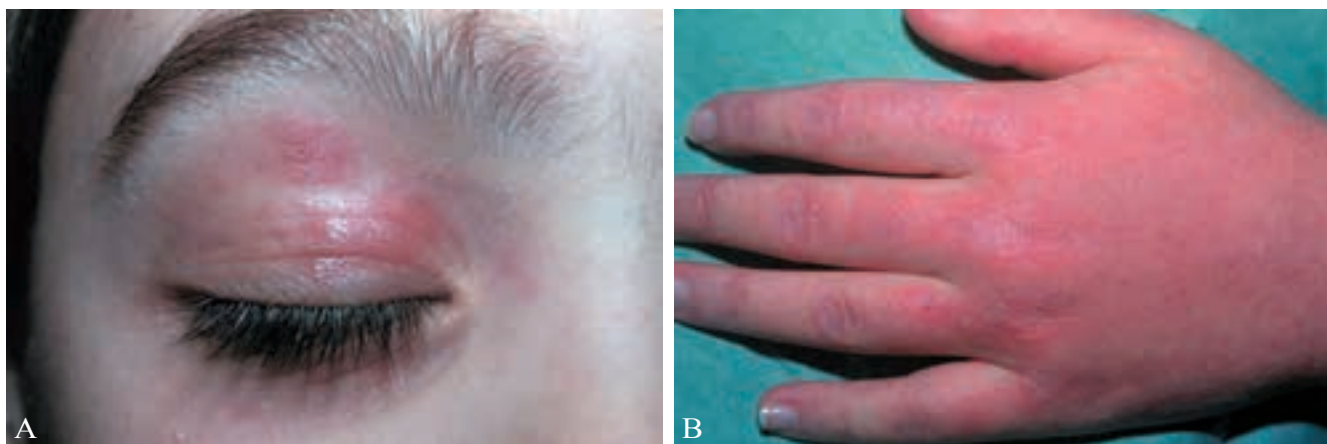


Figure 6.—A) Heliotropic rash of the eyelids with telangiectases, a typical sign of JDM; B) Confluent photosensitive erythema of the dorsal aspects of the hands in a girl affected by JDM.

Despite the fact that some decades ago²⁶ and also recently JDM is regarded as an autoimmune vasculopathy/vasculitis disease, histopathological evidence of such changes in the skin are lacking. In fact, involved JDM skin is not characterized by vasculitis/vasculopathy, and rather, by evidence of interface vacuolar changes, Civatte bodies, mild to moderate lymphocytic perivascular infiltrate with some neutrophils, and interstitial mucin deposits, all features of a collagen-vascular disease, much alike to SLE, rather than those of a true vasculitis/vasculopathy.

Even in cases in which periungual and gingival involvement is claimed to be a vasculopathic sign of JDM,²⁷ an histopathological demonstration is not shown, thus creating confusion between the clinical

evidence of telangiectatic bushy loops of JDM, and the histopathological features of a true vasculopathy, characterized by scant inflammatory infiltrate around vessels walls and endoluminal thrombi.

More consistently, when gastrointestinal involvement during JDM is reported, including dysphagia, bowel dismotility, and abdominal pain, the underlying condition of the bowel ulceration and perforation is a true thrombotic vasculopathy, involving multiple small and medium sized arteries with the features of significant luminal fibrinoid degeneration. The true vasculopathic nature has also been proved by immunophenotyping of the cells surrounding the vessels, but not within the vessel walls.²⁸

An example of the absence of vasculopathy in the

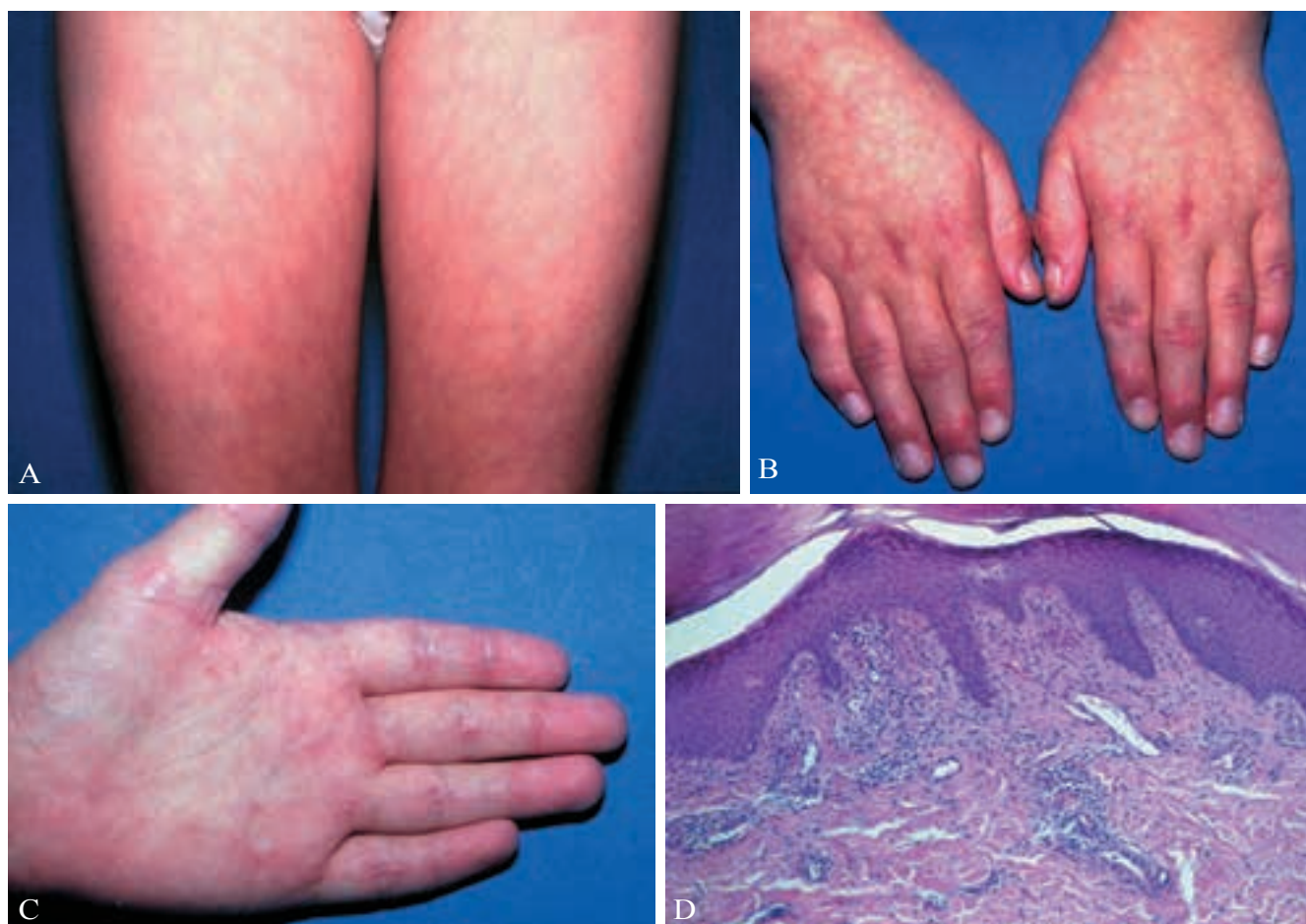


Figure 7.—A) Unusual livedoid chronic reticulated changes on legs of a 10-year-old boy affected by JDM; B) The same patient had livedoid changes on the dorsum of his hands with clear evidence of Gottron's papules, and C) reticulated livedoid features of his palms with tiny hyperkeratotic lesions on flexural areas of his fingers that showed histologically D) changes indistinguishable from those of a conventional Gottron's papule.

skin of JDM patients is given by the clinico-pathological correlation of a case of JDM sent in consultation by the Department of Pediatrics, University of Pavia, and reported here. A 10-year-old boy affected by JDM presented with unusual reticulated livedoid features on lower legs (Figure 7A), and on upper extremities. Both dorsal and volar aspects of his hands (Figure 7B, C) had livedoid appearance. Typical Gottron's papules were present. Tiny hyperkeratotic focal lesions were localized on flexural folds of his digits and on his palms. Histopathology of such a lesion showed (Figure 7D) hyperkeratosis, irregular acanthosis, and hypergranulosis, focal vacuolar interface changes with few necrotic keratinocytes, and a superficial lymphocytic perivascular infiltrate, without vasculitis or vasculopathy. Superficial vasodilation was remarkable. All the described histopathologic features are typical of Gottron's papules, otherwise unreported on palmar surfaces.

Behçet's disease: etiopathogenesis, clinical features and the problem in classifying the cutaneous changes in a neutrophilic/vasculitic disease.

The Greek ophthalmologist Benediktos Adamantiades in 1930 described the ophthalmologic changes of the disease as a case of "relapsing iritis with hypopyon";²⁹ later, Hulusi Behçet, a Turkish dermatologist, described in 1936 the complex cutaneous, ocular, mucosal, systemic features of the syndrome that would be later eponymically called by his name. Behçet's disease (BD) is a multisystem disease characterized by the classic triad of "recurrent oral aphthous ulcers, genital ulcers, and hypopyon uveitis".³⁰ According to the International Study Group for BD, the major criterion, *i.e.* oral aphthae recurring at least three times in a period of one year, has to be associated with at least two of the following signs, *i.e.* 1) recurrent genital aphthae; 2) ocular involvement; and 3) skin lesions (erythema nodosum, erythema nodosum-like plaques, papules, acneiform manifestations, sterile folliculitis) associated with a positive pathergy reaction. Behçet syndrome is a multisystem disease involving gastrointestinal tract, arteries and veins, central nervous system, joints and more rarely heart and kidney.

The highest prevalence is recorded in Far East, Middle East, Turkey, while is more rarely diagnosed

in Northern Europe and United States. In Italy, the prevalence of BD is higher in the Southern than in the Northern part of the country, as reported by Olivieri *et al.*³¹ BD is rarer in children than in adults, with an estimated prevalence of 1:600.000 children <15 years.³² Human leukocyte antigen B51 expression is frequently present in patients affected by BD in Mediterranean countries and in Japan, while this association is not found in patients from Northern Europe and United States.³²

In a series of 17 cases of BD in Turkish children reported by Borlu M *et al.*,³⁰ recurrent oral and genital aphthae, skin lesions, and ocular lesions are typically the most frequent manifestations of the disease. Vascular involvement has been recorded in one patient as a self-healing episode of thrombophlebitis. The authors refer that no cutaneous biopsy was done.³² In a series of 10 children affected by BD in UK, 90% of cases had skin manifestations, encompassing the entire spectrum of the clinical changes that may be found in BD, including palpable purpura. The authors conclude that BD in childhood has similar signs and symptoms to those found in adults.³³

From a clinico-pathological point of view, cutaneous involvement in BD may be characterized by both non vasculitic, and vasculitic changes.

Non vasculitic cutaneous changes in pediatric BD: a short report

Non vasculitic histopathologic changes are the demonstration that BD is substantially a neutrophilic dermatosis, with variations from diffuse neutrophilic infiltrate to spongiotic neutrophils collections to follicular and non follicular pustules. The clinical and histopathological correlation of a 18-month-old female baby are here described. The patient had continuous-remittent fever, unresponsive to systemic antibiotic treatments, with elevation of erythrocyte sedimentation rate (100 mm/h), and with neutrophilic leukocytosis. Persistent arthralgia involved her right knee. Cutaneous findings were characterized by persistent figurate and annular lesions on her limbs and abdomen (Figure 8A). No mucous involvement was present. A biopsy of a figurate erythematous lesion showed histopathological features of a dense superficial and mid dermal neutrophilic infiltrate without vasculitis and with neutrophilic exocytosis (Figure 8B). After an episode of asthma, the systemic steroid treatment induced a dramatic improvement of signs

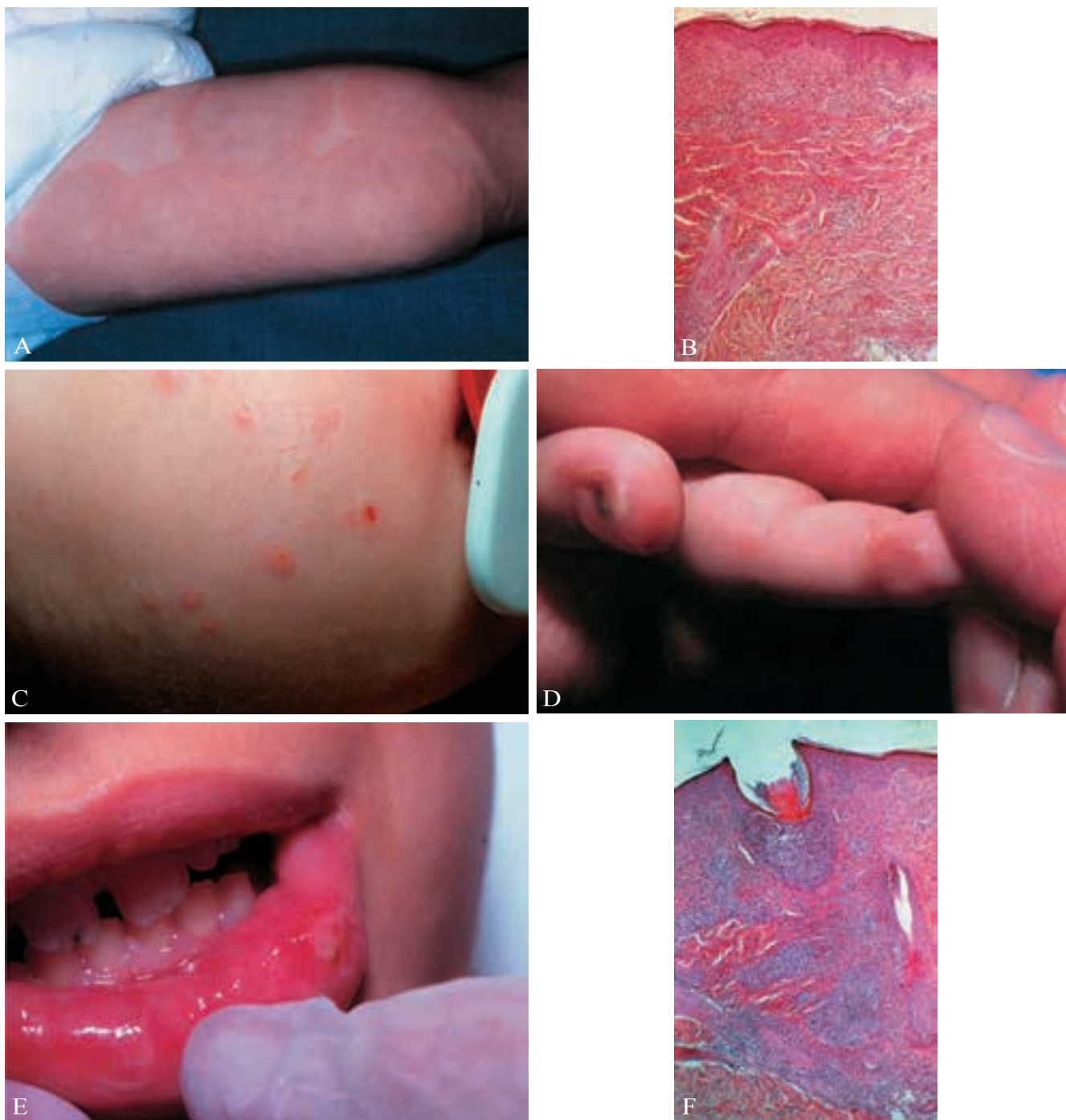


Figure 8.—A) Figurate and circinate centrifugal erythematous lesions involving lower legs and abdomen in a 18-month-old baby, who presented later the typical major diagnostic signs of BD; B) histopathology of a figurate lesion showed dense diffuse neutrophilic infiltrate consistent with an aspecific diagnosis of neutrophilic dermatosis without vasculitic involvement (hematoxylin and eosin, X 100); C) sterile pustules involving the cheeks of the baby and D) discrete pustules on her fingers, and E) typical aphthae on her labial mucosa. F) Histopathology of a pustule on her cheek demonstrated a ostio-follicular involvement with a diffuse neutrophilic infiltrate without vasculitis (hematoxylin and eosin, X 100).

and symptoms in the child, including rapid resolution of the cutaneous involvement. However, after steroid withdrawal, a recurrence of both systemic sign and symptoms, including fever, arthralgia, diarrhea, and skin involvement, rapidly arose again, with new cutaneous and mucous components, namely an sterile folliculitis on her cheeks (Figure 8C), discrete palmar (Figure 8D) and plantar pustules, and oral aphthae (Figure 8E). A biopsy of a tiny pustule on her cheek demonstrate the follicular involvement with an inner neutrophilic perivascular infiltrate without vasculitis (Figure 8F)

A diagnosis of BD was made at that point, with systemic signs, symptoms, and aspecific cutaneous neutrophilic non vasculitic involvement, preceding of some months the major clinical criterion of oral aphthae.

Vasculitic cutaneous changes in pediatric BD: a short report

A 18-year-old girl, satisfying the diagnostic criteria of BD (oral aphthae, cutaneous changes, and pathergy), had acne-like lesions on her cheeks. She also had multiple plaques on the extensor surfaces of her forearms. An isolated extensive Sweet-like plaque was present on her neck (Figure 9A). The cutaneous expression of BD are extremely polymorphous. Erythema nodosum, indeed, is one of the pathologic patterns that may be found in nodular lesions of BD. Erythema nodosum-like lesions of BD are con-

stantly associated with vasculitic changes.³⁴ In some cases the underlying histopathology expression is lobular panniculitis associated with small vessel vasculitis, either leukocytoclastic or lymphocytic.³⁵ In other cases, phlebitis is the histopathology counterpart of nodular lesions in BD.³⁶ Histopathology from the plaque on the neck of the *proposita*, was characterized by diffuse neutrophilic infiltrate with leukocytoclastic vasculitis of postcapillary venules, with evidence of endoluminal thrombi in small deep dermal vessels (Figure 9B).

Chen KR *et al.*³⁷ on the basis of the high frequency of histopathologic vasculitic changes found in a study of 20 adult patients, maintain that cutaneous vasculitis of BD is predominantly a venulitis and a phlebitis, that may be found approximately in 50% of the cutaneous lesions. A leukocytoclastic and/or a lymphocytic vasculitis may be associated histologically to the cutaneous lesions of BD. The authors conclude that rather than a neutrophilic dermatosis, BD should be regarded as vasculitic disease.³⁷

In our opinion, a true neutrophilic dermatitis without vasculitis may characterize, at least in some phases of the disease, the histopathologic expression of BD, and this is true in particular with pustular and figurate lesions. The presence or the absence of vasculitis in BD depends on several variables, such as the stage of the disease, at least of the cutaneous lesions (early, fully developed, long lasting), the type of lesions, and possibly by ethnic background, different antigenic triggers, and immunologic condition of the patient.

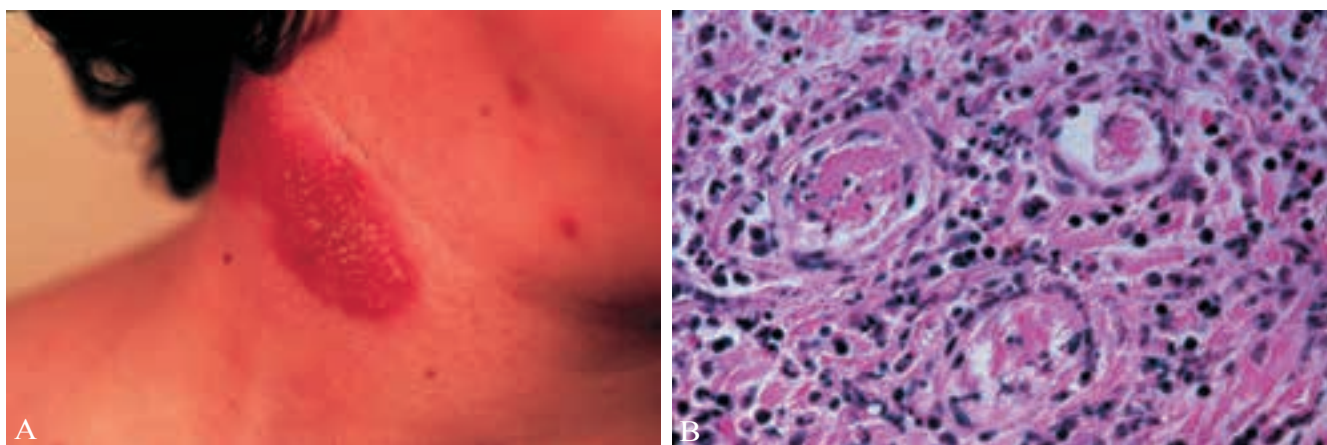


Figure 9.—A) Isolated extensive Sweet-like plaque was present on the neck of 18-year-old girl affected by BD (oral aphthae, cutaneous changes, and pathergy), she had also acne-like lesions on her cheeks, and multiple plaques on the extensor surfaces of her forearms; B) diffuse neutrophilic infiltrate with leukocytoclastic vasculitis of post-capillary venules, with evidence of endoluminal thrombi in small deep dermal vessels (hematoxylin and eosin, X 100).

WG: etiopathogenesis, clinical features, frequency of cutaneous vasculitis in a systemic vasculitis disease

WG is a systemic vasculitis mainly affecting the respiratory tract and kidney; cutaneous involvement is not infrequent. WG may occur at any age.

Despite the fact that WG is rarely observed in children, cutaneous involvement, according to Cabral *et al.*³⁸ and Akikusa *et al.*,³⁹ is reported in about 40% of the cases. Skin lesions may be the early sign of WG in a small percentage of cases,⁴⁰ and they include different types of lesions, such as nodules, purpuric patches, palpable purpura, or ulcers. Papulo-necrotic lesions are symmetrically distributed on knees, elbows, buttocks, and face. A higher prevalence of WG is reported in Caucasian and female children, while in adults a slightly preponderance of males has been recorded. The mean age at the diagnosis is about 14 years.³⁸ Hypersensitivity reactions to unknown antigens, respiratory tract sensitization to bacteria, and autoimmune pathogenesis may play a role in WG, inducing both a vasculitic component and granuloma formation.

At the onset of the disease, upper and/or lower respiratory tracts are the most frequently involved sites, with a reported higher risk of subglottic, tracheal, or endobronchial stenosis in children than in adults. In a study by Rottem *et al.*,⁴¹ at the onset of WG about 87% of pediatric patients present with involvement of ear, nose and/or throat, with signs and symptoms such as sinusitis, otitis media, hearing loss, emphysema, ear pain, and oral lesions. Glomerulonephritis is rarely present (about 9% of cases) in the early phase of the disease, but it is frequently found in about 61% of patients in a later phase, evolving in 1 out of 3 cases into a chronic renal failure. During the course of the disease, upper respiratory tract involvement (sinusitis, mucosal ulcerations, nasal septal perforation, saddle nose deformity), eye disease (dacryocystitis, scleritis, pain), arthralgias/arthritis are common findings.

Laboratory diagnosis of WG is based on detection of autoantibodies (usually of IgG class) reacting against cytoplasmic components of neutrophils (ANCA). In particular, two types of diagnostic ANCA may be found, namely cytoplasmic ANCA (c-ANCA), direct against the granular enzyme proteinase 3 (PR3)-ANCA, and perinuclear ANCA (p-ANCA), characterized by multiple antigenic af-

finities, among which myeloperoxidase is the best characterized.

From the point of view of systemic vasculitic involvement, ANCA positivity in children has been outlined by Lindsley CB and Laxer RM⁴² and it encompasses distinct diseases, such as WG, microscopic polyangiitis, Churg-Strauss Syndrome, and crescentic glomerulonephritis.

In children c-ANCA are positive in about 86% of cases, while PR3-ANCA are detectable in 68% of cases.³⁸ Other laboratory findings include leukocytosis, with moderate eosinophilia, marked elevation of erythrocyte sedimentation rate and C reactive protein level. About 50% of children with WG has rheumatoid factor positivity.

Histopathology

A true histopathologic necrotizing vasculitis with granulomatous changes does not exceed the 20% of cases of WG.⁴³ Other histopathological findings are characterized by dermal inflammatory changes, either involving the vessels or not. Extravascular changes show focal dermal fibrinoid degeneration, sometimes demarcated by palisading histiocytic infiltrate with multinucleated giant cells. The distinction of cases with vasculitic and without vasculitic

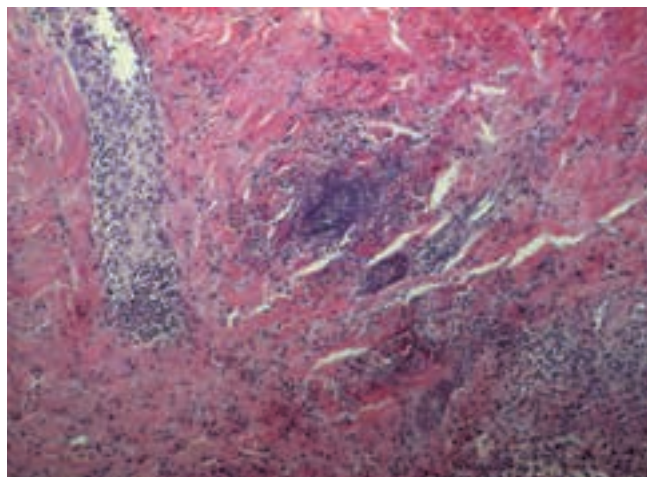


Figure 10.—Mid dermal vasculitic involvement in a case of pediatric WG. A postcapillary venule is characterized by heavy neutrophilic perivascular infiltrate, obscuring the vessel wall, and by the presence of two small vessels characterized by destruction of the vessel wall and basophilic degeneration of the surrounding dermis with diffuse leukocytoclasia and by a small vessel involvement characterized by an endoluminal thrombus (hematoxylin and eosin, X 100).

involvement in WG, has practical implications. In fact, according to the report by Barksdale *et al.*⁴⁴ on 75 cutaneous biopsies taken from 46 WG patients with skin involvement compared with 82 WG patients with no skin involvement, the histopathological subclass of leukocytoclastic vasculitis characterized a more severe and progressive course of the disease, in comparison to the cases with granulomatous inflammation or no cutaneous involvement. Furthermore, cutaneous vasculitic involvement denoted a phase of active disease. Leukocytoclastic vasculitis affects small and medium sized dermal vessels, including capillaries, postcapillary venules, and arterioles, thus involving upper, mid and deep dermis (Figure 10).

PAN: etiopathogenesis, clinical features and different presentations of cutaneous vasculitis in a systemic vasculitic disease

Etiology of PAN remains obscure. Despite the relation of PAN with *Hepatitis B* in adults, in children this association is very rare. In childhood the association of PAN with infectious agents is today taken into consideration, after the demonstration of the role of some bacterial superantigens.⁴⁵ From the pathogenetic point of view, the immunological mechanisms are likely to be more complex than simple immunocomplex type, including also cytokines, chemokines, cell-adhesion molecules, neutrophil and T-cell mediation.

According to Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis, PAN has been defined as a necrotizing multiorgan vasculitis associated with aneurysmal nodules, involving medium or small sized arteries, without vasculitis in arterioles, capillaries or venules.⁴⁶ This definition has been only partially applicable to the diagnosis of childhood PAN. In fact, after several revisions of the pediatric diagnostic criteria, finally the diagnosis of childhood PAN is now definable according to Ozen *et al.*³, as based on a major criterion, the histopathological one (necrotizing vasculitis in medium and small arteries) and/or the angiographic one (presence of aneurism, stenosis, or occlusion of medium or small sized arteries), plus one of the following criteria: 1) myalgia or muscle tenderness; 2) arterial hypertension; 3) peripheral neuropathy; 4) renal involvement; 5) skin involvement. Cutaneous changes

are characterized by livedo reticularis, skin nodules, and cutaneous necrosis.

In the field of childhood PAN an open issue with nomenclature, classification, prognosis and therapy implications, is proposed by a recent paper⁴⁷ that makes a distinction between systemic juvenile PAN and cutaneous juvenile PAN, in which cutaneous changes (cutaneous nodules, livedo and ulcerations) are present without systemic involvement. However, the same author⁴⁷ adds to the cutaneous changes in brackets, also myalgia and arthralgia.

Different from cutaneous juvenile PAN is childhood microscopic polyangiitis (MPA), that, according to Chapel Hill Consensus Conference,⁴⁶ is a distinct necrotizing vasculitis of the small sized vessels, involving the kidney, with progressive crescentic glomerulonephritis and pANCA positivity. Sometimes pulmonary capillaritis occurs, with no evidence of true granulomatous inflammation. MPA is included in the spectrum of ANCA-positive diseases and the skin manifestations are purpura (100%), and necrotizing cutaneous vasculitis (29%).⁴⁸ Histopathology of MPA cutaneous vasculitis is characterized by a neutrophilic acute involvement of arterioles with variables leukocytoclasia, focal fibrin degeneration of the vessels and erythrocytes extravasation with sparing of medium sized muscular arteries.

Cutaneous clinical features of childhood PAN are characterized by acral livedo reticularis (Figure 11A); by focal necrotic ulcers (Figure 11B, C), in the context of a preexisting livedo reticularis; by extensive acute necrosis of the fingers, rapidly occurring on the basis of macular and confluent recent livedo (Figure 11D); and by nodules. The underlying histopathological expression of the nodules is given by a mid-sized arterial involvement characterized, in early phase, by thickening of the vessel wall, by fibrin, and a mixed cell infiltrate composed of neutrophils, lymphocytes, and eosinophils. Later, lymphocytes predominate with a progressive intimal and mural fibrosis, leading to artery occlusion (Figure 11E). Medium sized arteries involvement may be observed at the deeper portion of the dermis or in the context of the subcutaneous tissue (Figure 11F). Scant, if any, mononuclear cell infiltrate involves the surrounding subcutaneous fat. Multiple biopsies taken from different PAN cutaneous lesions may show different stages of the arterial involvement at the same time.⁴⁹



Figure 11.—Cutaneous features of childhood PAN: A) acral livedo reticularis; B, C) focal necrotic ulcers in the context of a preexisting livedo reticularis; D) extensive acute necrosis of the fingers, rapidly occurring on the background of macular and confluent recent livedo (Figure courtesy of Prof. A. Martini). E) The stereotypical histological expression of the nodules of PAN is given by a mid sized arterial involvement that, in early phase, show thickening of the vessel wall, fibrin deposition and the presence of mixed cell infiltrate made of neutrophils, lymphocytes and eosinophils; later, lymphocytes predominate with a progressive intimal and mural fibrosis, leading to artery occlusion (hematoxylin and eosin, X 200). F) Arterial vasculitis is observed at the deeper portion of the dermis and in subcutaneous fat (hematoxylin and eosin, X 100).

KD: etiopathogenesis, clinical features and the role of cutaneous changes in the diagnosis of systemic vasculitis

KD, early described by Tomisaku Kawasaki in 1967, is one of the most common multisystem vasculitides in children. It is characterized by acute, subacute and recovery phases, and defined by diagnostic criteria, such as fever, lasting for more than 5 days, plus four of the following signs: 1) bilateral conjunctivitis; 2) pharyngeal and oral mucous membrane involvement, lips fissurations, strawberry tongue; 3) edema of distal parts, and later cutaneous desquamation; 4) polymorphous cutaneous rash involving primarily trunk, and cheeks, flexural areas, abdomen; 5) cervical lymphadenopathy.

The highest incidence is recorded in Asian patients with a peak incidence recorded in Japan in the first year of life, in both sexes. Etiology remains obscure: systemic vasculitis in KD may be caused by common antigens able to induce an immune response to the endothelial cells. The role of superantigens, such as some strains of *Streptococcus*, *Staphylococcus*, and mycobacterial antigen, may play a role in T-cell stimulation. Other authors have considered the role of different antigens, such as Epstein Barr virus and Rotavirus. However, humoral factors such as circulating immunocomplexes, anti-endothelial antibodies, and ANCA, are frequently implicated.⁵⁰ Evidence of increased serum levels of inflammatory cytokines, such as IL-6 and TNF α , has been proved and linked to the severity of the disease by Lin CY *et al.*⁵¹ Vasculitis of KD may affect the coronary, central nervous system and gastrointestinal tract, leading respectively to coronary artery aneurism, stroke and intestinal hemorrhages with visceral rupture. *Post-mortem* findings by Amano *et al.*⁵² on 37 Japanese patients demonstrated a necrotizing panarteritis, with aneurisms and thrombi formations observed mainly in the coronary district. The authors concluded that the vascular changes of KD involved both arteries and veins.

There is no mention in literature of a vasculitic process underlying the polymorphic cutaneous eruption of KD in the first phase of the syndrome. However, at least 15 cases of KD with cutaneous vasculitis and peripheral gangrene have been reported.⁵³ Gomez-Moyano *et al.* in their case, clearly demonstrate the livedoid, the purpuric and the gangrenous changes affecting the distal extremities of

the newborn, occurring after the previous polymorphous cutaneous changes that characterize the onset of the disease in the first phase. Histopathology of a purpuric lesion of that patient, was characterized by swelling of endothelial cells, fibrin deposition within and around the vessel walls, extravasation of erythrocytes and mild karyorrhexis.

Even an early and extensive paper by Hirose and Hamashima,⁵⁴ proposed after the original description by Kawasaki T in 1967, considering from an electromicroscopic point of view mucocutaneous lymphnode syndrome as a vasculitis, fails to add evidence of a true vasculitic nature of the exanthema of KD, although the authors claim that “*The vasculitis of MCLS begins in capillaries and small caliber vessels and these lesions then extend to larger vessels. [...] Subendothelial deposition of fibrinoid material in arteries and veins involved is slight and not significant. [...] The skin lesions of MCLS seem to be similar to those seen in delayed-type hypersensitivity*”.

Later, Sato *et al.*⁵⁵ described in 10 Japanese patients affected by KD immunopathology and histopathologic features of the polymorphous exanthema. Histopathologic changes were characterized by extensive edema of the papillary dermis with marked dilation of the capillaries. The infiltrate was made of mononuclear cells with very few neutrophils. The mononuclear cells were mainly macrophages and lymphocytes with some activated CD4 T lymphocytes. In the convalescent phase, the inflammatory infiltrate was absent.

The second phase of KD (subacute phase) is characterized by systemic signs and symptoms, such as arthritis and coronary arteries aneurism formation (25% of the untreated patients), the latter being the consequence of artery vasculitis and thrombosis. The cutaneous counterpart of this crucial phase is characterized by extensive cutaneous desquamation. Histopathology changes are, on the contrary, characterized, as in the case presented here, by the absence of vasculitis. A 9 year-old girl affected by KD had diffuse erythematous and scaly features (Figure 12A), with persistent edema of her hands (Figure 12B), with histopathology changes characterized by hyper/parakeratosis, regular psoriasiform hyperplasia, slight dermal lymphocytic infiltrate, with many melanophages in the upper part of the dermis (Figure 12C). In conclusion, cutaneous features of KD are not characterized by cutaneous vasculitis, except in

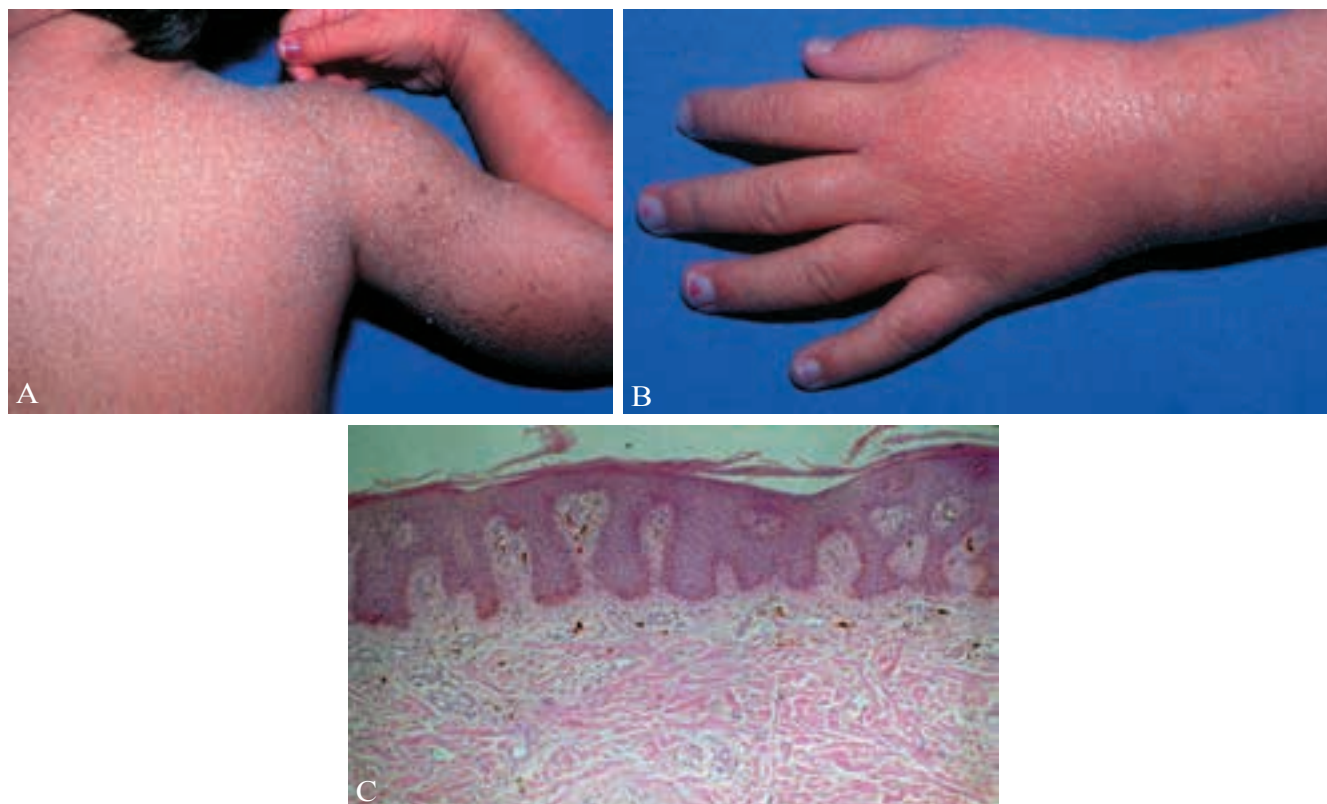


Figure 12.—A) A 9-year-old girl affected by KD, during the phase of diffuse erythematous and scaly changes, with B) persistent edema of her hands; C) histopathology changes are characterized by absence of vasculitis and by a psoriasiform pattern with hyper/parakeratosis, slight dermal lymphocytic infiltrate with many melanophages in the upper part of the dermis (hematoxylin and eosin, X 100).

the rare cases in which livedoid, purpuric and necrotic lesions superimpose to classic exanthema of the early phase.⁵³

Conclusions

A histopathological based approach to the diagnosis of vasculitides in childhood may be conveniently done upon:

- the type of the vessel involvement (arterial, venous);
- the anatomical level (papillary dermis, reticular dermis, pandermal, and subcutaneous fat involvement) with the vascular equivalent of its involvement (capillaries, post-capillary venules, veins, arterioles, arteries);
- the predominant type of its inflammatory infiltrate (neutrophilic with leukocytoclasia, granulomatous, mixed).

Furthermore the histopathology based approach to the diagnosis of pediatric vasculitides, with cutaneous involvement, can identify three groups of diseases.

— The first group has cutaneous changes with histopathological expression of a constant underlying vasculitis (HSP and AHEI less frequently).

— The second group is characterized by sporadic vasculitic involvement of the skin under different clinical patterns, in a group of autoimmune diseases in which the major diagnostic criteria do not include cutaneous vasculitis. This is the case of SLE under the clinical presentations of UV, purpuric lesions, cryoglobulinemic purpura and livedo vasculitis/vasculopathy.

Again, WG is a systemic vasculitis with a cutaneous granulomatous vasculitic expression in about 20% of the cases. In WG histopathologic changes may demonstrate a constant and more frequent extravascular involvement with dermal fibrinoid de-

generation, palisading arrangement and multinucleated giant cells.

PAN is a multisystem necrotizing vasculitis affecting medium and small sized arteries that includes, among its diagnostic criteria, also the skin involvement, namely livedo reticularis, skin nodules, and cutaneous necrosis, secondary to vasculitis. In pediatric patients cutaneous vasculitis may be proved in about 30% of the cases.

In the second group BD may also be included, accordingly to its protean clinical features, sometimes consistent with a neutrophilic histopathologic pattern, namely a diffuse neutrophilic dermal involvement and pustules, and sometimes consistent with a true vasculitis, namely leukocytoclastic vasculitis with diffuse dermal neutrophilic involvement.

— The third group is exemplified by childhood systemic vasculitides without cutaneous vasculitic involvement, as given by KD and by JDM. Yet, severe cutaneous vasculitis is seldom reported in these conditions.

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- Acknowledgments.*—The authors are indebted to Prof. Alberto Martini, Dr. Angelo Ravelli, Dr. Nicolino Ruperto and Dr. Stefania Viola, now at the Istituto Giannina Gaslini, Genoa, Italy, UOC Pediatria II – Reumatologia, for their invaluable help in sharing, discussing and diagnosing with competence and enthusiasm the clinical findings of pediatric rheumatology patients, when they worked at the Department of Pediatrics, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
- Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.
- Epub ahead of print on December 17, 2014.

Septic vasculitis and vasculopathy in some infectious emergencies: the perspective of the histopathologist

C. TOMASINI

Sepsis is a potentially life-threatening complication of an infection where cutaneous lesions often represent one of the early signs. A myriad of microorganisms including bacteria, fungi, yeasts, viruses, protozoas, helminths and algae can be implicated. A broad spectrum of clinical and histopathologic findings can be observed in the skin and the common denominator is a thrombotic vasculopathy. The pathogenesis of cutaneous septic vasculitis (SV)/vasculopathy is complex and includes five main mechanisms: disseminated intravascular coagulation, direct invasion and occlusion of blood vessel walls by microorganisms, hypersensitivity reaction with immune complex deposition into blood vessel walls, embolism from a distant infectious site and vascular effects of toxins. Herein we describe the clinicopathologic findings of some selected cases of SV recently observed in our hospital, including purpura fulminans, necrotizing fasciitis, cutaneous meningococemia, malignant syphilis and disseminated alternaria infection. Histopathologically, a wide spectrum of histopathologic changes was observed in skin specimens from the various entities, involving the intensity and composition of the inflammatory infiltrate, the degree of vascular changes and the presence of microorganisms, that ranged from a predominant not inflammatory, thrombotic-occlusive vasculopathy in purpura fulminans to leukocytoclastic vasculitis like changes in cutaneous meningococemia to a dermal angiomatosis-like pattern in disseminated *Alternaria* infection. The different pathologic presentations may be related to the microorganism involved, the main pathogenetic mechanism that induced the vascular injury and the individual immunologic burden. Early skin biopsy for histopathologic examination and microbiologic culture is a cornerstone in the diagnosis of life-threatening diseases that present with cutaneous septic vasculitis. Ancillary techniques, such as immunohistochemistry and polymerase chain reaction are ad-

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ditional novel and helpful tools to identify pathogens, leading to definite diagnosis in cases with challenging or ambiguous clinical and/or pathologic findings.

KEY WORDS: Sepsis - Vasculitis - Purpura fulminans - Fasciitis, necrotizing - Angiomatosis - Syphilis.

Sepsis is a potentially life-threatening complication of an infection with mortality rates of 40-80%.^{1, 2} It occurs when chemicals released into the bloodstream to fight the infection trigger inflammatory responses throughout the whole body. In turn, this inflammation can trigger a cascade of changes that can damage multiple organ systems, leading to their failure. If sepsis then progresses to septic shock, blood pressure drops dramatically and death may follow.¹

There seems to be a worldwide increase in the incidence of sepsis, which may also be due to the increase in the aging population, drug-resistant bacteria and/or weakened immune systems. Even if anyone can develop sepsis, it is most commonly observed and most dangerous in the very young or very old or those who are very sick, often in a hospital intensive care unit, or those with wounds or injuries, invasive devices and subjects with a compromised immune system. Any type of infection — bacterial, viral, fungal, protozoal, helminthal, algal — can lead to sepsis, but the most likely include pneumonia, ab-

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dominal, kidney and/or bloodstream infection (bacteremia). In immunosuppressed individuals, such as solid organ transplant recipients, high-dose corticosteroid regimen patients and HIV infected patients, organisms that are usually either not virulent or only slightly, may also invade the skin, producing significant localized or disseminated disease.^{2, 3}

Early diagnosis of sepsis is critical to properly manage it, as initiation of early specific therapy is key to reducing mortality. Among the specific evidences for infection (WBCs in normally sterile fluids, free air on abdominal X-ray or CT scan, signs of inflammation of the abdominal cavity lining, abnormal chest X-ray consistent with pneumonia), cutaneous abnormalities are frequently one of the first signs of this disease; therefore, their recognition can result in prompt diagnosis and the institution of effective therapy. Dermatological signs of sepsis include protean clinical lesions such as petechiae, purpura, papulonodules, pustules, vesicles, bullae and ulcers, which share a common pathologic substrate, *i.e.* an inflammatory-thrombotic vasculopathy involving mainly the small vessels of the dermis and sometimes the subcutaneous fat that can be broadly defined under the term septic vasculitis (SV). Therefore, early recognition of cutaneous lesions in the course of sepsis is very helpful for prompt treatment and prognosis.

Cutaneous SV, also referred to as non-leukocytoclastic vasculitis, is a variant of small vessel cutaneous vasculitis seen in association with various septicemic states where it may be one of the early events.⁴⁻⁸ Therefore, early recognition of cutaneous lesions in the course of sepsis is critical to allow for prompt treatment and prognosis. The pathogenesis of SV is complex and includes disseminated intravascular coagulation, direct invasion of skin blood vessels by microorganisms and their entry into the skin, hypersensitivity reactions with immune complex deposition in the blood vessel walls, bacterial embolism and the vascular effects of toxins.⁴⁻⁹ It must also not be forgotten that more than one mechanism may be involved in a single patient.

The various cutaneous manifestations of sepsis depend on the interplay of multiple factors, such as the microorganism and the immunological burden and/or the constitutional characteristics of the individual patient. Among the various presentations of SV, one may mimic leukocytoclastic vasculitis (LV) with the occurrence of purpuric macules and

papules and/or vesicopustules and bullae that may evolve into eschars or ulcers, sometimes distributed acraly. Unlike the case in LV, many lesions in SV are present above the thighs. Pathologically, SV is mainly a thrombo-occlusive vasculopathy affecting small vessels of the superficial and deep dermis and often hypodermis with variable inflammatory reaction, thus the term SV is used interchangeably.

Herein, we describe the clinicopathologic findings of some life-threatening examples of SV recently observed in our dermatology department and classified according to the main pathogenetic mechanism that was presumed to be involved. The role of the skin biopsy in early recognition of these conditions is emphasized.

Purely thrombotic SV

Disseminated intravascular coagulation (DIC) is an acquired, life-threatening condition characterized by the widespread activation of the clotting cascade due to different causes that result in the formation of blood clots in the small blood vessels throughout the body.¹⁰ As the coagulation process consumes clotting factors and platelets, normal clotting is disrupted and severe bleeding can occur from various sites. This leads to a compromise in the tissue blood flow and can ultimately lead to multiple organ damage, including renal, pulmonary, adrenocortical insufficiency (Waterhouse-Friderichsen syndrome), neuropathy, gastrointestinal bleeding and cutaneous lesions.¹¹

In septic states, the development of microvascular occlusive syndrome is often correlated with a severe protein C deficiency, or an acquired or congenital dysfunction due to the production of infection-triggered antibodies that interfere with the protein S function.^{12, 13} Whilst meningococcal infection and other Gram negative bacteria account for a relatively high percentage of cases of septic syndromes associated with DIC mainly through the release of endotoxins, a variety of bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *B-hemolytic streptococci*, *Staphylococcus aureus* groups A and B and *Pseudomonas sp.*, have been also implicated, although precise data as to their incidence are not yet available.¹²⁻¹⁶ The first signs of DIC in the skin include acrocyanosis, ecchymosis, bleeding from wounds and venipuncture sites, *purpura fulminans* (PF) and symmetrical peripheral gangrene (SPG)

and their prompt recognition is critical for both prognosis and treatment.

Purpura fulminans

PF, almost synonymous with acute meningococemia to most physicians, is not a specific diagnosis, but rather a syndrome that includes three distinct categories: 1) inherited or acquired abnormalities of protein C or other coagulation systems; 2) "acute infectious"

PF; and 3) "idiopathic" PF. Inherited and acquired abnormalities of the protein C and S anticoagulant pathway are thought to be responsible for the majority of PF cases, while gram negative organisms, especially *Meningococcus*, are the commonest cause of the acute infectious variety. In children under 4 years of age, the immaturity of the protein C system and factor V Leiden mutation may contribute to the rapid and more frequent development of the pathogenesis of PF in the course of bacterial and/or viral infections.^{12, 13, 16}

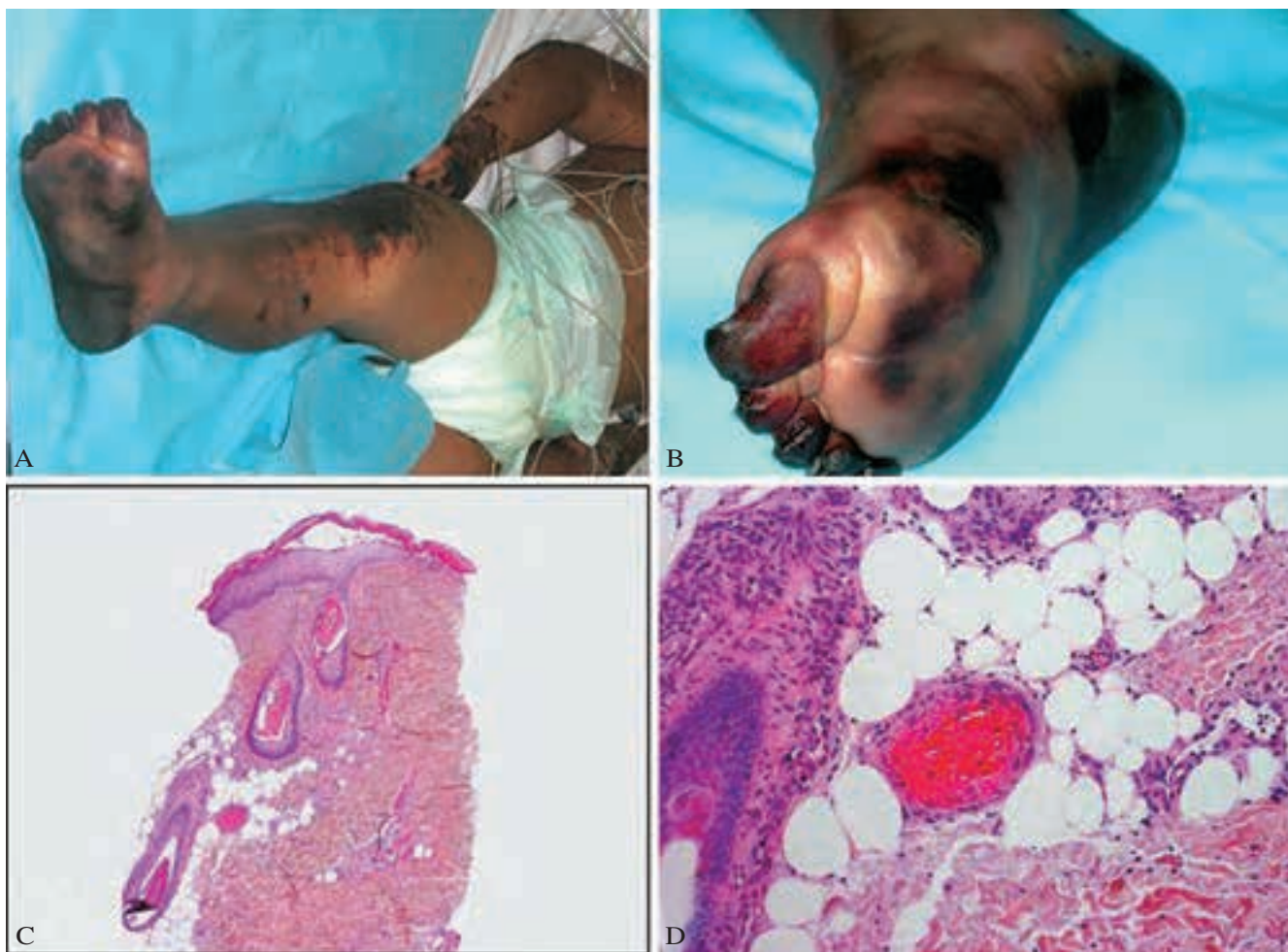


Figure 1.—*Purpura fulminans*. The patient was a 29 year-old male who presented with hypotension and a lethargic state. He had had a sore throat, headache, fever, nausea, vomiting and arthralgia for a few days. One day after admission, the patient's skin became mottled and purpura developed over his lips and knees. During the following 24 hours, the purpura progressed to cover most of his body. His coagulation parameters were consonant with DIC, with a marked reduction in proteins C and S. Cultures of blood samples obtained at the time of admission yielded no microorganism growth, although a later CSF culture was positive for *Meningococcus*. Ceftriaxone plus activated protein C concentrate was administered and the patient recovered slowly with heavy scarring on the distal parts of the extremities. A, B) Widespread hemorrhagic plaques on the upper and lower extremities. The lesions progressed to frank skin necrosis and gangrene on the distal part of the lower extremity. C, D) Skin biopsy showed thrombi in the capillaries and venules with no inflammatory infiltrate. Epidermal necrosis and intraepidermal bulla were also evident.

PF manifests as symmetrical, retiform, sharply demarcated branching or necrotic purpura, predominantly on the distal parts of the extremities and/or bland thrombi as the primary histological findings. The lesions may spread proximally and evolve rapidly into hemorrhagic bullae, which may, in turn, progress to overt skin necrosis and gangrene (Figure 1A, B) and, in severe forms, the whole of the skin surface can be involved. Histopathologically, biopsy from cutaneous lesions show intraluminal thrombi in the dermal small vessels, extravasated erythrocytes and a mild or absent perivascular inflammatory infiltrate (Figure 1C, D). In the late stage, subepidermal blood-filled bullae, epidermal necrosis and ulceration can be observed at this stage, whilst usually no microorganisms can be detected within the vessel walls.

Symmetrical peripheral gangrene

SPG is a rare, devastating condition with high rates of associated morbidity and mortality. It is most commonly observed in the course of septic states associated with DIC characterized by symmetrical distal ischemic damage at two or more sites in the absence of large vessel obstruction.¹⁷ Clinically, it manifests as extreme pallor, cold, and pain in the distal extremities, followed by acrocyanosis and, if not reversed, to frank gangrene within 24-48 hours. The ischemic changes may progress proximally to involve the entire extremity. The clinical changes of PF and SPG sometimes overlap, as in the case of the patient shown in Figure 1. The diagnosis of PF and SPG is based on characteristic clinical, laboratory and microbiologic findings. Laboratory abnormalities include anemia, leukocytosis and thrombocytopenia. Anemia is a feature of the disease and is due to a combination of tissue extravasation, external loss and microangiopathic haemolysis. Laboratory markers consistent with DIC include: prolongation of prothrombin time and the activated thromboplastin time (aPTT), low level of plasminogen, a rapidly declining platelet count and high levels of fibrin degradation products, including D-dimer.

PF and SPG must be differentiated from lesions of similar appearance, such as traumatic skin bleeding or purpuric rashes occurring in the setting of coagulopathies due to various causes, including immune thrombocytopenia, thrombotic thrombocytopenic purpura, inherited or acquired protein C and S deficiencies, coagulopathies associated with connective

tissue disease (*e.g.* lupus anticoagulant and antiphospholipid antibody syndromes), platelet thrombosis in heparin- or Warfarin- induced skin necrosis.¹⁸

PF may run a fatal course, with an overall mortality rate of about 50%, making prompt recognition and therapy critical. Recognition of the pathophysiological mechanism involved in this severe condition may provide a rational basis for treatment, that mainly includes immediate heparinization, replenishing the coagulating factors (protein-C or antithrombin concentrations), antibiotic therapy and stabilizing the cardiovascular system.^{14, 19} Extensive purpura in septic states may also occur in the absence of DIC and there may be no correlation between the severity of the purpura and the presence of DIC.²⁰ Furthermore, the coagulopathy that frequently occurs in sepsis may be attributed to causes other than those provoking DIC.²¹

SV from other pathogenetic mechanisms

In contrast to PF and SPG, other forms of cutaneous SV often contain profuse microorganisms, as revealed in histopathologic specimens and may be not associated with DIC. The most commonly observed pathogens in SV are gram-positive bacteria, such as *Staphylococcus aureus*, *Streptococcus sp.*, *Pneumococcus* and gram-negative bacteria like *Meningococcus*, *Gonococcus* and *Pseudomonas*, but *Mycobacteria*, *Spirochetes*, *Rickettsia*, fungi, protozoas, *rickettsiae* and viruses may also be implicated.^{3, 6-9, 22, 23}

The pathogenetic mechanisms that play a role in producing the cutaneous lesions are complex and have not yet been fully and clearly elucidated; they include direct invasion of skin blood vessels by microorganisms from the blood stream into the skin or from the skin into the systemic circulation, a hypersensitivity reaction with immune complex deposition in the blood vessel walls and infectious embolism.⁴⁻⁹ Noteworthy is the fact that more than one mechanism, including a local hypercoagulability state, may be involved in a single patient.

In chronic meningococemia, both *in vivo* and *in vitro*, data suggest that in the pathogenesis of cutaneous lesion microorganisms gain access from the capillary lumen to the peripheral extravascular compartment in the absence of vascular dislocation, through an active process of the internalization of the pathogen into the endothelial cells of the venules with subsequent translocation towards the perivascular com-

partment, followed by immune complex deposition within the vessel walls with complement cascade activation and vascular injury.²⁴ It is well known that consumptive coagulopathy is due to local vascular damage rather than a generalized activation of the coagulation system. Clinically, a wide spectrum of cutaneous lesions can be observed, partly depending on the microorganism involved, the port of entry, the immunologic burden of the patient and the pathogenetic mechanism. The course varies widely with two polar expressions: acute, fulminant forms resulting in a rapid death in many cases if untreated (sometimes even despite treatment) and chronic forms that can last for months. At onset, the cutaneous lesions usually begin as purpuric macules that may evolve into eschars or ulcers. In some chronic forms (e.g. gonococemia and subacute bacterial endocarditis), the lesions are more frequently vesicopustules with an acral distribution.

Septic embolism, like other emboli, is a life-threatening condition that may reach any organ, including the skin. It is a traveling, intravascular mass infected with bacteria detached from a focus of infection that is sometimes occult and carried by the circulation which is capable of clogging arterial capillary beds and creating an arterial occlusion at a site distant from its point of origin. Bacterial endocarditis, septic thrombophlebitis, periodontal and central venous catheter or implanted intravascular device infections constitute a group of primary disorders most frequently associated with septic embolism.⁹

Septic embolization in the skin may cause Osler's node, Janeway lesions, petechiae and splinter hemorrhages.²⁵ Osler's nodes are tender, erythematous papules and nodules with white centers that favour the finger/toe pads and thenar/hypothenar eminences, whereas Janeway lesions are painless erythematous macules to nodules on the palms or soles. Other cutaneous findings are vesicles, bullae and pustules and most patients have more than one type of skin lesion. Culture and examination of biopsy specimens of the embolic lesions typically demonstrate microorganisms.

Necrotizing fasciitis

Among the more difficult infectious skin diseases encountered by physicians and surgeons is necrotizing fasciitis (NF). It is a life-threatening condition and recent publications have reported significant morbidity and mortality rates of 25-35%^{26, 27} where

the pathogenetic mechanisms of the cutaneous lesions and sepsis include both direct invasion of the vessel walls and the release of toxins by the microorganisms, leading to local severe thrombotic vasculopathy that may eventually progress to DIC. Although the presentation is insidious, the progression is rapid with necrosis of the subcutaneous fat and superficial fascia with relative sparing of the skin and underlying muscles.

The diagnosis of NF is hindered by the fact that the disease progresses below the surface and the cutaneous manifestations misrepresenting the severity of the disease. Diabetics, immunosuppressed individuals, the obese, drug abusers and subjects with severe chronic illness run the highest risk of NF. However, minor surgical procedures, such as endoscopic saphenous vein harvesting, minor trauma, trivial scratches and even insect bites have also been involved. Group A beta-hemolytic streptococcus is the commonest etiologic agent involved in NF, even if the infection is also frequently of polymicrobial etiology.²⁷ Other causative organisms include *Clostridium*, *Peptococcus*, *E. coli*, *Pseudomonas*, *S. pyogenes*, *S. aureus*, and *S. marcescens*. Pathophysiologically, the bacteria multiply and release toxins and enzymes that result in thrombosis (clotting) in the blood vessels. This leads to the destruction of the soft tissue and fascia. Varying amounts of early or late systemic toxicity depend on the strain of the bacteria and the toxins produced. Typically, the infection has an innocuous onset, with swelling and erythema mimicking a wound infection or erysipela with local severe and constant pain, that is completely disproportional to the physical signs. Unlike erysipela, the infection margins are poorly defined, with tenderness extending beyond the apparent area of involvement. Within 1-2 days, the initial redness of the skin begins to fade and turns into a dusky blue (Figure 2A). At this point, the patient reports a numbness rather than pain, the involved tissue becomes progressively swollen with the development of haemorrhagic bullae and ecchymosis, followed by necrosis of the subcutaneous tissues. A foul smelling, thin, watery fluid, known as "dishwater pus", can be observed inside these purple bullae. On physical examination, there is a cracking sound at palpation, known as crepitus, due to the presence of gas producing bacteria, such as *Clostridium perfringens*.²⁸ With disease progression, by days 3-4, there is a systemic toxicity with high fever, diarrhea, vomiting and tachycardia, at which point the patient may be disoriented

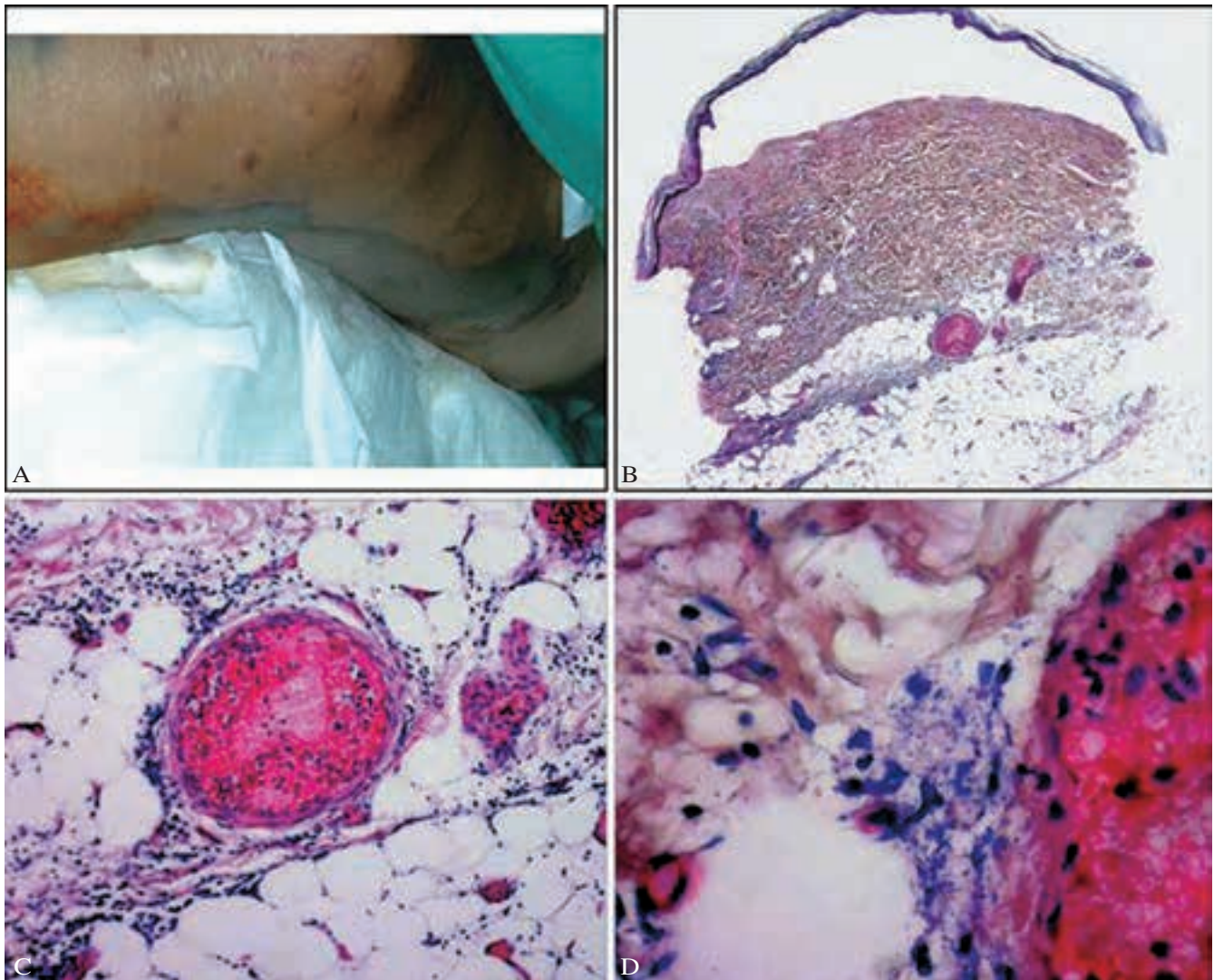


Figure 2.—Necrotizing fasciitis. A 57 year-old woman with a past medical history significant for coronary artery disease, myocardial infarction, type II diabetes mellitus, hypertension and hypercholesterolemia was admitted to intensive care unit after she had an off pump, 4-vessel coronary artery bypass graft. Six days postoperatively, she developed swelling and redness, associated with a low-grade fever on her right leg. Due to the semi-unconscious state of the patient, local symptoms were not referred. This patient's condition was caused by a polymicrobial infection, with *Staphylococcus Aureus* and *Escherichia coli*, confirmed by cultures from a skin biopsy of the lesional skin. A) Purplish, cold, sharply demarcated areas of swelling on the lower extremity; B) numerous thrombi within the lumen of the small blood vessels of the superficial and deep dermis in concert with scant inflammation and a subepidermal bulla were observed; C) neutrophilic infiltrate around a thrombotic vessel; D) numerous bacteria in a perivascular and intravascular location were apparent (600X).

and lethargic. Untreated, the tissue will soon become gangrenous, sloughing by the second week and releasing toxins into the bloodstream leading to sepsis, multisystem organ failure, toxic shock and even death within a few days. In unconscious or severely debilitated and/or immunosuppressed patients, both local and systemic symptoms may be subtle.

Early diagnosis of NF is critical for prognosis and treatment and is mainly based on the patient's symptoms, including medical and exposure history to infectious pathogens, followed by isolation of the organism(s) from the involved tissue by taking wound swabs and/or surgical samples from the deep tissues using both aerobic and anaerobic isolation

techniques and fungal cultures. A rapid skin biopsy in the evolution of a suspected NF may be extremely helpful in the recognition of the disease and differentiation from look-alike conditions such as cellulites, erysipela, Clostridial and non-Clostridial myositis and myonecrosis as well as thrombotic vasculopathies of non-infectious etiology. Early pathological changes include thrombosis of the small vessels of the deep dermis and subcutaneous fat, a scant inflammatory infiltrate of neutrophils and microorganisms within the vessel lumen or perivascularly (Figure 2B-D). It has been reported that imaging techniques, such as magnetic resonance, are useful in the early diagnostic stage for prompt recognition of the disease. In the late stages, blood tests may show leukocytosis, acidosis, an altered coagulation profile, hypoalbuminemia and abnormal renal function.

Therapy is based on radical surgical debridement

of infected tissues as delivery of antibiotics into involved tissues is ineffective due to ischemia, followed by administration of broad-spectrum antibiotic agents and intensive care with aggressive fluid replacement. The antibiotic therapy may be modified according to the culture and antibiogram results. Hyperbaric oxygen may also be an effective adjunctive therapeutic measure.

Cutaneous meningococemia

Meningococcal infection is a life-threatening condition that occurs worldwide, mainly affecting infants, adolescents and young adults.²⁹⁻³¹ When acute meningococemia develops, from one-third to one-half of patients present with a petechial eruption resembling LV, typically in association with a fever, chills, myalgia and headache. Endotoxin pro-

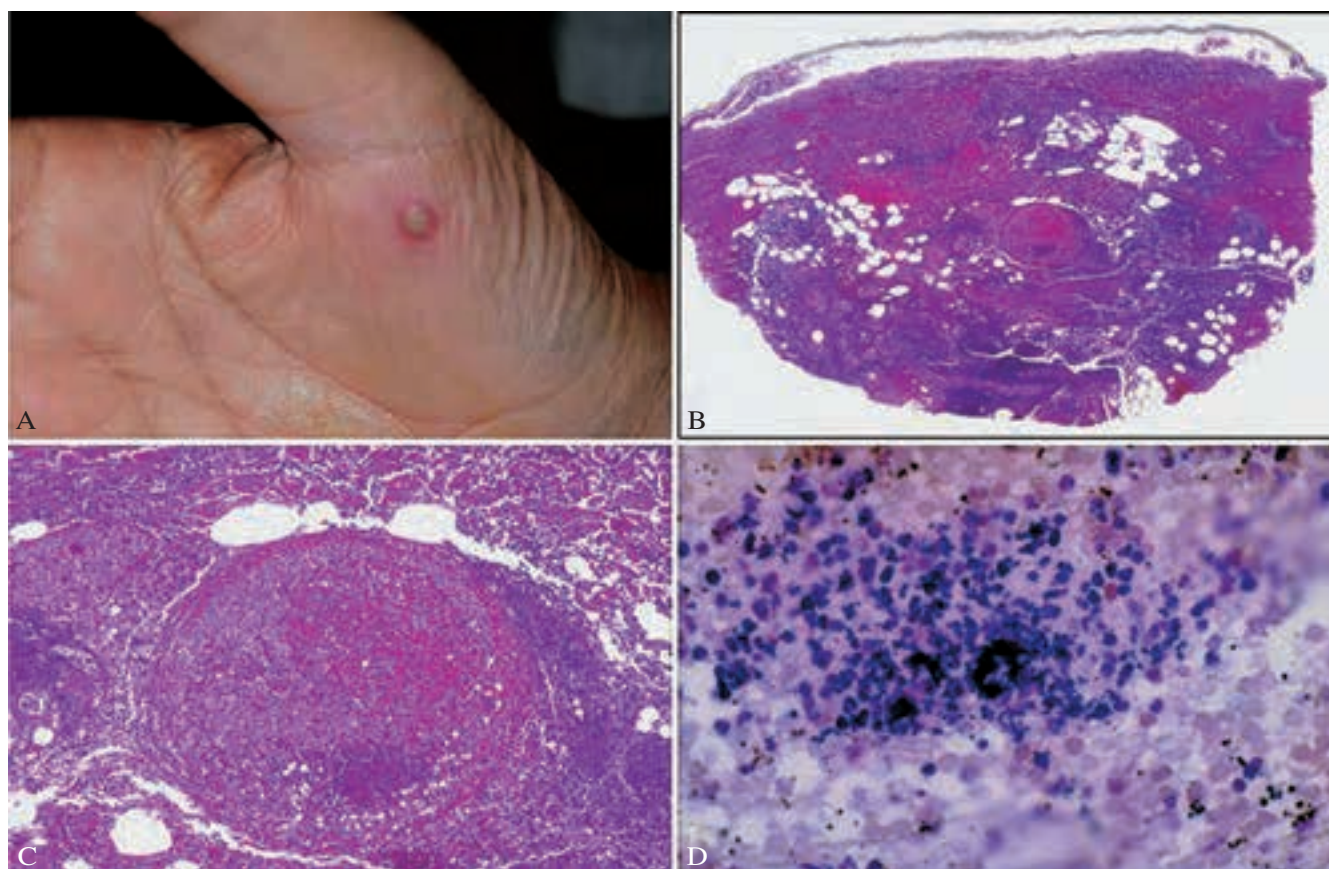


Figure 3.—Cutaneous meningococemia. A) A papulopustule with a haemorrhagic ring on the thenar eminence of the hand; B, C) Microscopic examination of a biopsy taken from this lesion showed occlusive luminal thrombi involving the small blood vessels of the superficial and deep dermis along with an inflammatory infiltrate of neutrophils with a scant leukocytoclasia. Subepidermal and intraepidermal pustules were also seen. D) Clumps of bacteria intermingled with fibrin were observed intravascularly (Gram stain).

duction by the bacteria is mainly responsible for the triggering of the inflammatory process, that in fulminant cases, may lead to shock, multiorgan failure and PF. The skin eruption may advance from a few ill-defined lesions, usually located on the trunk and legs, to a widespread petechial eruption within a few hours. Pustular and vesicular and bullous hemorrhagic lesions may also be present (Figure 3A).

Even if it remains to be clarified which type or what percentage of skin lesions actually contain microorganisms, the pathogenesis of the skin lesions has immunological, infectious and thrombotic components. Although cutaneous lesions of acute meningococemia do share some histopathological similarities with LV, intraluminal thrombi, involvement of deep vascular plexuses and the frequent presence of clumps of bacteria may allow for differentiation (Figure 3B-D).

Chronic meningococemia is much rarer than is acute meningococemia and is characterized by recurrent episodes of fever, arthralgias, and the development of nonspecific skin lesions with erythematopurpuric macules and papules that may develop into nodules and pustules. As blood cultures are often negative and histopathologic examination of skin lesions usually do not show bacteria, chronic meningococemia is a diagnostic challenge.

Although evaluation of skin biopsies is not an established component of the routine work-up, a skin biopsy for histopathologic examination, microbiologic culture and *N. meningitidis*-specific PCR testing may be a diagnostic tool that leads to the diagnosis of chronic meningococemia, a setting where the bacillary load is by far lower than in patients with acute meningococcal infection.^{32, 33}

Malignant syphilis

Malignant syphilis is a rare, severe form of SV, more commonly affecting individuals with poor health, malnutrition or HIV infection³⁴ and, at times, diagnosis is no easy feat. The cutaneous lesions are papulopustules that rapidly evolve into highly infectious, round or oval, cutaneous ulcerations with sharp borders, covered centrally by a dark – sometimes rupioid – crust resembling pyodermitis or ecthyma gangrenosum (Figure 4A). Constitutional symptoms are pronounced and the mucous membranes are usually affected.^{35, 36}

Although a high titre of positivity for serologic tests for syphilis is usually confirmatory, in rare cas-

es serology may be negative,³⁷ or the positive results may be erroneously interpreted, especially when the patient has a recent history of syphilis and the clinical suspicion is low. A skin biopsy is a helpful tool for the diagnosis of malignant syphilis and histopathology reveals an intact or ulcerated epidermis, with a dense, nodular and/or diffuse dermal infiltrate of lymphocytes, plasmacells and macrophages. Changes in the small vessel vasculitis, such as endothelial swelling, hyaline thrombi and fibrinoid deposition in the vessel walls are almost invariably observed (Figure 4B, C). Historically, spirochetes have been rarely identified, if at all, in skin biopsy specimens of malignant syphilis by Warthin-Starry stain. It has, therefore been argued that lesions due to malignant syphilis can be highly organism depleted and treponemas cannot be detected in all secondary syphilitic lesions.³⁸ Recently it has been demonstrated that an appropriate immunohistochemical study with anti-Treponema antibodies can identify high numbers of the etiologic agent in a skin biopsy, increasing the diagnostic sensitivity and specificity (Figure 4D).³⁹

Despite the name “malignant”, this severe form of syphilis usually responds rapidly to proper therapy; HIV-infected patients should be treated by the same recommendations as those indicated for HIV-uninfected patients.

Disseminated alternariosis

Fungal pathogens, some previously unknown or considered saprophytes, are increasingly identified as etiologic agents of cutaneous and subcutaneous infections, not only in solid organ recipients, but also in other immunocompromised patients, where they show a propensity to soft-tissue destruction and invasion of blood vessels with systemic spread.^{40, 41} Primary cutaneous and subcutaneous mycoses, often caused by saprophytic organisms, include mainly sporotrichosis, chromoblastomycosis, histoplasmosis, coccidioidomycosis, blastomycosis, cryptococcosis, aspergillosis, mucormycosis, and fusarial infection. As these organisms often have early manifestations on the skin in the early stages of disease, or in the course of dissemination, prompt recognition of cutaneous lesions with isolation of the pathogen from skin or mucosal biopsy is critical, not only for prognosis and therapy, but also to predict the individual's immune status.⁴²

Phaeohyphomycosis (PHM) is a rare infectious disease caused by dematiaceous fungi which are

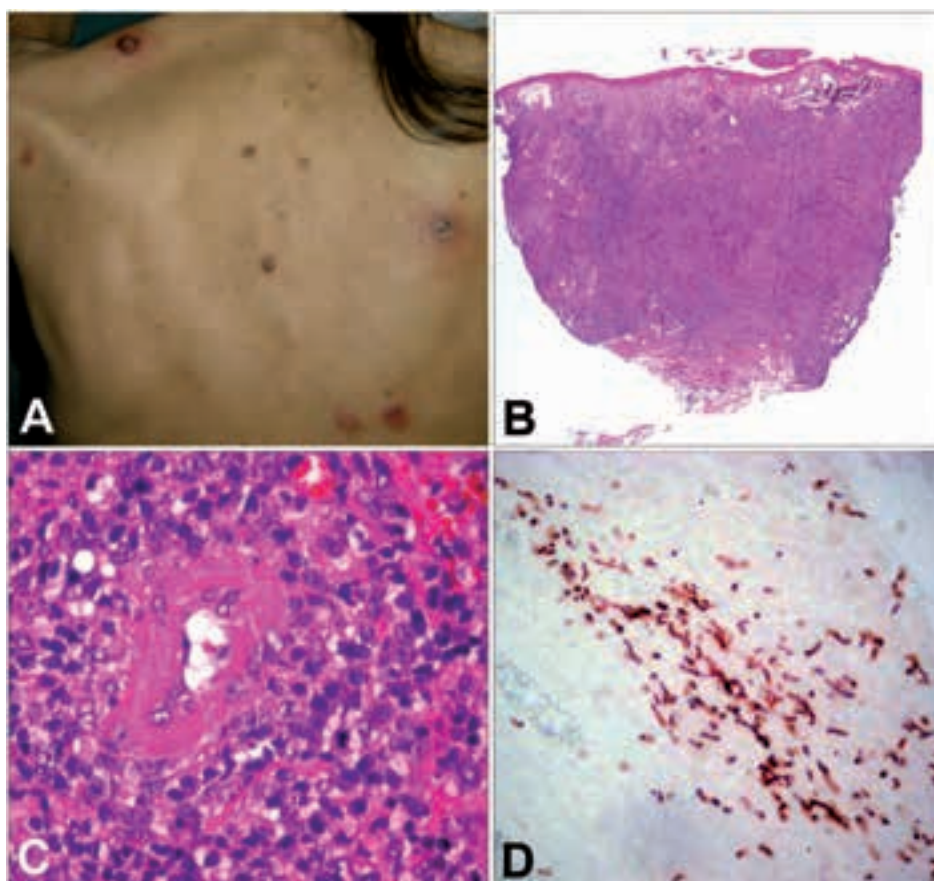


Figure 4.—Malignant syphilis. The patient was a 36 year-old man with advanced HIV infection who presented with fever, malaise, and ulcero-necrotic lesions on the trunk and extremities. Due to a recent syphilis infection, the highly positive serology for syphilis was erroneously interpreted and the clinical diagnosis was ecthyma gangrenosum. A) Numerous erythematous plaques with necrotic center and ulcers covered by a dark rupioid crust on the trunk and upper extremities; B) sections of the skin samples taken from lesions on the right forearm revealed epidermal hyperplasia and a dense and diffuse dermal infiltrate of neutrophils, lymphocytes, macrophages and plasma cells; C) necrotizing vasculitis with fibrinoid necrosis and endothelium swelling was apparent; D) immunohistochemical study with anti-*Treponema* antibodies revealed a numerous spirochetes within the dermis and was confirmatory for the diagnosis of syphilis.

characterized by the presence of melanin in the cell wall of hyphae and conidia. They have a worldwide distribution and numerous species are common saprophytes in soil, air and a variety of other habitats; some are ubiquitous agents of decay and plant pathogens. However, only a few species, including *Alternaria*, *Phialophora* and *Exophiala*, are implicated in human diseases. These mostly affect immunocompromised hosts, such as those with autoimmune diseases and post-transplant patients.⁴³⁻⁴⁷ The portal of entry of the infection is usually through corneal trauma or a breakdown of the skin barrier. Most clinical manifestations involve cutaneous and subcutaneous infections, although other types of infections like

oculomycosis, sinusitis, onychomycosis and systemic disease, have also been less commonly reported.

Although the genus *Alternaria* includes over 80 species, only few are pathogens for humans, *Alternaria alternata*, *Alternaria cathartum* and *Alternaria tenuissima* being the most frequently described. The main clinical manifestation due to *Alternaria* is a respiratory disease, usually allergic, due to the inhalation of the spores. Less frequently, the inhalation of the spores may cause sinusitis, which may exceptionally be complicated by granulomatous lung disease.⁴⁸ Cutaneous involvement is rare and dissemination exceptional⁴⁹ with multiple, painless, violaceous papulonodular lesions, resembling Kapo-

si's sarcoma (Figure 5A, B). Central nervous system phaeohyphomycosis has also been reported.⁵⁰

The diagnosis of *Alternaria* infection is based on histological findings of fungal characteristics identifiable as phaeohyphomycetes and the growth of typical colonies in cultures of biopsy specimens in Sabouraud's dextrose agar without cycloheximide. Early biopsies should be performed for histopathology and microbiological analysis, as mortality is high

if should the appropriate treatment be delayed. The typical histopathologic lesion shows a mixed suppurative and/or granulomatous infiltrate in the dermis, intermingled with the presence of pigmented oval or round fungal cells and hyphae that can be better visualized by special stains for fungi, whilst vasculitis is usually not a feature.

In a renal transplant recipient with systemic alternariosis, recently observed by us and shown in

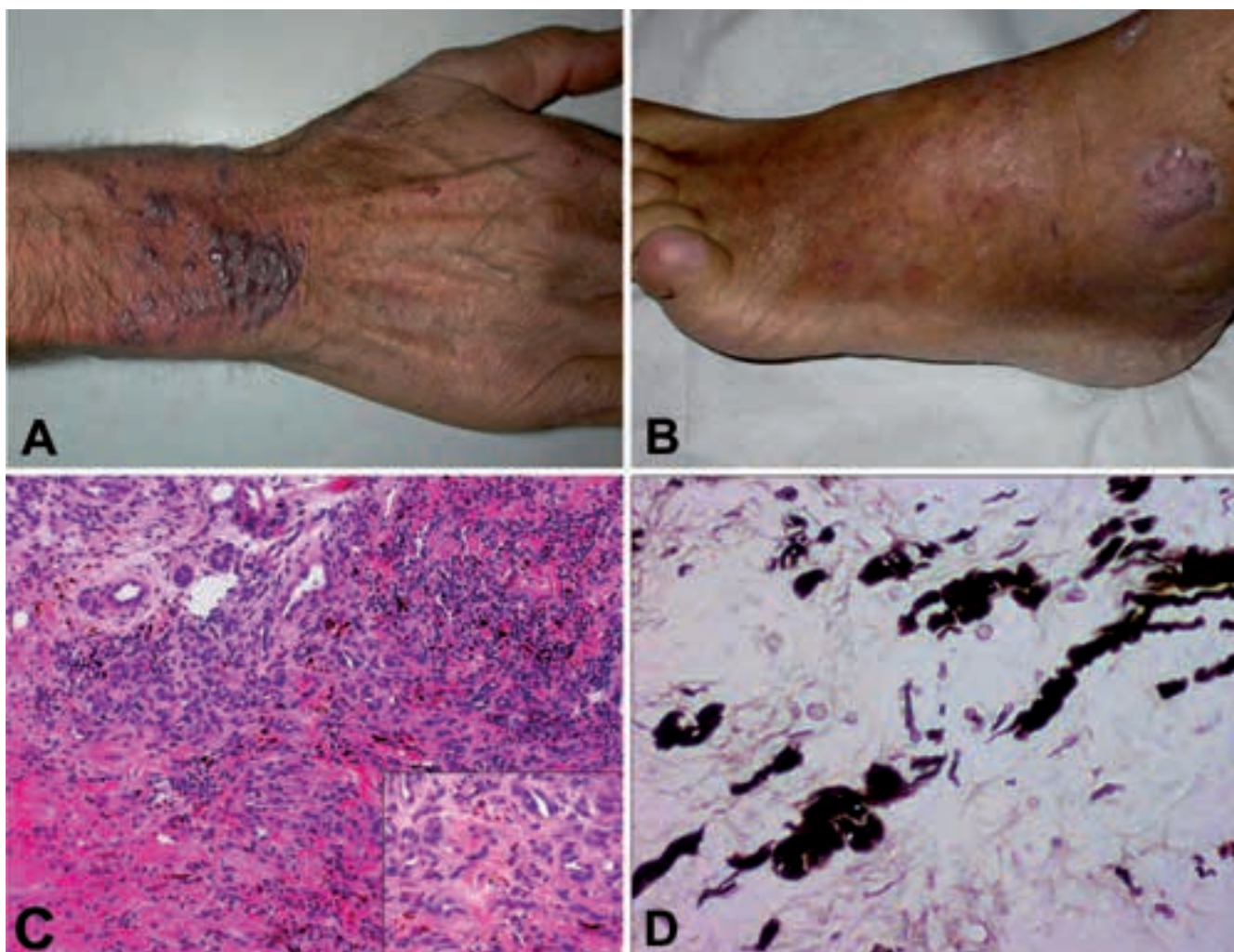


Figure 5.—Systemic (cutaneous and pulmonary) alternariosis. The patient was a 63 year-old man on corticosteroids and steroids after a liver transplant. He presented with a cough and disseminated cutaneous lesions. Based on histopathology and microbiological culture, the patient was diagnosed with an infection by *Alternaria alternata*. Treatment with Itraconazole led to complete resolution of the skin and pulmonary lesions. A, B) Purple papules and nodules, reminiscent of Kaposi's sarcoma on the upper and lower extremities. Chest X-ray and computed tomography scan revealed a mass in the right lung. C) Skin biopsy revealed a proliferation of mildly hyperplastic endothelial cells within the reticular dermis lining capillary sized vessels intermingled with a scant inflammatory infiltrate of neutrophils and pigmented hyphae and spores; D) Gomori's methenamine silver stain confirmed the fungus showing broad, septate, branching hyphal forms and large spores.

Figure 4, the port of entry of the fungus was a penetrating trauma of the hand, followed by the development of a livid ulcerated plaque. Shortly afterwards, multiple violaceous nodules and plaques developed on the extremities (Figure 5A, B) and there was also lung involvement. A biopsy of a skin lesion, distant from the infectious primary site, produced specimens characterized histopathologically by a highly vascularized dermis with endothelial cell proliferation, reminiscent dermal angiomatosis, intermingled with a mixed-cell infiltrate and nuclear dusts of neutrophils (Figure 5C). Irregular pigmented hyphae and spores were identified within this pathological background and were then better visualized by special stains (Figure 5D). Therapeutic options for cutaneous and/or systemic alternariosis include itraconazole, voriconazole or posaconazole.

Discussion

SV is a severe medical condition and sometimes a true emergency that can be caused by a myriad of microorganisms including bacteria, fungi, yeasts, viruses, protozoas, helminths, or algae. A systematic review of the literature on this topic is problematic as no series considers this entity as a whole. Therefore, the true frequency of cutaneous manifestations in the course of sepsis remains unknown and variable rates have been reported, depending mainly on the infectious agent and the individual immunological burden.

Clinical presentation of SV varies widely and depends on multiple factors, including the microorganism, the pathogenic mechanism and the individual immunologic burden, with the exception of PF and SPG, which are commonly associated with DIC. Histopathologically, it is essentially a thrombo-occlusive vasculopathy of variable morphology.

Herein, we reported our experience in some cases of rare, infectious, life-threatening diseases where emergence of cutaneous lesions allowed for a rapid diagnosis. Remarkably, in all cases, final diagnosis was obtained by the integration of clinical, microbiological and histopathologic results.

A skin biopsy is easy to perform, can be completed within minutes, requires little equipment, and is safe, even in patients with severe clotting disorders.

Regardless of the rationale for performing a skin biopsy in the suspicion of a septic disease, it is impor-

tant to realize that the process of securing appropriate tissue involves more than the mere mechanical removal of a specimen. It is a multistep process, which is to be done with forethought, precision and care, so as to obtain the maximum amount of useful information. There are at least four main prerequisites to obtain useful information in this clinical setting. Firstly, a biopsy diagnosis of suspected SV cannot stand alone: it must be correlated with clinical history, physical and laboratory findings and microbiologic studies, such as blood and/or tissue cultures and/or PCR analysis. Secondly, the choice of clinical lesions, timing and biopsy technique used type for histopathological assessment have great impact on the diagnosis. In general, an early biopsy (<48 h after appearance of clinical lesion) by a 5-6 mm punch or scalpel extending into the subcutis taken from the most tender, reddish or purpuric lesional skin may well provide the most useful information. If only superficial ulcers are present, it is advisable to include also the edges. Thirdly, a lesional biopsy for microbiologic studies (culture, PCR) should be performed at the same time whenever possible. The specimen should be placed in a sterile container, containing 1 ml of sterile isotonic saline and immediately transported to the microbiologic laboratory for rapid processing. Fourthly, if the specimen has been taken from an immunocompromised and/or severely ill or unconscious individual, a histopathologist should assume an infectious etiology is present until proven otherwise.

Microbiological tests for the diagnosis of infectious diseases are important for the clinical management of patients with life-threatening conditions, but the sensitivity of cultures of blood, CSF, or other body fluids may vary greatly or even be low, particularly in patients that have been treated with antibiotics before collection of diagnostic samples.^{50, 51} Retrospective studies suggest that examination of the skin biopsies may allow for a rapid diagnosis and that cultures of skin biopsies are often positive even after antimicrobial treatment has commenced.^{50, 51}

Innovative molecular techniques, including immunohistochemistry, polymerase chain reaction and in situ hybridization have recently emerged and have been proven to be useful tools in the diagnosis of cutaneous infections, improving diagnostic accuracy, particularly in cases where conventional histopathology is challenging or ambiguous.⁵³⁻⁵⁵ The judicious use of these ancillary techniques may not only represent a diagnostic tool in diagnosis of infectious

disease, but may also open new perspectives on the pathogenesis of cutaneous lesions of infectious origin including SV as – for example – those occurring in malignant syphilis, which historically believed to be the result of an immunologic reaction and depleted of treponemas,³⁸ should be reconsidered as a true infectious vasculitis.³⁹

Traditionally SV has been considered a great imitator of LV. Indeed, as about 22% of all cases of cutaneous vasculitis are associated with infection,¹⁸ it is a must that an infectious process be ruled out in the valuation of a LV. Histopathologically, compared with non-infectious LV, SV shows a greater frequency of intraluminal thrombi, intraepidermal and subepidermal pustules and has relatively less nuclear dust (leukocytoclasia), less eosinophils and lymphocytes and may show predominant IgA vascular deposits on immunofluorescence. The presence of microorganisms is highly variable.

Our study included a wide spectrum of histopathologic changes in skin specimens from various SV. These involved the intensity and composition of the inflammatory infiltrate, the degree of vascular changes and the presence of microorganisms, ranging from a predominant noninflammatory, thrombotic-occlusive vasculopathy (PF) to authentic neutrophilic vasculitis, to a diffuse dermal angiomatosis-like pattern (disseminated alternariosis). These different pathologic presentations might be related to the microorganism involved, the main pathogenetic mechanism by which infection injured the vessels and/or the individual immunologic burden.

Interestingly, biopsy specimens in our cases of systemic alternariosis showed prominent dermal proliferation of the endothelial cells in a pattern reminiscent of diffuse dermal angiomatosis in the background of a neutrophilic infiltrate and debris with no overt changes of vessel damage (*i.e.* fibrin in vessel walls or intraluminal thrombi).

Diffuse dermal angiomatosis is a distinctive cutaneous entity that belongs to the spectrum of reactive angioendotheliomatoses, characterized histopathologically by an intravascular and/or perivascular endothelial proliferation that may develop as a consequence of a thrombotic occlusive vasculopathy in the process of the organization of thrombi and recanalization.⁵⁶⁻⁵⁹ This distinctive reaction pattern has been associated with various pathologic conditions, including bacterial endocarditis and septic states. It is likely that in our patient with systemic alternariosis,

the development of cutaneous lesions at sites distant from the portal of entry of the fungus were the consequence of an embolic mechanism that led to a cutaneous thrombotic vasculopathy. The process of organizing of the septic thrombi and recanalization that followed may have been responsible for the reactive endothelial proliferation observed in the skin biopsy.

In conclusion, cutaneous SV is a potentially life-threatening inflammatory syndrome that can present with protean clinical and histopathologic aspects, the common denominator of which is a thrombotic vasculopathy. Skin biopsy and proper interpretation of histopathologic changes in the context of clinical and laboratory findings is of high practical value as it may lead to a probable diagnosis for a seriously ill patient at an early stage. As various organisms are identified in skin lesions, the use of ancillary methods, such as immunohistochemistry, culture or PCR, alone or in combination, may well enhance diagnostic accuracy.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Epub ahead of print on January 16, 2015.

Chronic localized leukocytoclastic vasculitis: clinicopathological spectrum of *granuloma faciale* with and without extrafacial and mucosal involvement

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Granuloma faciale (GF) is a rare cutaneous condition of unknown origin, that usually presents as one or more brown-purple papules, plaques and/or nodules, localized mostly on the face, although extrafacial lesions can also occur. Eosinophilic angiocentric fibrosis (EAF) is regarded as the mucosal counterpart of GF. Histologically, it has been described as a persistent leukocytoclastic vasculitis, with a dense polymorphous inflammatory infiltrate in the superficial and mid dermis, typically sparing the subpapillary dermis, the so called *grenz zone*. The presence of eosinophils is considered a characteristic feature of the disease. All the cases of GF seen at the Dermatology Unit from 2002 to 2013 were considered and reviewed, both clinically and histopathologically. Only cases with consistent clinical findings of GF, and accurate patient's history were considered. Ten cases of GF were reviewed for both histological specificity and clinicopathological correlation. Two patients presented extrafacial lesions. One patient had involvement of nasal mucosa. Two patients suffered from associated rheumatological diseases. The most frequent histopathologic features were the presence of a *grenz zone* and eosinophils in the infiltrate, but also adnexal involvement was often present; vascular changes were constant, yet leukocytoclastic vasculitis could be recorded only in four cases. Fibrosis or sclerosis were always absent. Clinical pictures of the patients treated demonstrated a complete remission of the lesions, without scarring. However, a complete enduring healing was observed only in two patients, and relapse or incomplete remission of the disease was the rule. In conclusion a review of clinicopathological findings of ten patients affected by GF was made and new details of the disease presented.

KEY WORDS: Granuloma faciale - Vasculitis, leukocytoclastic, cutaneous - Skin diseases.

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In 1945 Wigley first described a 46-year-old woman with four “greyish-brown, smooth, infiltrated lesions, varying in size up to that of a silver three-penny piece” on her forehead and nose. According to Wigley’s original description, these lesions clinically resembled the sarcoid of Boeck, but the histopathological findings were different, showing the presence of an inflammatory infiltrate made of histiocytes and many eosinophils both arranged in foci and diffusely scattered among the histiocytes.¹ In 1950, Lever and Leeper distinguished this entity from other eosinophilic granulomas, and two years later Pinkus termed it “granuloma faciale”.^{2,3} In spite of the fact that this definition is now considered a misnomer, because no granulomatous infiltrate is usually seen, it still remains as a common reference. *Granuloma faciale* (GF) is an uncommon disease characterised by well-circumscribed brown-erythematous papules, plaques or nodules, that typically affects the face. Extrafacial lesions may also occur, and even a mucosal (nasal) variant has been described. Its etiology is unknown. Once fully developed, GF usually does not change and has a chronic, indolent course. It occurs predominantly in middle-aged white men, but it has been observed also in black and Asian male patients as well as in female patients.^{4,5} Lever *et al.*

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were the first to report extrafacial involvement when they incidentally found lesions on the upper back of one patient.² As a rule, extrafacial lesions are confined to the trunk or upper extremities, they are associated to facial lesions, and usually appear from 1 to 9 years after the facial eruption.^{4, 6, 7} In rare cases, a primary and exclusive extrafacial involvement has been reported.⁸ Both facial and extrafacial, solitary or multiple lesions are not associated with symptoms, sometimes only mild pruritus or mild burning sensation maybe present. GF is a chronic disorder, non-associated with systemic diseases.⁸ GF has been traditionally included in the histopathological group of chronic cutaneous leukocytoclastic vasculitides (LCCV).

The stereotypical histopathological presentation is a diffuse dermal involvement with neutrophils, eosinophils, extravasated red-blood cells and leukocytoclastic vasculitis. The mucosal variant is also known as Eosinophilic Angiocentric Fibrosis (EAF) because, in chronic lesions, fibrosis is the most prominent finding. First described in 1983 by Holmes and Panje, EAF most commonly affects the sinonasal cavity; despite the nose and sinuses are the most involved sites, other localizations, such as the eye orbit, gums, larynx, and upper trachea, have been described as well.^{9, 10} In EAF, females are more commonly affected (male-to-female ratio = 1:1.3) with a mean age of 48 years at diagnosis. The disease has a submucosal pattern of growth, and nasal endoscopic examination may reveal mucosal thickening. Because of its rarity, photographic documentation is scant. In previous studies, CT scans have detected bony sclerosis, and also focal destruction of the surrounding structures with invasion of the orbit has been reported.¹¹ Symptoms are non-specific and include nasal obstruction, sinusitis and pain.¹² The pathogenesis of GF and its relationship to other forms of LCCV such as erythema elevatum diutinum (EED) are not fully established.⁵ Ackerman and Mones claimed that GF and EED are the same condition considered under different names, and Zimer *et al.* stated that they are histologically almost indistinguishable.^{13, 14} Conversely, other authors maintain them as separate entities, suggesting that there is space for further insight into the subject. LeBoit considers them as two different entities belonging to the same family, *i.e.*, LCCV. This is supported especially by their clinical presentation and outcome and also, from an histological point of view, EED presents a

distinctive pattern of fibrosis (long, parallel arrays of collagen bundles with intermingled neutrophils) that GF do not have.¹⁵ We report the study of ten patients affected by GF with both clinical features and histopathological findings, in particular the presence/absence of leukocytoclastic vasculitis, that is considered a clue of the disease.

Methods

The patients with a diagnosis of GF were retrieved from the files of the Dermatology Unit, Department of Medical, Surgical, Diagnostic and Pediatric Science, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia. Ten patients were diagnosed as having GF between 2002 and 2013 and were studied retrospectively. The diagnosis of GF was made in all cases on the presence of typical clinical and histopathological findings. We considered only the patients with complete clinical data, including clinical pictures. The biopsy material was fixed in 10% formalin, processed routinely, and stained with hematoxylin and eosin. All cutaneous samples were analyzed for the following histopathological features: inflammatory infiltrate and its distribution/extension, rate of eosinophils, grenz zone, vasculitis signs, adnexal involvement, fibrosis, epidermal changes. In three cases, direct immunofluorescence (DIF) revealed linear deposits of immunoglobulin (IgG and IgM) around small vessels of superficial and mid dermis.

Results

Clinical features

Five women and five men were considered: the youngest was 30 years old and the oldest was 73. The clinical data are summarized in Table I and illustrated in Figure 1. Nine patients had facial lesions at presentation and one of them developed extrafacial localization. A woman presented only with extrafacial involvement on her back. One patient had GF of the skin and mucous membrane of her nose, demonstrated by magnetic resonance imaging. The most common sites of involvement were the cheeks (four patients), forehead (four patients), nose (four patients). The lesions were usually purple-brown

TABLE I.—*Clinical data of the patients included.*

Patient	Age	Sex	Variant	Involved sites	Comorbidities	Duration	Clinical response
1	39	F	Classic (localized)	Face (malar region)	//	4 yrs	Partial with topical tacrolimus; complete regression with dapsone
2	30	M	Classic (localized)	Face (nose)	//	3 months	Complete regression with topical tacrolimus
3	63	M	Classic (localized)	Face (forehead)	Rheumatoid arthritis, Allergic asthma, Hypertension; Steroid-induced diabetes	2 months	Complete regression with systemic steroid and topical tacrolimus
4	38	F	Extrafacial granuloma	Back	Metabolic syndrome, diabetes mellitus, Hashimoto's thyroiditis, fibromyalgia	4 yrs	Partial with topical tacrolimus
5	67	M	Classic (localized)	Nose	Hypertension	5 yrs	Partial response with topical tacrolimus
6	32	F	Classic (localized)	Cheeks	//	1 yr	Partial response with topical tacrolimus
7	28	F	Eosinophilic angiocentric fibrosis	Cutaneous, subcutaneous and mucosal involvement of the nose	// (Corneal ulcer preceding the occurrence of skin and mucosal manifestations)	2 yrs	Partial regression with dapsone
8	45	M	Classic (multiple lesions)	Face, multiple eruptive lesions:	Allergic asthma	1 yr and a half	Poor response with systemic steroid. Complete regression with dapsone.
9	73	M	Classic (multiple lesions)	Face: forehead, nose	// (Previous basal carcinomas)	1 yr	Complete regression with topical tacrolimus
10	56	F	Facial and extrafacial granuloma	Shoulder, face (multiple lesions)	//	15 yrs	Partial regression with dapsone; complete regression adding and topical tacrolimus

plaques, less often papules. In two patients, the lesions had a more intense erythematous component. Older papules were usually brownish and had a firmer consistency and more prominent follicular openings. The duration of the GF varied from 2 months to 15 years. The association of GF with other diseases in our series included two cases with hypertension. One patient had a history of metabolic syndrome, type II diabetes mellitus, Hashimoto's thyroiditis and fibromyalgia. One patient suffered from rheumatoid arthritis, allergic asthma, steroid-induced diabetes and developed GF while under methotrexate treatment. One female patient had a 15 year history of slowly progression of the disease, with the appearance of new plaques every two-three years. The majority (six patients) had no associated systemic disease (Table I).

Five patients were treated solely with topical tacrolimus: an improvement could be seen in four of them patients, while one young patient with a recent

lesion on his nose showed complete regression (Figure 2). A further case with localized disease achieved a complete response with a combination of topical tacrolimus and systemic steroid. Two cases responded to a therapy consisting of topical tacrolimus and diaminodiphenylsulfone. Finally, two patients with more widespread disease received diaminodiphenylsulfone and one of them healed completely (Figure 3).

Histopathological and immunopathological findings

The histopathological data are summarized in Table II and shown in Figure 4. A dense inflammatory infiltrate involved the superficial and mid dermis in all cases. The infiltrate was always both perivascular and interstitial. In five patients it extended to the deep dermis and in four cases the infiltrate reached the hypodermis. The infiltrate was composed in all cases by lymphocytes; neutrophils were found in seven bi-



Figure 1.—The most relevant clinical data are here represented: nine patients presented facial lesions while only one patient, a woman, developed lesions of GF with an exclusive extrafacial involvement. In five cases lesions were multiple, while in the remaining five cases a solitary lesion could be detected. In all the cases the typical lesion was represented by a purplish round or oval-shaped plaque or papule with a smooth surface, follicular accentuation and superficial telangiectasia. Lesions could be both asymptomatic or associated with mild pruritus.



Figure 2.—Patient 2 before and after topical treatment with tacrolimus: complete regression of the lesion without scarring.



Figure 3.—Patient 3 before and after systemic treatment with dapsone: complete regression of cutaneous lesions without scarring.

TABLE II.—*Histopathological data of the treated patients.*

Patient	Inflammatory infiltrate (predominant cells)	Eosinophils rate	Adnexal involvement	Grenz zone	Vasculitis signs	Inflammatory infiltrate extension	Fibrosis	IFD
1	+++ (neutrophils, histiocytes)	++ (25%)	absent	present	infiltration of vessel walls with inflammatory cells. No leucocytoclasia	superficial and medium dermis	absent	+
2	+++ (lymphocytes, histiocytes)	+/- (5%)	present	present	infiltration of vessel walls with inflammatory cells. Hemorrhagic extravasation. No leucocytoclasia	deep dermis	absent	//
3	++ (lymphocytes)	+ (10%)	present	present	infiltration of vessel walls with inflammatory cells. Hemorrhagic extravasation. Focal leucocytoclasia	hypodermis	absent	+
4	++ (histiocytes, neutrophils, plasmacells, lymphocytes)	+/- (5%)	absent	present	infiltration of vessel walls with inflammatory cells. No leucocytoclasia	deep dermis	absent	//
5	+++ (lymphocytes, neutrophils)	++ (20%)	present	present	infiltration of vessel walls with inflammatory cells. Hemorrhagic extravasation. No leucocytoclasia	deep dermis	absent	//
6	++ (lymphocytes, neutrophils, histiocytes)		absent	present	infiltration of vessel walls with inflammatory cells. Focal leucocytoclasia	hypodermis	absent	//
7	++ (lymphocytes, neutrophils, histiocytes)	+ (10%)	present	present	infiltration of vessel walls with inflammatory cells. Hemorrhagic extravasation. No leucocytoclasia	hypodermis	absent	//
8	++ (lymphocytes)	+/- (5%)	present	present	infiltration of vessel walls with inflammatory cells. No leucocytoclasia	deep dermis	absent	//
9	+++ (lymphocytes, plasmacells, neutrophils)	+/- (5%)	present	present	infiltration of vessel walls with inflammatory cells. Hemorrhagic extravasation. Leucocytoclasia	deep dermis	absent	//
10	++ (lymphocytes, neutrophils)	+/- (5%)	present	present	infiltration of vessel walls with inflammatory cells. Focal leucocytoclasia	hypodermis	absent	+

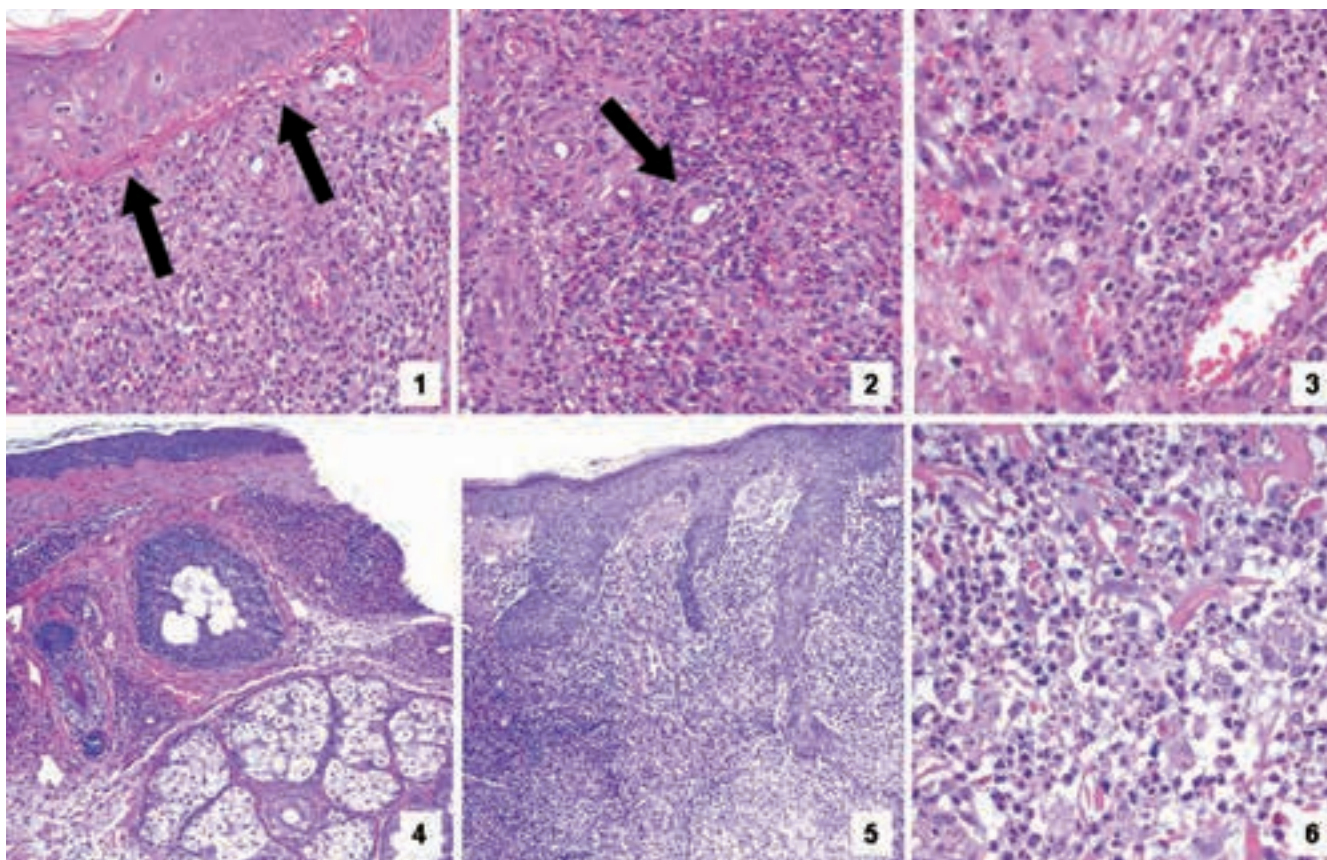


Figure 4.—The most relevant histopathological findings observed are here listed: in all the cases a grenz zone (1) was detected. A dense polymorphous inflammatory infiltrate with variable amount of eosinophils was observed: in three cases adnexes were spared (4), while in all the other cases there was adnexal aggression (5). In almost all the cases analyzed, signs of vasculitis, such as infiltration of vessel walls (2) and haemorrhagic extravasation (3) were observed, but only in 4 cases also leukocytoclasia (6) could be detected.

opsy specimens; scattered plasma cells in two biopsy specimens, and few histiocytes were evident in five cases. No multinucleated histiocytes were observed. Eosinophils in variable numbers were present in all cases: there were few of them in half of cases, while they were prominent in three cases and up to 25% of the infiltrate in two patients. The grenz zone was a constant finding in all patients, and it was characterised by a narrow band-like zone of uninvolved superficial dermis that separated the inflammatory infiltrate from the overlying epidermis. An inflammatory infiltrate involving the adnexal structure could be described in most cases (seven out of ten). In particular, exocytosis of lymphocytes and eosinophils could be observed in follicular epithelia, especially in the infundibulum and isthmus; an involvement of sebaceous gland was present in two patients. Although the presence of inflammatory cells in the wall of ves-

sels could be always demonstrated, frank leukocytoclastic vasculitis was seen in only four specimens. Extravasation of erythrocytes was present in five patients. Two of the biopsy specimens that contained nuclear dust nevertheless did not display deposits of fibrin within or around vessels. No fibrosis was seen in all cases. Epidermal changes were unremarkable. In three cases direct immunofluorescence was made, with evident blood vessels involvement.

Discussion

Despite the fact that small vessel vasculitis of the skin is often considered a sign rather than an entity itself, GF has been traditionally seen as a unique model of chronic leukocytoclastic vasculitis limited to the skin. GF consists of papules plaques or nodules that,

at an earlier stage, present signs of leukocytoclastic vasculitis, i.e. neutrophils, nuclear dust and fibrin in the wall of venules. Later, a prominent eosinophilic infiltrate is described. In 1993 Smoller and Bortz¹⁶ suggested that GF would be a chronic inflammatory disease characterized by a dermal infiltrate of skin specific memory T-helper lymphocytes, attracted to the skin by γ -interferon-induced mechanisms; these lymphocytes would fail to migrate into the overlying epidermis because of the lack of ICAM-1 expression on the overlying keratinocytes, thus creating the characteristic grenz zone. Gauger *et al.*¹⁷ focused on a local, cutaneous, clonal expansion of a CD4⁺ T-cell population which would produce IL-5, attracting eosinophils. EED has been considered either a rarer variant or a separate, albeit similar, entity of GF. In fact, GF and EED are both chronic LCCV and, in early and fully-developed stages, they cannot be distinguished on the basis of the histopathological findings alone.¹³ The clinical background of the two entities are different, one (EED) being characterized by the constant findings of associated systemic diseases and the other (GF) by the absence of it. Cesinaro *et al.*,¹⁸ in their immunohistochemical study, found some differences between GF and EED, and proposed GF as a disease part of the spectrum of IgG4-related sclerosing diseases (IgG4-RD). Clinically EED presents with smooth plaques which evolve in fibrotic plaques with scant erythema; we could not find these features in our group of patients.

We described ten patients affected by GF, with facial, extrafacial and, in one female patient, contemporary cutaneous and mucosal involvement.

Clinically, they presented a variety of cutaneous manifestations, ranging from small erythematous papules through classic singular or multiple plaques with prominent follicular openings. One patient presented with two coalescent nodules on his nose, with superficial telangiectases, mimicking basal cell carcinoma, which is one of the clinical differential diagnosis reported. A woman had a fifteen-year history of evolving plaques, without association with internal systemic disease: it represents the characteristic indolent, chronic course of GF. However in two patients rheumatological diseases were present: rheumatoid arthritis and fibromyalgia. A report of one patient affected by rheumatoid arthritis and Sjögren syndrome has already been described.¹⁹ Our male patient was under treatment with methotrexate that could not inhibit the development of cutaneous GF, suggesting that this would not be a possible therapy. One female patient with extrafacial involvement was also affected by fibromyalgia and Hashimoto thyroiditis; her cutaneous extrafacial lesions appeared on her back, while the other female patient with extrafacial GF had one large plaque on her arm. In fact, the trunk and upper extremities are the usual localization of the extrafacial GF.²⁰ A female, Egyptian lady, with contemporary GF of the nose and nasal mucosa, had a peculiar clinical presentation, characterized by a brown-violaceous plaque with poor-defined margin, localized on the bridge of her nose (Figure 5). At the beginning she was visited by otolaryngologist because of nasal inspiration/expiration difficulties, and a magnetic resonance imaging demonstrated inflammatory process involving both

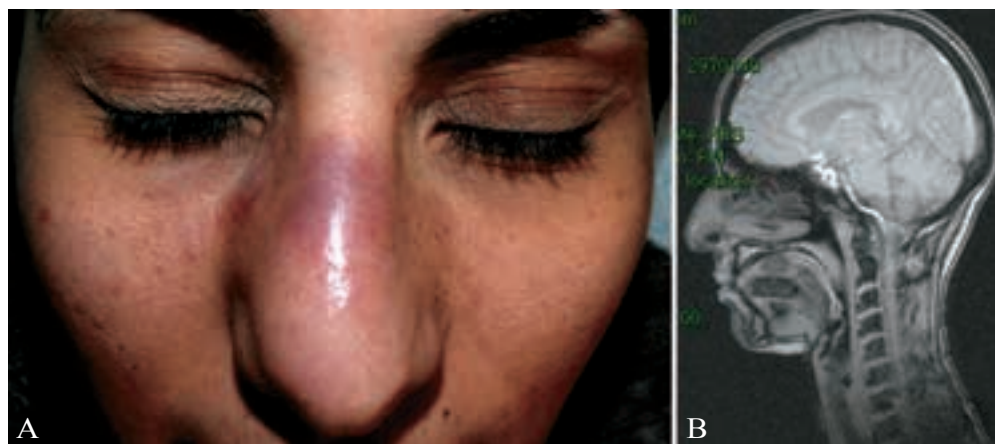


Figure 5.—Patient 7, edema and erythema of the dorsal part of the nasal pyramid. According to RM imaging, oedema and inflammatory infiltrate involved also nose cartilage, the lower right turbinate and its mucous membrane.

the skin and mucosa. The skin biopsy clarified the diagnosis; diaminodiphenylsulfone therapy orally and topical tacrolimus had prompted a good clinical response, with a complete resolution of the mucosal localization and with partial regression of the skin lesion. The patient presented good general health and all blood clotting analysis and different clinical and instrumental examinations did not demonstrate any other disease. In two patients a complete resolution of GF could be documented also by clinical pictures (Figures 2 and 3). It is evident that no scar ensued.

GF is usually described as a sclerosing disease; however, no signs of cicatricial outcome neither clinically nor histologically were found. The histological findings were consistent with a diagnosis of GF, *i.e.*, characterized by a dense, polymorphous, inflammatory cell infiltrate localized in the upper two-thirds of the dermis, with a narrow, uninvolved Grenz zone beneath the epidermis. The infiltrate, perivascular and interstitial, was made of eosinophils, usually quite numerous, together with neutrophils, lymphocytes, histiocytes, and a few plasma cells. In our series of patients an involvement of adnexal structures was observed, and this finding has not been usually described. In particular, an inflammatory infiltrate was present in the epithelia of the isthmus and infundibular tract of the hair follicle. Inflammatory infiltrate around and inside sebaceous glands was present in two patients. No cytooid bodies in the adnexal structures were evident. We could observe frank LCCV only in four cases, confirming that the LCCV represent an early or, however, not always evident feature of GF.¹⁵ Three patients had also a biopsy for direct immunofluorescence; in all the cases, IgG, IgM and complement (C3) were present confirming a vasculitic involvement and a vascular damage in the pathogenesis of the lesions. These findings turn out to be very relevant since they were detectable in three cases (respectively patient 1, 3 and 10), which in turn displayed no or few histopathological aspects of LCCV.

Conclusions

In sum, GF shares many histopathological features with EED, and differs from that because none of the lesions of GF in our series showed fibrosis or sclerosis. Even in those patients with well-documented resolution of the lesion, a clinical scarring outcome

was not present. Small vessel leukocytoclastic vasculitis appears to have a relevant pathogenetic role in GF, albeit its distinctive histological changes may not be fully manifest and constant.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Epub ahead of print on January 16, 2015.

Angiocentric and intravascular lymphomas

D. TOMASINI ¹, E. BERTI ²

Under the generic diagnosis of angiocentric and intravascular lymphomas are included several subtypes of lymphomas histopathologically characterized either by the predominantly endovascular-endoluminal presence of neoplastic lymphocytes of B-T or NK/T cell origin, or by a pathologic process centered around a blood vessels secondarily infiltrated and invaded by the spreading infiltrate. This group of lymphoproliferative disorders is heterogeneous regarding phenotype, but they share common features that are multiorgan involvement, worse prognosis, and, frequently Epstein-Barr virus (EBV) genomic integration. At onset, some of these rare lymphomas, *e.g.* intravascular large cell lymphoma or lymphomatoid granulomatosis (Liebow diseases), are misdiagnosed as inflammatory diseases. The actual treatments of these disorders are based upon chemotherapy and/or chemotherapy plus bone marrow transplantation with variable results. Therapeutic approaches for EBV related angiocentric and intravascular lymphomas, similarly to those employed for other viral induced lymphoproliferative disease would comprise the employment of chemotherapy together with drugs able to interfere with viral infection. Such an approach has been used in rare cases of EBV-positive diffuse large B-cell lymphoma of the elderly, a lymphoproliferative disorders which development is linked to immunosuppression due to senescence. The present review will focus on intravascular and angiocentric lymphomas providing histopathologic, immunophenotypical and molecular data useful to overcome to a specific diagnosis and to differentiate them from other lymphoproliferative disorders showing a secondary vascular engulfment and infiltration and some vasculitides showing overlapping histopathologic features.

KEY WORDS: Lymphoma, non-Hodgkin - Lymphoma, large B-cell, diffuse - Diagnosis.

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Under the generic diagnosis of angiocentric and intravascular lymphomas several lymphomas with different clinicopathologic, immunohistochemical, and prognostic features have been included. Although is easier to define intravascular lymphomas from a histopathologic point of view, *i.e.* lymphoproliferative disorders characterized by the predominant endovascular-endoluminal presence of neoplastic lymphocytes either of B-T or NK/T cell origins, the definition of angiocentric lymphomas is more difficult. Angiocentrism would suggest a pathologic process centered around a blood vessels that is secondarily infiltrated and invaded by the spreading infiltrate. This group of lymphoproliferative disorders is heterogeneous regarding phenotype, but they share also common features that are: multiorgan involvement, worse prognosis and EBV genomic integration.¹ Epstein-Barr virus (EBV) has been clearly demonstrated in some of these disorders either with a type II or type III latency pattern. It has been shown that there are three different EBV latency patterns in EBV-related malignant disorders. These are the result of differential promoter activity and are influenced by host cell factors; the more the immunosuppression, the higher the latency states.^{2, 3} EBV, which presence can be detected in

about the 95% of general population, exists in latency I state (infected cells express EBNA antigen) in healthy individual and there is no latent membrane protein 1 (LMP1) expression, which is the essential transforming viral oncoprotein in EBV infected cells. Latency II (EBNA and some LMP proteins) and latency III (EBNA and several LMP proteins) appear in hosts with increasing degrees of immunosuppression, such as organ transplantation and HIV/AIDS patients. EBV pattern of latency suggest that immunosuppression, not induced by virus or treatments but linked to still unknown factors, such as age, or, simply, to the oncogenic effect mediated by intracellular viral proteins plays a pivotal role in lymphomagenesis. The actual treatments of these disorders are based upon chemotherapy and/or chemotherapy plus bone marrow transplantation with variable results. In EBV related disorders other treatments are under investigation. Therapeutic approaches, similarly to those employed for other lymphoproliferative diseases such as other types of B-cell non-Hodgkin lymphoma induced by hepatitis C virus (marginal zone lymphoma and diffuse large B-cell lymphoma) or Kaposi sarcoma herpes virus (primary effusion lymphoma), would comprise the employment of chemotherapy and drugs able to interfere with viral infection, such as ganciclovir, valganciclovir, arginine butyrate or EBV specific cytotoxic T-cell lymphocytes. This approach has been used in rare cases of EBV-positive diffuse large B-cell lymphoma of the elderly, a lymphoproliferative disorders which development is linked to immunosuppression due to senescence.

The present review will focus on intravascular and angiocentric lymphomas providing histopathologic, immunophenotypic and molecular data useful to overcome to a specific diagnosis and to differentiate them from other lymphoproliferative disorders showing a secondary vascular invasion and infiltration and some vasculitides showing overlapping histopathologic features.

Intravascular large cell B-cell lymphoma

In 1959 Pflieger and Tappeiner⁴ described under the name of “angioendotheliomatosis proliferans systemisata” an unusual cutaneous disorder characterized by erythematous subcutaneous nodules, as well as telangiectasia, cellulitis, and lymphedema,

sustained, at microscopic level, by the presence of cells restricting the lumen of small vessels, particularly capillaries. The neoplastic cells initially were believed to be of endothelial origin, but subsequent studies clearly demonstrated the lymphoproliferative nature of the disorder.⁵⁻⁸ At the present time, this disease has been renamed intravascular lymphoma (IVL) or “angiotropic lymphoma” and has been recognized as a subtype of diffuse large B-cell lymphoma (IVDLBL) in the World Health Organization (WHO) although rare forms with a T-cell and NK-T cell phenotype do exist.⁹

Definition and incidence

IVDLBL has to be considered a disseminated disease at diagnosis. Clinical manifestations are extremely variable and most of signs and B-symptoms are related to the involved organs. Clinical differences have been explained mainly in relation to the geographical origin of the patients. Cases diagnosed in Western countries display a relatively high frequency of central nervous system (CNS) and skin involvement,¹⁰ while patients from Asian countries preferentially show hemophagocytic syndrome, bone marrow involvement, fever, hepatosplenomegaly and thrombocytopenia.¹¹ The median age is 70 years (range: 34-90), with a male/female ratio of 0.9, whereas the “cutaneous variant”¹² involves predominantly females and is associated with a younger age if compared to the “systemic variant”.

Clinical features

Cutaneous lesions encompass painful indurate erythematous eruption, violaceous plaques (Figure 1A), livedo reticularis-like lesions, cellulitis, large solitary plaques, painful blue-red palpable nodular discolorations, tumors, ulcerated nodules, small red palpable spots and erythematous and desquamative plaques.¹³ IVDLBL lesions are commonly situated on the upper arms, thighs and legs, lower abdomen, breast and sub-mammary region. Colonization of preexisting cutaneous vascular malformation has been reported.^{14, 15} Cutaneous lesions may be single or involving multiple sites. Skin eruption in the cutaneous variant is not associated with hematologic alterations (normal red blood cells and platelets count); B-symptoms (fever, chills, night sweats, and weight loss) are detected in the 30% of cases. An increase

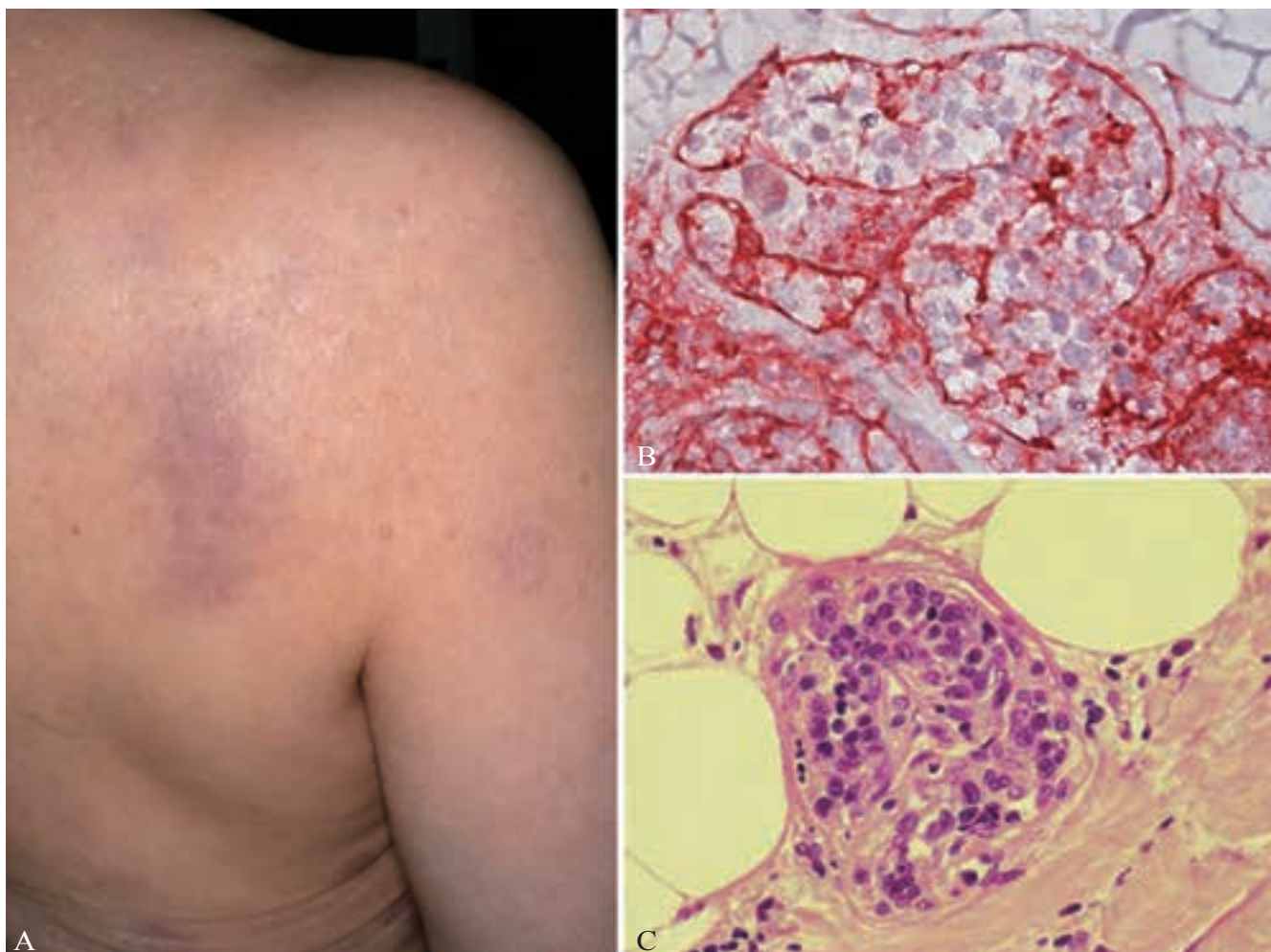


Figure 1.—A) Violaceous plaques involving the back; B) CD31 staining of vascular channels lining neoplastic lymphocytes. (PAP technique, 20x). C) A capillary showing endoluminal presence of large neoplastic B -lymphocytes (EE, 40x).

of ESR, LDH and β 2-microglobulin is constantly observed in the cutaneous variant. The presence of concomitant hematologic alterations, neurologic symptoms (paresthesias, hypostenia, aphasia, dysarthria, hemiparesis, seizures, myoclonus, transient visual loss, vertigo, sensory neuropathy and altered conscious state) and B-symptoms in the context of a histopathologically proven IVDLBL should alert the clinician to search for other organ involvement besides the skin, and, specifically for CNS involvement (MRI and/or whole-body CT-PET).

Hemophagocytic syndrome is rarely reported in the “cutaneous variant” and in Western patient,^{10, 12} whereas is a frequent finding in Asian patients.¹¹

Histopathology, immunophenotype and molecular genetics

Small dermal and subcutaneous vessels are filled with large B cells with blastic cytomorphology, and abundant cytoplasm (Figure 1B, C). Recent reports suggest that the cytologic spectrum of tumors cells may be broader and, in some instances, smaller than usual. Nonetheless these findings, IVDLBL, according to the 2008 WHO classification, is classified among the group of mature B-cell neoplasms and considered by most of the authors to be a rare subtype of diffuse large cell B-cell lymphoma (DLBL). Immunoprofile of neoplastic cells is typified by expression of CD20,

CD79a, Bcl-2, PAX5 and, variable positivity of Bcl-6, CD5, CD10, MUM1/IRF4. These data shed light on the heterogeneity of immunophenotype among IVDLBL cases. Indeed, in the literature, the reported frequency of CD5 and CD10 positivity in IVDLBL varies considerably, suggesting that this disease may represent a heterogeneous group with a post germinal center cell derivation (cases showing a MUM1/IRF4, CD5 positive phenotype) and, more rarely, a germinal center cell derivation (cases showing CD10 and Bcl-6 positivity).^{16, 17} Kappa or lambda monotypic restriction is reported in some cases. "Cutaneous" and systemic forms do not show any difference in immunoprofile. Loss or malfunction of both beta-1-integrin (CD29) and ICAM-1 (CD54) was shown to promote the angiogenic character in IVDLBL.¹⁸ Monoclonal rearrangement for B-cell receptor is frequently detected, whereas EBV is rarely reported in IVDLBL.¹⁶

Rare published cases display a histiocytic, NK/T or T cell phenotype, but only in a very small number of these cases immunoprofile is broad enough to permit a precise classification and, according to literature data, most of these cases are of NK/T cell derivation with a cytotoxic phenotype and EBV positivity. Additionally, an "intravascular" variant of primary cutaneous anaplastic large cell lymphoma has been recently described.

Differential diagnosis

As previously stated, cutaneous presentation of IVDLBL is extremely variable, representing in most of the cases an unexpected histopathologic finding. IVDLBL deserves clinical differential diagnosis from different inflammatory skin conditions such as: trombohepatitis, erythema nodosum, panarteritis nodosa, leukocytoclastic vasculitis, septic vasculitis, erysipelas, livedo racemosa and skin metastasis. At microscopic level, intravascular neoplastic lymphocytes can be observed in lymphoproliferative disorders associated with a predominant extravascular component (B-cell chronic lymphocytic leukemia, mantle-cell lymphoma). Small tumoral cell size, the clinical context and immunophenotype allow a distinction between these lymphomas and IVDLBL. Rare cases of intravascular large cell lymphomas exhibiting T-cell or NK/T cell phenotype have been reported. These patients should not be misdiagnosed as IVDLBL and immunoprofile plays a critical role in differential diagnosis. Finally, undifferentiated carcinomas

can spread as intravascular tumors especially involving the skin. Immunohistochemistry allows the final diagnosis using a limited panel of reagents, such as anti-CD45/common leukocyte antigen, CD3ε-chain (polyclonal CD3), CD79a, CD30, CD56, CD34, D2-40 and anti-cytokeratin antibodies. IVDLBL must be kept distinct, by definition, also from those lymphoproliferative disorders showing angiotropism, such as lymphomatoid granulomatosis, extranodal NK/T-cell lymphomas nasal and nasal type (ENKTL), and, very rarely, from intralymphatic cutaneous anaplastic large cell lymphoma.

Staging evaluation and prognosis

Once a diagnosis of IVDLBL is reached, it must be kept in mind by the clinician, that IVDLBL is always retained a systemic disease and every effort must be done to precisely staging the patient. Clinical presentation together with hematologic findings (anemia and thrombocytopenia) and presence of neurologic alteration are strongly suggestive of a disseminated form. Work up studies must comprise: neurologic evaluation, bone marrow aspirate and biopsy, total body CT scan, contrasted whole-brain magnetic resonance imaging, positron emission tomography with ¹⁸Fluorideoxyglucose (¹⁸F).

Treatment

IVDLBL is retained a systemic lymphoproliferative disease with a short survival time and a 3-yr overall survival rate of 32%, excluding those with the "cutaneous variant". Anthracycline-based chemotherapy gives a 60% of rate response. Rituximab following CHOP chemotherapy are effective in some series.^{10, 17} Encouraging results have been reported using autologous stem cell supported high-dose chemotherapy as a first or second line of treatment against IVDLBL.^{19, 20} However, only a limited number of patients can receive this treatment considering the median age of the patients and poor performance status at diagnosis.

Intravascular large T-cell and NK/T-cell lymphomas

In the 2008 WHO, the only lymphoma classified according to its intravascular location is IVDLBL.⁸

Different case series of intravascular cytotoxic, EBV+NK/T-cell lymphomas and cytotoxic T-cell lymphomas presenting in the skin and, seldom, in other organs are reported too, but they are not included as distinct entities in the WHO classification of hematolymphoid neoplasms. They are briefly mentioned within the section on IVL as rare occurrence.

Furthermore a subset of intravascular T-lymphoproliferative disorders presenting in the skin shows morphologic and immunohistochemical findings of ALK-anaplastic large cell lymphoma (ALCL) or other CD30+ lymphoproliferative disorders without evidence of systemic involvement. In the following chapters, intravascular NK/T cell lymphoma and intralymphatic ALCL will be briefly described.

IVL of T-cell and NK/T origin seem to slightly differ from IVDLBL regarding occurrence in younger individuals with a male predilection (median age 61 years, ranging from 17 to 84 years old).²¹⁻³² Skin is the organ most frequently involved by this subset of lymphoproliferative disorder, but other extranodal sites (brain, lung, testis, appendix, bowel) can also be involved. Cutaneous lesions are very similar to those described for IVDLBL with diffuse painful indurate erythematous eruption, violaceous plaques, livedo reticularis-like lesions, solitary plaques, painful blue-red palpable nodular discolorations, tumors, ulcerated nodules, small red palpable spots, and erythematous and desquamative plaques. Neurologic findings may also occur, including dementia, polyneuropathy, myalgia, and muscle weakness. Considering the cases reported so far and our experience, histology is characterized by a proliferation of medium-sized to large-sized pleomorphic cells confined within the lumina of capillaries and post capillary venules throughout the dermis (Figure 2A, B). Some of the lumina are completely filled by neoplastic cells. A sparse inflammatory infiltrate is sometimes observed around the vessels. Immunoprofile of tumor cells is heterogeneous with some of the reported cases showing a derivation from NK/T cells (Figure 4C)^{5, 25, 27, 28, 29, 30} whereas other present a CD8+ cytotoxic T-cell^{26, 31} origin and a possible γ/δ T-cell origin.³² Notably, EBV, as detected by *in situ* hybridization (Figure 4D) or other techniques, is frequently reported, suggesting that EBV episomal integration plays a role in the induction of intravascular NK/T cell lymphomas. EBV is generally absent in the IVL of B-cell origin, having been reported only in rare cases, two of which occurred in

immunosuppressed patients. The mean survival time is very short. Patients rapidly die with progressive disease. A prolonged survival time has been reported in about the 40% of case, but the follow-up period was relatively short (12 months). Similarly to IVDL-BL, prognosis is better for patients presenting with involvement of one organ only compared with those showing lesions in 2 or more organs. Some authors, considering the lack of clear-cut prognostic differences between intravascular large cell lymphoma of B and T-cell origin and, on the opposite, the strong similarities between organ of involvement and intravascular arrangement of neoplastic cells, suggest to classify intravascular lymphoma into a single specific entity regardless of phenotype of neoplastic cells.³⁰ Various treatment have been reported (CHOP chemotherapy and autologous stem cell supported high-dose chemotherapy)³⁰ but, due to the paucity of cases, no specific treatment guidelines exist for this subset of lymphoproliferative disorder.

Intralymphatic cutaneous ALCL

ALCL is a well known entity and according to the 2008 WHO classification it can be sub-classified into three distinct subtypes according to the site of involvement and to the presence of the t(2:5) (p23;q35).³³⁻³⁵ This translocation, which is important in lymphomagenesis, determines a fusion of the anaplastic lymphoma kinase (ALK) gene, located on chromosome 2, with the nucleophosmin, whose gene in turn is located on chromosome 5, with the production of a chimeric protein of 80kD called p80. An ALK+³³ and ALK-³⁴ nodal variants are recognized together with a primary cutaneous form that is, by definition, ALK- and show an indolent clinical behavior if compared to the nodal counterparts.³⁵ Rare cases of extranodal ALCL showing a preferential endovascular localization (IVALCL) have been reported.³⁶⁻⁴³ Intravascular distribution is taken as *de facto* evidence of systemic rather than primary cutaneous origin. Some of the aforementioned cases showed a secondary cutaneous spread. Additionally, 10 cases showing exclusive skin involvement have been reported.³⁸⁻⁴³ Cutaneous lesions are very similar to those described for IVDLBL (violaceous plaques, livedo reticularis-like lesions, and erythematous and desquamative patches and plaques).¹³ Histology is characterized by an endovascular proliferation of

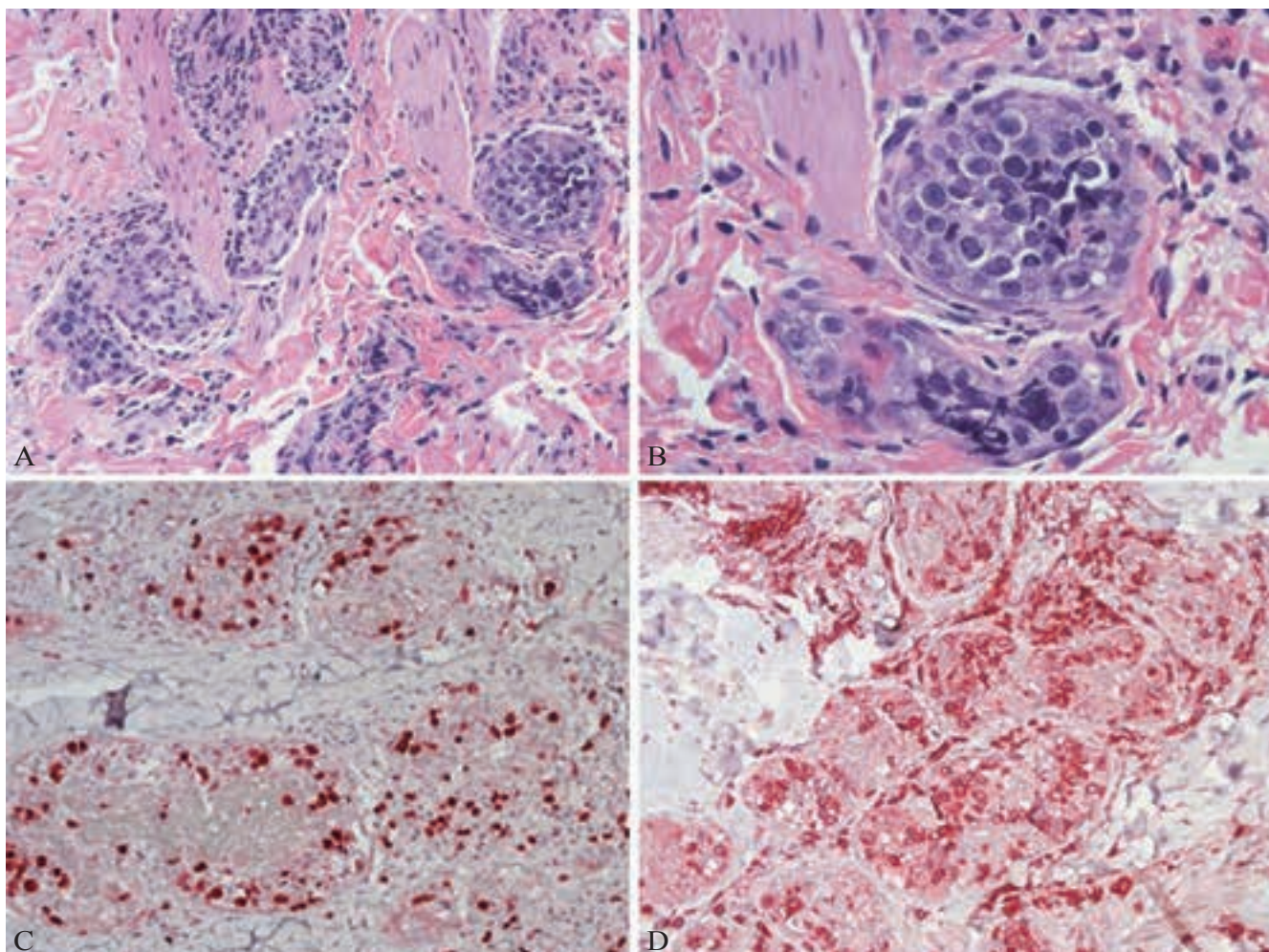


Figure 2.—A, B) Postcapillaries venules showing endoluminal presence of neoplastic lymphocytes (NK cells) (EE, 20x, 40x). C) EBER nuclear staining of large atypical cells (NK/T). D) CD56 membranous staining of large atypical cells (NK cells).

cohesive medium-sized to large-sized pleomorphic cells filling single-layered thin-walled dermal vessels. Characteristic “hallmark” cells with reniform, sometimes bilobed or wreath-like nuclei indented by eosinophilic inclusion-like cytoplasm are present. Immunoprofile of cutaneous IVLALCL is characterized by CD30 constitutive expression, ALK-p80 negativity and variable expression of T-cell restricted antigens and cytotoxic molecules. EBV is not detected. Some of these cases were tested for the DUSP22-IRF4 locus.⁴³ The translocation was present in 2 of the 4 tested cases. The DUSP22-IRF4 (6p25.3) translocation is most closely associated with primary cutaneous ALCL,^{44, 45} lymphomatoid papulosis⁴⁶ and

peripheral T-cell lymphomas.⁴⁷ This data suggested to the authors a strict relationship between cutaneous ALCL involving the lymphatics and primary cutaneous ALCL. It must be kept in mind that this translocation may be seen in some systemic ALK-ALCLs. Interestingly, IVLALCL CD30+, as tumor cells colonized single layered thin-walled dermal vessels that are D2-40+, a monoclonal antibody reputed to selectively stain lymphatic vessels,⁴⁸ has been called intralymphatic. Systemic ALCL has a preference for lymphnode sinuses, the site of regulation of egress of T lymphocytes into the lymphatics. This could explain the lymphatic tropism of cutaneous IVLALCL. Relapse has been reported in some cases, but

it was always confined to the skin. Clinical behavior of cutaneous cases is more indolent if compared to nodal and extranodal IVALCL.^{36, 37} The latter entity, according to literature data, show an aggressive clinical behavior with a short survival time similar to that reported for IVDLBL¹⁰ or IVLNK/T.³⁰ It is mandatory, considering that cutaneous IVLALCL is ALK-, to ascertain whether it really belongs to the group of primary CD30+ lymphoproliferative disorders or whether it is an extranodal IVLALCL with cutaneous spread. Workup studies (neurologic evaluation; CT scan and emission tomography with ¹⁸F in search of hypermetabolic foci outside the skin) more than immunoprofile, are essential to solve the issue. Additionally, intralymphatic cutaneous ALCL must be differentiated from benign atypical intravascular CD30+ T-cell proliferation, intralymphatic histiocytosis and from aggressive intravascular T/NK lymphomas. The former lymphoproliferative disorder may be characterized by the endovascular presence of atypical large CD30+ T-cell showing a polyclonal rearrangement of TCR.^{49, 50} Intralymphatic histiocytosis, first reported in 1994 by O'Grady *et al.*,⁵¹ is histopathologically characterized by dilated dermal vessels with collections of mononuclear histiocytes expressing immunohistochemical markers for macrophages/histiocytes (CD68, KP1, PGM1, Mac 387). The endothelial cells of the dilated vessels stain for D2-40/podoplanin suggesting their lymphatic nature.⁵² Intralymphatic histiocytosis is sometimes reported in the context of rheumatoid arthritis, Klippel-Trenaunay syndrome and solid tumors.⁵² Intravascular T/NK lymphomas are usually EBV+, CD30- and involve the blood vasculature rather than lymphatics.³⁰

Due to its rarity, no treatment guidelines exist but, when an exclusive cutaneous involvement is demonstrated without any doubt, local radiotherapy of single regional lesions could be the choice.

Lymphomatoid granulomatosis

Lymphomatoid granulomatosis (LYG) was first described by Liebow *et al.* in 1972.⁵³ From its inception, there were questions as to whether it represented an inflammatory process similar to Wegener granulomatosis or it was a lymphoma. Liebow believed that this disease was a unique condition with overlapping features of Wegener granulomatosis and

lymphoma, but the author retained that it required the presence of lymphnode involvement as a criterion for diagnosing lymphoma in cases of LYG. Early studies of LYG used mainly frozen-section preparations and cell suspensions; but these techniques yielded ambiguous findings, and, initially, LYG was interpreted as a T-cell lymphoproliferative process. The terms angiocentric immunoproliferative lesion and angiocentric T-cell lymphoma were proposed for the process.^{54, 55} In 1994, Guinee *et al.*, by immunohistochemical staining of paraffin embedded formalin-fixed tissue, highlighted that the large cells were clonal B cells infected by EBV and that the small lymphocytes were reactive T cells.⁵⁶⁻⁵⁸ Further studies validated EBV genomic integration in clonal B lymphocytes.⁵⁷ Nowadays, as evidence of fact, LYG grade 2 and 3 is retained a variant of large cell B-cell lymphoma,⁵⁹ sharing many features with T-cell rich B-cell lymphoma (an uncommon morphologic variant of diffuse large B-cell lymphoma).⁶⁰ The debate is still open regarding the nosologic classification of LYG grade 1, the histopathologic variant characterized by predominance of reactive T cells over EBV+ neoplastic large B-cell.

Clinical features

LYG involved predominantly male with a male-to-female ratio of nearly 2:1 showing a peak of incidence in the fourth to sixth decade of life.⁶¹⁻⁶³ LYG has been reported in association with a number of immunodeficiency states, including immunosuppressive therapy for rheumatologic disorders, and in patients with primary and acquired immunodeficiency (acquired immunodeficiency syndrome, common variable immunodeficiency, X-linked agammaglobulinemia and hypogammaglobulinemia). LYG has been reported in organ transplant recipients, and, interestingly, the WHO considers allogeneic organ transplantation as "predisposing condition" for LYG.

The skin is, together with nervous system (both peripheral and central), the most common extrapulmonary site of involvement, and cutaneous LYG has been reported in about the 40-50% of cases.⁶¹ The lesions of cutaneous LYG are variable and can present as dermal and/or subcutaneous nodules (Figure 3A), multiple papules and/or atrophic plaques, and macular erythema.^{64, 65} Ulceration is seen in larger lesions. The trunk and/or extremities are more frequently involved than the head, neck. Cutaneous involvement



Figure 3.—A) Nodular lesions covered by serous and necrotic crusts involving the nose and the chins. Radiographic aspect of the same patient showing pulmonary bilateral involvement.

can precede, be seen concurrently, or develop years after the recognition of pulmonary LYG, and it can also herald disease relapse. Fever and cough, suggestive of a pulmonary involvement (Figure 3B), are the most common presenting complaints.

Histopathology

The histopathologic hallmark of LYG is a nodular mixed mononuclear cell infiltrate (Figure 4A, B).⁶⁵ Although the features have been described as “angiocentric,” the process really does not center around the blood vessels. Rather, blood vessels are secondarily engulfed and infiltrated by the spreading infiltrate. A mixture of small lymphocytes, large lymphocytes with variable cytologic atypia (atypical lymphoreticular cells), histiocytes, and occasional plasma cells comprise the infiltrate. The infiltrates have a periadnexal and/or perivascular-angiocentric distribution. A lymphohistiocytic lobular panniculitis, often with poorly formed granulomas, is sometimes seen. A mild exocytosis of lymphocytes can be detected in papular or nodular lesions. “Angiocentric” distribution of lymphocytes involving vessels in the superficial and deep dermis is another finding (Figure 4C, D). Angiodestruction, necrosis, and variable degree of atypia are also consistent features

in nodular lesions. The necrosis varies from extensive central necrotic zones with only a thin rim of viable cells to small fibrinoid foci within or adjacent to dense cellular infiltrates. Inflammatory cells, such as neutrophils, eosinophils, and multinucleated giant cells are generally absent.

The WHO has proposed a classification for grading LYG into 3 different histopathologic subsets⁵⁹ taking into consideration the number of atypical B cells and EBER (EBV) positive cells. Grade 1 LYG is characterized by the predominance of reactive cells and a low number of atypical large B cells and, on the opposite, large cluster of atypical B cells dominate the microscopic features in LYG grade 3.

Immunophenotype and molecular genetics

The large cells stain as B-lymphocytes with CD20.⁵⁶⁻⁵⁸ The background small lymphoid cells stain with CD3 and have been further characterized as cytotoxic T-lymphocytes expressing CD8, TIA-1, and granzyme B. Clonality of the large B cells has been examined in several studies, although the total number of cases reported is small.^{57, 67, 68} Myers *et al.* noted light chain restriction by immunohistochemistry in 4 of 11 cases, and clonal heavy-chain gene rearrangement in 1 of 4 tested by

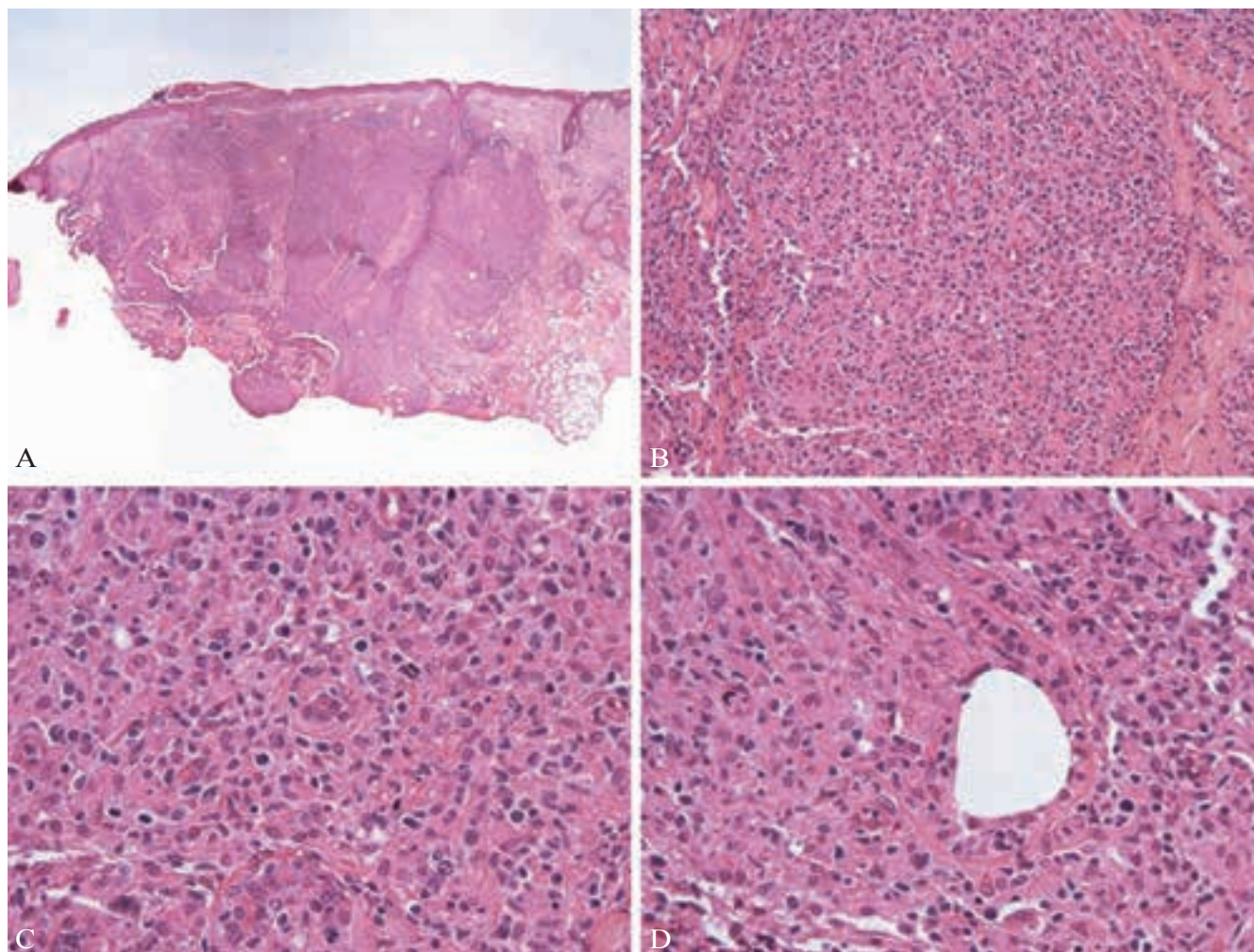


Figure 4.—A) Scanning magnification showing a nodular dermatitis reminiscent of a granulomatous process (EE, 2,5x); B) small and large lymphoid cells appear to composed the infiltrate (EE, 10x); C) the angiocentric distribution of the infiltrate is apparent. Mitosis can be observed (EE, 20x). D. Infiltration and engulfment of a blood vessel by the spreading infiltrate (EE, 20x)

Southern blot.⁶⁶⁻⁶⁸ Others using the more sensitive PCR technique have reported heavy-chain gene rearrangements in 25% to 100% of cases. Katzenstein *et al.*, on the basis of the histologic similarity to post transplant lymphoproliferative disorders, investigated 29 cases of LYG for evidence of EBV infection using PCR, and they identified EBV DNA in 21 patients.⁶⁶ The association with EBV infection was subsequently confirmed in several reports by *in situ* hybridization (ISH) for EBV RNA (EBER), which showed positive staining in the large B cells in 57% to 100% of cases. Importantly, evidence of EBV infection may be present in biopsies from some

sites, whereas absent in others⁶⁹ simultaneously, and some initially negative cases may be positive in subsequent biopsies.

Differential diagnosis

The differential diagnosis of cutaneous LYG includes Wegener's granulomatosis. The clinical presentations of LYG and WG can be very similar, but leukocytoclastic small vessel vasculitis or necrotizing granulomatous inflammation, both characteristic histologic features of cutaneous Wegener's granulomatosis, are not detected in LYG.

Screening for ANCA antibodies may be useful in this circumstance. Distinction from extranodal NK/T lymphoma (ENKTL), another “angiocentric” lymphoma often involving cutaneous sites, is based upon the different pattern of EBV-positive cells as identified by *in situ* hybridization. In LYG the EBV-positive cells are rare to sparsely scattered CD20+ B-cells; whereas in NK/T-cell lymphoma the majority of the infiltrating cells are EBV-positive cells with an NK/T cell phenotype (CD2+, CD3e+, CD4-, CD8-, CD56+, Granzyme-B+, TIA-1+). Pulmonary involvement is also uncommon in NK/T-cell lymphoma. Because cutaneous LYG is commonly associated with lobular panniculitis, the differential diagnosis also includes subcutaneous panniculitis-like T-cell lymphoma (SPTCL). In contrast to LYG, the infiltrate is more monomorphic, with cytologically atypical cytotoxic T-cells rimming fat spaces or invading blood vessels. Conversely, in LYG although occasional large atypical cells are seen, they are always associated with a marked polymorphous background. Immunohistochemical studies will be helpful in this differential diagnosis because CD8-positive lymphocytes are sparse and scattered in LYG and they usually predominate in SPTCL. Finally, SPTCL is consistently negative for EBV.

Staging evaluation and prognosis

Skin lesions are the initial manifestation of LYG in up to one third of the patient. A careful search for lung involvement is essential in all patient suspected for LYG. Some authors have further observed that skin lesions are frequently detected in LYG patients with a multiorgan involvement. Other authors retain that the diagnosis of LYG in the skin in the absence of other organ involvement (lung, CNS central and peripheral) should be made with caution. Work up studies must comprised: neurologic evaluation, bone marrow aspirate and biopsy, total body CT scan, contrasted whole-brain magnetic resonance imaging, positron emission tomography with ¹⁸F.

Prognosis is strictly linked to the grading of the disease. Grade 1 patients have a better outcome, whereas grade 2 and 3 LYG have a worse prognosis with two-thirds of patients dying within 1 year of diagnosis.

Treatment

Fauci *et al.* advocated a regimen of cyclophosphamide and prednisone similar to that used for the treatment of the Wegener granulomatosis.⁶² This study included 15 patients, and mortality remained high. More recently, different combination chemotherapy regimens used for lymphoma such as cyclophosphamide, vincristine, and prednisone (CVP), cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), CVP or CHOP combined with rituximab (the anti-CD20 monoclonal antibody), cyclophosphamide, vincristine, prednisone, and procarbazine (C-MOPP), and etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH), have been used, mainly in the grade 3 and some grade 2 cases.⁷⁰ Some success has been reported with interferon α -2b in lower-grade LYG, also in combination with chemotherapy regimens or as maintenance therapy.⁷¹ Successful treatment has also been reported with autologous stem cell transplantation.⁷² Notwithstanding LYG is actually managed by a combination of chemotherapy and immunotherapy, its outcomes still remains poor.

EBV-positive DLBL of the elderly

EBV-positive diffuse large B-cell lymphoma (EBV-positive DLBL) of the elderly was described in 2003 by Oyama *et al.*,⁷³ and is included as a provisional entity in the 2008 WHO classification of hematopoietic and lymphoid tissues.⁷⁴ It involves patients older than 50 years with no predisposing immunodeficiencies outside the impairment of the immune system occurring naturally with ageing. EBV-positive DLBL of the elderly interest nodal and extra-nodal sites. According to the data of Oyama *et al.*, the skin is one of the most frequent extranodal site of involvement, detected at least in the 13% of cases.⁷⁵ Skin involvement may be either with single or multiple lesions ranging from deep seated nodules to ulcerative lesions. Constitutional symptoms such as fever, malaise, and weight are frequently observed together with peripheral lymphadenopathy. Histopathologically, a diffuse and polymorphic subtype and a monomorphic large cell variant, resembling diffuse large B-cell lymphoma (with presence of immunoblasts and Reed-Sternberg-like cells) are described. Variably, reactive

cell, necrosis and an angiocentric-angiodestructive pattern, may be seen.^{74, 75} All the cases showing skin involvement described by Oyama and coworkers in their seminal paper⁷³ showed angiocentricity together with extensive necrosis. Martin *et al.*, referring on a single skin case, did not observe angiocentricity but only extensive necrosis.⁷⁶ The atypical cells show immunohistochemical expression of CD20, CD79a, CD30, and MUM-1, whereas CD10, Bcl-2 and Bcl-6 are usually negative, suggesting a non germinal center B-cell derivation of tumor cells.⁷⁷ Although a polymorphic variant based on the broad range of B-cell maturation and the scattered distribution of large cells is well known, it is extensively accepted that EBV-positive DLBL of the elderly should be differentiated from DLCL, either showing a primary or secondary skin involvement, Hodgkin's disease and other angiocentric lymphoproliferative disorders such as LYG and ENKTL. The neoplastic cells are negative for CD15 and strongly positive for EBV. These data are of paramount importance in the differential diagnosis between EBV-positive DLBL and, respectively, Hodgkin's disease and DLCL. The clinical context and the reactive T-cell infiltrate of LYG are different from those of EBV-positive DLBL of the elderly. Large cells of EBV-positive DLBL of the elderly are CD56 negative and EBER positive, permitting an easy differentiation from ENKTL involving the skin. Work up studies must comprise total body CT scan and positron emission tomography with ¹⁸F. Treatment of the disease is based upon CHOP regimen chemotherapy together with rituximab, whenever it is possible.^{78, 79} Rare cases with exclusive cutaneous involvement and single lesion, were treated with local radiotherapy with no relapse after a 13 months period of follow-up.⁷⁶ The disease usually runs an aggressive course with a median survival of 2 years but, due to the small number of cases reported so far, the prognosis of this newly recognized type of DLBL remains uncertain.

Extra-nodal nasal type NK/T-cell lymphoma

Extra-nodal nasal and nasal-type NK/T-cell lymphoma (ENKTL and ENNKTL), according to the 2008 WHO classification,⁸⁰ is a predominantly extranodal lymphoma with vascular damage and de-

struction, prominent necrosis, cytotoxic phenotype and association with EBV. It is still named NK/T-cell lymphoma because, although most of the cases are reputed to be of NK origin, some of the cases demonstrate a cytotoxic T-cell phenotype. ENKTL-ENKTL is relatively common in Asia, Mexico, Central America, and South America, but rare in Europe.⁸¹ ENKTL occurs predominantly in extranodal tissues, especially in the nasal cavity and nasopharyngeal region, but also in the skin, soft tissues, and intestine; the spread to lymph nodes is uncommon.⁸² In the past, similar ulcerative skin lesions, with slow expansion, localized to the nose and prolabium, were also defined as a "malignant midline granuloma". Patients usually have multiple extranodal locations of the lymphoma, systemic symptoms, and involvement of peripheral blood; hemophagocytic syndrome is a possible complication.

Clinical features

Skin involvement is typically characterized by plaques, nodules and tumoral lesions of large size (Figure 5), with an hemorrhagic hue, and a tendency to a terminal necrotic and ulcerative phase. However, at onset, there can be slightly infiltrated patches like in MF, or maculopapular, exanthematous-like, purpuric, bullous or nodular subcutaneous panniculitis-like lesions. The most frequent cutaneous localizations include: the face, trunk, and extremities. Nasal involvement may follow over time the cutaneous localization.⁸³⁻⁸⁶



Figure 5.—Necrotic tumoral lesions encircled by a hemorrhagic hue halo in a patient with ENKTL.

Histopathology

The histopathologic aspects of this variety of lymphoma, angiocentrism and necrosis, are similar, whatever is the site primarily affected by the tumor (nasal region, compared to extranasal regions).⁸⁰ The tumor cells infiltrate the dermis and subcutaneous tissue, showing a growth pattern that is initially interstitial-angiocentric and then diffuse (Figure 6A).⁸⁴⁻⁸⁶ Angiodestructive aspects are frequent and associated with fibrin deposits, coagulative necrosis (Figure 6A) and presence of numerous apoptotic bodies. Lymphoid cells show a very variable cytological appearance, from small-medium (Figure 6B)

to large cells. Generally, the dominant cell population consists of medium/large-sized cells, with irregular, vesicular or elongated nuclei; the cytoplasm is normally scarce or pale. In addition to tumor cells, there can be, initially, a significant inflammatory infiltrate consisting of macrophages, plasma cells, and eosinophils, which makes the histopathological diagnosis difficult, with scleroderma-like aspects.

Immunophenotype and molecular genetics

Tumor cells have a characteristic phenotype ^{85, 86} CD2+, CD3ε+ (cytoplasmic), CD43+,

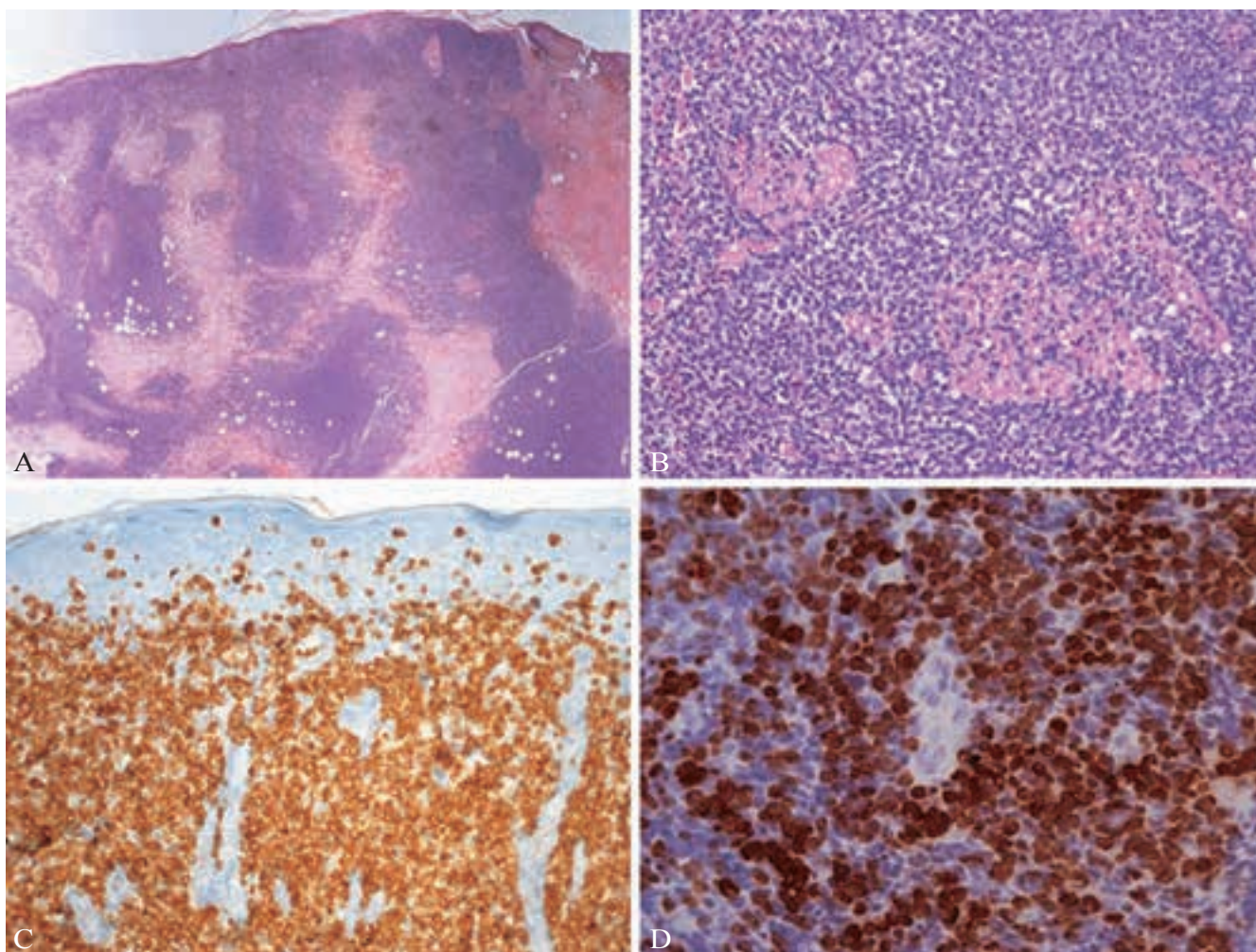


Figure 6.—A) Scanning magnification of a tumoral necrotic lesion showing a nodular infiltrate involving the entire dermis and subcutaneous tissue. A necrotic area can be observed in the upper right angle (EE, 2.5x). B) The infiltrate is predominantly composed by small and medium lymphocytes. Presence of extravasated red blood cells. (EE, 20x). C) Tumor cells showing membranous staining for CD56 (Pap technique, 20x). D) Nuclear staining for EBER. (Pap technique, 20x).

CD45+, CD45RO+, CD56+ (Figure 6C), EBV+ (Figure 6D), while they are negative for CD3s (membrane) and other T or NK cell markers (CD4, CD5, CD8, CD16, CD57). Specific markers for NK cells, such as CD94, PEN-5 (CD162R), and Nkp46 (CD335), have been found positive, but can be currently tested only on cell suspensions or on sections of “fresh” tissue and not on histopathologic sections of formalin fixed paraffin-embedded tissues. CD7 and CD30 antigens may be expressed sporadically. The markers of cytotoxic granules (TIA-1, perforin, granzyme) are expressed in almost all cases. Usually, TCR genes and immunoglobulin genes do not present monoclonal rearrangement. The presence of EBV virus can be detected using various techniques (immunohistochemistry, *in situ* hybridization, and quantitative molecular analysis on DNA extracted from lesions) and it is positive in the vast majority of cases with a type II pattern of latency.⁷⁸ Specific genomic alterations of ENKTLNT have been recently identified by our group and other researchers suggesting a close relationship concerning lymphomagenesis between ENKTLNT involving the skin and other extranodal sites.^{87, 88}

Differential diagnosis

The cutaneous onset is initially associated with scarce symptoms and may mimic an inflammatory disease (*i.e.* vasculitis) or other forms of lymphoproliferative lesions showing an angiocentric and angiodescriptive pattern of involvement. As previously described, immunoprofile plays a critical role in differential diagnosis between LYG and cutaneous ENKTLNT. Cutaneous ENKTLNT also share some similarities with primary cutaneous γ/δ T-cell lymphoma. Both commonly present with ulcerated masses that demonstrate angio-invasion, necrosis, and a similar basic paraffin section immunophenotype, with CD56 molecule significantly expressed by primary cutaneous γ/δ T-cell lymphoma. Moreover rare EBV+ primary cutaneous γ/δ T-cell lymphoma are reported.⁸² In this specific setting, the evaluation of expression of TCR γ -c1 chain by tumor cells together with a PCR analysis of TCR for monoclonal rearrangement are useful data to distinguish CD56+ primary cutaneous γ/δ T-cell lymphoma from cutaneous ENKTLNT.

Staging and prognosis

Based on the diagnosis, the patient has to undergo to complete blood staging (tests on peripheral blood and bone marrow aspirate and biopsy), total body CT scan and PET, like in other aggressive lymphomas. Prognosis is poor with a very aggressive clinical course and high mortality rate, despite aggressive polychemotherapy protocols, also if followed by bone marrow transplant. Cases localized to the skin are reported to have a better prognosis in some but not all studies. Survival of patients with cutaneous ENKTL is poor, with a median/mean survival of about 7 to 13 month.

Treatment

Recommended therapy is multi-agent polychemotherapy associated with autologous bone marrow transplantation.

Angioinvasive lymphomatoid papulosis - lymphomatoid papulosis type E

Common features of “angiocentric,” lymphoproliferative disorders is, at microscopic level, the infiltration and invasion of the blood vessel by the spreading infiltrate and, clinically the development of papulonodular lesions evolving in necrotic lesions leaving atrophic scars. Necrotic skin lesions are the clinical hallmarks of skin disorders, either inflammatory or



Figure 7.—LyP type E, a necrotic lesion on the face.

neoplastic, sustained by vascular damage or by an immunologically mediated activation of cytotoxic T cells as it can be detected in reactive conditions such as *pityriasis lichenoides e varioliformis acuta* or cutaneous lymphomas of cytotoxic T-cell origin. Wu *et al.*,⁸⁹ and, recently, Kempf *et al.*⁹⁰ reported patients suffering with LyP presenting unusual manifestation simulating, histopathologically, highly aggressive angiocentric and angi-destructive T-cell lymphoma. This group of patients is characterized by recurrent papular lesions (Figure 7) rapidly evolving into hemorrhagic necrotic eschar-like lesions (this the reason why the authors named this subtype of LyP as LyP

type E) and spontaneous regression often leaving a scar and by an infiltrates of CD30+, CD8+ lymphoid cells with an angiocentric and angi-destructive pattern (Figure 8A, B). Medium-sized lymphoid cells are detected within the walls of veins (Figure 8C, D) and small arterioles in the mid and deep dermis together with eosinophils arranged interstitially or around blood vessels. Immunoprofile of intravascular lymphocytes is predominantly that of TCR α/β T-cells showing expression of CD8, CD30 and cytotoxic related proteins such as TIA-1. Lymphoid cells are negative for ALK-1 and TCR- γ/δ , without loss of CD2 or CD5; while CD56 is rarely detected. A mon-

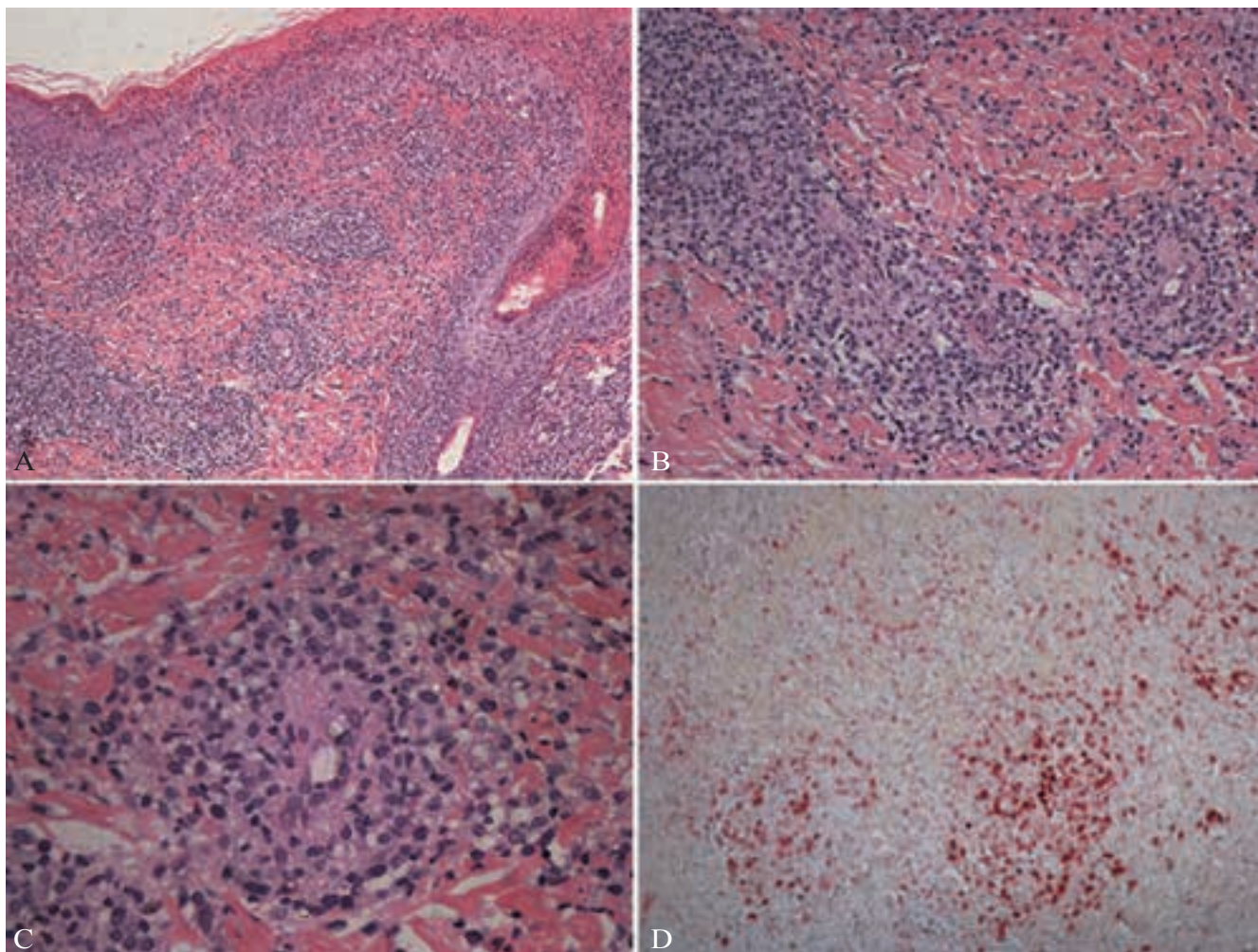


Figure 8.—A) Necrotic epidermis with dense angiocentric infiltrates in the dermis and epidermotropism of atypical lymphocytes (EE, 10x); B) angiocentric distribution of atypical lymphocytes (EE, 20x); C) close up view showing infiltration and engulfment of the vessel wall by the spreading infiltrate; D) atypical lymphocytes with a high proliferation index as detected by Ki-67/Mib-1 nuclear staining (Pap technique, 10x).

oclonal TCR rearrangement is present in about the 60% of cases.⁹⁰ Clinical presentation and histological findings suggest differential diagnosis with different lymphoproliferative disorders of the skin showing highly aggressive clinical behaviour and, namely, ENKTLNT, and other primary cutaneous cytotoxic T cell lymphomas such as cutaneous $\gamma\delta$ positive T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma, and, obviously, cutaneous and nodal ALCL. CD30 expression is rarely detected in ENKTLNT, and, above all, tumor cells are positive for EBV as detected by EBER staining.⁸⁰ Additionally CD8 antigen is not a constant findings. LyP type E proliferating cells are EBV negative and they rarely stain for CD56.⁹⁰ More problematic is the distinction between LyP type E and primary cutaneous $\gamma\delta$ positive T-cell lymphoma, as CD30 expression is sometimes reported in this kind of skin lymphoma.⁹¹ Kempf *et al.* did not detect TCR γ chain in any of the tested case by using gamma3.20, a monoclonal antibody able to detect $\gamma\delta$ T lymphocytes on formalin fixed paraffin-embedded tissue section. Rare case of LyP with a supposed $\gamma\delta$ T-cell origin have been reported too, but they did not show a similar angiotropism.⁹² The mutual combination of clinical features, necrotic lesions undergoing spontaneous resolution, histopathological data and immunoprofile are essential to overcome to a specific diagnosis in this scenario. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma share many features with LyP type E and an angiocentric distribution of the infiltrate can be observed. Tumor cells are CD30 negative and, in our experience, eosinophils are never detected.⁹³ Nonetheless we believe that mutual combination of clinical histological and immunohistochemical data are of paramount importance also in this case to overcome to a precise diagnosis. Clinical presentation and workup studies are essential to differentiate LyP type E from nodal and cutaneous ALCL. Treatment of LyP is similar to the other clinico-histological variant of LyP ranging from skin directed treatment (steroid ointment, PUVA therapy) to the use of systemic drugs as methotrexate or IFN α -2b in patients with a widespread cutaneous involvement.

Hydroa vacciniforme-like lymphoma

In 1995 Ruiz-Maldonado *et al.* described a peculiar vesiculo-papular skin eruption observed in

children from Mexico.⁹⁴ These lesions were associated with facial edema, vesicles, crusts, and large ulcers, with severe scarring and disfigurement in sunexposed and nonexposed skin areas. Systemic symptoms, fever, weight loss and asthenia, together with hepatosplenomegaly and lymphadenopathy were frequently observed in the acute phase. It was also noted hypersensitivity to mosquito bites (HMB). Because panniculitis and/or vasculitis were among the histological features this entity was called edematous scarring vasculitic panniculitis just to separate it from hydroa vacciniformis a rare, chronic photodermatosis of unknown origin occurring in childhood. Subsequent report from specific geographic area (Asia, Mexico and Peru) demonstrated that there was an association with EBV infection and often T-cells showed a monoclonal rearrangements of the T-cell receptor in some of these patients.⁹⁵ Some of these cases evolved to a systemic lymphoproliferative disorder with a high mortality rate.⁹⁶ Thereafter, it was introduced the term hydroa vacciniforme-like lymphoma (HVLL). Nowadays HVLL lymphoma” is incorporated in the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues in the subgroup of EBV-positive T-cell lymphoproliferative disorders of childhood, and defined as an EBV-positive cutaneous T-cell lymphoma that occurs in children and less often in young adults and may be associated with hypersensitivity to insect bites.⁹⁷ This peculiar form of cutaneous T-cell lymphoma is mainly observed in children living in Latin America and East Asia, being not described in western countries and in Europe. Clinically, patients present with facial edema and recurrent vesiculopapular rash followed by ulceration and crusting.⁹⁷ The infiltrate is distributed around adnexae and blood vessels, often with angiodestructive features. Spongiotic foci may be observed. The intensity of the infiltrate and atypia are variable from case to case. Not infrequently large cells with irregular nuclei, prominent nucleoli, and abundant clear cytoplasm can be observed. Most cases reveal a CD8 T-cell phenotype and in a small proportion of cases a natural killer (NK)-cell phenotype.⁹⁷ The lymphoid cells are positive for cytotoxic markers, such as granzyme B and TIA-1. CD30 expression was found in a portion of the reported cases. Notwithstanding the identification of monoclonal rearrangements of the T-cell receptor and EBV genomic integration,

several issues remain to be clarified. Many doubt concern whether HVLL is a true lymphoma from its first clinical presentation or a disorder with high risk of developing into a systemic lymphoma. Recently Quintanilla-Martinez *et al.*,⁹⁸ reviewed the clinical, histological, immunohistochemical and molecular features of 20 young patients suffering from HVLL and they showed, similarly to other reports for Peru and Japan⁹⁹ that HVLL is a lymphoproliferative disorder showing in a third of cases a NK-cell phenotype and that such cases had a more indolent clinical behavior if compared to cases of T-cell derivation. These patients according to the data of Quintanilla-Martinez are at high risk of developing systemic lymphoma such as NK-cell leukemia or ENKTLNT.¹⁰⁰ They concluded that the long waxing and waning clinical course and the relatively good response to immunomodulating therapy challenge the concept of a full-blown malignant lymphoma at onset. In order to avoid unnecessarily aggressive treatment and the stigma of a lymphoma diagnosis, they suggest for clinical usage the term “HV-like EBV+ LPD” to encompass the different clinical manifestations of the EBV-associated HV-like cutaneous lesions both of T-cell and NK-cell origin.⁹⁸ Treatment of these group of patient is problematic; chemotherapy and/or radiotherapy have been shown to be of little or no benefit with a transient effect without sustained remission in most cases. On the opposite, immunomodulating therapies, such as prednisolone, cyclosporine, interferon, chloroquine, and thalidomide have been shown temporary remission or improvement of symptoms. These results indicate that a conservative approach should be recommended as first-line therapy in these patients.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding.—None.

Epub ahead of print on December 22, 2014.

Diffuse dermal angiomatosis: a clinical mimicker of vasculitis associated with calciphylaxis and monoclonal gammopathy

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Diffuse dermal angiomatosis is a form of cutaneous reactive angiomatosis characterized clinically by painful erythematous or violaceous lesions with ulcers that may mimic cutaneous vasculitis/vasculopathy. Histologically it shows a benign, diffuse proliferation of endothelial cells with tiny blood vessels in the papillary and reticular dermis. Herein, we report four patients with diffuse dermal angiomatosis in the setting of calciphylaxis and monoclonal gammopathy and review the cases previously published in the literature. Comorbidities and management will also be discussed.

KEY WORDS: Angiomatosis - Calciphylaxis - Monoclonal gammopathy of undetermined significance.

Diffuse dermal angiomatosis (DDA) has been described as a variant of cutaneous reactive angioendotheliomatosis in 1994.¹ Most cases present with asymptomatic or painful violaceous, purpuric, and occasionally ulcerated plaques mainly on the lower extremities of patients with peripheral vascular atherosclerotic disease, diabetes and hypertension or on the forearm secondary to iatrogenic arteriovenous fistulas in the setting of chronic hemodialysis.²⁻⁸ In addition, calciphylaxis^{9, 10} and antiphospholipid syndrome¹¹ have been also associated with DDA. Involvement of the breast is a rare event that has previously been described in women with large breasts who are heavy smokers.^{12, 13} Histologically, diffuse dermal angiomatosis shows a diffuse proliferation of endothelial cells interstitially arranged between the collagen bundles within the full thickness of the dermis.

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Herein, we report four patients with DDA in the setting of calciphylaxis and monoclonal gammopathy and review the cases previously published in the literature. Our main aim is to describe the clinical and histopathological characteristics of this rare skin disorder that mimics vasculitis or vascular disease in the setting of cutaneous reactive angiomatoses.¹⁴ Comorbidities and management will also be discussed.

Case series

Table I summarizes the clinical presentation of the 4 cases.

Case 1.—A 66-year-old woman presented with a 6-month history of skin plaques and ulceration. Her past medical records pointed out chronic renal failure, diabetes mellitus and excess weight. On physical examination, the patient had livedoid erythematous plaques on her abdomen, right upper thigh and leg with small areas of ulceration on his lower abdomen (Figure 1 A, B). The patient was lost to follow-up.

Case 2.—A 69-year old man presented with a progressively painful plaques on his leg during a 2 month period.

TABLE I.—Clinical features of our patients with DDA.

Gender/age	Clinical presentation	Comorbidities	Suspected diagnosis
Female/66	Painful, erythematous-violaceous, livedoid nonhealing plaques with painful ulcers on the abdomen and extremities since 6 months	Diabetes Chronic renal failure	Calciphylaxis? Kaposi sarcoma?
Male/69	Painful non healing plaques with necrotic ulcers on the legs and abdomen since 2 months	Diabetes Severe chronic renal failure on hemodialysis	Vasculopathy/Vasculitis? Calciphylaxis?
Female/70	Painful erythematous, purpuric plaques with ulceration on the leg since 3 months	IgG lambda monoclonal gammopathy Thrombophlebitis	Vasculopathy/Vasculitis?
Female/59	Erythematous papules and plaques, sometimes with central crusts since 3 months	IgG lambda monoclonal gammopathy	Vasculitis?



Figure 1.—A) Livedoid erythematous plaques on abdomen and right upper thigh and leg with small areas of ulceration on the abdomen; B) small ulceration on the abdomen.

He had developed chronic renal failure and had started maintenance peritoneal dialysis at the age of 65. The patient had been diagnosed with type 2 diabetes mellitus, atherosclerotic disease of the legs and cerebrovascular disease. On physical examination, an irregular, ulcerated lesion with crusting and background livedo reticularis-like changes were seen on his left leg (Figure 2). At the time of consultation, he also had two further, smaller lesions more distally on his anterior abdominal wall. Laboratory calcium was normal and phosphate levels were high 5.9 mmol/L (n.v: 2.4-4.1) as well as parathormone 154 pmol/L (10-60).

Case 3.—A 70-year-old woman suffered since 3 months from some painful erythematous purpuric plaques with central ulceration on her left leg (Figure 3) that evoked clinically a diagnosis of vasculopathy/vasculitis. She was a heavy smoker (a pack per day for 50 years). Her past

medical history was relevant for a IgG lambda monoclonal gammopathy and an episode of thrombophlebitis of the same leg 2 years before the consultation. During this time period, the lesions had increased slightly in volume without signs of regression. A discrete elevation of D-Dimers and fibrinogen suggested activation of the coagulation pathway. All other laboratory tests, in particular immunologic markers including antinuclear body, rheumatoid factor, anticardiolipin body, cryoglobulin, cANCA and pANCA antibodies resulted absent or in normal ranges. Following the histologic diagnosis of DDA, the patient received oral corticotherapy and the lesions improved markedly.

Case 4.—A 59-year-old woman suffered since 3 months from painful erythematous papules and plaques on her lower extremities (Figure 4) that evoked clinically a diagnosis of vasculitis. Some lesions showed a crusted center. Her past medical history was noncontributory. The diagnosis of



Figure 2.—Patient 2. Irregular, ulcerated lesion with crusting on the left leg. The red color is due to the application of eosin.



Figure 3.—Patient 3. Painful erythematous purpuric plaques with central ulceration on the leg that evoked clinically a diagnosis of vasculopathy/vasculitis.

DDA was reached at the histologic examination. A monoclonal gammopathy of IgG lambda type was disclosed following the histologic diagnosis. All other laboratory tests, in particular immunologic markers including antinuclear body, rheumatoid factor, anticardiolipin body, cryoglobulin, cANCA and pANCA antibodies resulted absent or in normal ranges. There was no clinical evidence for peripheral atherosclerotic disease. After oral prednisone (1/2 mg/kg/day) lesions resolved.

Discussion

Cutaneous reactive angiomatoses encompass a group of rare benign reactive angioproliferations



Figure 4.—Patient 4. Painful erythematous papules and plaques on her lower extremities that evoked clinically a diagnosis of vasculitis.

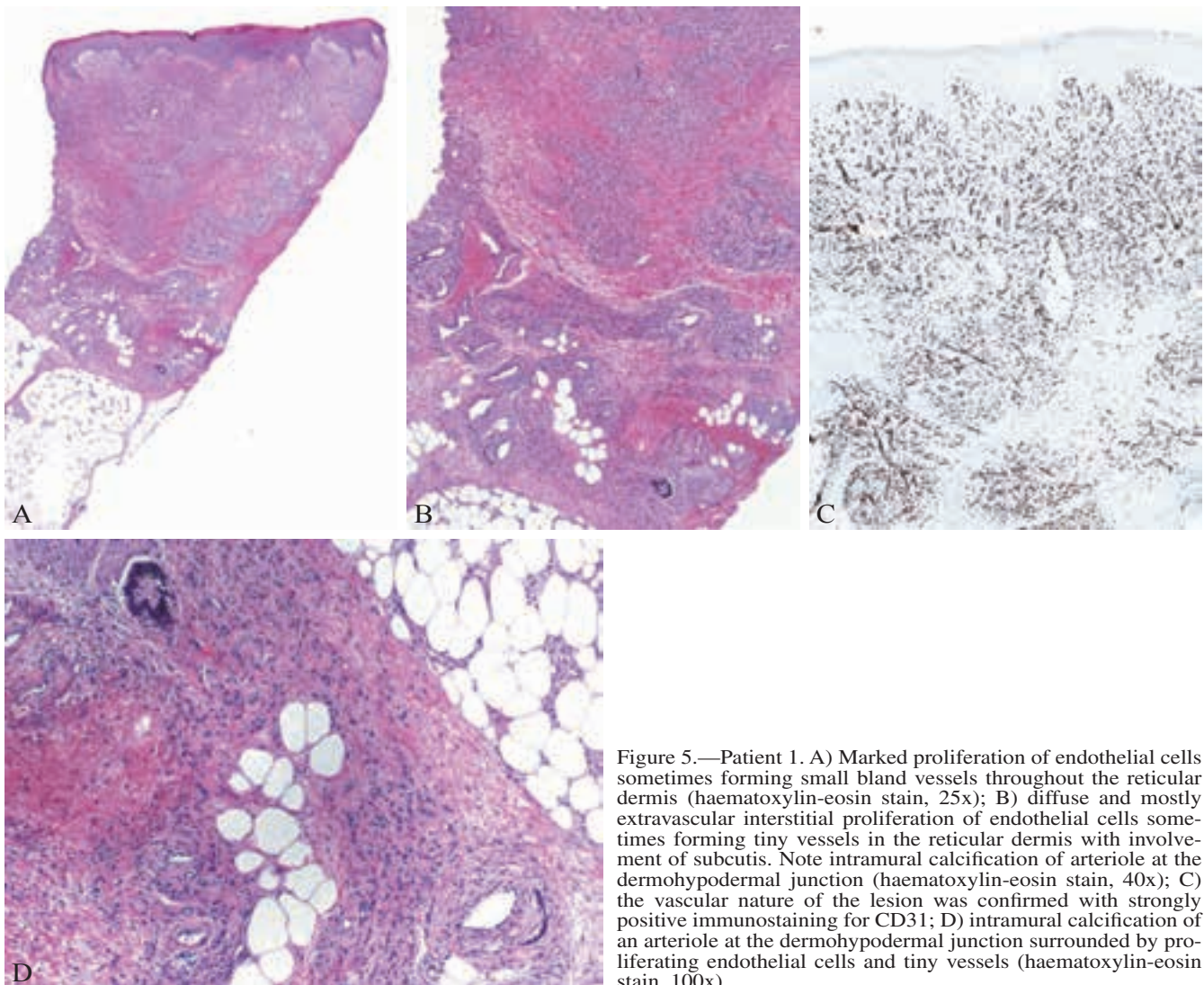


Figure 5.—Patient 1. A) Marked proliferation of endothelial cells sometimes forming small bland vessels throughout the reticular dermis (haematoxylin-eosin stain, 25x); B) diffuse and mostly extravascular interstitial proliferation of endothelial cells sometimes forming tiny vessels in the reticular dermis with involvement of subcutis. Note intramural calcification of arteriole at the dermohypodermal junction (haematoxylin-eosin stain, 40x); C) the vascular nature of the lesion was confirmed with strongly positive immunostaining for CD31; D) intramural calcification of an arteriole at the dermohypodermal junction surrounded by proliferating endothelial cells and tiny vessels (haematoxylin-eosin stain, 100x).

including at least 6 entities such as reactive angioendotheliomatosis, acroangiodermatitis (pseudo-Kaposi sarcoma), diffuse dermal angiomatosis, intravascular histiocytosis, glomeruloid angioendotheliomatosis, and angiopericytomatosis (angiomatosis with cryoproteins).¹⁴ From a clinical point of view, all of them present with multiple, erythematous-violaceous and purpuric patches and plaques, sometimes evolving toward necrosis and ulceration with a wide distribution but a propensity to involve limbs mimicking cutaneous vasculitides. Histologically, they are characterized by intravascular and extravascular hyperplasia of endothelial

cells, histiocytes and pericytes. All the variants have been consistently associated with systemic conditions in which (sub)occlusive or inflammatory vasculopathic processes occur in the vascular tree. They include infections (mainly bacterial endocarditis), peripheral vascular diseases, autoimmune, hemolymphoproliferative diseases and solid tumors (Table II). Although the exact pathogenesis of cutaneous reactive angiomas has not been fully elucidated, all the different forms may represent a continuum of the same regeneration mechanism after a (sub)occlusive or inflammatory vascular process.^{14, 15} In fact, the common characteristic among

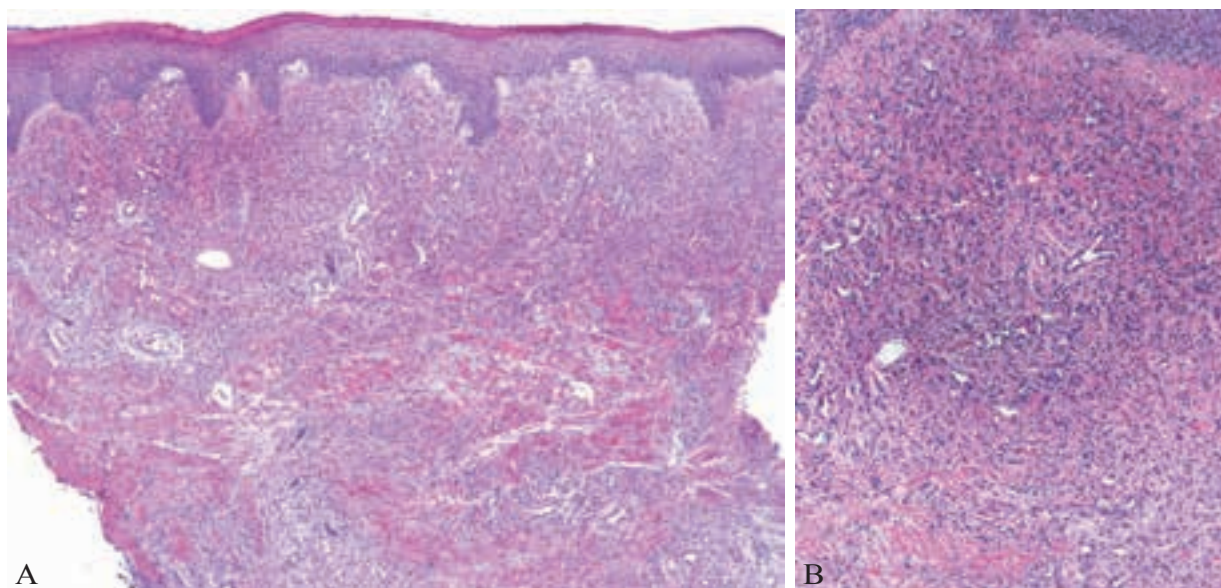


Figure 6.—Patient 3. A) Diffuse proliferation of benign endothelial cells in the superficial and deep dermis associated with few vascular structures in the absence of sign of calciphylaxis (hematoxylin-eosin stain, 40x). B) Proliferation of endothelial cells and tiny vessels (hematoxylin-eosin stain, 100x).

TABLE II.—Clinical and pathological features of cutaneous reactive angiomatoses.

Type	Clinical presentation	Histologic features	Proliferating cells	Localized or systemic changes
Reactive angioendotheliomatosis	Erythemato-violaceous, papules and plaques, localized or extensive, occasionally ulcerated and necrotic	Endoluminal (intravascular) proliferations	Endothelial cells (with or without pericytes) CD31+ CD34+ Other endothelial markers+	Infections (endocarditis), cholesterol emboli, arteriovenous shunt, antiphospholipid syndrome, renal disease, rheumatoid arthritis, monoclonal gammopathy, hepatitis
Diffuse dermal angiomatosis	Ulcerated violaceous plaques with or without necrosis and ulceration	Interstitial clusters in the reticular dermis	Endothelial cells CD31+ CD34+ Other endothelial markers+	Atherosclerosis, arteriovenous shunt Calciphylaxis Antiphospholipid syndrome
Acroangiodermatitis (pseudo-Kaposi sarcoma)	Coalescent red-brown macules or violaceous papules and plaques (usually on the legs)	Periluminal lobular proliferation with thick-walled vessels in the papillary dermis	Endothelial cells (and pericytes)	Venous insufficiency (Mali type), arteriovenous shunt (Bluefarb-Stewart type), limb paralysis, amputation stump, thrombophilia, syndrome Klippel-Trénaunay
Intravascular (intralymphatic) histiocytosis	Erythema with unclear border around joints, Erythematous-violaceous patches and plaques, papules and induration	Intraluminal proliferations with occlusion	Histiocytes CD68+	Monoclonal gammopathy, vascular insufficiency, rheumatoid arthritis, orthopedic metal implant
Reactive glomeruloid angioendotheliomatosis	Erythematopurpuric patches and ulcerated necrotic plaques	Intraluminal glomeruloid-like tufts of capillaries	Endothelial cells CD31+ CD34+ Other endothelial markers+	Cold agglutinins, lymphoma
Angiopericytomatosis (angiomatosis with cryoproteins)	Ulcerated necrotic plaques and erythematous patches and papules	Periluminal proliferation with or without thrombi	Pericytes (with or without histiocytes)	Myeloma, cryoproteinemia

Modified from Rongioletti F *et al.*¹⁴

these entities is the tendency to develop either a vasculopathic occlusive or subocclusive process or an inflammatory vascular reaction that generates a localized hypoxic stimulus causing the endothelial neovascularization. The neovascularization process in the organization of microthrombi involves different stages. Each stage may reflect a different form of cutaneous reactive angiomatoses,^{14, 15} which in the early stages is characterized by an intravascular proliferation of histiocytes or endothelial cells and in the late stages by an endothelial and pericytic cell proliferation. The spectrum of lesions, seen mainly on histopathological grounds, is dependent on the time of the biopsy and on the severity of the underlying pathological condition. Some recent cases showing different simultaneous patterns of cutaneous reactive angiomatoses in the same lesions favor this pathogenetic mechanism.¹⁵

Among the cutaneous reactive angiomatoses, DDA is a rare variant with only 14 cases reported worldwide in the medical literature that most commonly affects patients with severe atherosclerotic vascular disease and other comorbidities, such as arteriovenous fistula.¹⁴ From a clinical point of view, it is usually characterized by painful livedoid plaques with central ulceration on lower extremities; however, the clinical presentation may be variable with single or multiple erythematous or violaceous papules and plaques without ulceration widely distributed. Histologically, DDA exhibits a diffuse endothelial cell hyperplasia found interstitially in the papillary and reticular dermis. The development of this reactive pattern of angiomatosis on the breast with several violaceous, livedoid, poorly demarcated plaques is another presentation of DDA that involves middle-aged women who had large pendulous breasts and a personal history of a heavy smoking habit.^{12, 13}

DDA has been reported in association with a variety of diseases that cause vaso-occlusion or subocclusion, including calciphylaxis.^{9, 10} Calciphylaxis is a life-threatening condition characterized by progressive cutaneous necrosis due to vascular calcification seen in the setting of end-stage renal disease. Patients with calciphylaxis clinically present with firm plaques with stellate purpura and ulceration. Histopathologically, calciphylaxis is characterized by calcification of arterioles in the dermis and subcutaneous tissue with accompanying thrombosis and cutaneous necrosis. The association of calciphylaxis

with DDA has been rarely reported and we added two further examples of this association. The lower-grade ischemia or sub-occlusive process that leads to DDA may precede the frank ischemia seen in calciphylaxis, and DDA may represent an early pathologic sign that heralds the subsequent development of calciphylaxis. Alternatively, the vascular occlusion of larger dermal/hypodermal vessels in calciphylaxis may induce an increase in levels of VEGF as a compensatory mechanism, suggesting that DDA may occur as a secondary response to calciphylaxis. Angiomatosis of skin has also been associated with local intravascular immunoglobulin deposits and with monoclonal gammopathy that may represent the (sub)occlusive trigger as it occurs in our third and fourth patients who clinically has been suspected to have a vasculopathy/vasculitis.¹⁶ It has been suggested that DDA may represent a residuum of leukocytoclastic vasculitis, but strong evidence for such a hypothesis is lacking. It is possible that deposition of complement and immunoglobulins may induce vascular injury.¹⁷ If the triggering agent is a circulating immune complex, it might be expected that evidence of systemic involvement would occur, including glomerulonephritis, arthralgia, and/or uveitis. There was no such evidence documented in our cases.

The microscopic differential diagnosis of DDA includes vascular tumors such as Kaposi sarcoma and angiosarcoma.¹⁴ Features mimicking KS have been described, but several histological features, including frank atypia of cells, a diffuse slit-like lumen formation with the promontory sign, the inflammatory lymphoplasmacytic component and the positive immunostain for HHV8, are not features of DDA. Cutaneous angiosarcoma shows multiple vascular channels of different sizes, lined by endothelial and atypical cells, and disposed in one or more layers.

Management of DDA includes an accurate search and treatment of the possible associated systemic diseases (Table II). Early correction of the associated ischemic peripheral vascular disease promotes resolution of DDA.¹⁸ Furthermore, systemic steroids, as in our third case, and/or antiaggregation and isotretinoin, based on their inhibitory effect on neoangiogenesis have been successfully used.¹⁴ Cessation of smoking led to a substantial improvement, especially in patients presenting with DDA of the breast.¹² Finally, self-improvement and healing of DDA are also possible.

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Conflicts of interest.-The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Epub ahead of print on December 11, 2014.

Degos disease: report of a case and review of the literature

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We report the case of a 20-year-old woman with one-year history of asymptomatic pink papules on the abdomen, with central atrophy. Fever and symptoms suggesting involvement of other organs were absent. Histological examination revealed wedge-shaped area of cutaneous ischemia extending into the deep dermis with superficial and deep perivascular lymphocytic infiltrate. On this basis, we diagnosed malignant atrophic papulosis. Laboratory tests and instrumental investigation did not reveal any systemic involvement. The rarity of this disease makes early diagnosis challenging, even if clinical and histological patterns of the skin lesions are peculiar.

KEY WORDS: Malignant atrophic papulosis - Skin - Diagnosis.

Degos disease, also known as Köhlmeier-Degos or malignant atrophic papulosis (MAP), is an extremely rare vasculopathy involving the tunica of small and medium size arteries and veins.^{1, 2} Skin lesions are often the first symptoms of the disease, even if systemic involvement can manifest several years later. In these cases the prognosis is extremely severe with intestinal perforation and peritonitis being the main causes of death.^{1, 3} Here we report the case of a 20-year-old woman with malignant atrophic papulosis only involving the skin.

Case report

A 20-year-old woman was admitted to our hospital in August 2010 with a one-year history of multiple non pruritic, non painful papules that had appeared progressively.

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The eruption began suddenly and the papules were distributed mainly on the trunk. The palms, soles, face and scalp were spared. The lesions were slightly raised pink papules surrounded by a pale rim with a central white spot. Fever and symptoms suggesting involvement of other organs were absent. A dermatologist obtained a skin biopsy and the histological report indicated a generic finding of vasculitis, on the basis of which the patient was treated with systemic corticosteroids, without improvement of the rash. The patient was referred to our Department for further evaluation.

On admission, general health was apparently good. Family medical history was unremarkable. Body temperature was normal (36.6 °C) with an initial blood pressure of 120/70 mmHg, pulse rate 93 bpm and respiratory rate 15 breaths/minute. Organ manifestations were absent. Multiple popular skin lesions, ranging from 3-7 mm in diameter, were only observed on the trunk. The lesions were pink dome-shaped papules, some of which had a telangiectatic rim and a central porcelain-white atrophic scar (Figure 1A, B). Systemic examination was normal. Lymphadenopathy, clubbing and cyanosis were absent. Neurological examination was unremarkable. Cardiovascular examination revealed regular first and second heart sounds. Breath sounds were normal. The abdomen was soft, nontender and nondistended. Peripheral pulse was equal bilaterally and pedal edema was absent.

Laboratory parameters were within normal limits or

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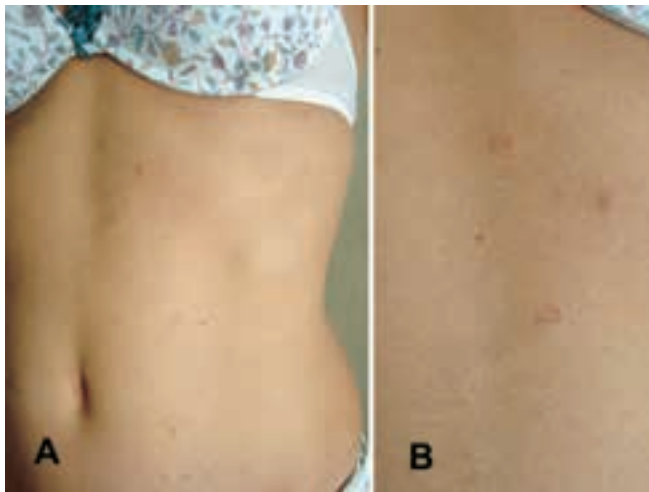


Figure 1.—Pink dome-shaped papules, some with a telangiectastic rim and a central porcelain-white atrophic scar (A); details (B).

not specific. Notably, complement levels, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasm antibody and other coagulation studies, including protein C and S, factor V Leiden, antithrombin III, anticardiolipin and antiphospholipid antibodies, lupus anticoagulant, prothrombin time and activated partial thromboplastin time were normal. ECG was normal. Chest and cranial radiographs showed no abnormalities. Abdominal ultrasonography only showed small kidney cysts. EEG showed no abnormalities. Ophthalmic examination showed visual acuity 10/10 in the right eye and 9/10 in the left. Color vision was normal. Anterior segment findings were unremarkable and intraocular pressure and fundus examination were normal.

Histological review of the skin biopsy specimens was then performed. It revealed an atrophic epidermis with thinning and initial necrosis of dermal papillae; in the dermis a superficial and deep perivascular lymphocytic infiltrate with abundant mucin deposition was also present (Figure 2A, B). On these basis a diagnosis of Degos disease was made and initial treatment with 325 mg aspirin once a day was started. The patient was also advised to avoid smoking (positive association between smoke and thrombosis). After about 6 months we observed no new lesions and all the investigations did not reveal any alteration.

Discussion

Kohlmeier described a case of malignant atrophic papulosis as a form of thromboangiitis obliterans in 1941.¹ Degos recognized it as a specific entity in 1942.¹ Since then, fewer than 150 cases have been

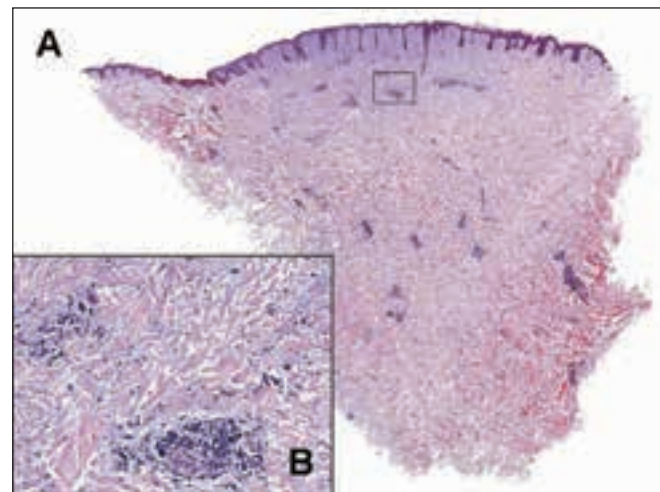


Figure 2.—Skin biopsy of our patient revealed atrophic epidermis with thinning and initial necrosis of dermal papillae (A); a superficial and deep perivascular lymphocytic infiltrate with abundant mucin deposition were also recognized in the dermis (B) (H & E stain).

reported 4-5 and the epidemiology of MAP is therefore still unclear. The disease affects all ages and both sexes. About 75% of patients are male and the disease is most frequent in the third and fourth decades of life.² Etiology is still unknown and the exact nature of the disease is controversial. The three most accepted etiopathogenetic theories are that MAP is a form of vasculitis, a clotting disorder, and/or a primary endothelial cells disease.^{4, 6} Recently other pathogenetic mechanisms have been reported. In particular Passarini *et al.* suggested that the disease could be caused by a viral trigger (Parvovirus B19), with cross-reactivity due to molecular mimicry or epitope formation between viral antigens and the host.⁵ The disease has a purely cutaneous variant and a systemic one (Table I).³ Both have similar cutaneous manifestations, characterized by erythematous, pink or red papules (2-15 mm), which evolve into scars with typical porcelain white atrophic center. Purely cutaneous MAP is a benign condition that can be life-long. However at any time later of life patients may develop systemic disease, which is usually fatal within three years from the onset.⁷ For this reason all patients should receive regular follow-up.

From a systemic point of view the disease must be differentiated from inflammatory bowel disease, cryoglobulinemia, coagulopathies, dermatomyositis, progressive systemic sclerosis, polyarteritis nodosa and systemic lupus erythematosus, though clini-

TABLE I.—*Clinical presentation, description, laboratory findings and histopathology.*

Clinical presentation	Description	Laboratory findings	Histopathology
Skin-limited disease	<ul style="list-style-type: none"> – Early-fully developed stage: slightly elevated, small flesh-colored papules with porcelain-white Centers (+ umbilication) surrounded by an erythematous border. – Late-stage: flat and atrophic porcelain-white centers without surrounding erythema 		<ul style="list-style-type: none"> – Late-stage: epidermal atrophy with wedge-shaped zone of dermal necrosis. Low degree of inflammation and dermal mucin deposition
Systemic involvement Mostly preceded by skin lesions; prognosis is poor	<ul style="list-style-type: none"> – Gastrointestinal: abdominal, nausea, vomiting, diarrhea, bowel perforation, intestinal bleeding and peritonitis can appear several weeks, months or years after the initial skin lesions. – Neurologic: A wide range of manifestations can be found due to involvement of both central and peripheral nervous systems (cerebrovascular accidents, seizures, mononeuritis multiplex, transverse myelitis and amaurosis fugax), meningo-encephalitis and dementia, visual field defects, posterior subcapsular cataracts, optic neuritis and optic atrophy, congenital glaucoma due to angle dysgenesis and retinochoroidal colobomas. – Mucus membrane involvement: bulbar conjunctivae, sclera and episclera. – Intrathoracic: constrictive pericarditis, pleurisy, pleural adhesion, pleural and pericardial effusions, fibrous thickening of the pleura. 	<ul style="list-style-type: none"> – Abdominal film/CT: free air/signs of peritonitis – Abdominal laparoscopy: intestinal lesions similar in appearance to skin lesions – Head CT: cerebrovascular accident – EMG: demyelinating polyneuropathy – Chest film/CT: atelectasis, pleural effusions, and pulmonary infarcts – Electrocardiographic and echocardiographic signs of pericardial effusion and constrictive pericarditis 	<ul style="list-style-type: none"> – Gastrointestinal infarcts – Brain and spinal cord hemorrhagic and ischemic infarcts – Mesothelial surfaces inflammation. Calcified and scarred pleura, hemorrhagic pleural infarcts and fibrous pericarditis

CT: computed tomography; EMG: electromyogram.
Modified from Fernandez-Perez ER *et al.*³

cal and histological patterns of the skin lesions are diagnostic.¹ Differential diagnosis of the cutaneous manifestations of MAP is necessary with respect to atrophie blanche, atrophie blanche-like papules of systemic lupus erythematosus/dermatomyositis, dermal mucinosis, rheumatoid arthritis, lichen sclerosis et atrophicus, guttate morphea, and scleroderma.¹ Clinicopathologic correlation is necessary for definite diagnosis.

There is no specific medical treatment for MAP. Antiplatelet drugs (*e.g.* aspirin and dipyridamole) may have a role in the treatment of all variants.^{1, 8} Heparin has been administered in acute cases, but other anticoagulant, fibrinolytic and immunosuppressive agents have been tried without any success.^{2, 8} A recent case report advocated bevacizumab, a recombinant human monoclonal antibody against vascular endothelial growth factor, and provided in-

direct evidence of therapeutic response.⁹ Systemic corticosteroids are ineffective and have been associated with early intestinal perforation and sepsis.¹⁰

In conclusion, MAP is a rare and potentially life-threatening disease. Its prognosis depends on the development of the systemic involvement. The probability of benign course increase with the duration of monosymptomatic skin disease.¹¹

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on December 14, 2011.

Accepted for publication on June 9, 2014.

In vivo confocal microscopy for eyelids and ocular surface: a new horizon for dermatologists

TO THE EDITOR: *In vivo* confocal microscopy (IVCM) is an emerging non-invasive diagnostic technique that offers the evaluation of external body tissues at real time, with cellular resolution, and is increasingly used in dermatology for the examination of the skin.^{1,2} Until now dermatologists did not use IVCM to investigate the eye, although the eyelid, the ciliary margin and the conjunctiva also belong to the dermatologic field. Two IVCM are currently available in ophthalmology: the Confoscan 4 slit scanning confocal microscope (Nidek, Gamagori, Japan) and the laser scanning confocal microscope Heidelberg Retina Tomograph^{3,4} equipped with the Rostock Cornea Module (Heidelberg engineering GmbH, Heidelberg, Germany). These devices are mainly used to visualize cornea and more rarely the conjunctiva located near the sclero-corneal limbus. Because of limitations in the handiness of both microscopes, the rest of the conjunctiva, the ciliary margin and the entire eyelid have never been extensively studied.

We used for the first time the two IVCM dedicated to skin (VivaScope 1500 and 3000, Lucid Inc, Rochester, New York, distributed in Europe by MAVIG GmbH, München, Germany) to explore eyelid and conjunctiva.

The handled camera (HC) VivaScope 3000, thanks to its good handiness, enables an easy exploration of the whole ocular area, in particular the palpebral conjunctiva (Figure 1), the ciliary margin, the lacrimal punctum, the internal and external canthi, and both surfaces of the eyelids comprising the Meibomian glands. All these regions have almost never been explored by IVCM before because of the limited mobility of devices available at present for ophthalmology. Of course, like both ophthalmology IVCM, the HC also enables examining cornea and bulbar conjunctiva. The IVCM aspect of the conjunctiva is analogue to the skin (Figure 1) due to the similar anatomy of these tissues. The conjunctiva is formed by a stratified squamous epithelium with polygonal cells with hyper-reflective membranes that are analogue to skin keratinocytes, and by a stroma (lamina propria) with collagen fibers and vessels that is similar to the skin dermis. The main differences are that the

epithelium is non-keratinized and therefore no stratum granulosum and corneum are present, that there are no hair follicles, and that the conjunctival stroma is less reflective than dermis under IVCM.

The multilaser camera (MLC) VivaScope 1500 per-

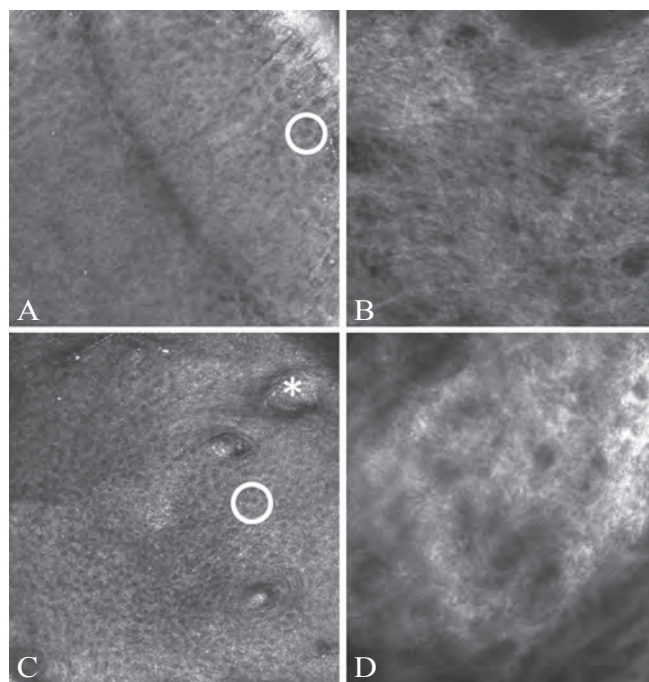


Figure 1.—*In vivo* confocal microscopy (IVCM) (VivaScope 3000) aspect of normal conjunctiva (A, B) compared with normal skin (C, D). The conjunctiva is composed by a stratified squamous epithelium (A) with polygonal cells with hyper-reflective membranes (circle) that are analogue to skin keratinocytes (circle) (C), and by an underlying stroma (B) that is similar to the skin dermis (D). Unlike the conjunctiva, in the skin hair follicles are present (C) (asterisk), and the dermal collagen (D) is more thick and more reflective.

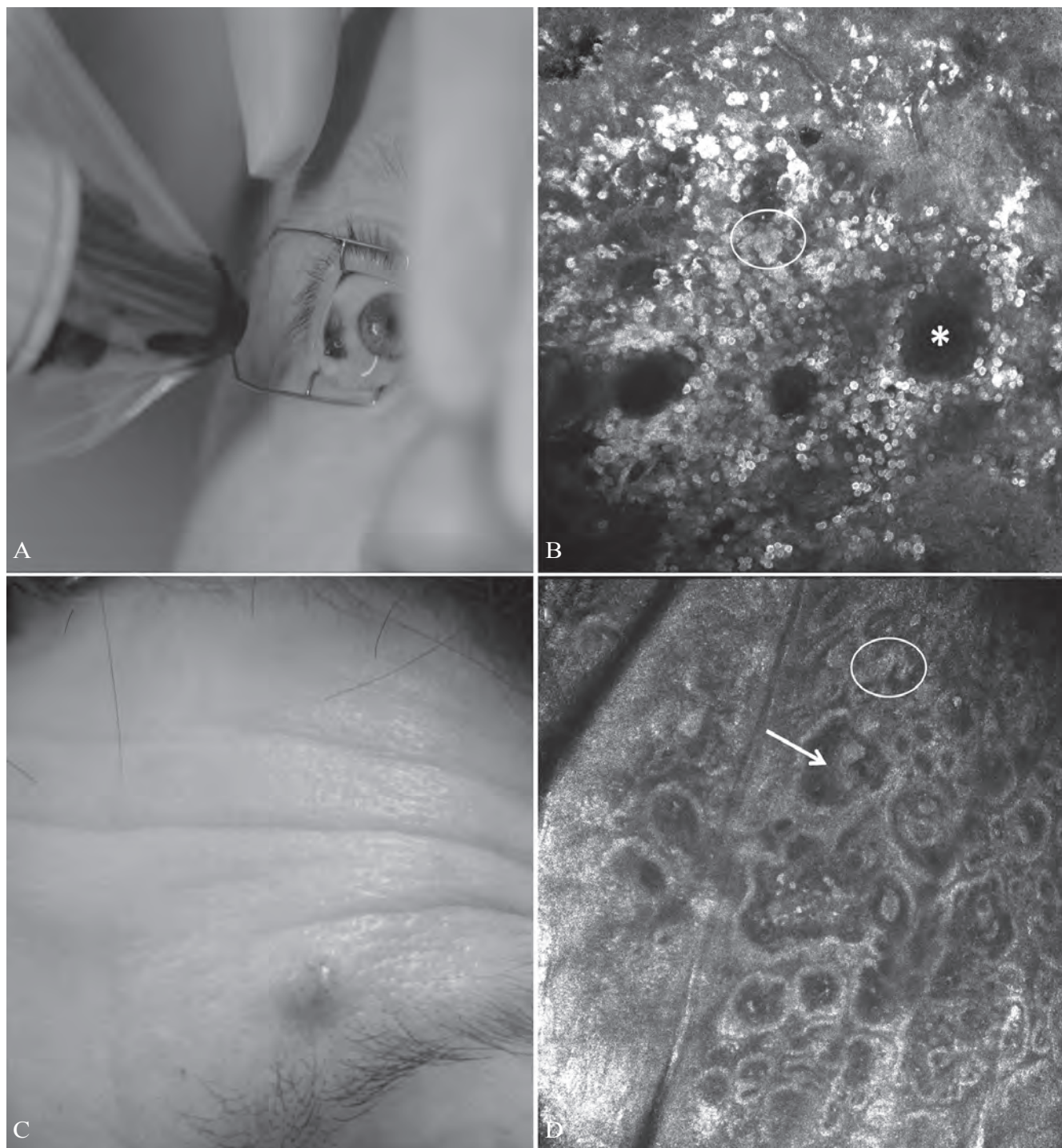


Figure 2.—Clinical and IVCM aspect of a conjunctival compound nevus (A, B) compared with a skin (C, D) compound nevus. Under IVCM, conjunctival nevus (B) shows sheets and small nests (circle) of hyper-reflective nevocytes in the epithelium and lamina propria, and dark cysts (asterisks) characteristic of benign conjunctival nevi. Under IVCM, skin nevus (D) shows nests of hyper-reflective melanocytes at the dermoepidermal junction (circle) and in the dermal papillae (arrow).

mits examination in both reflectance and fluorescence with three different wavelength (488, 658 and 785 nm), thus fundamentally differing from the previous devices that have only one light source and do not allow fluorescence acquisition. In order to use the MLC, we created an adapter between its tip and the ocular surface to reduce the diameter of the current tip made for the skin, while preserving its optic qualities. In addition, to avoid abrupt or involuntary movements of the patient, the investigator and the head of the camera, which could be dangerous for the ocular surface, we use a chin support for the patient and created a hinged support for the MLC that allows 5 degrees of liberty and therefore a precise alignment in front of the region of interest.

We explored normal eyelid, conjunctiva and cornea, and neoplastic (squamous cell carcinomas, basal cell carcinomas, lentigos, nevi and melanomas), inflammatory, infectious and storage disease with ocular involvement. All the suspected malignant lesions have been excised and the histological examination confirmed the IVCN diagnosis in all cases.

We obtain high resolution images, comparable to those achievable with the skin (Figures 1, 2), but contrary to what happens in the skin, the lack of the stratum corneum on the mucosal surface enables to preserve the same optical resolution on the deeper layers.

The MLC allows to explore the fluorescence characteristics of the ocular apparatus either spontaneously or after topical instillation or intravenous injection of fluorochromes already used in routine by ophthalmologists. Fluorochromes specifically stain cellular or tissular components that are unlikely to be discriminated only by reflectance confocal images.

In addition, there is a medico-economic interest of the ophthalmology applications of the IVCN devices initially dedicated to the skin: the same machine can be shared by dermatologists and ophthalmologists with a better cost benefit ratio for medical centers.

In conclusion, our preliminary experience suggests that IVCN used until now to examine the skin can be employed for the ocular surface and ocular adnexa analysis, establishing a connection between dermatology and ophthalmology in this field. Larger studies are now needed to evaluate these applications.

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G ITAL DERMATOL VENEREOL 2014;150:127-9

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Legionellosis and psoriasis in biologic era

TO THE EDITOR: Psoriasis is a chronic dermatosis with a prevalence of 2-3% in the world's population, whereas of 1-2% in Europe.¹ About one third of patients have either severe or moderate psoriasis (involving more than 10% of body surface area), for which a number of biologic agents, including tumor necrosis factor (TNF)- α antagonists (etanercept, adalimumab and infliximab), are available. Even if TNF- α has been shown to play an important role in the pathogenesis of psoriasis, it also contributes to host immune defense. Indeed, the main concern about biological agents is the effect of long-term chronic immunosuppression and the consequent possible increased risk of infection and cancer. *Legionella pneumophila* is a Gram-negative facultative intracellular parasite of mononuclear phagocytes and the etiologic agent of legionnaires' disease (LD). Infection with *Legionella spp* ranks among the three most common causes of severe pneumonia in the community setting and is isolated in about 1-40% of cases of hospital-acquired pneumonia.² Legionellosis mortality rates are highly variable, ranging from less than 1% to as high as 80%. We report the case of a 56-year-old male patient affected with psoriasis since 11 years. Moreover, he suffered from high blood pressure, familial hypercholesterolemia (in treatment) and chronic obstructive pulmonary disease (not in treatment). Over the years psoriasis has been treated with topical therapies (calcipotriol monohydrate and betamethasone, without results), with acitretin (35 mg/day, stopped due to the onset of fatigue, headache, and nausea), with ciclosporin (250 mg/day, discontinued because of headache, dizziness, and increased blood pressure) and intermittently with narrow band (nb)-UVB phototherapy or heliotherapy, achieving a clinical improvement. At the time of our examination Psoriasis Area and Severity Index (PASI) was 23.4, the value of Body Surface Area (BSA) was 30%, and Dermatology Life Quality Index (DLQI) was 15. Furthermore, the patient reported pain in the distal interphalangeal joints of hands and in the feet, which appeared edematous. The suspicion of psoriatic arthritis was confirmed by clinical and instrumental examinations (ultrasound scans). On the basis of the clinical history, therapy with infliximab (5 mg/kg bodyweight every 8 weeks) was started after screening tests (routine examinations, viral and tumor markers, Mantoux and Quantiferon TB gold tests, chest X-ray). The patient showed a progressive clinical improvement. After 19 months of infliximab treatment he was hospitalized with fever (up to 41 °C), cough, tachycardia and cardiac arrhythmia, preceded by a period of flu-like illness. Laboratory findings showed an increased number of white blood cells (22.000 mmc, normal range 4000-10.000 mmc) with a percentage of neutrophils of 84% (normal range 53-69%), increases

in erythrocyte sedimentation rate (36 mm/h, normal range 0-19 mm/h) and C-reactive protein (29 mg/L, normal range 0.1-6 mg/L). Electrocardiogram demonstrated hyperkinetic arrhythmia and atrial fibrillation. Chest X-ray showed an inhomogeneous infiltrate in the left lung, diffuse pleural thickening, and obliteration of cost-phrenic field. Thoracic computerized tomography (CT) showed parenchymal consolidation of the left lung, with ground-glass appearance. Emogasanalysis values were as follows: pH 7.45 (normal range 7.38-7.42), pO₂ 37.5 mmHg (normal range 80-100 mmHg), pCO₂ 37.5 mmHg (normal range 35-45 mmHg). Through bronchoscopy whitish secretions were revealed in the inferior lobes of both lungs. Microbiological analysis were negative for pathogen common flora and *M. tuberculosis*. The diagnosis of *L. pneumophila* pneumonia was established by the detection of specific antigen in the urine. Infliximab treatment was immediately discontinued and the patient was treated with ciprofloxacin 500 mg twice a day for 15 days, prednisone 25 mg (1/2 cpr for 7 days - 1/4 cpr for other 7 days) and tiotropium 10 μ g (3 consecutive inhalations per day). The patient responded rapidly to the treatment with resolution of symptoms within a week. After fifteen days, laboratory findings changed back to normal ranges and after thirty days thoracic CT showed no active infiltrates. With regard to psoriasis, nb-UVB phototherapy and a non-steroidal anti-inflammatory drug to relieve joint pain (aceclofenac 200 mg per day) were prescribed, while every immunosuppressant therapy was discontinued as suggested by the pneumologist advice.

TNF- α seems to play an important role in fighting the infection by *L. pneumophila*, that causes pneumonia replicating, invading, and destroying pulmonary tissues by affecting specific cells, such as alveolar macrophages and alveolar epithelial cells. McHugh SL *et al.* demonstrated that pretreatment of macrophage cultures *in vitro* with TNF- α induces resistance of the macrophages to infection by *L. pneumophila*. Moreover, addition of small amounts of monoclonal antibody to TNF- α restores susceptibility of the macrophages. TNF- α is also secreted by *L. pneumophila* infected macrophages *in vitro* and is detected in lung lavage fluid during *L. pneumophila* infection.³

In literature, more than 30 cases of *Legionella* infection after anti-TNF- α treatment have been reported. In most cases, the infection was community-acquired by patients receiving anti-TNF- α treatment for rheumatic, gastrointestinal and dermatological diseases. Among these cases, only a few suffered from psoriasis and were all treated with infliximab (Table I).^{4,5} Actually, no screening test has been established in clinical practice. Of the various methods available for the diagnosis, culture is the most specific and is accepted as the gold standard. However, in routine and

clinical laboratory work, legionellosis is rarely proven by culture and the most common laboratory test used is the detection of *Legionella* antigenuria.² Because of its reasonable sensitivity and high specificity with rapid results, it is to be considered the first-line diagnostic test, with the limit to detect only *L. pneumophila* serogroup 1; such disadvantage can be overcome through molecular techniques detecting other serogroups and species. LD can endanger patient's life if not promptly diagnosed and treated. Physicians should take special care of patients with several risk factors, such as exposure to smoke and combination therapy with immunosuppressive agents. A quick notification of such cases should help to define more precisely the relationship between the anti-TNF- α agents and infections as well as the effectiveness of preventive strategies. More studies are needed to determine the role of molecular techniques able to detect all serogroups and species of *Legionella*, in order to manage in the best way this life-threatening but curable infection.

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Trichilemmal carcinoma of the lower eyelid in a oculocutaneous albino patient

TO THE EDITOR: Trichilemmal carcinoma (TLC) is a rare cutaneous adnexal neoplasm deriving from the outer root of the hair follicles. It represents the malignant counterpart of trichilemmoma and occurs as vegetating, often ulcerated or crusted nodule or plaque usually arising in the sun-exposed areas of the elderly population. Head, neck and dorsum of the hand are the most frequently involved sites.¹ Oculocutaneous albinism is characterized by the lack of enzyme tyrosinase, essential for the production of melanin. These patients are born with bluish eyes and white hair and skin, and they maintain these features when growing old. They show an increased risk of skin cancer, mainly squamous and basal cell carcinomas.² We describe the case of a 70-year-old oculocutaneous albino patient that presented with a firm 15x7 mm right lower eyelid

nodule (Figure 1). The patient referred that this nodule arose three months before as a little papule and grew very quickly to the actual size. The patient was also affected by psoriasis. The anamnesis revealed an exaggerated sun exposure in the past: the patient worked outdoor as bricklayer in Africa for 30 years. The patient developed several basal and squamous cell carcinomas and his whole face was affected by severe actinic keratoses. We treated the patient with numerous surgical excisions for the tumours and with methyl aminolevulinic acid-photodynamic therapy for the severe field cancerization of his sun exposed areas. We decided to surgically remove the nodule and we repaired the minus with an advancement flap. Histologically the neoplasia is lobulated, follicle centred, focally in continuity with epidermis. It is composed of irregular nests and cords



Figure 1.—Clinical aspect of the nodular lesion.

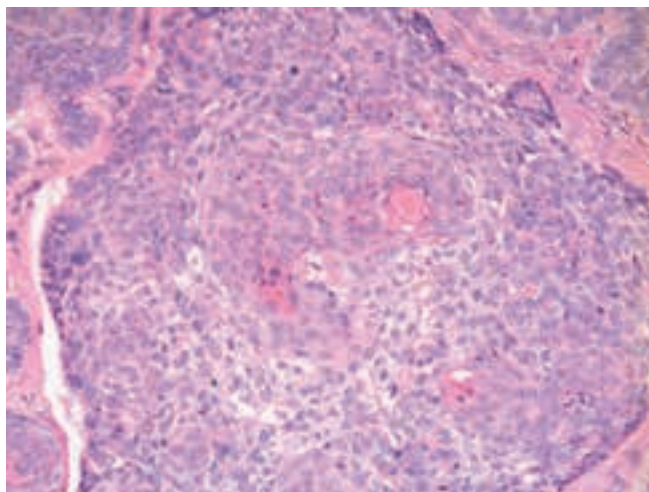


Figure 2.—Histological aspect of the lesion demonstrating a neoplasm composed of eosinophilic clear cell, peripheral nuclear palisading and trichilemmal keratinisation. Several mitotic figures are represented.

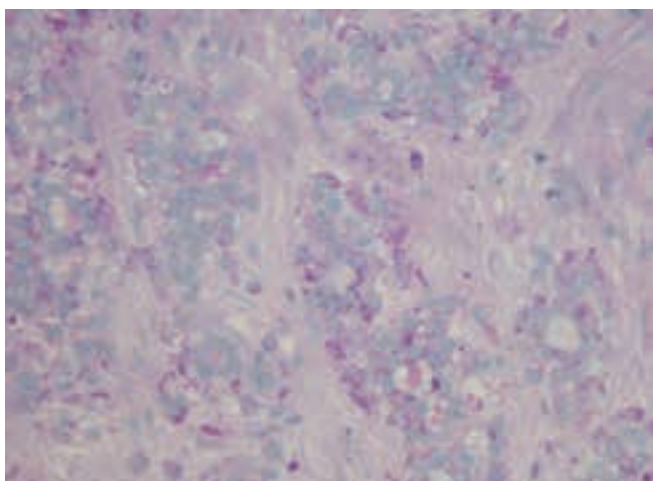


Figure 3.—Immunohistochemical PAS stain.

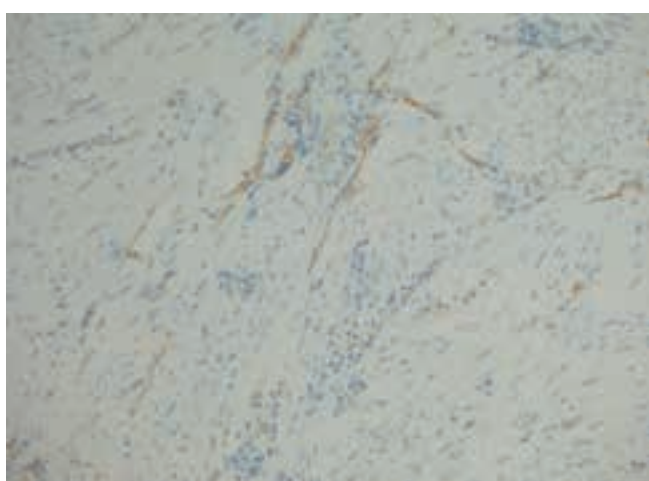


Figure 4.— Immunohistochemical CD34 stain.

of eosinophilic cells with clear cytoplasm, high mitotic index, focal necrosis, picnosis and with invasive aspect involving the adjacent dermis irregularly with surrounding chronic inflammation and desmoplasia. Some of the tumor cells usually have PAS positive and diastase labile clear cytoplasm. Peripheral nuclear palisading is frequent at the periphery of the neoplastic lobules. Areas of trichilemmal keratinisation are disposed irregularly throughout the neoplasm which resembles squamous carcinoma. Perineural infiltration is also frequent (Figure 2). TLC is a rare cutaneous adnexal neoplasm usually occurring in the sun-exposed areas of the elderly population; it originates from the external root sheath of the hair follicle³ and can

be considered a malignant variant of trichilemmoma. The pathogenesis of TLC involves actinic damage,⁴ low dose, transformation from benign trichilemmoma. This malignancy that can be seen in both immunocompetent and immunosuppressed hosts. The clinical appearance resembles basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, keratoacanthoma and nodular melanoma and usually manifests as a single nodule measuring <2 cm. Histology reveals multiples intradermal lobules and trabeculae with a peripheral palisade of basaloid cells continuous with the epidermis. Tumoral cells present a cytoplasm rich with glycogen and The cell membrane is pas positive and well defined (Figure 3). In Figure 4 a immunohistochemical

stain with CD34 (marker of differentiation from the outer hair sheath is provided. Usually a malignant appearance, characterized by cytological atypia and high mitotic index, gives the impression of a high-grade malignant neoplasm. Trichilemmal keratinisation, defined as an abrupt keratinisation without a granular layer, is a common finding in TLC. Another feature of TLC is the epidermal spread, with an abrupt or pagetoid interface with normal keratinocytic layer. Despite of cytological malignant appearance, TLC has an indolent clinical course and shows no tendency to metastatize. Due to his local aggressive growth and frequent local recurrences, the recommended treatment for TLC is a wide surgical excision. When available, Mohs micrographic surgery should be performed to ensure complete removal of the malignancy. Albinism is characterized by a reduction in melanin pigment biosynthesis. Six different genes have found to be involved in Albinism. The main enzymatic defect is the lack of tyrosinase, a key enzyme in melanin synthesis. This deficiency results in an increased sensitivity to ultraviolet (UV) radiation and to a predisposition to skin cancer. Albino patients are also affected by photophobia, myopia and other visual problems including nystagmus and strabismus. These problems are due to the lack of retinal pigment required for the normal development of the visual system. UV exposure in hypopigmented skin causes severe skin damage. Most of the lesions are localized in sun-exposed areas as face, ears, neck and shoulders and include sunburns, blisters, solar elastosis/keratosis, ephelides, lentiginosis, and superficial ulcers. As said before, our patient spent most of his life working outdoor in Africa, and can be compared to these patients. Squamous cell carcinoma is the most increased skin cancer in albino patients, followed by basal cell carcinoma.⁵ Although non-melanomatous skin cancers are more common in patients with albinism, pigmented lesions can be difficult to evaluate in this patients because of their

hypopigmented appearance. Interestingly, the pattern of skin cancer incidence changes occurring in albino patients has similarities with the immunosuppressed population, although the mechanisms causing skin cancer's incidence increase are different.

To the best of our knowledge, this is the first case of TLC in a patient affected by oculocutaneous albino syndrome.

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G ITAL DERMATOL VENEREOL 2014;150:131-3

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