

Cutaneous vasculitis and their differential diagnoses

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ABSTRACT

Vasculitis is defined as an inflammatory cell infiltration and destruction of blood vessels identified upon histologic examination. Cutaneous manifestations are frequent during the course of many systemic vasculitis. Lesions are often not specific, the most frequent being palpable purpura. They may be the first and only manifestation of the disease or be a part of a systemic condition. Histology is mandatory to confirm the diagnosis of vasculitis to avoid a delayed and inappropriate diagnosis that could lead to improper management. Cutaneous histology gave some data that may help to classify the vasculitis without determining precisely its type. A histological examination of all other skin lesions is necessary. The result of the biopsy has to be correlated to DIF data, medical history, physical examination, laboratory and radiological findings leading to the correct diagnosis and effective treatment.

In this review, we discuss the diagnosis of cutaneous vasculitis (CV) and the pitfalls related to the cutaneous pathology. We also describe the essential features of the major categories of skin vasculitis.

Introduction

Vasculitis is defined as an inflammatory cell infiltration and destruction of blood vessels identified upon histologic examination. Cutaneous manifestations may be the first and only manifestation of the disease or be a part of a systemic condition (1).

In this review, we discuss the diagnosis of cutaneous vasculitis (CV) and the pitfalls related to the cutaneous pathology. We also describe the essential features of the major categories of skin vasculitis.

Diagnosis of cutaneous vasculitis

Physical cutaneous signs of vasculitis are wide and non-specific. Vasculitis affects the skin with varying intensity,

depth and distribution. Even though a certain number of syndromes have been described, a patient may present with symptoms that overlap with another clinical diagnosis making a diagnosis “at first sight” impossible. Vasculitis has a histopathologic definition, therefore its confirmation comes only from the microscopic examination of the lesion.

The diagnosis of CV is made by microscopic examination of hematoxylin-eosin stained biopsies (2). A list of criterias allows a trained pathologist to diagnose and distinguish an active vasculitis, from chronic and healed lesions of vasculitis and changes that are adjacent to vasculitis and may help to define a subtype or the etiology of the CV (2). Inflammatory infiltrates within and around the vessel walls associated by intramural and/or intraluminal fibrin deposition (fibrinoid necrosis) confirm the diagnosis of vasculitis. Some changes are suggestive of active vasculitis such as red blood cell extravasation, perivascular nuclear dust (leukocytoclasia), eccrine gland necrosis, ulceration, necrosis/infarction. In the absence of fibrinoid necrosis, the diagnosis of CV becomes more difficult. Lamination of the adventia, media and/or intima; perivascular nuclear dust (leukocytoclasia) without fibrinoid necrosis; loss of the elastic lamina with acellular scar tissue; or, subendothelial intramuscular and/or advential inflammatory cells in large vessels are all other argues for vessel wall damages (2).

A direct immunofluorescence examination (DIF) is also mandatory in case of CV. It does not confirm the diagnosis of CV but allows to orienter for one or another diagnosis. Absence of immune complex is in favor for pauci-immune vasculitis: Wegener’s granulomatosis (WG), Churg-Strauss syndrome (CSS), Microscopic Polyangiitis (MPA). Immunoglobulin (Ig) G, IgM, IgA and/or C3 in or around the vessels may be

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found in immune mediated vasculitis like cryoglobulinemia. In all case of CV, immune depositions of Ig and complement may be found especially C3 and IgM. However, the older the biopsied lesion is, the less immunoglobulins are found. After 72h, only C3 is detected. Therefore, a negative DIF does not rule out the diagnosis of CV. Predominance of IgA is highly in favor for Henoch-Schönlein purpura (HSP) without being constant or specific (3). IgM depositions are observed, specially in case of circulating rheumatoid factor or cryoglobulinemia. IgA deposits are absent in case of cryoglobulinemia. Of note, positive DIF without pathological assessment of CV is not relevant.

After confirmation of the diagnosis of CV itself, vasculitis may be defined more accurately by vessel size involvement (small; small and medium vessel and medium to large vessel), the extent of the lesions (superficial perivascular to dermal and/or subcutaneous) and the predominant inflammatory cell infiltration. The finding of small-vessel vasculitis with predominance of neutrophilic infiltrate and positive DIF is indicative of cutaneous leukocytoclastic vasculitis, HSP, urticarial vasculitis or erythema elevatum diutinum. More rarely, other cells may predominate such as eosinophils or lymphocytes. Presence of both small and medium sized vasculitis favors ANCA associated/pauci immune vasculitis (with negative DIF): CSS, MPA, WG or cryoglobulinemia, connective tissue disease (lupus, rheumatoid arthritis) or hypocomplemental vasculitis if DIF is positive. Polyarteritis nodosa is characterized by a neutrophilic infiltration associated with a medium vessel arteries vasculitis.

Some extravascular histologic pattern found in the surrounding tissue may be helpful to indicate a specific disease. Thus, palisading granulomatous dermatitis ("Winkelmann granuloma") is in favour for WG, CSS, rheumatoid arthritis or systemic lupus erythematosus (2). Presence of eosinophils and flame figures associated with such granulomas are found in CSS while neutrophils and basophilic debris in WG and rheumatoid vasculitis. Vacuolar interface dermatitis with sometimes dermal mu-

Table I. Differential diagnoses of vasculitis: cutaneous pseudovasculitis, modified from (4).

HEMORRHAGE

Thrombopenia
Congenital and acquired thrombopathy
Scurvy
Solar/senile purpura
Pigmented purpuric dermatoses
Arthropod
Viral and drug reactions
Ehler Danlos syndrome
Gardner-Diamond syndrome

EMBOLISM

Cardiac myxoma
Fibrinocutaneous emboli
Cholesterol Emboli
Other emboli (gaseous, fat, neoplastic...)

THROMBOSIS

Purpura Fulminans
Intravascular coagulation
Vitamin K antagonists and heparin induced skin necrosis
Antiphospholipid Syndrome
Cryoglobulinemia type I
Thrombocytaemia
Livedoid vasculopathy/atrophie blanche
Other coagulation disorder (protein C, protein S deficiencies...)
Calcephylaxis

VASOSPAMS

Drug induced
Cocaine

VASCULAR TRAUMA

cin deposition is associated with lupus erythematosus and dermatomyositis. Intraepidermal or dermal pustules with neutrophils small vessel vasculitis is related to an infectious related vasculitis (2). Skin biopsy allows to exclude pseudovasculitic disorder, a wide group of heterogeneous diseases that may mimic cutaneous vasculitis (Table I) (4).

Pitfalls

In order to enable the diagnosis of vasculitis, the choice of the "best" lesion is crucial. A lesion of cutaneous vasculitis should be analyzed within the first 48h after its appearance, otherwise typical signs of vasculitis may be absent. A fresh purpuric lesion displays within the 24 first hour fibrin deposits in the vessel wall, neutrophilic infiltration, surrounding hemorrhage and intranuclear debris. After 24 hours, lymphocytes and macrophages replace neutrophils. After 48 hours, lymphocytes predominate. Moreover, skin biopsy of an infiltrated

lesion must include the epidermis, dermis and hypodermis to precise the size of the affected vessels. Some CV affect typically the upper part of the dermis like HSP. Therefore, a punch skin biopsy will permit to show the lesions. In the case of polyarteritis nodosa, deep muscular vessels of the dermis-hypodermis and the hypodermis are affected which imply a deep incisional biopsy. Similarly, a livedo should be biopsied on its infiltrated or necrotic areas.

In some specific cases, an *incidental vasculitis* may be found on the skin biopsy. This pathologic statement should not mislead to diagnose a vasculitis. Thus, neutrophilic small vessel vasculitis may be observed if a biopsy is performed on an ulcer (2), while the surrounding vessels are normal. Besides, vessel damage induced by neutrophils is observed in lesions related to neutrophilic dermatoses such Sweet's syndrome (5).

Clinical pathologic correlation

The cutaneous lesions correlate sometimes with the size of the affected vessels. Palpable purpura, infiltrated erythema, urticaria, vesicles, blisters are mainly related to small vessel vasculitis of the dermis, while subcutaneous nodules, ulceration, gangrene are related frequently to medium sized vessel vasculitis located at the dermo-hypodermal junction or in the subcutaneous fat. Necrosis and livedo occur when either small and/or larger vessels are involved.

Clinical manifestation

Cutaneous vasculitis displays a wide range of elementary lesions that may be associated and lead to a pleomorphic appearance of the eruption. CV may manifest variously as urticaria, purpura, infiltrated erythema, hemorrhagic vesicles, ulcers, nodules, livedo, infarcts, digital gangrene (1). Lesions affect primarily the lower limbs. Upper extremity, trunk, head and neck involvement are not usual and may be considered as a sign of severity and/or of a systemic vasculitis

Palpable purpura is unquestionably the most frequent manifestation. It is localized on the lower limbs, dependent sites or underlying tight-fitting clothes (Figs. 1 and 2). Elementary lesion ranges

from tiny red macules and pinhead to coin-sized petechia, but also sometimes to more extensive plaques and ecchymoses. Colour range may change from red to purple to brownish yellow as extravasated blood is progressively broken. Purpura may disclose a necrotic evolution leading to vesicles, blisters, erosions, ulcerations and ulcer. There is often an association of different lesions in a same patient simultaneously: erythematous to purpuric macules, papules and necrotic lesions (Fig. 3). In the case of mixed cryoglobulinemia associated with hepatitis C, purpura may be absent or masked by a residual chronic pigmented brown ocre post-inflammatory purpura ("dermite ocre"), sign of former flare-up of the disease without any venous insufficiency.

Papules may present variously. Purpuric papules may be noted but also atypical urticaria with distinctive feature from common urticaria: duration of the lesions longer than 24 hours, presence of purpura, postinflammatory pigmentation, symptoms of burning rather than itching (6). Papules may display an annular erythema multiformis like eruption without any predominance on the lower limbs.

Dermal or hypodermal nodules (so-called "subcutaneous nodules") are always palpable, typically inflammatory, tender, red and small-sized. They should be looked after on the vessel territories of the lower limbs, where they can be surrounded by livedo reticularis, but are also observed on other sites such as the dorsal aspect of upper limbs or rarely the trunk. Nodules may also gather in groups along the course of superficial arteries and may evolve into necrosis and ulceration.

Livedo reticularis is a reddish-blue mottling of the skin in a "fishnet" reticular pattern frequently localized on the lower limbs. It may also affect the lower trunk and the upper limbs. Livedo reticularis of CV displays specific findings that distinguish it from physiological cutis marmorata: it is typically irregular with broken meshes with some infiltrated areas on careful examination. When associated with CV, livedo persists indefinitely with some fluctuations in intensity and extensiveness as

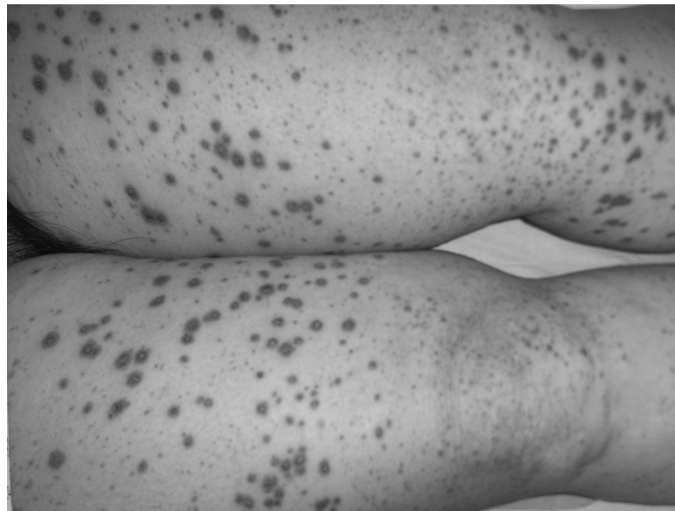


Fig. 1. Palpable purpura of the lower limbs during leukocytoclastic vasculitis.



Fig. 2. Purpura of the lower limbs disclosing cutaneous vasculitis. Notice the respect of the dorsum of the feet related to the shoe pressure of the patient.



Fig. 3. Association of different lesions in a same patient simultaneously: purpuric macules, papules and necrotic lesions (known as "trisymptôme de Gougerot").

temperature varies. It may be isolated or associated with other symptoms, especially nodules and necrosis.

Necrotic lesions are the final event of

previous cutaneous lesions, resulting from the occlusion of dermal vessels. Its extension and depth are highly variable depending on extension and depth

of involved vessels. Localized necrotic lesions lead to vesicles, then to pustules due to secondary infection. When necrosis is extensive, painful purpura is followed by a black necrotic plaque with active purpuric border and bullous lesions. After removal of necrotic tissue, ulcerations of various sizes take place. Ulceration/ulcer is the final step of necrosis.

Non-follicular pustules (pustular vasculitis) with a purpuric rim may be the manifestation of small vessel vasculitis, especially during Behçet's disease or inflammatory diseases of the bowel (Fig. 4) (2). Other frequently observed pustules may result from secondary infection of necrotic lesions.

Recently, a new entity was described as "macular arteritis" characterized by *asymptomatic hyperpigmented macules* with a chronic and indolent course. Pathology discloses lymphocytic arteritis at various stages of evolution ranging from fibrinoid necrosis to endarteritis obliterans (7-9).

Other skin manifestations associated with systemic vasculitis

Extravascular necrotizing granuloma

Initially described by Churg and Strauss in 1951 as a manifestation of allergic angiitis (Churg-Strauss syndrome), the extravascular granuloma has been further reported in a large variety of other systemic vasculitis and connective tissue diseases (Winkelman). Papular or nodular lesions vary in size, from 2 mm to 2 cm or more, and colour, from red to purple. Central crusting and/or ulceration are frequent. Rarely, other aspects are reported like vesicles, pustules, arciform plaques or firm mass. Sites of involvement are the extensor aspects of the elbows, the fingers where they are usually multiple, often symmetrical, and less frequently the buttocks, the scalp, the knees, the hands, the dorsum of feet, the neck, the forehead, the ears.

Histological features include endothelial necrosis and oedema, fibrinoid necrosis of the collagen and granulomas containing eosinophils, histiocytes and lymphocytes. The center of the granuloma consists of basophilic fibrillar necrosis in which bands (some-

times linear) of destroyed tissue are interspersed with poly-morpho-nuclear leukocytes and leukocytoclastic debris. This necrotic area is surrounded by a granulomatous mass of histiocytes, often in a palisade array. Decrease or absence of elastic fibers is observed in foci of degenerated collagen. No relationship is noted between the clinical appearance of lesions, the histological features and the associated systemic disease. However, tissue eosinophilia is more frequently reported in patients with Churg-Strauss syndrome (2).

Panniculitis

Cutaneous eruption consists of recurrent crops of erythematous, oedematous and tender subcutaneous nodules. The nodule size is around 1 or 2 cm but could be much larger. In lobular panniculitis, lesions are usually of symmetrical distribution on the thighs and the lower legs. They usually regress spontaneously with hypo-pigmented and atrophic scar due to fat necrosis. Occasionally, they may suppurate. In septal panniculitis, nodular lesions are primarily located over the extensor aspects of the lower limbs. They regress spontaneously without atrophic scar. A lobular infiltrate of lymphocytes, plasma cells and histiocytes with fat necrosis is common in lobular panniculitis while in septal panniculitis the infiltrate surrounds vessels of the septa.

Pyoderma gangrenosum

Pyoderma gangrenosum lesions usually begin as deep-seated, painful nodules or as superficial hemorrhagic pustules, either de novo or after minimal trauma. They further break down and ulcerate discharging a purulent and hemorrhagic exudate. Ulcers reach 10 cm or more, spread, partially regress or remain indolent for a long period. The irregular edges are raised, red or purplish, undermined, soggy and often perforated. The most commonly affected sites are the lower extremities, the buttocks and the abdomen but other areas of the body may be involved. Lesions are usually solitary, but may arise in clusters which then coalesce to form polycyclic irregular ulcerations. When healing occurs, an atrophic and often cribriform

scar is left. The histological features consist of a large, sterile abscess in which thrombosis of small- and medium-sized vessels, haemorrhage and necrosis are present. Polymorph neutrophils are numerous but epithelioid, giant and moonuclear cells are also seen especially in more chronic forms. Leukocytoclastic or lymphocytic vasculitis may be observed, particularly in the active border of the lesion. These changes are not pathognomonic and the diagnosis is essentially based on the clinical aspects.

Granuloma

Granulomatous lesions with neither vasculitis nor central necrosis may be observed in systemic vasculitis, especially WG. Clinical aspect is highly variable ranging from papules, nodules, subcutaneous infiltration, pseudo-tumour to chronic ulcers. Any site of the body may be involved: breasts, scrotum, face, gums, etc. Other granulomatous diseases have to be considered in the differential diagnosis like sarcoidosis, metastatic Crohn's disease, mycobacterium infections and foreign bodies granulomas.

Superficial thrombophlebitis

Thrombophlebitis of a superficial vein is sometimes clinically evident due to the presence of painful induration of the vein with redness and increased heat. In other cases, the clinical aspect is a non-specific red nodule and diagnosis is only confirmed by histological examination of a deep skin biopsy. Such lesions are essentially observed in thromboangiitis obliterans, Behçet's disease, Crohn's disease and relapsing polychondritis.

Gangrene

Gangrene resulting from arterial occlusion may be observed in all vasculitis involving medium or large-sized arteries. It is initially characterized by a sharply demarcated blue black colour of the extremities. The main differential diagnoses are thrombosis without inflammation of the vessel walls and emboli. Angiography visualizes occlusion or stenosis of arteries and does not help distinguishing these different

pathologic processes. The presence of other skin lesions with histologically proven vasculitis is in favour of vasculitis although thrombosis, vasculitis and emboli may be concomitant as in atheromatous emboli.

Raynaud's phenomenon

Bilateral Raynaud's phenomenon may occur in 5 to 30% of randomly questioned population. It is classically associated with all types of vasculitis. However, its prevalence is unknown in many vasculitis and its diagnostic value is very low. In contrast, unilateral Raynaud's phenomenon suggests an obstructive arterial disease and is mainly observed in Takayasu's arteritis.

Classification

Classification of vasculitis is a real brain-teaser. Existence of overlapping clinical features, lack of knowledge regarding precise etiopathogenic process of each vasculitis, lack of "pathognomonic" clinical or laboratory or radiologic findings make almost impossible to have a perfect classification. Several classifications have been proposed, each of them presenting advantages and weaknesses. The most commonly used criteria for the classification of vasculitis are those of the American College of Rheumatology (ACR) criteria established in 1990 (10) and the Chapel Hill Consensus Conference (CHCC) in 1992 (11). A "classical" example taken by authors to show the weakness of the ACR criteria and the CHCC is the PAN / MPA distinction. Indeed, the ACR classification recognizes only polyarteritis nodosa as a medium-sized vessel vasculitis that could affect also small vessel too. Conversely, the CHCC definitions – based on pathological considerations – exclude small vessel involvement in PAN. Consequently, any patient with PAN and purpura will be considered as having MPA or another small vessel vasculitis (6). Classification criteria should be restricted to their primary use, *i.e.* stratify uniform populations who carry a diagnosis. In clinical practice, a final diagnosis should rely on the interpretation of clinical, laboratory, radiologic and pathological findings.



Fig. 4. Pseudo-folliculitis related to pustular vasculitis.

Table II. Approach to the diagnosis of isolated, biopsy-proven, cutaneous vasculitis.

ESTABLISH THE SEVERITY : SYSTEMIC INVOLVEMENT ?

Complete physical examination

- General manifestations : fever, night sweats, weight loss
- Joint (arthralgias), muscles (myalgias), lung (hemoptysis, cough, shortness of breath, wheezing), heart (chest pain, murmur) gastrointestinal tract (abdominal pain, gastro-intestinal bleeding), ear, nose, throat (sinusitis, rhinitis) and ocular symptoms (scleritis, sicca syndrome), peripheral (paresthesia, numbness) and central (cephalgia, seizures) nervous system, urologic and genital symptoms (hematuria, testicular pain)

Laboratory studies

- Kidney function every 3 months : urinalysis, proteinuria, blood urea/creatinine
- Electrocardiography
- Chest x-ray

IDENTIFY A POTENTIAL CAUSE

Recently introduced drug ?

Laboratory studies recommended in the absence of clinical relevant symptoms

- Blood cell count, C-reactive protein, erythrocyte sedimentation rate
- Serum electrophoresis
- Liver tests: transaminases, hepatitis B and C virus serologies
- Cryoglobulins
- Antinuclear antibodies, anti-dsDNA, anti-extractable nuclear antigens (Ro/Ssa, La/SSb, RNP, Sm...), rheumatoid factors
- Antineutrophils cytoplasmic antibodies (ANCA)
- Complement levels (CH50, C3, C4)
- Anti-streptolysin O titers

Complementary exams according to medical history and clinical findings

- HIV test
- Blood culture
- Lumbar puncture
- Echocardiography
- Viral serologies (parvovirus B19, Epstein Barr virus, CMV...) proposed in case of pregnancy or in immunocompromised hosts
- Sinus CT scan and teeth examination

Approach to the diagnosis of cutaneous vasculitis

The first step being completed - having proved by a skin biopsy the presence of cutaneous vasculitis and analyzed his precise subtype (cell infiltration, size of the involved vessel, DIF) - the physician collect all the relevant data that will help him 1) to establish the severity of the CV by the absence or the presence of systemic involvement that will

prompt to initiate immunosuppressive treatment and 2) to identify a potential curable cause (Table II). The precise diagnosis is made by the combination of clinical history, clinical, laboratory and radiologic findings. Therefore, patients precise past medical data, history of the disease including newly introduced drugs or episode evocative for acute infection, are mandatory. Indeed, any cutaneous vasculitis occurring in a

patient with a known systemic vasculitis should prompt to look after intercurrent triggering factor like infection or a newly introduced drug before diagnosis of flare-up the disease. Full physical examination will include search for: fever, weight loss, night sweat, arthralgias, myalgias, hemoptysis, cough, shortness of breath, wheezing, murmur, chest pain, sicca syndrome, photosensitivity, eye or ear symptoms, sinusitis, numbness, paresthesia, abdominal pain, gastro-intestinal bleeding, hematuria and testicular pain (1, 6). A certain number of complementary examinations are compulsory like urinalysis, proteinuria, blood urea/creatinine, chest x-ray and electrocardiography. Urinalysis and proteinuria should be performed from a weekly to a monthly basis during at least 3 months. In the absence of clinical relevant symptoms that allow to suspect a precise diagnosis, authors recommend the following laboratory studies: blood cell count, C-reactive protein, ESR, liver tests, cryoglobulins, antinuclear antibodies, anti-dsDNA, anti-extractable nuclear antigens (Ro/Ssa, La/SSb, RNP, Sm), rheumatoid factors, antineutrophils cytoplasmic antibodies (ANCA), complement levels (CH50, C3, C4), anti-streptolysin O titers. According to clinical findings, HIV test, blood culture, echocardiography and/or lumbar puncture will be performed. For some authors, viral serologies like parvovirus B19, Epstein Barr virus, CMV should be systematic but we do not recommend this attitude as no therapy will be proposed except in case of pregnancy or in immunocompromised hosts. Sinus CT scan and teeth examination can be suggested in the absence of any found cause. Physicians should not loose from sight and warn the patients that in 50% of all cases of cutaneous vasculitis, no specific cause is found (12).

Small vessel vasculitis

Cutaneous leukocytoclastic angiitis (CLA)

CLA, as defined by CCHC in 1992 in replacement of the former hypersensitivity vasculitis, is characterized by an isolated cutaneous vasculitis affecting the small vessels (mainly post-capillary

venules) without any systemic involvement. Diagnosis of CLA is therefore a diagnosis of exclusion. Patients usually present with a crop of lesions (infiltrated purpura, papules, vesicles, urticaria) affecting the declive areas, tight-fitting clothes and trauma sites. Arthralgias may be present and should not rule out the diagnosis. Biopsy will show a neutrophilic infiltrate affecting small vessels with fibrinoid necrosis. Lesions resolve spontaneously within weeks or months and episode remain isolated. In most cases, no cause is detected. Approximately 10% of the patient will experience chronic evolution (6). However, systemic disease (HSP, WG, MPA) may disclose initially CLA presentation before renal vasculitis occurs (13). This confirms the outmost importance of proteinuria and urinalysis several months after the disease. Of note, a specific condition was recently described under various names (Golfer's vasculitis and exercise induced vasculitis) in healthy individuals, mostly women, who developed cutaneous vasculitis after prolonged exercise during hot weather without any systemic involvement (14-18).

Urticarial vasculitis (UV)

UV is a rare, chronic, and unpredictable condition, that affect 5 to 10% of the patients with chronic urticaria. In most cases, UV remains idiopathic. Nonetheless, it may be associated with connective tissue diseases (mainly Sjögren's syndrome, systemic lupus erythematosus), mixed cryoglobulinemia, hepatitis C infection, drugs, viral infection, monoclonal gammopathy (Schnitzler's syndrome) and malignancies (Fig. 5). Distinguishing the hypocomplementemic form of UV (HUV), noted in 20-30% of the cases, from normocomplementemic UV (NUV) is useful. NUV (70-80% of the UV) is idiopathic, restricted to the skin and self resolving. HUV is more often associated with connective tissue diseases. HUV syndrome is characterized by lupus-like manifestations (arthralgias, arthritis, uveitis, scleritis, glomerulonephritis and obstructive lung disease) and circulating anti-C1q antibodies. Serum levels of C1q, C3 and C4 are variable.

ESR may be elevated and antinuclear antibodies may be positive (6, 19).

Histology of UV usually shows a sparse neutrophilic infiltrate with focal small vessel neutrophilic vasculitis or perivascular nuclear debris, fibrin deposits, with or without red blood cells in the superficial dermis. HUV display sparse interstitial and perivascular neutrophilic infiltrate while eosinophils are more common during NUV. C3 deposits with or without immunoglobulin IgM are seen on DIF. DIF and a lupus band test (basement membrane deposits of C3 and/or immunoglobulins) are more frequently seen during HUV (2).

Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP, also known as anaphylactoid purpura, allergic purpura and haemorrhagic capillary toxicosis) is a small vessel vasculitis associated with IgA-immune deposits representing approximately 10% of all cases of cutaneous vasculitis (2). HSP mainly affects young boys aged from 4 to 8 years old with a seasonal winter predominance following an acute upper respiratory tract infection in half of the cases. Initially described as the combination of palpable purpura, arthritis, gastro-intestinal involvement and glomerulonephritis, HSP was then defined by CHCC according to IgA vascular deposits (11). However, the latter are neither sensitive nor specific of HSP. They may be found in other various conditions such as cryoglobulinemia, livedoid vasculitis and other vasculitis. The skin is always affected. Its presentation and histology are undistinguishable from CLA (Fig. 6) (2). Lesions occur in successive waves then resolve spontaneously.

The biopsy of an early lesion shows a small vessel neutrophilic vasculitis of the superficial and mid dermis. In the later stages, mononuclear cells may predominate. In fresh lesions, DIF may show IgA and C3 deposits. Joint involvement with arthritis, abdominal pain, gastro-intestinal bleeding and mesangial glomerulonephritis are other features that increase the likelihood of such diagnosis. A long-term follow-up for children and adult is mandatory as they may develop later on a chronic renal failure

especially in case of preexisting nephrotic syndrome, hypertension, renal failure in children, fever, purpura affecting the trunk and elevated ESR (20).

Infantile acute haemorrhagic oedema is characterized by the following features: febrile onset in children younger than 2 years of age; oedema of the scalp, hands, feet and peri-orbital tissue preceding purpura; lack of renal and gastrointestinal involvement. Recovery is expected within 3 weeks. Oedema probably results from an increased capillary permeability due to an underlying vasculitis. This entity is considered by some as a distinct clinical entity, especially for its better prognosis, and believed by others to be a variant of HSP.

Essential cryoglobulinemic vasculitis (21-26)

Cryoglobulins are immunoglobulins that persist in the serum, precipitate with cold temperature, and resolubilize when rewarmed. Only mixed type II and III cryoglobulinemia are responsible for vasculitis. Type I cryoglobulinemia is responsible for thrombosis rather than vasculitis.

Skin manifestations occur in 60% to 100% of patients with symptomatic cryoglobulinemia. They are a frequent presenting complaint and often come along with arthralgia and weakness. The disease has a tendency to wax and wane. Women outnumber men with a sex ratio W/M of 1.3/1. The average age of onset is 50 years. The interval between the first skin manifestation and diagnosis of cryoglobulinemia varies from 0 to 10 years. Palpable purpura of the lower extremities is the main manifestation, present from 30 to 100% of the patients. The lesions may extend progressively to the abdomen. Purpura often displays seasonal triggering (winter time, cold exposure) or related to prolonged standing, physical exertion, or trauma. Purpuric lesions can first start by a preceding burning sensation and leave a brown residual pigmentation ("dermite ocre") within 10 days. Lesions are more commonly observed on the head and mucosal areas (ears, nose, mouth) in type I cryoglobulinemia. Post-inflammatory pigmentation is noted in 40% of patients



Fig. 5. Urticarial vasculitis.



Fig. 6. Purpuric lesions of the buttocks during Henoch-Schölein purpura.

and can retrospectively evoke the diagnosis. Infarction, haemorrhagic crusts and ulcers are present in 10 to 25% of patients. Widespread necrotic areas, head and mucosal involvement, livedoid vasculitis, Raynaud's phenom-

enon and cold induced acrocyanosis are relatively more common in type I cryoglobulinemia. Mixed cryoglobulinemia is more often responsible for urticaria or purpura (25). On histology, purpura corresponds to a leukocyto-

clastic vasculitis of the small dermal vessels. DIF studies have shown IgM, IgG, and C3 deposits in some patients with acute vasculitis. In type I cryoglobulinemia, thrombosis is the main histological feature, sometimes associated with vasculitis. Globally, the clinical and histological aspects of purpura are not different whether HCV infection is present or not.

Drug-induced vasculitis (27-30)

Approximately 15 to 20% of the cutaneous vasculitis may be induced by drug intake (2). Time schedule is highly variable after drug intake, ranging from hours to years. Drugs from almost every class may be implicated in sporadic cases of vasculitis (27), but some pharmaceutical classes are more frequent: propylthiouracil, hydralazine, colony-stimulating factors, allopurinol, cefaclor, minocycline, D-penicillamine, phenytoin, isotretinoin, and methotrexate (27). Moreover, chemicals, food, vitamins, nutritional supplements may also cause vasculitis. There is no specific clinical or laboratory pattern. Of note, a specific subset of cases of CV associated with ANCA was separated (28) and recently used anti-tumor necrosis factor alpha may also be responsible for cutaneous vasculitis (29). Vasculitis usually occurs after drug dosage increases and after rechallenge with the culprit drug. Drug-induced vasculitis may be restricted to the skin or at worse be life threatening in case of multiple organ systems involvement. Death rate of drug induced vasculitis is estimated to 10% (30). Drug-induced vasculitis is considered as an exclusion diagnosis. However, we suggest that a newly introduced drug should be always looked after any flare up of CV, even if the patient has already an identified cause (primary vasculitis, CTD).

Infection-induced vasculitis (31, 32)

All microorganisms (virus, bacteria, fungi, parasites) may be responsible for cutaneous vasculitis, especially in case of a subacute or chronic infection. Twenty percent of cutaneous vasculitis are related to an infection. Hepatitis B and C are known cause of PAN and cryoglobulinemia.

In *septic vasculitis*, dermatologic lesions occur abruptly in a context of septicaemia secondary to bacterial infection such as *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus* and *Candida*. They are characterized by pustular purpura, vesicles, blisters and erythematous macules with small pustules of the extremities. Histology displays occlusive luminal thrombi of platelets, blood cells, fibrins and neutrophils, less nuclear debris, deep dermal and arteriolar involvement, hemorrhage, subepidermal and intraepidermal pustules with necrosis. Micro-organisms are rarely seen with Gram staining.

Malignancy-induced vasculitis (33-38)

Cutaneous vasculitis is rarely associated with malignancies (less than 5% of the cases).

Blanco *et al.* found only 4 patients with an underlying malignancy in a study including 303 unselected patients with cutaneous vasculitis. Moreover, these patients displayed clinical and laboratory data suggestive of the associated disorder (33). In most of the cases, vasculitis is often the consequences of circulating monoclonal antibodies during lymphoproliferative disorders *i.e.* cryoglobulins. Thus, recently, Fain *et al.* reviewed 60 cases of vasculitis associated with malignancy with cutaneous involvement in 78% of the cases. Cutaneous leukocytoclastic was found in 45% of the cases, polyarteritis nodosa in 36.7%, WG in 6.7%, MPA in 5%, and HSP in 5%. Malignancies were hemopathies (63%) with myelodysplastic syndrome in 32% and lymphoma 30%. Solid tumors represented 37% of the cases. Synchronous diagnosis occurred in almost 40% of the cases (34). According to a small series of 15 patients with vasculitis and solid tumor, the commonest malignancies were carcinomas of urinary organs, lung, and gastrointestinal tract (35).

Some rare associations deserve to be known. Vasculitis with leukaemic cell infiltration ('leukaemia vasculitis') occurs while neoplastic cells mediate vessel injury. Patients with such lesions do have an aggressive clinical course and a poor prognosis (36). Hairy-cell leukaemia may be associated with cutaneous

vasculitis, especially with PAN (37). Concurrent malignancy during giant cell arteritis (GCA) is not a rare as observed in up to 7.4% of the cases, with solid malignancies and hematological disorders, especially myelodysplastic syndromes. Clinical features are not specific (38).

Connective tissue disease associated vasculitis

Vasculitis is an uncommon but important manifestation that may complicate CTD, mainly systemic lupus erythematosus (SLE), rheumatoid arthritis and Sjögren's syndrome (SS), but also dermatomyositis, scleroderma and polychondritis.

Systemic lupus erythematosus

Four percent of all the cutaneous vasculitis are related to systemic lupus erythematosus (SLE).

Cutaneous vasculitis is the most frequent manifestation with purpura, urticarial vasculitis and livedo reticularis. According to a recent series (39), patients with SLE related vasculitis have a higher prevalence of livedo reticularis. A characteristic feature of cutaneous vasculitis during SLE is the palmar and digital pulp infarcts as small tender purpuric macules or depressed punctated scars of the palmar surfaces and fingertips. Histology will show a small vessel neutrophilic vasculitis. Vascular deposits of IgG and/or IgM deposits with complement are seen often with basement membrane depositis on DIF in half of the patients (2, 6).

Rheumatoid vasculitis (RV) (40, 41)

RV is a rare inflammatory condition of the small- and medium-sized vessels that affects a subset of approximately 1 to 5% of the patients with established rheumatoid arthritis (RA) (40). It is defined as an exclusion diagnosis after having ruled out all other causes of vasculitis during RA (infection, drug hypersensitivity, malignancy, or other vasculitides: WG, cryoglobulinemia, PAN). The skin is the most commonly affected in 90% of the cases with focal digital infarcts with nailfold involvement appearing as dark perinungual macules (Bywaters lesions), maculopapular ery-

thema, palpable purpura, haemorrhagic blisters, ulcers, and gangrene. Petechiae and purpura occur mostly in the lower extremities and have no specific characteristics. Ulcers are usually deep, painful, with a punched-out aspect and tend to be found in the lower extremities in unusual locations, such as the dorsum of the foot or the tibia. Moreover, subcutaneous nodules, livedo reticularis, atrophie blanche, pyoderma gangrenosum and erythema elevatum diutinum have been also reported. Chen *et al.* described three different pathological patterns upon histology of cutaneous lesions of RV: i) dermal necrotizing venulitis with predominance of neutrophilic infiltrates (leucocytoclastic vasculitis) characterised clinically by purpura, haemorrhagic bullae, maculopapular erythema and erythema elevatum diutinum; ii) acute or healed arteritis at the junction of dermis and subcutis, histologically resembling cutaneous polyarteritis nodosa, in nodules, livedo reticularis and ulcerations and iii) co-existence of arteritis and dermal venulitis in subcutaneous nodules, atrophie blanche and purpura. DIF disclosed dermal small vessel wall depositions of immunoglobulin (IgM) and/or C3 (41). Cutaneous RV overlaps both the characteristics of cutaneous necrotizing venulitis and cutaneous polyarteritis nodosa. Leucocytoclastic vasculitis in RA patients does not necessarily indicate a favourable prognosis (41).

Primary Sjögren's syndrome (SS) (42)

Cutaneous vasculitis represents almost 60% of the cutaneous manifestations during SS.

Vasculitis occurs mostly in female patients at a mean age of 50 years. Symptoms are non-specific (palpable purpura, urticarial lesions, erythematous maculopapules). Vasculitis is often, but not always, related to circulating cryoglobulin. Small-sized vessels (leucocytoclastic vasculitis) are mainly affected, while medium-sized vessel vasculitis are uncommon. Compared with SS patients without vasculitis, patients with cutaneous vasculitis had a higher prevalence of articular involvement, peripheral neuropathy, Raynaud's phenomenon, renal involvement, and im-

munologic features of SS. Severity of the vasculitis is directly correlated with circulating cryoglobulins. CV during primary Sjögren's syndrome may be associated with lymphoma.

Behçet's disease (40-42)

In 1937, a Turkish dermatologist, Hulusi Behçet, described an entity associating oral aphthosis, genital aphthosis and ocular inflammation. Since then, various other manifestations have been related to this disease, known as Behçet's disease (BD). Skin lesions are frequent and helpful for the diagnosis. This entity is unique as it may involve any blood vessel from aorta to capillary veins.

Complex aphthosis is the mucosal hallmark of this disease. Oral aphthae occur as the first manifestation in 25 to 75% of cases. They are usually undistinguishable from ordinary aphthae. They form a 1 to 3 cm, painful ulceration of variable depth with a yellow fibrinous base surrounded by erythema. Patients may have single or multiples ulcers spontaneously healing in 1 to 4 weeks without scarring. Ulcers may also be herpetiform with pinpoint lesions occurring in coalescing clusters. The usual affected sites are lips, gums, cheeks and tongue and less frequently pharynx and palate. Frequency of recurrences is highly variable. In the diagnostic criteria of the International Study Group on Behçet's disease, at least three recurrences per year are required. Pathologic features are usually non-specific with rarely a lymphocytic or leukocytoclastic vasculitis. Genital aphthae are present in 60 to 80% of cases. They are similar to oral aphthae but do not usually recur as often. In men, they are mainly localized on the scrotum with a permanent residual scar, more rarely on the sheath or the meatus. In women, vulva is predominantly involved; aphthae resolve without scar. Ocular or perineal aphthae are rarely reported.

Pseudo-folliculitis is the most frequent skin lesion, observed in 39 to 60% of cases (Fig. 4). It presents as non-follicular erythematous papules that become pustular, then secondly resolve or ulcerate. They are mainly located on the trunk, the lower limbs, the buttocks and the genitalia but may occur on other parts of the body like palms and soles.

On histology, there is an amicrobial neutrophilic infiltration with a lymphocytic infiltrate and an inconstant leukocytoclastic vasculitis. Non-bacterial folliculitis can be histologically undistinguishable from a bacterial folliculitis.

Cutaneous aphthae are less frequent, mainly observed in folds.

Nodules are present in 30 to 50% of cases, sometimes resembling erythema nodosum, on the anterior aspects of lower limbs. Histology shows a septal or lobular infiltration of hypodermis consisting of lymphocytes, histiocytes and neutrophils. Rarely a lymphocytic or a leukocytoclastic vasculitis is described. These nodules correspond sometimes to a superficial thrombophlebitis.

In a few patients, tender erythematous papules and plaques resembling those of Sweet's disease may be present on the face and neck. Pyoderma gangrenosum-like lesions have also been reported in some cases. The association with gastrointestinal involvement raises the difficult problem of the differential diagnosis with inflammatory enterocolitis. Other manifestations have been occasionally described: livedo reticularis, purpuric lesions, erythema multiforme-like lesions.

The pathergy test is an induced cutaneous reaction resembling pseudo-folliculitis. When the skin is pricked by a needle or injected with saline, an erythematous papule or pustule develops within 24 to 48 hours. Pathergy is a characteristic response in Turkish, Israeli, French and Japanese patients but is uncommon in North American and British patients. The use of needles of large diameter with a blunt point seems to increase the sensitivity of this test. On histology, a lymphocytic and neutrophilic dermal infiltration has been observed in the first 24 hours. Vasculitis is rare. Immunoglobulin and/or complement deposits in vessels wall may be obvious using DIF techniques. Of note, positive pathergy is not pathognomonic of BD, as 8% of the patients with inflammatory bowel disease may present such positive reaction (46). On a physio-pathological point of view, BAFF and its signalling in B cells were shown to be implicated in the development of skin disease in patients with BD (46).

Churg-Strauss syndrome

In 1951, Churg and Strauss defined allergic granulomatosis as a distinct entity occurring in asthmatic adults and associated with fever, eosinophilia, systemic vasculitis and extra-vascular granulomas.

Skin lesions have been observed in 40 to 75% of cases depending on series. They are rarely the presenting symptom (6%) (48, 49). Palpable purpura, petechia, ecchymoses, hemorrhagic bullae on lower extremities is the most frequent cutaneous manifestation (50%). Cutaneous nodules (30%) or papules are also very frequent, sometimes with an urticarial appearance, located on the lower limbs or on the extensor side of the elbows, fingers, scalp and/or breast (Fig. 7). Lesions of the fingers are usually multiple, often symmetrical, and most commonly localized at both lateral sides of the distal interphalangeal joint. These nodules or papules of the upper limbs have frequently central crusting or ulceration. Their consistence is usually firm. A pustular or vesicular component is rarely noted. Various other dermatologic lesions have been reported: maculo-papules resembling erythema multiforme, ulcerations, livedo reticularis, patchy and migratory urticarial rash, nail fold infarction with splinter haemorrhages, and facial oedema (49).

Histologically, three distinct patterns that can be associated on a biopsy are noted during CSS: i) a small vessel eosinophil rich neutrophilic vasculitis of the superficial and mid dermis and eosinophilic rich neutrophilic muscular vessel vasculitis, ii), dermal eosinophilia and iii) palisading neutrophilic and granulomatous inflammation with degenerated collagen bundles (so called "red" granulomas). Nodules correspond to granulomatous vasculitis, or necrotizing vasculitis of arterioles of the deep dermis or hypodermis (similar to those observed in PAN) or to extra-vascular granuloma. In fact extra-vascular granuloma correlates, in the majority of patients, with papules and nodules on the extensor aspects of the elbows. Finally, histological findings of skin lesions can be disappointing, typical granuloma and eosinophilia not being detected in

more than half of patients. Skin lesions rapidly respond to systemic corticosteroids and eosinophilia may be absent. DIF is negative.

Microscopic polyangiitis (50, 51)

The microscopic form of PAN, now called microscopic polyangiitis (MPA), is defined as a systemic vasculitis of small-sized vessels (*i.e.* capillaries, venules or arterioles) without extravascular granuloma. MPA is associated with segmental necrotizing glomerulonephritis and anti-neutrophil cytoplasm antibodies of the myeloperoxidase type.

Dermatologic manifestations occur in 25 to 60% of patients (50). Purpuric lesions of the lower limbs are the most frequent. Other lesions have been reported such as erythematous macules, vesicles, bullae, splinter haemorrhages, annular purpura, nodules, palmar erythema, erythema elevatum diutinum, oral ulcers, facial oedema and pyoderma gangrenosum-like lesion. Leukocytoclastic vasculitis of the small vessels of the dermis is usually observed. Sometimes, arterioles or smaller vessels of the deep dermis and subcutaneous fat are also involved, explaining the nodular appearance of skin lesions. DIF is usually negative but the presence of vascular deposits of immunoglobulins and complement does not exclude the diagnosis. Of note, neither the cutaneous manifestations, or the skin histological studies contribute to the distinction between PAN and MPA (51).

Wegener's granulomatosis (52-58)

Wegener's granulomatosis (WG) is characterized by granulomatous necrotizing inflammatory lesions of the upper and lower respiratory tractus, usually accompanied by rapidly progressing glomerulonephritis.

Skin lesions occur in 14 to 77% of cases depending on series (52, 53). They are inaugural in about 10% of cases and are exceptionally isolated as the presenting symptom (54). Palpable purpura of the lower extremities is undoubtedly the most frequently observed. Necrotic papules of the extensor aspects of the limbs are less frequent but more suggestive of WG. Facial involvement has been reported and would be more sug-

gestive of WG than other vasculitides (55). Skin features are exceptionally similar to erythema elevatum diutinum with IgA paraproteinemia (56). Nodules are quite frequent, mainly localized on the limbs. Extensive and painful cutaneous ulcerations may precede by weeks to years other systemic manifestations. These ulcers are sometimes described as "pyoderma gangrenosum-like lesions", especially when they follow a localized traumatism or the breakdown of painful nodules or pustules. However, they usually lack the typical raised, tender, undermined border of pyoderma gangrenosum. Sometimes numerous, they are located on the limbs, the trunk, the face (pre-auricular area), the breasts (mimicking adeno-carcinoma with possible nipple retraction and galactorrhea) and the perineum. Digital gangrene are occasionally reported. Florid xanthelasma is associated with longstanding granulomatous orbital and periorbital infiltration. In contrast to PAN, livedo reticularis is unusual in WG.

Frequency of oral manifestations is difficult to estimate from literature series since they are often included in ear-nose-throat symptoms and not described separately. Oral ulcers are sometimes reported independently of other oral manifestations. They are undoubtedly frequent, present in 10% to 50% of cases depending on series. Unlike aphthae, they are persistent and not recurrent. Their number and localization are highly variable. Hyperplastic gingivitis is usually not mentioned in the largest series. However well-documented case-reports have been published. Gingival changes include a granular aspect and red to purple colour with many petechiae (Fig. 8). The entire peri-odontium and gingival mucosa may be involved resulting in tooth mobility and loss of teeth or palate ulceration (Fig. 9). Significant but incomplete improvement is observed with empiric antimicrobial therapy. Genital ulcers are uncommon although penile necrosis has previously been described.

As usual, purpuric papules correspond to leukocytoclastic vasculitis of small vessels; necrotic and purpuric lesions could result from necrotizing vasculitis

of superficial and/or deep dermal and subcutaneous vessels. Others lesions are more frequently associated with granulomatous inflammation. Papules or papulonecrotic lesions correspond to leukocytoclastic or granulomatous vasculitis of small vessels or extra-vascular granuloma. Nodules correspond to necrotizing or granulomatous vasculitis of medium-sized arterioles or extra-vascular granuloma. All these lesions may lead to ulceration with a secondary mixed inflammatory pattern. Pathologic findings of oral ulcerations are often non-specific showing acute and chronic inflammation. In other cases, a granulomatous infiltration is present. Gingival hyperplasia corresponds to a chronic histiocytic inflammation with inconstant vasculitis, necrosis and giant cells infiltrate. Pseudo-epitheliomatous hyperplasia and micro-abscesses with polymorpho-nuclear leukocytes and eosinophils are occasionally encountered.

Except xanthelasma, all clinical or histological types of skin lesions are associated with active systemic disease. They disappear in few weeks or months after treatment onset and are reported in about 50% of relapses. Cutaneous WG vasculitis is associated with an active, rapidly progressive diseases compared to patients without cutaneous vasculitis and with granulomatous lesions (57).

Since 1966, limited and sub-acute forms of WG have been individualized without kidney involvement. In our experience, the most frequently observed skin lesions in these forms are nodules with granulomatous infiltration or granulomatous vasculitis on histology (58). DIF of skin lesions may reveal IgM and complement deposits.

Polyarteritis nodosa (PAN)

According to the names and definitions of vasculitis adopted by the Chapel Hill consensus conference on the nomenclature of systemic vasculitis, classic polyarteritis nodosa (PAN) is characterized by a necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.

Systemic PAN is actually very rare; its evolution is acute with skin manifestations different of those observed in cutaneous PAN which is a chronic disease.



Fig. 7. Granulomatous lesions during Churg-Strauss vasculitis.

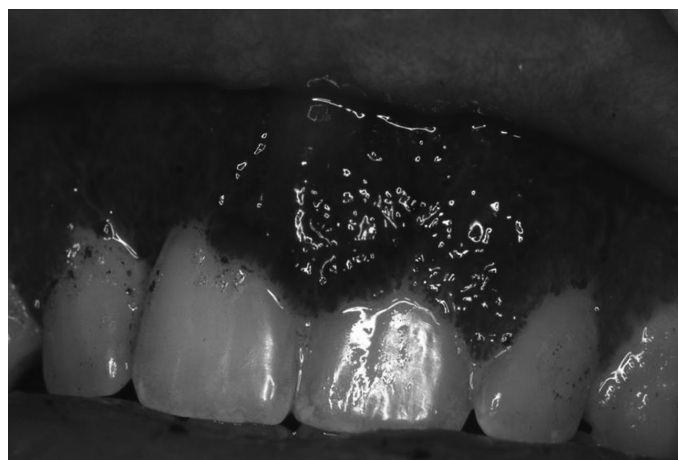


Fig. 8. Gingival hyperplasia during Wegener's granulomatosis.

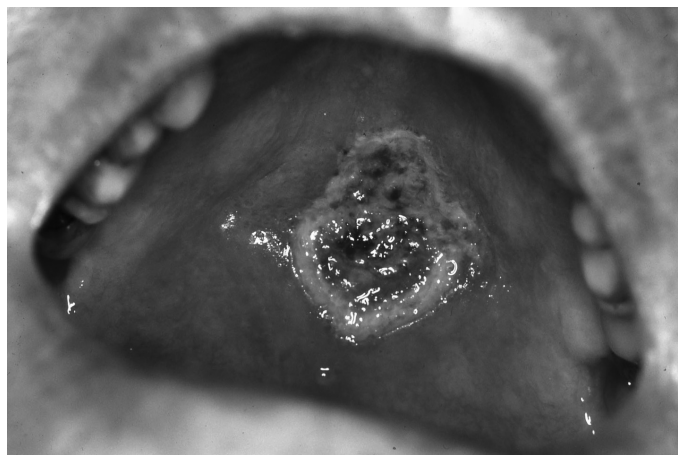


Fig. 9. Palate ulceration during Wegener's granulomatosis.

The skin hallmarks of cutaneous PAN are nodules. These cutaneous or subcutaneous nodules are the first sign of the disease and appear in groups along the course of superficial arteries. They measure between 5 and 25 mm in diameter and are mainly located on the lower legs, especially around the knees

and on the feet. Arms, trunk, head, and buttocks also can be involved. The number of nodules is highly variable according to each flare and display a course ranging from a few days to more than 2 months. Nodules may leave a violaceous livedoid colour or pigmentation that persist for months to

Fig. 10. Cutaneous nodules during polyarteritis nodosa.

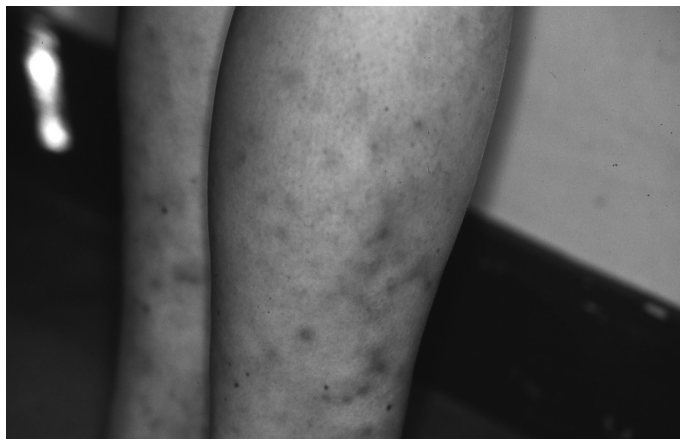


Fig. 11. Chronic painful fibrinous ulcerations during cutaneous polyarteritis nodosa. (Notice the “atrophie blanche” lesions around the ulcerations).



years (Fig. 10). Livedo reticularis may precede come along or follow the onset of nodules. In PAN, livedo reticularis is typically suspended, located on the lower limbs, the dorsal aspects of upper limbs and rarely the trunk. The fishnet reticular pattern is irregular with broken meshes. On careful examination, infiltrated areas of the fishnet pattern are found. Painful ulcerations are frequently associated with tender and firm plaques resulting from coalescent nodules (Fig. 11). Lastly, some patients may present atrophic, ivory-coloured, stellate-shaped scars (atrophie blanche) (59). These clinical features are characteristic of cutaneous PAN which, by definition, only affects small arteries of the skin. A full-thickness excision of an active inflammatory nodule will show a necrotizing arteritis with variable amounts of fibrinoid necrosis and leukocytoclasia, edema, and inflammatory cells (Fig. 12). Focal panniculitis

surrounding the involved artery is characteristic, in contrast with the more diffuse panniculitis usually found in other nodular diseases. Presence of eosinophil among the infiltrate should not rule out the diagnosis. Evolved nodules may only show reparative signs in the panniculus and mild chronic inflammation and fibrosis of the artery wall. Therefore, old lesions should not be biopsied. DIF may show non-specific immunoglobulins IgM and complement deposits (60). For some authors, the recently described “macular arteritis” may be a form of latent cutaneous PAN (7, 8).

These chronic, benign limited cutaneous forms of periarteritis nodosa are in fact frequently associated with arthralgia and pure sensitive neuropathy. Systemic acute disease rarely occurs in the course of cutaneous PAN.

Cutaneous manifestations occurring during systemic PAN have been re-

ported with variable prevalence in the large series of the literature. This prevalence has ranged from 28% to 60% for PAN series (51). In the series of Agard *et al.* (61), skin involvement (purpura, nodules) was the first presenting sign in 11% of their patients with PAN. They are less frequently observed in patients older than 65 years. We found in our recent series of patients with systemic PAN that the most frequent skin lesions observed were palpable purpura (19%), livedo (17%) and nodules (15%) (51). Although this systemic disease mainly affects the medium-sized arteries of the kidney, liver, heart and gastrointestinal tract, the most common cutaneous finding is palpable purpura corresponding to a small vessel vasculitis. Other manifestations have been reported such as urticaria, transient erythema, superficial phlebitis, Raynaud's phenomenon, splinter haemorrhages. Localized oedema is usually associated with underlying muscular involvement.

Granulomatous vasculitis

Granulomatous vasculitis (Fig. 13) is associated with heterogeneous diseases and/or conditions, mostly represented by Takayasu's arteritis (TA) and giant cell arteritis (GCA). Other rare causes of granulomatous vasculitis include sarcoidosis, metastatic Crohn's disease, ulcerative colitis, CTD (SLE, RA), lymphoproliferative processes, hepatitis C, herpes and zoster-related vasculitis (4, 62). Their clinical aspect vary greatly ranging from papules, nodules, subcutaneous infiltration or pseudo-tumor to chronic ulcer developing at any site of the body.

Takayasu's arteritis (63-66)

TA is a rare chronic inflammatory arteriopathy of unknown origin that predominantly affects the aorta and its main branches. Two, eventually overlapping, stages of this disease have been distinguished: a first systemic non-specific inflammatory stage followed by an occlusive stage characterized by inflammation of the media and adventitial layers of the large vessels wall resulting in vascular stenosis and/or aneurysm formation.

Skin manifestations have been reported

in 2.8 to 28% of patients. Some are directly related to large vessels occlusion such as unilateral Raynaud's phenomenon, digital gangrene or unilateral digital clubbing. Other skin manifestations were frequently thought to be related to this vasculitis *i.e.* ulcerated or non-ulcerated nodules of the lower limbs, pyoderma gangrenosum, livedo reticularis, papular or papulo-necrotic lesions, superficial phlebitis, Sweet's lesions. Other manifestations are occasionally related without evident relationship with TA: urticaria, angioedema, erythema multiforme, erythematous eruptions and "dermatitis". The prevalence of these different skin lesions greatly varies from Asian to European countries. In northern America and Europe, acute or sub-acute inflammatory nodules are the most commonly observed skin lesions. Erythema induratum corresponds to ulcerated sub-acute nodular lesions. The histological features of these nodules are variable. They may correspond to granulomatous or necrotizing vasculitis of small-sized or medium-sized arterioles of the dermis or hypodermis, extra-vascular granuloma, septal or lobular panniculitis. Usually, there is no correlation between the localization of the nodules and alterations of large vessels revealed by angiography. Furthermore, these nodules can occur at any stage of the disease. Tuberculoid infiltration has been reported in biopsies from papular or papulo-necrotic lesions raising the problem of an infectious origin of the disease. These lesions mainly occur at the occlusive stage of the disease. In Japan, pyoderma gangrenosum-like lesions are frequent, especially at the occlusive stage; this type of lesions has also been reported in patients from northern Africa. The relationship between skin manifestations and TA is based on the absence of other aetiology and on the parallel course of skin lesions and vasculitis. Whatever is the stage of the disease, recurrence of skin lesions is strongly suggestive of arteritis reactivation.

Giant cell arteritis (GCA) (67-71)

GCA is a systemic vasculitis with a predilection for small- to medium-sized cranial arteries in elderly patients. It

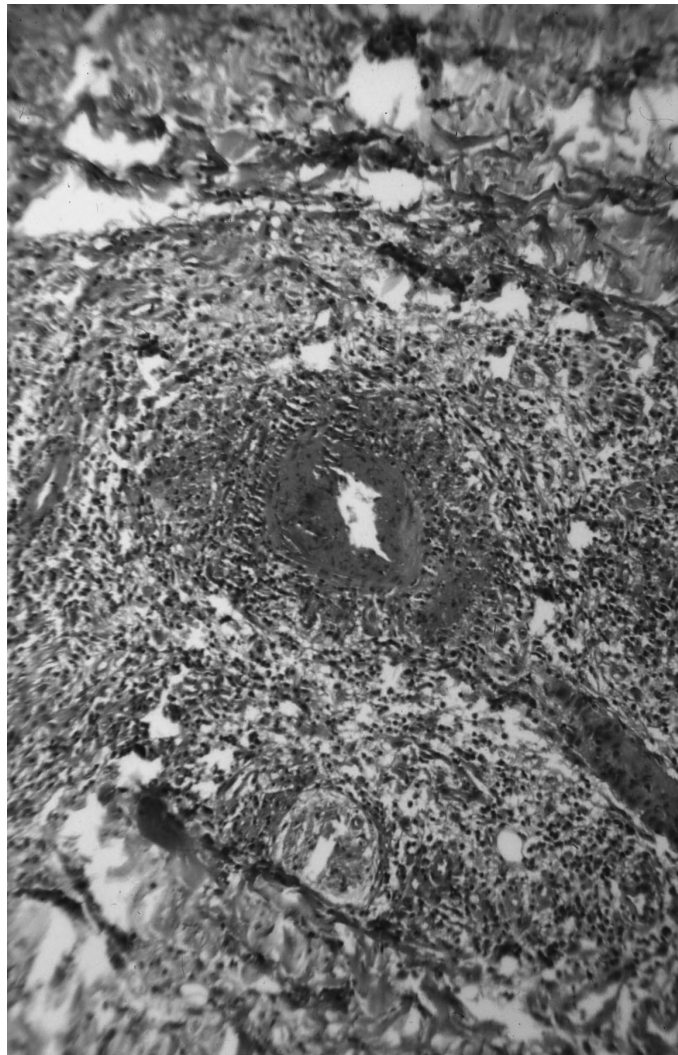


Fig. 12. Microscopic examination of a cutaneous nodule during PAN: necrotizing arteritis with fibrinoid necrosis and leukocytoclasia, edema, and inflammatory cells.

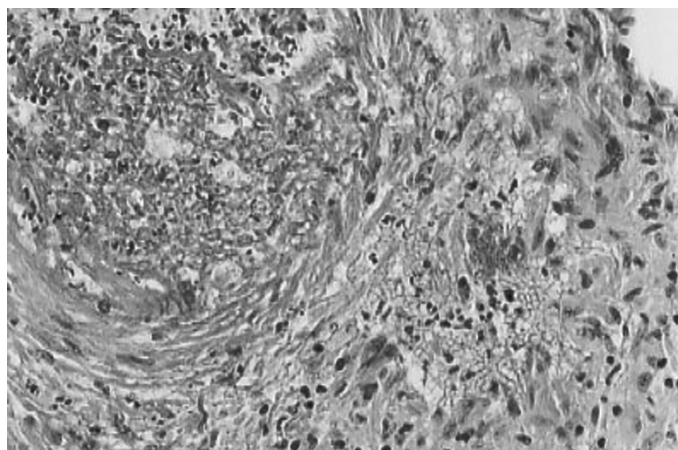


Fig. 13. Microscopic examination of granulomatous vasculitis.

represents less than 1% of all cutaneous vasculitis. Skin manifestations are often observed in the late stages of the disease. Therefore, they are actually rare due to an early diagnosis. According to a french retrospective study of 260

patients, cutaneous symptoms represent only 2% of the inaugural symptoms and they don't occur isolated (69). Classically, scalp and temples are tender and red. Tender cordlike nodules are palpable over the course of temporal, occipital

or facial arteries. Pulsations in these arteries are diminished or absent. Exceptionally, multiple scalp aneurysms have been reported.

The majority of other skin lesions are the consequence of ischemia related to cranial arteries occlusion and localized on the tongue and the scalp. Glossitis occurs in 10% of patients, and may sometimes be revealing. The tongue has a red, raw-beef colour and may become blistered, scaling or gangrenous. Necrosis usually occurs in the anterior two-thirds. Lesions may start as crusts of the scalp that misdiagnosed for herpes zoster lesions. Bullae, ulcers or massive necrosis may then affect the scalp. Patients with scalp necrosis represent a subgroup of severe GCA with older age of onset and frequent serious complications such as visual loss, gangrene of the tongue or nasal septum necrosis. The mean interval between onset of symptoms of GCA and scalp necrosis is 3.0 months. Under treatment, scalp healing is complete or satisfactory in 75% of cases. In other cases, skin grafts are possible. Less severe chronic ischemia of the scalp leads to thinning or loss of hair. Ischemic skin lesions of the neck or the cheeks are occasionally reported. Rarely, vessels of the lower limbs are involved leading to ischemic ulcerations or distal gangrene. Skin biopsy of the border of ulceration or necrotic tissue is rarely contributive since granulomatous vasculitis has been shown in only 2 of 24 biopsies from patients with scalp necrosis. Other skin manifestations have been published as case-reports: nodules of the lower limbs with granulomatous vasculitis in the hypodermis or septal panniculitis, butterfly rash with transient oedema. Senile purpura is frequent on sun-exposed skin areas in elderly patients, especially when treated with corticosteroids. However, palpable purpura of the lower limbs due to vasculitis is exceptional.

Management of cutaneous vasculitis

Management of isolated, biopsy-proven, CV without clinical manifestation in favor for systemic involvement or for a specific cause, include : i) to

look for the presence of systemic involvement (heart, lung, kidney) and ii) to identify a potential curable cause. However, complementary explorations should be orientated by clinical context (Table II). Moreover, any patient with a known underlying disease that may be responsible for CV should be asked about any new drug intake, infectious like episode and carefully examined to rule out an other potential cause of vasculitis.

In most of the cases, CV remains restricted to a single, self-limited and short-lived episode of purpura of the lower limbs without any visceral involvement and relapse. In this frequent situation, treatment is not compulsory. However, support stockings or panty hose are recommended. Aspirin or anti-inflammatory agents can be given for symptomatic relief. If the disease persists, worsen or is symptomatic (burning sensation, pain) with a restriction to the skin, various drugs can be given, usually colchicine at the dose of 1 to 2 mg/day for one month. Alternatives include dapsone titrate (25-50 mg/day) or pen-toxyphililine (400 mg, 3 times a day). Extensive, recurrent skin disease with persistent lesions, vesicles, ulcers, nodules; intractable symptoms or systemic vasculitis with other organ involvement may prompt initiation of immunosuppressive therapies such as corticosteroids, methotrexate, azathioprine, cyclosporine or cyclophosphamide (1).

Conclusion

Cutaneous lesions are frequent during the course of many systemic vasculitis. Lesions are often not specific, the most frequent being palpable purpura. Histology is mandatory to confirm the diagnosis of vasculitis to avoid delayed and inappropriate diagnosis that could lead to improper management. Cutaneous histology gave some data that may help to classify the vasculitis without determining precisely its type. An histological examination of all other skin lesions is necessary. The result of the biopsy has to be correlated to DIF data, medical history, physical examination, laboratory and radiological findings leading to the correct diagnosis and effective treatment.

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