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Cutaneous Vasculitis: Review on Diagnosis and Clinicopathologic Correlations

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Abstract

Cutaneous vasculitis is an inflammatory disease affecting the dermal blood vessel walls. The skin is a privileged organ in the setting of vasculitis since it is easily accessible for physical examination and safe biopsy, allowing an accurate characterization of inflammatory lesions. The skin is often involved. Also, cutaneous vasculitis can reflect a cutaneous component of a systemic vasculitis, a skin-limited or skin-dominant expression or variant of a systemic vasculitis, or be a single-organ vasculitis per se. Vasculitis lesions are multiple and polymorphic. They may induce a wide spectrum of clinical manifestations depending on the location and the size of the vessels involved. The depth of affected vessels is correlated with the type of cutaneous lesions. Involvement of small superficial vessels results mostly in urticarial, but relatively persistent plaques, papules, and palpable purpura. Involvement of vessels in the dermohypodermic junction or hypodermis results in ulcers, nodules, or livedo. The type of inflammatory infiltrate is also a key finding for the diagnosis of cutaneous vasculitis. Leukocytoclastic vasculitis is not a disease per se but the result of a pathophysiological process common to different causes. A better knowledge of the vascular anatomy of the skin, elementary lesions, and histological characteristics of dermatologic manifestations would allow a more relevant and more efficient diagnostic approach. We also propose a list of additional exams to be performed in front of skin lesions suggestive of vasculitis. The aim of our article is to provide an overview of elementary skin lesions and clinicopathologic correlations in cutaneous and systemic vasculitis.

Keywords Skin · Cutaneous vasculitis · Nodules · Purpura · Livedo

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Introduction

Vasculitis is a heterogeneous group of diseases characterized by the presence of inflammation of blood vessels. In 1990, the American College of Rheumatology established diagnostic criteria for seven vasculitis based on clinical, biological, and histologic findings, namely polyarteritis nodosa (PAN) [1], granulomatosis with polyangiitis (GPA) formerly named Wegener's granulomatosis [2], eosinophilic granulomatosis with polyangiitis (GEPA) formerly named Churg-Strauss syndrome [3], hypersensitivity angiitis [4], IgA vasculitis formerly named Henoch-Schönlein purpura [5], giant cell arteritis (GCA) [6], and Takayasu arteritis [7]. The first International Chapel Hill Consensus Conference (CHCC) on the Nomenclature of Systemic Vasculitides in 1994 reached consensus on names and definitions for the most common forms of vasculitis [8], with an update in 2012 to improve the previous nomenclature, change names and definitions, and add categories of vasculitis that were not included in the CHCC1994 [9]. Vasculitis may affect a wide range of tissues at the same time or during the follow-up or predominantly

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affect one organ more than the others as various expression of a systemic vasculitis. In contrast, vasculitis can be limited to a single organ and define a single-organ vasculitis. Cutaneous vasculitis reflects the inflammation of dermal blood vessels and may induce a wide spectrum of clinical manifestations depending on the location and the size of the affected vessels. Along with this line, a dermatologic addendum to the CHCC2012 was proposed in 2018 to standardize the names and definitions for cutaneous vasculitis and provide a standard framework both for clinicians [10]. The aim of our article is to provide an overview of elementary skin lesions and clinicopathologic correlations in cutaneous and systemic vasculitis.

Vascular Anatomy of the Skin

Better knowledge of the vascular anatomy of the skin is required to understand the different clinical aspects of cutaneous vasculitis (Fig. 1). The vascular system of the skin consists of two interconnected plexuses: a deep plexus and a superficial plexus. Nourishing arteries of the skin are located in the hypodermis and engage into the deep dermis where arterioles and venules communicate to form the deep vascular plexus. The deep plexus is at the dermohypodermic junction and is also called cutaneous plexus. The branches of this plexus irrigate the adipose tissue of hypodermis, the deep part of dermis, and the capillary network surrounding hair follicles, deep sebaceous glands, and sweat glands. Then, these branches pass vertically through the dermis (candelabrum-like arteries). In the superficial dermis, arterioles and venules form a second plexus, the superficial or subpapillary plexus, from which an arteriole ascends towards the most superficial part of the dermis, in front of the dermal papillae, and then descends by venules to reach the plexus. Therefore, the subpapillary plexus feeds the superficial part of the dermis and the capillary network surrounding superficial annexes. Conversely, the epidermis is not vascularized and is nourished by imbibition from the capillary networks of the dermal papillae. Such vascular anatomy is important because cutaneous inflammatory infiltrates during vasculitis are located along these vessels, as localized, regrouped and perivascular infiltrates, differentiating them histologically from diffuse inflammatory infiltrates. However, it is common not to visualize the wall of the vessels because of their destruction or the infiltrates.

In terms of classification, it is important to note that medium-sized vessels according to the CHCC nomenclature are not present in the skin. However, there are in the deep layers of the skin some vessels with a smooth muscle wall which are considered medium-sized vessels. Nevertheless, it seems more accurate to talk about small vessels and vessels with smooth muscular wall in the skin.

Finally, the cutaneous functional vascular unit is a cone-shaped zone for which the base is at the surface of the epidermis and the apex at the level of the nourishing artery at the dermohypodermic junction. This vascular anatomy explains the clinical aspect of livedo, where the obstruction of the nourishing artery leads to a venous stasis drawing the contours of the cone and assuming a reticulated aspect.

Details on Histologic Features for the Analysis of Vasculitis

Type of Inflammatory Infiltrate

The type of inflammatory infiltrate is a key finding for the diagnosis of cutaneous vasculitis.

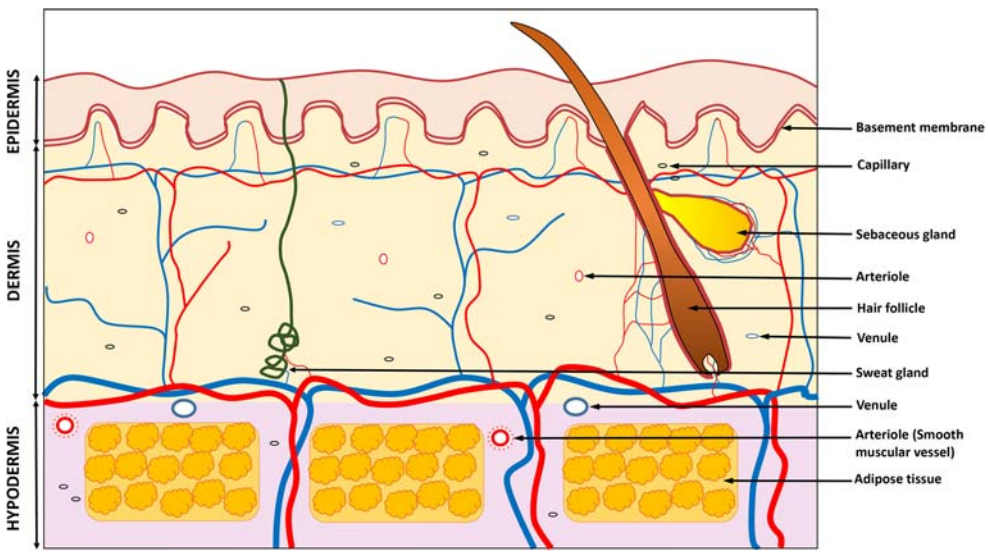

Fig. 1 Vascular anatomy of the skin

Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis is not a disease per se but the result of a pathophysiological process common to different causes. Leukocytoclastic vasculitis reflects a damage related to circulating immune complexes that are deposited in the wall of small vessels and activate the complement cascade. Cutaneous lesions related to leukocytoclastic vasculitis are mostly localized in the lower limbs due to venous stasis.

Histological differential diagnoses of leukocytoclastic vasculitis are infections and neutrophilic dermatoses. Diagnosis of neutrophilic dermatosis is based on dermal infiltrates composed of neutrophils with or without leukocytoclasia pictures. Some neutrophilic dermatoses such as pyoderma gangrenosum or Sweet's syndrome may be accompanied by foci of vasculitis as an epiphenomenon, but the density and the absence of angiocentricity of the neutrophilic infiltrate allow correct diagnosis.

Lymphocytic Vasculitis

Lymphocytic vasculitis may correspond to an evolutionary stage of leukocytoclastic vasculitis, marking the transition from an acute to a subacute stage. However, some vasculitis can be primarily lymphocytic, as seen in macular lymphocytic arteritis. True lymphocytic vasculitis must be differentiated from perivascular lymphocytic infiltrates without fibrinoid necrosis of the vessel wall.

Necrotizing Vasculitis

Necrotizing vasculitis is defined by vasculitis accompanied by fibrinoid necrosis. Tissue necrosis is called fibrinoid necrosis when it is associated with a homogeneous, eosinophilic, periodic acid-Schiff-positive extracellular substance, due to the penetration into the vascular wall and the interstitial tissue of serum proteins, like fibrin, immunoglobulins, or complement, especially when immune complexes are present. Fibrinoid necrosis may not be always visible, mainly because of the segmental or focal involvement as in PAN or the thinness of the wall of the affected vessel compared with the intensity of inflammatory infiltrates as in leukocytoclastic vasculitis.

Thrombosing Vasculopathy

During an inflammatory process, various consequences can be observed, as the extravasation of red blood cells or the secondary thromboses due to endothelial cell damage. However, thrombosing vasculopathy may also result from a primary thrombotic process causing necrosis that will secondarily induce inflammation. Also, a thrombosing vasculitis associated with a mixed or neutrophilic infiltrates should suggest an infectious origin, especially if leukocytoclasia is absent.

Granulomatous Vasculitis

Predominance of macrophages with or without giant cells characterizes granulomatous vasculitis. Granuloma may be located into the vessel wall like in GCA, or be extra-vascular like in GPA. Differential diagnoses include infectious and non-infectious disorders such as sarcoidosis, cutaneous metastasis, and Crohn's disease.

Direct Skin Immunofluorescence

Direct skin immunofluorescence may reveal immunoglobulins (IgA, IgM, IgG), complement (C3, C1q), or fibrinogen deposits within the vessel wall. All leukocytoclastic vasculitis are the consequence of immune complex deposits into the vessel wall, and therefore with positive direct immunofluorescence on skin biopsy. Nevertheless, such deposits evolve over time and the biopsy of a lesion more than 72 h old usually reveals only C3 deposits on the vascular wall. Therefore, negative direct immunofluorescence does not eliminate leukocytoclastic vasculitis. Direct immunofluorescence may be an additional feature supporting the diagnosis of IgA vasculitis in case of predominant IgA deposits into the capillary wall, though it is not specific [11]. Also, IgM deposits are not specific and are conventionally mentioned in the presence of rheumatoid factor or cryoglobulinemia [12]. Conversely, immunoglobulin deposits into the vascular wall without any evidence of vasculitis have no pathological significance.

Diagnostic Approach According to the Size of the Affected Vessels and the Elementary Lesions

Cutaneous lesions have a major interest for the diagnosis of vasculitis but they do not allow etiological diagnosis. Lesions are multiple and polymorphic, but they can provide some valuable information on the size of the affected vessels and the type of vasculitis involved. Approximately half patients with cutaneous vasculitis with dermal or hypodermic vessel involvement have systemic vasculitis [13]. Conversely, half patients with systemic vasculitis will develop cutaneous manifestations. The depth of affected vessels is correlated with the type of cutaneous lesions. Involvement of small superficial vessels results mostly in urticarial, but relatively persistent plaques, papules, and palpable purpura. Involvement of vessels in the

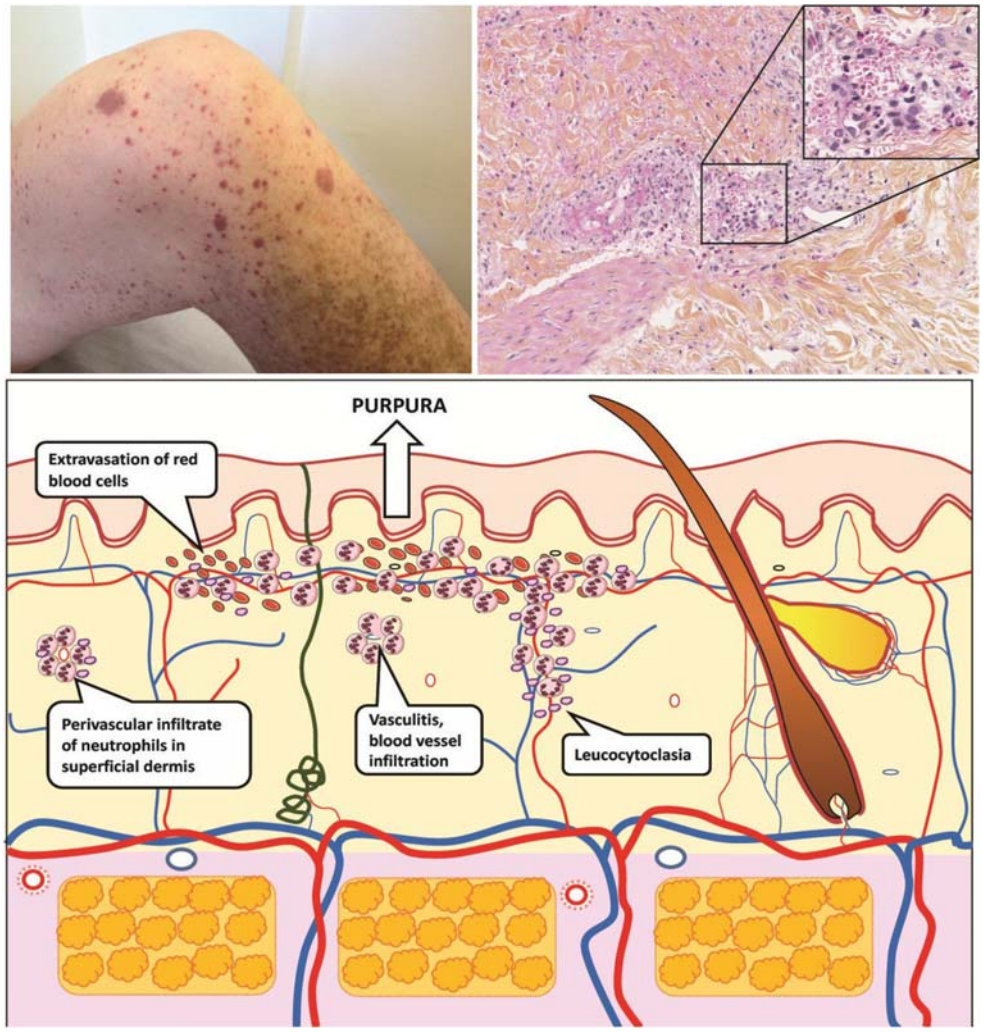

Fig. 2 Clinicopathologic correlations of nonthrombocytopenic purpura

dermohypodermic junction or hypodermis results in ulcers, nodules, or livedo [14].

Involvement of Small Vessels

Purpura

Purpura is the clinical expression of red blood cell extravasation in the dermis (Fig. 2). Purpura is not always synonymous with vasculitis related to damage of the vessel wall. Purpura may occur in the absence of inflammation of the vessel wall. A purpura not initially palpable, dark, with necrotic evolution, translates more often thrombosing vasculopathy than vasculitis (Table 1). In contrast, a palpable purpura usually reflects the presence of an inflammatory cell infiltrate [13]. Papulous or polymorphic purpura is usually the clinical expression of leukocytoclastic vasculitis. However, some vasculitis may result in nonpalpable purpura.

Nonpurpuric Papules

Within vasculitis, papules usually reflect the involvement of small-sized vessels of the dermis. Papules correspond to palpable and solid lesions measuring of less than 1 cm. Vasculitis lesion becomes palpable due to the intensity of the inflammatory infiltrate, usually within the perivascular superficial and/or deep areas. These lesions are almost always erythematous because of vasodilatation caused by the perivascular infiltrate. Also, associated edema of the dermis may be responsible by itself of the palpable lesion, as it is in urticaria, or coexist with a cellular infiltration. Papules may also reflect granulomatous lesions associated with vasculitis, especially during GPA or GEPA. In these situations, papules are erythematous or purple, located on the elbow and finger extension areas, and usually multiple and symmetrical (Fig. 3). These lesions may resemble to vesicles, nodules, or ulcerations. Histologically, there is an endothelial necrosis with an extra-vascular granulomatous

Table 1 Main causes of nonpalpable purpura and palpable purpura (adapted from [15])

Nonpalpable purpura
Bacteremia et septicemia
Purpuric and pigmentary capillaritis
Disseminated intravascular coagulation
Purpuric annular granuloma
Langerhans cell histiocytosis
Paraproteinemia (cryoglobulinemia)
Parvovirus B19 (and other viruses)
Stasis
Rickettsiosis
Talon noir
Thrombocytopenia
Drug reactions
Ecchymotic lesions (with or without petechiae)
Amyloidosis
Disseminated intravascular coagulation
Ehler Danlos syndrome
Angioimmunoblastic T cell lymphoma
Pseudohematoma
Mechanic purpura (Bateman)
Thrombotic livedo
Superficial pyoderma gangrenosum
Scurvy
Thrombocytopenia
Anticoagulant
Traumatism
Vasculitis
Palpable purpura
Vasculitis lesions
Bacteremia
Langerhans cell histiocytosis
Paraproteinemia
Rickettsia, typhus…
IgA vasculitis
Leukocytoclastic vasculitis
Granulomatous vasculitis
Nonvasculitis lesions
Angioma
Kaposi's disease
Angiokeratoma
Pyogenic granuloma

infiltrate composed of eosinophils, lymphocytes, and histiocytes, and necrobiosis of collagen bundles is usually basophilic in GPA and eosinophilic in GEPA [16].

Pustules

Pustules are caused by the detachments of the epidermis whose content is made of neutrophils (Supplementary data Fig. 1). Pustules are sometimes secondary to purpura and the intensity of the inflammatory infiltrate. Follicular or nonfollicular pustules with purpuric contour reflect small-vessel vasculitis, and are typically observed in Behcet's disease or inflammatory bowel diseases [14]. They may also occur during infectious endocarditis or gonococcemia.

Involvement of Smooth Muscle Wall Vessels (Medium-sized Vessel)

Nodules

Nodules correspond to palpable and solid lesions measuring of more than 1 cm. Usually, nodules are located in the dermis or hypodermis. In the context of vasculitis, they reflect the involvement of vessels of the dermohypodermic junction or the hypodermis (Supplementary data Fig. 2). Nodules can be located alongside an artery or a superficial vein, and can evolve into an ulcer or necrosis.

For an adequate pathological evaluation of a nodule, a deep biopsy with the scalpel, carrying out the hypodermis, is required. Vasculitis associated with cutaneous nodules involves vessels with a smooth muscle wall as in PAN, or vasculitis involving both capillary and smooth muscle wall vessels as ANCA-associated vasculitis.

Livedo

Livedo corresponds to a reticulate (network-like) erythema of vascular origin (Fig. 4). Livedo is secondary to vasomotor disturbances or obstructive vascular pathology, with or without parietal involvement (Table 2). It is not synonymous with vasculitis. Clinically, there are different types of livedo:

- Livedo reticularis, with fine, regular, and closed meshes, frequently physiological;
- Livedo racemosa (branched livedo), with broken, branched, discontinuous, and irregular meshes, always pathological and characteristic of the Sneddon syndrome;
- Livedo with infiltrated meshes, frequently encountered during vasculitis (PAN);
- Purpuric livedo or retiform purpura which directs towards a thrombosing pathology of the dermal vessels such as a disseminated intravascular coagulation or catastrophic antiphospholipid syndrome.

Overall, livedo reticularis is most often physiological, whereas a livedo racemosa is always pathological and requires a thorough assessment. The skin biopsy is not systematic and its interest remains debated. There is no interest of skin biopsy in livedo reticularis, whereas in livedo racemosa with infiltration or necrosis, the biopsy of the infiltrated zone sometimes can reveal vasculitis. In the presence of a non-infiltrated and non-necrotic livedo racemosa, limited to the lower limbs, the biopsy is frequently not contributive but may sometimes show a picture of endarteritis obliterans directing towards a diagnosis of Sneddon syndrome, or an intense hyaline fibrinoid

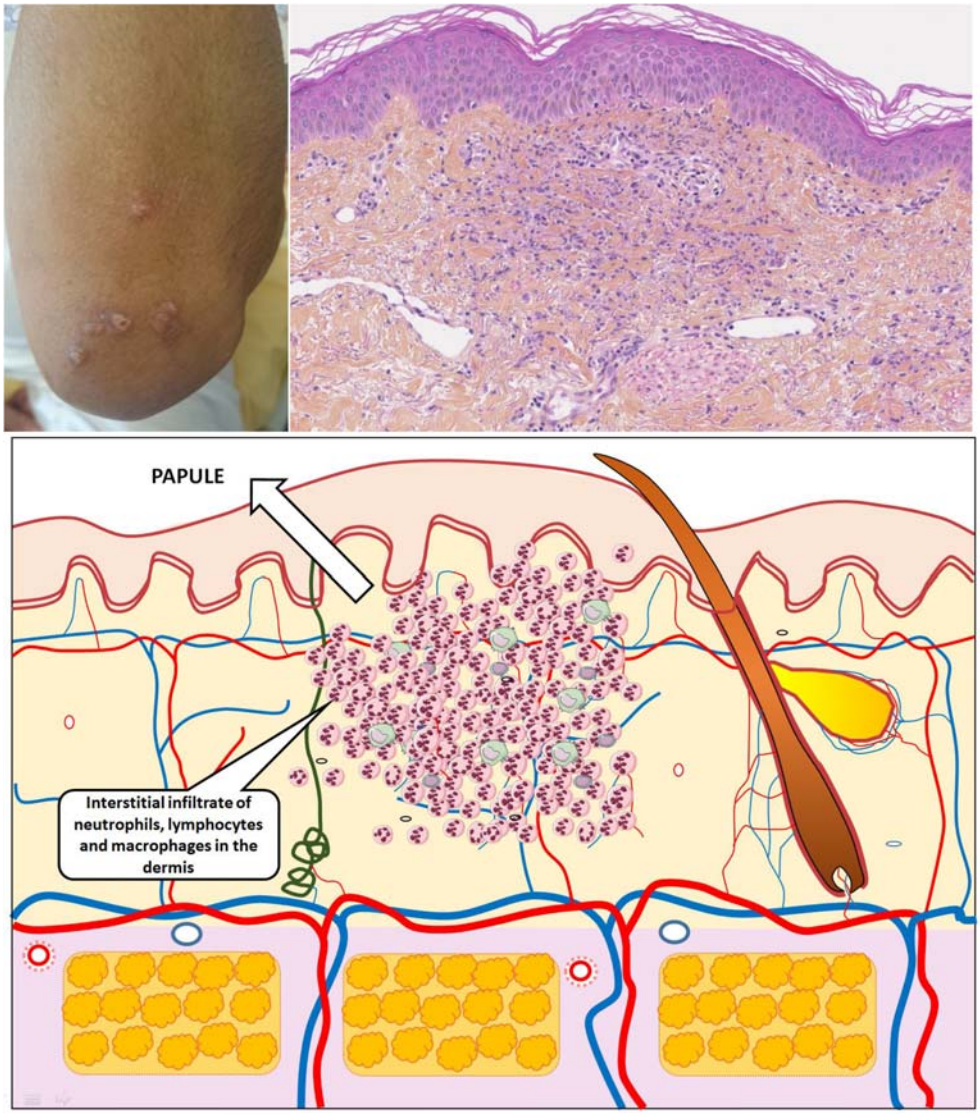

Fig. 3 Clinicopathologic correlations of papules. Picture showing papules of the elbow in a patient with granulomatosis with polyangiitis; histopathologically, there is a circumscribed area in the upper part of the dermis with a mixed interstitial infiltrate and necrobiotic collagen bundles (courtesy Dr. François Chasset)

aspect of the wall of a muscular arteriole observed in macular lymphocytic arteritis.

Ischemic Manifestations: Gangrene or Necrosis of the Extremities, the Scalp, or the Tongue

Skin necrosis results from the occlusion of skin vessels. The extent of necrosis depends on the type and depth of the affected vessels. Necrotic lesions are frequently seen in type I cryoglobulinemia [35] [36], where the main mechanism is a thrombosing vasculopathy. Such lesions can also be observed during ANCA-associated vasculitis and necrotizing digital arteritis during PAN. Necrosis of the scalp and/or the tongue occurs in GCA.

Other Manifestations Associated with Vasculitis

Pyoderma Gangrenosum

Pyoderma gangrenosum is a painful cutaneous ulceration, locating predominantly in the lower limbs, with progressive centrifugal extension that can reach more than 10 cm, and which initially starts as a pustule or subcutaneous nodule de novo or after a mild trauma, with inflammatory and purplish raised borders and some zones with *purulent hutches*. Pyoderma gangrenosum often occurs in patients with inflammatory bowel disease, but it can also occur in patients with GPA [37] and Takayasu arteritis [38].

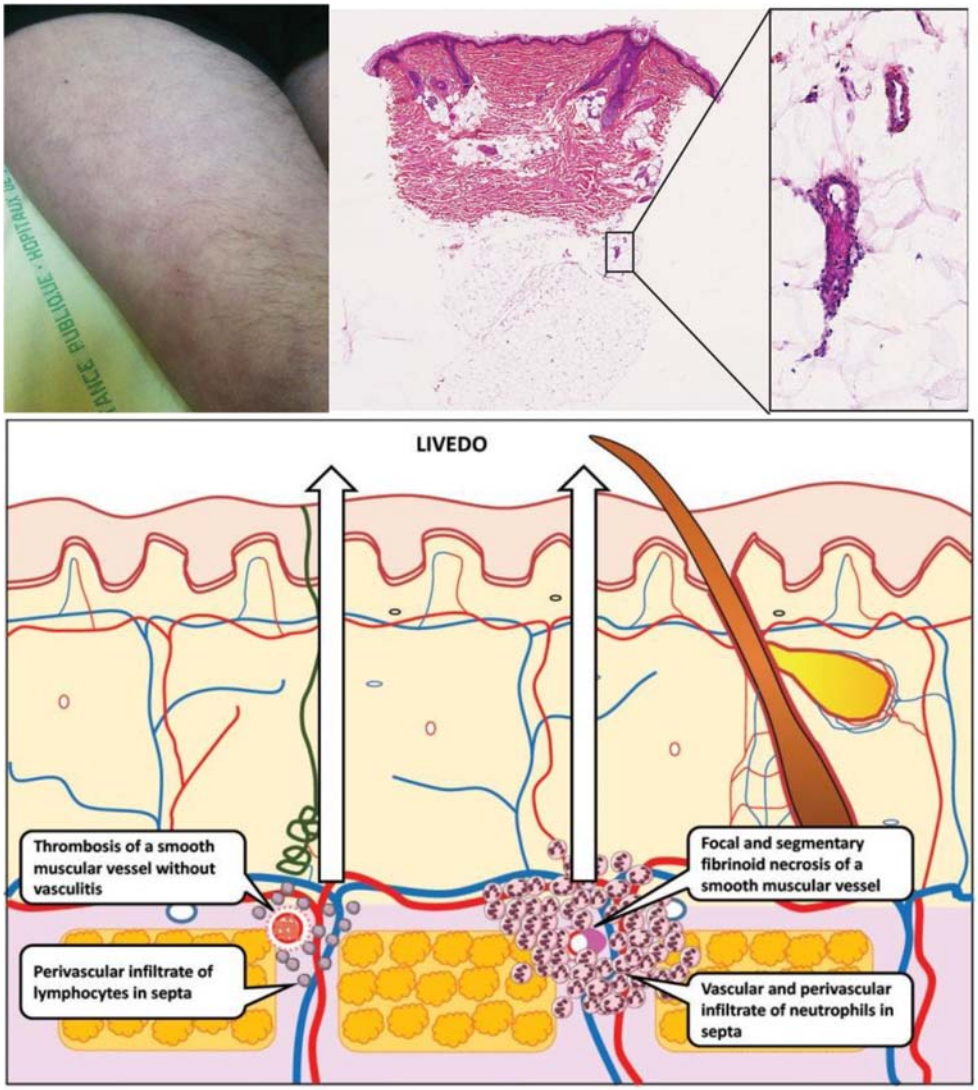

Fig. 4 Clinicopathologic correlations of livedo. Picture showing a livedo in a patient with PAN

Superficial Thrombophlebitis

Superficial thrombophlebitis must be distinguished from deep thrombophlebitis and varicose vein thrombosis. The clinical picture includes sensitive nodules, sometimes as a deep linear lesion or poorly limited cord. Such lesions can be seen in thrombophilic disorders as antiphospholipid syndrome or protein C or S deficiency, or in vasculitis, mainly Behçet's disease. Elsewhere, they may be the revealing mode of solid cancers, especially the stomach or the pancreas.

Gingival Hypertrophy

Gingival hypertrophy, displaying a raspberry appearance, was described as a mucosal manifestation of GPA, which is the only vasculitis associated with this feature.

Oral, Genital, or Anal Ulcers

Oral ulcers are rare manifestations of vasculitis, except for Behçet's disease in which it represents the most common manifestation. Oral ulcers can also be observed rarely in GPA (5% of patients) or in relapsing polychondritis, especially within the mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome.

Splinter Hemorrhages

Splinter hemorrhages, small areas of hemorrhages under the fingernails or toenails, are rare in vasculitis and are more likely to be due to thromboembolic or thrombotic pathology, especially during catastrophic antiphospholipid syndrome or infectious endocarditis.

Table 2 Mechanisms and causes of livedo (adapted from [15])

Vasomotor disorder: most often livedo reticularis
Physiological
State of shock, low circulatory flow
Pheochromocytoma, carcinoids
Medicinal: amantadine [17], noradrenaline [18], gemcitabine [19]
Heart dermatitis or erythema ab igne [20]
Pellagra [21]
Hypothyroidism, Cushing's syndrome
Central nervous system disorders: multiple sclerosis, encephalitis, poliomyelitis, Parkinson's disease, stroke, cerebral traumatism...
Livedo of inflammatory origin
Sarcoidosis [22] [23]
Susac syndrome [24], [25] [26]
Systemic lupus erythematosus [27]
Macular lymphocytic arteritis [28]
PAN, cutaneous PAN
ANCA-associated vasculitis: GPA, EGPA, MPA
Cryofibrinogenemia, cold agglutinates
Hypocomplementemic urticarial vasculitis [29]
Subcutaneous injection of buprenorphine [30]
Basin's disease or nodular vasculitis [31]
Livedo of emboligenous origin: livedo purpuric and purpura
Embolism of cholesterol crystals
Adenopathy emboligene
Crude embolisms (associated with myxoma of the atrium and endocarditis)
Gas emboli
Infectious endocarditis
Malignant embolism: angiotropic lymphomas, visceral cancers
Paradoxical embolisms on foramen oval
Intra-lymphatic histiocytosis (associated with rheumatoid arthritis)
Emboli of hydrophilic polymer after vascular catheterization [32]
Nicolau's Disease
Livedo of thromboembolic origin
Antiphospholipid syndrome
Cryoglobulin
Disseminated intravascular coagulation
Livedo of infectious origin
Capnocytophaga canimorsuss, due to an ICDD [33]
Escherichia coli [34]
Blood hyper viscosity: branched livedo
Myeloproliferative syndrome (essential thrombocythemia, Vaquez's disease, myeloid leukemia, myeloid splenomegaly)
Cryoglobulinemia, cryofibrinogenemia
Cold agglutinins
Pancreatitis
Crystal deposits: purpura retiform
Calciphylaxis
Oxaluria, homocystinuria
Livedo of thrombotic origin:
ADA2 deficiency
White cutaneous atrophy
Sneddon syndrome
Monoclonal cryoglobulinemia

Raynaud's Phenomenon

Raynaud's phenomenon is mainly seen in connective tissue diseases, mainly systemic scleroderma, mixed connective tissue disease, and inflammatory myopathy. In vasculitis, Raynaud's phenomenon directs towards cryoglobulinemic vasculitis, in up to 30% of patients with in type I cryoglobulinemia [36], and roughly 20% in mixed cryoglobulinemic vasculitis.

Interstitial Granulomatous Dermatitis

Interstitial granulomatous dermatitis may clinically present as linear cords of axillary regions, but also papules and plaques [39]. Histologically, deep dermal necrobiosis foci are typically observed, affecting one or a few collagen bundles and surrounded by histiocytes organized in *rosettes*. This entity is nosologically related to the so-called Churg-Strauss granulomas and is associated with

many disorders, such as GEPA and MPA [40], rheumatoid arthritis, systemic lupus erythematosus, and adult onset Still disease [39].

Description of the Main Cutaneous Vasculitis

Skin Small-Vessel Vasculitis

Cutaneous Leukocytoclastic Angiitis

The hypersensitivity vasculitis or cutaneous leukocytoclastic angiitis has been individualized in the CHCC1994 and the CHCC2012 and belongs to the single-organ vasculitis. Clinically, cutaneous manifestations of cutaneous leukocytoclastic angiitis are polymorphic and include purpura, urticarial plaques, nodules, vesicles or bulla, pustules, and/or ulceration.

Urticarial Vasculitis

Urticarial vasculitis is defined histologically by inflammation of capillaries of the dermis and post-capillary venules, and is divided into 2 groups accord the complement fraction level: normocomplementemic urticarial vasculitis and hypocomplementemic urticarial vasculitis.

Lesions of urticarial vasculitis differ from classical urticaria because they are more fixed, they are less pruriginous, and they persist for more than 24 h. They have a chronic evolution, leaving hyperpigmented maculas, and are associated with angioedema in half cases, purpura in one third, and livedo in 14% [29]. Extra-cutaneous manifestations may occur, mainly arthralgias, and ocular, pulmonary, gastrointestinal, and/or renal involvement. Most normocomplementemic urticarial vasculitis are idiopathic, whereas hypocomplementemic urticarial vasculitis are frequently associated with connective tissue diseases. Urticarial vasculitis must be distinguished from neutrophilic urticarial dermatosis, as many cases of UV have been reclassified as NUD during the last decade.

IgA Vasculitis (Henoch-Schönlein Purpura)

IgA vasculitis is characterized by palpable purpura, arthralgia, and abdominal pain, and accounts for 10% of cutaneous vasculitis [16]. IgA vasculitis is the most frequent vasculitis in childhood, with an annual incidence of 3 to 26 per 100,000 children, often occurring between 4 and 7 years [41]. The disease is less common in adults, with an estimated incidence between 0.1 and 1.8 per 100,000 individuals [38]. The dermatologic manifestation of both leukocytoclastic vasculitis and IgA vasculitis is palpable purpura. Michel et al. [42] described clinical criteria for differentiating IgA vasculitis and cutaneous leukocytoclastic angiitis. Presence of 3 of the following 6 criteria correctly classifies a patient as having IgA vasculitis in 87%: palpable purpura not related to thrombocytopenia, post-prandial diffuse abdominal pain typically associated with bloody diarrhea, gastrointestinal hemorrhage, hematuria, age less than 20 years, and absence of drugs at the beginning of the disease that could have precipitated the affection.

Histologically, IgA vasculitis displays no specificity, showing typical leukocytoclastic vasculitis. However, direct immunofluorescence reveals predominant IgA deposits in the capillary wall. Thus, predominance of perivascular IgA deposits on skin biopsy is an additional positive argument for the diagnosis of IgA vasculitis, without being specific [11], since other vasculitis as cryoglobulinemic vasculitis may have IgA deposits [12].

Cryoglobulinemic Vasculitis

Cryoglobulinemia is defined by the presence of immunoglobulins which precipitate with cold temperatures and resolubilize with warming. Classification is based on the immunochemical analysis, defining three types [43]. Type I cryoglobulins are single monoclonal immunoglobulins always linked to a B cell lymphoproliferative disorder. Type II cryoglobulins consist of polyclonal IgG with monoclonal IgM with rheumatoid factor activity. Type III cryoglobulins are comprised of polyclonal IgG and polyclonal IgM with rheumatoid factor activity. Type II and III are often referred to as mixed cryoglobulinemia (MC), and may be linked to B cell lymphoproliferative disorder, autoimmune disorders, and/or infections.

Mixed cryoglobulinemia is responsible for vasculitis with cryoglobulin immune deposits affecting small vessels (capillaries, venules, or arterioles). Vascular purpura is the most frequent manifestation, often indicative of the disease, whereas peripheral neuropathy occurred in half patients and renal involvement in one third of patients. In contrast, type I monoclonal cryoglobulinemia is responsible for vascular occlusion with frequent Raynaud phenomenon, ulcers and distal necrosis, pain and swelling in the extremities, or hyperviscosity syndrome. Histologically, cryoglobulinemia presents mostly with a perivascular mononuclear cell infiltrate, without affecting the vessel wall by itself. However, leukocytoclastic vasculitis is possible, especially within the skin, with fibrinoid necrosis of the wall of small-sized vessels and inflammatory infiltrate of neutrophils, some of them being pycnotic (leukocytoclasia). Intravascular hyaline deposits can be observed, with the presence of immunoglobulin and complement deposition using direct immunofluorescence.

Skin Small-Vessel and Smooth Muscle Wall Vessel Vasculitis

Association of vasculitis lesions of small vessels and vessels with smooth muscle wall is strongly suggestive of ANCA-associated vasculitis, i.e., GPA, MPA, and EGPA.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis is histologically characterized by inflammation of the vessel wall with peri- or extra-vascular granulomas. Clinically, GPA is characterized by ear, nose, and throat manifestations, pulmonary involvement, and glomerulonephritis. ANCA are positive in more than 90% of cases, directed against proteinase 3. Yes the most common skin finding is palpable purpura related to leukocytoclastic vasculitis.

Microscopic Polyangiitis

Microscopic polyangiitis is responsible for a segmental and focal necrotizing glomerulonephritis, associated with extracapillary proliferation, and no extra-vascular granuloma. Other clinical manifestations include arthralgias, peripheral neuropathy, alveolar hemorrhage, or gastrointestinal manifestations. ANCA are positive in more than 80% of cases, directed against myeloperoxidase.

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis is a necrotizing vasculitis defined by the association of asthma, blood and tissue eosinophilia, and systemic vasculitis. Clinical manifestations include multiple mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates, sino-nasal abnormalities, and cardiomyopathy. Cutaneous manifestations are frequent occurring in up to 50% of patients [40], especially purpura, subcutaneous nodules, and urticaria. Less frequent manifestations were reported, as Wells cellulitis [44], Kimura disease, and Lever granuloma, all belonging to the spectrum of eosinophilic dermatoses. Histologically, Wells phenomenon may be present, as the eosinophilic flame figures corresponding to collagen destruction by degranulation of eosinophils. ANCA are positive in only 30–40%, usually directed against myeloperoxidase.

Skin Vasculitis of the Smooth Muscle Wall Vessels

Polyarteritis Nodosa

Polyarteritis nodosa is a segmental and focal necrotizing vasculitis affecting medium and small arteries and arterioles of the deep dermis and septums, with an inflammatory neutrophilic infiltrate frequently responsible for vascular thrombosis. The disease can be systemic with cutaneous involvement (systemic PAN), and limited to the skin as a single-organ vasculitis (cutaneous PAN); in the latter, regional neurological involvement nevertheless frequently occurs.

Skin manifestations of systemic PAN are described in almost 50% of cases, dominated by purpura (19%), livedo (17%), nodules (15%), urticaria (6%), and ulcers or cutaneous necrosis (4%) [45]. Although purpura is often mentioned in clinical studies, it is incompatible with the current definition of the CHCC2012 since it is a manifestation of small-vessel vasculitis, the type of vessel which are spared in PAN. Possible explanations would be that these PAN with purpura would be MPA or cryoglobulinemic vasculitis, or conversely, an inaccurate definition of PAN in CHCC2012.

During cutaneous PAN, skin manifestations are mainly livedo, nodules, and ulcers predominantly affecting the lower limbs. Other manifestations were described, including atrophie blanche [46], Raynaud's phenomenon, and inflammatory plaques surrounded by nodules. Triggering factors of cutaneous PAN have been identified, such as viral, bacterial or mycobacterial infection, inflammatory bowel disease, or drugs (minocycline).

Another entity, called macular lymphocytic arteritis (MLA) or macular arteritis or lymphocytic thrombophilic arteritis, was described in 2003. Authors initially reported the association of a macular and pigmented rash with lymphocytic arteritis in the hypodermis or deep dermis on skin biopsy. Clinically, skin lesions are erythematous and/or pigmented macules, reticulated, sometimes associated with nodules and purpura. Lesions are always located in the lower limbs and less frequently in the upper limbs (44%) and more rarely in the trunk. MLA preferentially occurs in women in 70–80% and median age is 40 years. Histologically, the epidermis and dermis are normal; a dense peri- and intravascular lymphocytic infiltrate surrounding small arterioles in the reticular dermis or hypodermis is observed. No destruction nor necrosis is seen within the arterial wall, but a very homogenous fibrinous and hyaline circumferential arterial ring is characteristic of MLA. Autoantibodies can be found, mainly anticardiolipin and antinuclear antibodies, sometimes with anti-SSA specificity. However, this entity remains controversial and a real distinction between cutaneous PAN and MLA has not been established. In 2015, Buffiere-Morgada et al. retrospectively and blindly assessed the frequency of clinical and histologic features of MLA in patients given the diagnosis of cutaneous PAN. Predominantly lymphocytic arteritis, a paucity of neutrophils, concentric fibrin ring, and absence of internal lamina elastic disruption were present in 60%, 20%, 18%, and 23% of patients, respectively. The incidence of complete remission was not different between patients having a predominant lymphocyte infiltrate or few neutrophils. These data did not favor the classification of cutaneous PAN and MLA as distinct entities [28].

Kawasaki Disease

Kawasaki disease is a vasculitis of large and medium vessels, of unknown etiology, affecting preferentially children of less than 5 years, and more rarely adult. Kawasaki disease results in febrile adenocutaneous-mucosal syndrome. Its severity is related to cardiac involvement and the development of coronary aneurysms.

Behçet's Disease

Behçet's disease is a multisystemic inflammatory vasculitis affecting the arteries and veins of variable size, and preferentially young men aged around 30 years. Besides frequent buccal and genital ulcers, cutaneous manifestations include inflammatory nodules locating in the lower limbs and resembling erythema nodosum, "pseudofolliculitis," and superficial thrombophlebitis. Ocular, gastrointestinal, vascular, or central nervous system attacks are less frequent but much more serious.

Drug-Induced Vasculitis with Immune Complex Deposition

Drug-induced vasculitis with immune complex deposition has been individualized in the CHCC2012 as a vasculitis of defined cause. It occurs most often within 7–21 days after initiation of the suspected drug. Drugs most frequently involved are fosphenytoin, quinidine, sulfonamides, penicillins, allopurinol, or granulocyte-colony stimulating factor [11]. Overall, approximately 15–20% of cutaneous vasculitis are drug-induced [16].

How I Manage a Patient with Suspected Cutaneous Vasculitis

When a cutaneous vasculitis is suspected, a careful diagnostic approach is mandatory to look for potentially severe organ manifestations and to establish as quickly as possible the etiological diagnosis [12]:

1. Perform a skin biopsy of an early lesion with standard histology and direct immunofluorescence
2. Determine the severity of vasculitis by looking for systemic manifestations: constitutional symptoms, arthralgias, myalgias, pulmonary manifestations, gastrointestinal symptoms, ear, nose, and throat manifestations, ocular signs, peripheral neuropathy, renal involvement, and urogenital manifestations (abnormal urine analysis, testicular pain)
3. Identify a cause:
   (a) Recent drugs initiation?
   (b) Recent infection?
   (c) Neoplasia, malignant hemopathy?
   (d) Laboratory tests: CBC, platelets, CRP, PT, APTT, fibrinogen, serum electrolytes, urea, creatinine, liver function tests, serum protein electrophoresis, HIV, HBV, and HCV serologies, parvovirus B19 serology (and/or other viruses according to clinical and epidemiological setting), cryoglobulin, rheumatoid factor, complement fractions levels, antinuclear antibodies and if positive anti-ENA, ANCA testing, proteinuria, and urine analysis
   (e) Morphological investigations: chest X-ray
   (f) Investigations to discuss depending on clinical context and disease course: blood cultures, echocardiography, CT scan and sinuses, brain imaging and lumbar puncture.

Conclusion

Cutaneous vasculitis constitutes a large and heterogeneous group of diseases, for which the analysis of cutaneous elementary lesions and skin biopsy provide important findings on the size of the affected vessel and possibly on the type of vasculitis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed consent Yes.

Research Involving Human Participants and/or Animals None.

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