Cutaneous vasculitides and vasculopathies

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Summary

Cutaneous vasculitides are classified into four main forms: inflammatory vasculitides, livedoid vasculopathies, capillary chronic pigmented purpura and endothelitis. These conditions may have quite similar presentations, and sometimes they are overlapping.

Cutaneous vasculitides are a heterogeneous group of inflammatory disorders affecting skin blood vessels. They may be triggered by several factors, such as infection or drug, or may be related to underlying disease, notably connective tissue or malignancies. The most widely used classification of cutaneous vasculitides is based on the size of the vessels concerned, and makes a distinction between small-vessel, small- and medium-vessel, medium-to-large vessel and largest-vessel vasculitis (arteritis).

Small-vessel vasculitis

The most common form is small-vessel vasculitis, that is clinically characterized by the presence of purpuric papules, sometimes accompanied by hemorrhagic bullae or necrotic areas, mostly localized in the lower extremities (Figures 1, 2).

Small-vessel vasculitis may also present as petechiae and, less frequently, as persistent urticarioid lesions with hyperpigmentation, vesicles and pustules (5). The typical histopathological finding of these forms is a leukocytoclastic vasculitis, with fibrinoid necrosis of the vessel wall, a neutrophil-rich inflammatory infiltrate – sometimes also with eosinophils – with nuclear dust. It is usually recommended to perform a biopsy of recently developed palpable lesions, within 24-48 hours from appearance. If a biopsy of a less recent lesion is performed, there may be a different presentation because lesions are of evolutive nature: in a late stage of leukocytoclastic vasculitis, a more pronounced lymphomonocyte component may be detected. The pathogenetic mechanism involves a damage

Vasculitides and cutaneous vasculopathies are classified into four main forms: inflammatory vasculitides (with a typical cutaneous manifestation), livedoid vasculopathies (of non-inflammatory and microthrombotic nature), capillary chronic pigmented purpura and endothelitis (most frequently caused by viral infections, typically due to Parvovirus B19). These conditions may have quite similar presentations, and sometimes they are overlapping.

Cutaneous vasculitides are a specific pattern of skin vessel inflammation; they may be limited to the skin, develop at first at the skin level and then proceed to systemic involvement, or be a cutaneous manifestation of a systemic vasculitis. Both the arterial and the venous districts can be affected, with varying clinical manifestations that often require histological confirmation (1-4). They may affect the arteries and the veins, with a great clinical variability. The most widely used classification of cutaneous vasculitides is based on the size of the vessels concerned, and makes a distinction between small-vessel, small- and medium-vessel, medium-to-large vessel and largest-vessel vasculitis (arteritis) (Table 1).

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mediated by circulating immunocomplexes, with neutrophil-predominant vessel wall damage. Urticarial vasculitis can be either hypocomplementemic or normocomplementemic: hypocomplementemic forms are often associated with a systemic involvement, especially at kidney and pulmonary level (6). Hypocomplementemia is not necessarily detected steadily, as it may vary over time. Urticarial vasculitis – especially hypocomplementemic forms – is sometimes associated with connective tissue diseases: a proportion of these cases may fulfill the criteria for a diagnosis of systemic lupus erythematosus. Other conditions that may cause or be associated with small-vessel vasculitis include: infections (hepatitis B and C, infectious mononucleosis, Lyme disease), drugs (diltiazem, cimetidine, procarbazine, fluoxetine, etanercept, methotrexate), hematological diseases (leukemia, lymphoma, polycythemia, etc.). A particular form of leukocytoclastic vasculitis is Schönlein-Henoch purpura, a common form in children, characterized by perivascular deposits of IgA and a tendency to extra-cutaneous involvement with arthritis and gastrointestinal and renal manifestations.

A not so rare form in very young children – usually below two years of age – is acute hemorrhagic edema of infancy: it is characterized by hemorrhagic lesions particularly in the face and extremities, and creates great anxiety among parents (7). In spite of the appearance, it is a benign condition, usually secondary to infections, and resolves spontaneously without any therapy (Figure 3).

Some forms of vasculitis are characterized by the presence of an infiltrate with a prevalent lymphocyte composition, and this is the reason why they are called lymphocytic vasculitis (8, 9). In this case, too, there is a wide pathogenic spectrum, but the most typical forms are those associated with Rickettsiosis, use of certain drugs, or to conditions that may appear during connective tissue diseases or other disorders (Table 2).

Sneddon disease, which mainly affects young women, is a rare condition characterized by findings of a lymphocytic vasculitis associated with livedo racemosa and relapsing cerebrovascular complications. If a vasculitis is clinically suspected, a crucial step for confirmation of diagnosis is the histologic examination, to be performed – as previously said – on recent-onset lesions. The extent of the disease beyond the skin should be also assessed, i.e. possible involvement of the kidneys, nervous system (also the peripheral system which is often the main cause of pain), joints, gastrointestinal tract and pleuropericardial district. The next step is to determine etiology: this disease is most frequently caused by infections, drugs or associated conditions that induce the production of immunocomplexes, e.g. connective tissue diseases, tumors, or
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Diseases associated with immune complexes
- Infections (viral, bacterial, fungal, other)
- Drugs

Attempt to establish etiology
- Drugs
- Infections (viral, bacterial, fungal, other)
- Diseases associated with immune complexes (e.g. connective tissue vascular diseases, malignancy, inflammatory bowel disease, chronic active hepatitis, etc.)
- Idiopathic - 50%

Table 3 - Clinical evaluation of patients with vasculitis.

<table>
<thead>
<tr>
<th>Confirm clinical diagnosis histopathologically</th>
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<tr>
<td>• Punch biopsy of a lesion at the appropriate stage</td>
</tr>
<tr>
<td>• Realize that “lesions have life spans” and that therapy affects the histopathologic findings</td>
</tr>
<tr>
<td>• Incisional biopsy for larger vessel vasculitis</td>
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Assess extent of disease
- General
  - Myalgias
  - Arthralgias
  - Fever
- Kidney glomeruli
  - Proteinuria/hematuria
- Nervous System
  - Central or peripheral
  - Diffuse or local findings

Attempt to establish etiology
- Drugs
- Infections (viral, bacterial, fungal, other)
- Diseases associated with immune complexes (e.g. connective tissue vascular diseases, malignancy, inflammatory bowel disease, chronic active hepatitis, etc.)
- Idiopathic - 50%

Small- and medium-sized vessel cutaneous vasculitides

Small- and medium-sized vessel cutaneous vasculitides include cryoglobulinemia (Table 4). This condition is characterized by three subtypes: monoclonal type I (more frequently IgM), associated with B-cell lymphoproliferative disorders (multiple myeloma, Waldenstrom macroglobulinemia), clinically characterized by manifestations of gangrene, ulcers, acrocyanosis and Raynaud’s phenomenon; type II, composed of polyclonal IgG and monoclonal IgM with rheumatoid factor activity, associated with infections (HCV, HIV), autoimmune diseases and lymphoproliferative diseases (11). Type II is clinically characterized by the development of palpable purpura, sometimes accompanied by arthralgia, peripheral neuropathy and glomerulonephritis. Type III is composed of polyclonal IgG and IgM, the latter with a rheumatoid factor activity. In addition to leucocytoclastic presentations – with neutrophil-rich infiltrates around the vessel and fibrinoid necrosis of the wall – cryoglobulinemias may also present non-inflammatory conditions (especially of type 1) with vessel occlusions due to cryoprecipitates, although vasculitis is not necessarily present. In this case, the clinical presentation is not inflammatory but directly of the ulcerative type. The most relevant of medium-sized vessel vasculitides is polyarteritis nodosa (12). Classical polyarteritis nodosa is a very rare systemic disease characterized by a number of symptoms including fever, myalgia, fatigue with body weight loss, necrotizing glomerulonephritis, ischemic cardiac disease, hypertension, polyneuritis and ocular involvement. Cutaneous involvement may be observed in 20-30% of cases, with typical painful nodules in lower extremities – with a tendency to ulceration – palpable purpura, livedo reticularis and digital gangrene. Besides this classical form, there is also a cutaneous polyarteritis nodosa that presents with systemic symptoms as well, including low-grade fever, myalgia, arthralgia and peripheral neuropathy, but especially with very painful erythematous nodules in the legs that have an ulcerative progression and leave pigmentation and scars; it is more common during infancy and has a benign nature, although a chronic and relapsing course can be reported, and is associated with infections (HBV, HIV, Parvovirus B19) and bowel chronic inflammatory diseases (8-10). Over 50% of cases usually remain idiopathic (Table 3). From a therapeutic point of view, data from controlled studies on small-vessel cutaneous vasculitides are relatively limited. Overall, this is a rather rare disease, and therefore most treatment recommendations are based on case series; generally, the starting therapy is colchicine, pentoxifylline or cortisone, sometimes methotrexate; in the most severe forms, cyclophosphamide is the most frequently used drug.

Table 5 - Polyarteritis nodosa (PAN): main cutaneous and systemic clinical features.

<table>
<thead>
<tr>
<th>Classical (systemic) PAN</th>
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<tbody>
<tr>
<td>• Systemic disorder (fever, myalgias, asthenia, weight loss, necrotizing glomerulonephritis, cardiac ischemic disease, hypertension, neuritis, ocular involvement)</td>
</tr>
<tr>
<td>• Skin (20-30%) Erythematous and painful nodules (legs) which may ulcerate; palpable purpura, livedo reticularis, digital gangrene</td>
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Cutaneous PAN
- Mild fever myalgias, arthralgia, asthenia, peripheral neuropathy
- Erythematous and painful nodules (legs), ulcers, palpable purpura, livedo reticularis, digital gangrene
- Most common form in children
- Benign but chronic relapsing course
- Associated with infection (Strep; Parvovirus B19, HBV, HIV) and IBD
Livedoid vasculopathies

Livedoid vasculopathies develop in patients with a pre-disposing thrombophilic state at baseline (13, 14). This may be of different origin, since there are inherited and acquired thrombophilic forms, all characterized (from a pathogenic point of view) by a tendency to generate microthrombi in small skin vessels. A microthrombus can be histologically documented, without inflammatory events affecting the vessels. It is important to document the microthrombus histologically with intravascular fibrin deposition: biopsy should be performed on the healthy skin around the ulcerative lesions, presumably next to the obstructed vessel that runs through the surrounding skin. The examination reveals ulcerative manifestations that leave ivory-white stellate scars (atrophie blanche), often associated with livedo reticularis, intense pain, more frequently in young patients (in this case, they are often inherited thrombophilias) and particularly affecting the lower extremities. Typical manifestations include livedo reticularis or racemosa, with a large and highly irregular branching pattern, possibly accompanied by ulcerations; they usually affect very young patients who do not have a history of venous insufficiency or thrombophlebitis. Table 6 shows the main inherited and acquired causes of venous thrombosis. The treatment is based on antiplatelet, anticoagulant or antithrombotic therapy: in case of severe forms, the initial treatment is heparin followed by anticoagulation.

Pigmented purpuric dermatosis

The most common forms of pigmented purpuric dermatosis include Schamberg disease and lichen aureus (a localized, unilateral and well-circumscribed form) (Table 7). They are characterized by the appearance of flat, non-palpable macular lesions that begin as erythematous forms and then evolve into hyperpigmentation, usually in lower extremities; they are common in young women but also in elderly males. These forms are usually mistaken for vasculitis, but in fact they are chronic capillaritis (15). There is no vasculitis, but a perivascular inflammatory infiltrate with red blood cell extravasation that results into hemosiderin deposition and hyperpigmentation. These forms usually resolve spontaneously within a few months (but are sometimes relapsing) and do not need to be investigated from a systemic point of view like for vasculitis. The most typical diagnostic criteria include a superficial perivascular inflammatory infiltrate without vascular damage, with red blood cell extravasation and the presence of melanophages.

In the majority of cases, viral endothelitis is caused by parvovirus B19, which typically infects endothelial cells and determines several hemorrhagic conditions that include fifth disease, papular-purpuric gloves and socks syndrome (Figure 4), or purpuric manifestations with or without an association with vasculitis and with an atypical localization (16). These forms present as a viral infection, with polyarthralgias, fever, malaise, fatigue and possible neurological manifestations. From a clinical

### Table 6 - Causes of venous thrombosis.

<table>
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<th>Inherited</th>
<th>Common:</th>
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<tr>
<td>• G1691A mutation factor V gene (Factor V Leiden)</td>
<td></td>
</tr>
<tr>
<td>• G20210A mutation prothrombin (factor II) gene</td>
<td></td>
</tr>
<tr>
<td>• Homozygous C677T mutation MTHFR gene</td>
<td></td>
</tr>
<tr>
<td>• Increased levels of factor VIII, factor IX, or fibrinogen* (Probably inherited)</td>
<td></td>
</tr>
<tr>
<td>Rare:</td>
<td></td>
</tr>
<tr>
<td>• Antithrombin deficiency</td>
<td></td>
</tr>
<tr>
<td>• Protein C deficiency</td>
<td></td>
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<tr>
<td>• Protein S deficiency</td>
<td></td>
</tr>
<tr>
<td>Very rare:</td>
<td></td>
</tr>
<tr>
<td>• Dysfibrinogenemia</td>
<td></td>
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<tr>
<td>• Homozygous homocystinuria</td>
<td></td>
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<tr>
<td>• Increased levels of factor XI</td>
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### Table 7 - Pigmented purpuric dermatoses.

| Schamberg' disease |
| Purpura annularis teleangectodes of Majocchi |
| Pigmented purpuric lichenoid dermatitis of Gougerot and Blum |
| Lichen aureus |
| Eczematide-like purpura of Ducas and Kapetanakis |
| Linear pigmented purpura |
| Granulomatous pigmented purpura |

Figure 4 - Papular-purpuric gloves and socks syndrome: clinical manifestations.
cutaneous point of view, they appear as superficial, non-palpable purpuric lesions, sometimes spreading on acral sites, with a possible involvement of mucous membranes and with the appearance of petechiae and hyperemia that is particularly evident in the oral cavity and the pharynx. The histological examination shows a perivascular inflammatory infiltrate mainly consisting of lymphocytes, with no signs of vasculitis and with red blood cell extravasation into the dermis.

References