

Dermatologic Aspects of Systemic Vasculitis



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KEYWORDS

• Infection • Dermatology • Vasculitis

KEY POINTS

- Systemic and localized vasculitis affects the skin and subcutis, due to their large vascular beds as well.
- Initial cutaneous manifestations of vasculitides include discoloration, swelling, hemorrhage, and necrosis.
- Affected patients present with localized, self-limited disease to the skin without any known trigger or associated systemic disease.
- Cutaneous vasculitis manifests as urticaria, erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, livedo racemosa, deep punched-out ulcers, and digital gangrene.
- Skin biopsy and dermatopathology contribute relevant information.

INTRODUCTION

Systemic and localized vasculitis affects the skin and subcutis, due to their large vascular beds as well as hemodynamic factors, such as stasis in lower extremities, and environmental influences, as occur in cold exposure. The initial cutaneous manifestations of vasculitis includes diverse and dynamic patterns of discoloration, swelling, hemorrhage, and necrosis. One-half of affected patients present with localized, self-limited disease to the skin without any trigger or associated systemic disease, known as idiopathic cutaneous leukocytoclastic vasculitis (LCV).¹ Cutaneous vasculitis manifests as urticaria, erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, livedo racemosa, deep punched-out ul-

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cers, and digital gangrene.² Skin biopsy and dermatopathology contribute relevant information; however, they require correlation with the clinical history, physical examination, and laboratory findings to reach an accurate diagnosis in a given affected patient. This article reviews the dermatologic aspects of primary and secondary vasculitides.

GENERAL CONCEPTS AND NOSOLOGY

The skin receives its blood supply from penetrating vessels from within the underlying subcutaneous fat, which contains medium-sized vessels.³ Branches of medium-sized vessels give rise to 2 vascular plexuses that intercommunicate, the deep vascular plexus lying at the interface between the dermis and subcutaneous fat and the superficial plexus located in the superficial aspects of the reticular dermis. Further distally, the papillary dermis forms by capillary loops.

The type of cutaneous lesions closely correlates with the size of vessel affected by vasculitis. For example, in cutaneous LCV, immune complexes deposition and inflammation targeting postcapillary venules result in small palpable purpura (**Fig. 1**).

Inflammation that targets arterioles and arteries results in large purpuric lesions with irregular borders (**Fig. 2**). Ulcers, nodules, pitted scars, and livedo reticularis are



Fig. 1. Typical palpable purpura, some with central necrosis in a patient with idiopathic cutaneous vasculitis of the legs.



Fig. 2. Large purpuric lesions with irregular borders affecting the left wrist of a patient with idiopathic systemic vasculitis.

associated with arterial muscular vessel involvement localized to the dermal-subcutis interface or within the subcutis.⁴

EPIDEMIOLOGY

The incidence of cutaneous vasculitis ranges from 15.4 to 29.7 cases per million per year, affecting adults more than children of all ages, with slight female predominance, and up to 90% of children diagnosed with Henoch-Schönlein purpura (HSP)/IgA vasculitis (IgAV).¹ Approximately one-half of patients presenting with cutaneous vasculitis have idiopathic LCV skin lesions, whereas the remainder are attributed to recent infection and drug ingestion. LCV that results from drugs or infection is termed, *hypersensitivity* or *allergic vasculitis*. The antinuclear cytoplasmic antibody (ANCA)-associated vasculitides (AAV) include eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome), microscopic polyangiitis, and granulomatosis with polyangiitis (GPA) (previously known as Wegener granulomatosis) which may present with cutaneous vasculitis.³ The onset of cutaneous vasculitis may be an indication of secondary vasculitis in association with connective tissue disease (CTD), such as systemic lupus erythematosus vasculitis (LV),⁵ and rheumatoid arthritis (RA)-related vasculitis (RAV).⁶

The evolution of cutaneous vasculitis occurs in 3 phases. The first is a single acute, self-limited episode that resolves in less than or equal to 6 months in association with drug exposure or an infectious trigger, so noted in 60% of patients. The second is relapsing disease with symptom-free periods, usually found in patients with HSP/IgAV and cryoglobulinemic vasculitis (CV), so noted in 20% of patients. The third is chronic, unremitting disease most often associated with primary systemic and secondary vasculitides in association with CTD, CV, or malignancy, altogether in approximately 20% of patients. The duration of vasculitis ranges from 1 week to 318 months, with mean and median durations of 28 months and 3.7 months, respectively. Fewer than 20% of cutaneous vasculitis cases have extracutaneous or visceral vasculitis. Fatal disease occurs in fewer than 7% of patients.⁴

CLINICAL PRESENTATION

Systemic symptoms of fever, malaise, weight loss, arthritis, and arthralgia most often accompany cutaneous vasculitides. The resulting lesions affect dependent sites of the legs, especially under tight fitting clothes, less so along the arms, trunk, head, and neck, signifying more severe disease or coexisting systemic vasculitis.⁷ Cutaneous vasculitis commonly manifests as palpable purpura and infiltrated erythema, indicating dermal small vessel vasculitis (SVV), and less frequently as nodular erythema, livedo racemosa, punched-out ulcers, or digital gangrene due to muscular-vessel

vasculitis. The type of cutaneous lesions closely correlates with the size of vessel affected by vasculitis. Sparse superficial perivascular neutrophilic infiltrates associated with nuclear debris and extravasated red blood cells result in urticarial papules and plaques, which last greater than 24 hours, burn rather than itch, and resolve with residual pigmentation. A predominant SVV results in purpuric macules and infiltrated erythema, whereas deeper dermal SVV correlate with palpable purpura and vesiculobullous lesions. Ulcers, nodules, pitted scars, and livedo reticularis are associated with arterial muscular vessel involvement located at the dermal-subcutis interface or within the subcutis.⁸

LABORATORY EVALUATION

Histopathologic Studies

A diagnosis of cutaneous vasculitis of small and medium-sized muscular vessels is established by biopsy and examination of hematoxylin-eosin–stained sections followed by direct immunofluorescent (DIF) studies. Fibrinoid necrosis is composed of fibrin deposition within and around the vessel wall and is a feature of nearly all early vasculitic lesions. Inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition (**Fig. 3**) may be accompanied by endothelial damage in the form of endothelial swelling and shrinkage due to apoptosis and sloughing. The finding of inflammatory cells infiltrating the adventitia and media and disrupting the endothelium or endothelialitis is a de facto sign of vasculitis (**Fig. 4**). Secondary changes that suggest underlying vasculitis include extravasation of red blood cells causing purpura, necrosis leading to infarction, and ulceration secondary to the ischemia and vessel obstruction. Circumstantial evidence of vessel wall damage includes lamination of the adventitia, media, and/or intima of vessels or so-called onion skinning; perivascular nuclear dust or leukocytoclasia without fibrin deposits, such as in early evolving LCV; sharply defined loss of the elastic lamina associated with acellular scar tissue in the healed stage of muscular vessel vasculitis; and subendothelial, intramuscular, and adventitial inflammatory cells. Neovascularization of the adventitia and the formation of small capillaries are prominent features of mature and older lesions in chronic

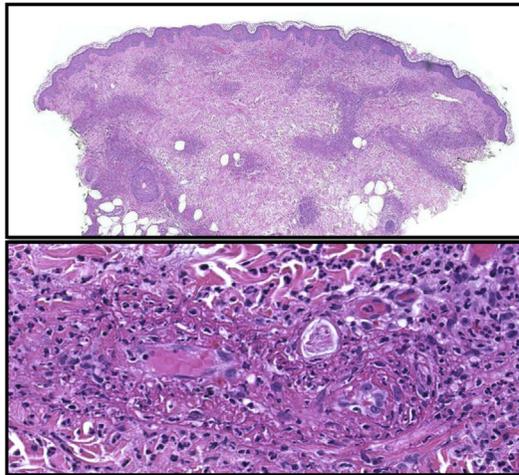


Fig. 3. Inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition indicative of vasculitis, seen in low magnification (*upper panel*) and higher magnification (*lower panel*).

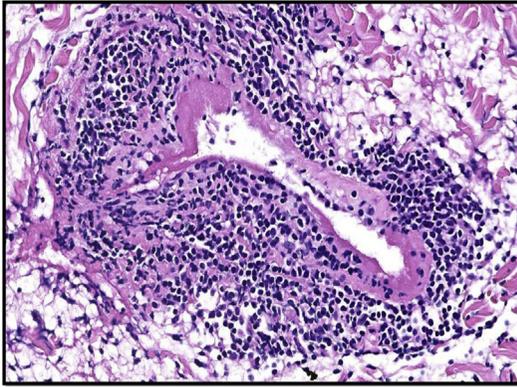


Fig. 4. Lymphocytes infiltrate the adventitia and media of a small vein and the intima shows extensive fibrin deposits.

localized SVV, such as erythema elevatum diutinum; medium vessel vasculitides, such as polyarteritis nodosa; and large vessel vasculitides, such as giant cell arteritis. Immunofluorescence analysis of a tissue biopsy of involved skin lesions is indispensable. The most common immunoreaction found in vessels by DIF is C3, followed by IgM, IgA, and IgG and fibrin deposits.^{1,8} The type of immunoglobulin and pattern of deposits in DIF are of additional diagnostic value. For example, predominance of IgA in HSP/IgAV directs attention to renal involvement. Basement membrane zone or keratinocyte nuclear or in vivo ANA and IgG immunoreactions found in vasculitides associate with CTD, such as LV. The finding of basement membrane zone immunoreactions occur especially in those with CTDs. IgM deposition in blood vessels, circulating RF, and monoclonal production of IgM occur in CV and RA-related vasculitis.

Drug-Induced Cutaneous Vasculitis

Hypersensitivity vasculitis due to adverse drug reactions manifests as superficial dermal neutrophilic or lymphocytic SVV on skin biopsy and represents approximately 20% of cases of cutaneous vasculitis.^{1,8-10} Tissue eosinophilia is a useful indicator of drug-induced cutaneous SVV.

Tumor necrosis factor α

Tumor necrosis factor (TNF)- α inhibitors used in the treatment of autoimmune and rheumatic diseases were the reported cause of cutaneous vasculitis in 8 patients so treated for 2 months to 72 months,¹¹ 4 patients with RA, 3 patients with ulcerative colitis, and 1 patient with Crohn disease. The most common presenting manifestation of the patients was palpable purpura, followed by ulcerated lesions, erythematous macules, and blisters. After discontinuation of anti-TNF- α , none had recurrent vasculitis. Appearance of ANCA titers in patients under anti-TNF- α therapy should prompt excluding AAV overlap, for which anti-TNF- α is not efficacious and that requires switching to disease-specific therapy.

Levamisole

Levamisole was originally introduced as an anthelmintic agent and later used in Behçet disease and RA for immunosuppression. It has been used in colon cancer, enhancing the immunity by potentiating the T-cell-mediated immune response. More recently levamisole was added to cocaine to potentiate the stimulant effects because it has a dopamine agonistic effects provoking a synergistic effect with

cocaine.⁵ Affected patients have constitutional symptoms, arthralgia, leukopenia, agranulocytosis, and cutaneous vasculitis with purpuric lesions of the ears, nose, cheeks, and extremities. The lesions have bright-red borders with central necrosis (Fig. 5). Despite the severe and dramatic clinical appearance of these lesions, they usually resolve spontaneously within a few weeks of drug discontinuation but can recur with subsequent contaminated cocaine abuse. Subsequently, clinicians need to differentiate this presentation from other forms of vasculitis, particularly with GPA, because the degree of immune suppression differs between both. The degree of skin necrosis has been as severe and large as to require skin grafting and removing the offender combined with a short course of corticosteroids suffice to control the disease, contrasting with the management for GPA, which requires more aggressive immune suppression. One-half of affected patients demonstrated positive anti-MPO or positive anti-PR3 antibodies.⁶ In addition, cocaine contaminated with levamisole by unclear mechanisms is the mediator of ANCA-mediated vasculitis. The target, differing from AAV, was found the neutrophil elastase within the granules, eliciting an atypical ANCA-positive antibody response. Furthermore, elastase, a constituent of neutrophil extracellular traps (NETs), is a target of patients exposed to cocaine/levamisole. It has been suggested that the programmed cell death of neutrophils by NETs release, which is the extrusion of nuclear (chromosomal material) and mitochondrial DNA containing proinflammatory and thrombogenic peptides, is potentiated by cocaine/levamisole. This combination of drugs induces the release of highly immunogenic NETs, containing high concentrations of elastase.¹²

TNF receptor-associated periodic fever syndrome (TRAPS) is an autosomal dominant disorder consisting of periodic fever episodes lasting from 3 days to 21 days and in which manifestations show pleuritic chest pain, abdominal pain, conjunctivitis, periorbital edema, monoarthritis, testicular pain, myalgia, and papulomacular and urticarial rash. A report revealed SVV and panniculitis in a 66-year-old patient diagnosed with TRAPS with migratory macular erythematous rash and with positive ANCA against elastase, successfully treated with etanercept.

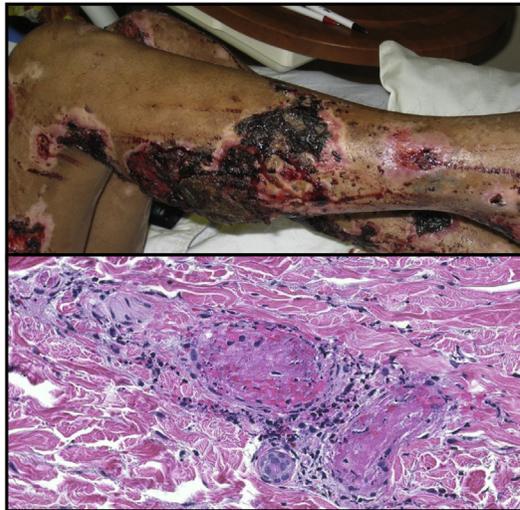


Fig. 5. Levamisole-induced vasculitis shows histologic signs of a vaso-occlusive disorder and vasculitis. The *upper panel* shows the site of clinical vasculitis and the *lower panel* shows the associated histopathology.

SYSTEMIC MALIGNANCY

Lymphoproliferative, myeloproliferative, and carcinomatous tumors comprise less than 5% of cases of paraneoplastic cutaneous vasculitis (Fig. 6), a diagnosis that may be considered in patients with recurrent purpura; hematologic abnormalities, including cytopenia, monoclonal gammopathy, and immature blood cells; hematuria, abnormal tissue, or nodal masses on imaging studies; and refractory responses to immune therapies. There are 3 such categories of patients, including those with true paraneoplastic vasculitic syndromes wherein the vasculitis improves with extirpation or treatment of the tumor; vasculitis masquerading as malignancy, such as lung masses in GPA; and malignancy masquerading as vasculitides, as in emboli from an atrial myxoma and superficial migratory thrombophlebitis with pancreatic cancer. Most paraneoplastic cutaneous vasculitic syndromes are the result of a paraproteinemia secondary to lymphoproliferative disorders, including cryoglobulinemia in association with lymphocytic lymphoma and Waldenström macroglobulinemia.

PROGNOSIS

The distinction between localized cutaneous vasculitis and systemic vasculitis is important because the former carries a relatively favorable outcome, whereas the latter conveys the likelihood of permanent organ damage and increased morbidity and mortality. Approximately 20% to 40% of patients with cutaneous vasculitis



Fig. 6. Myelodysplastic syndrome presenting as erythema elevatum diutinum. A large ulcerative tumor shows localized fibrosing leukocytoclastic vasculitis. The *left panel* shows the site of clinical vasculitis. The *upper and lower right panel* shows the associated histopathology. (Courtesy of Juan Carlos Graces, MD, Guayaquil, Ecuador.)

have concomitant limited systemic vasculitis, notably in the kidney, such as renal-dermal vasculitis, whereas the likelihood of chronicity and systemic progression is enhanced when there is coexisting CTD, cryoglobulinemia, frank ulceration, arthralgia, more than 1 form of cutaneous vasculitic lesion such as ulceration and palpable purpura, putative muscular vessel vasculitis and SVV, normal serum IgA levels, paresthesia, fever, painless lesions, and cutaneous necrosis.¹² Histologically, the severity of vessel injury in cutaneous vasculitis correlates with the clinical severity and course.^{13,14} Up to 60% of patients presenting with cutaneous vasculitis on skin biopsy have SVV restricted to the dermis whereas the remainder have deep dermal and pannicular SVV and muscular vessel involvement.¹⁵

THERAPY

Therapy depends on the nature and severity of the vasculitis. Mild hypersensitivity due to drug reactions should be treated with discontinuation of the offending agents, antihistamines for urticaria-associated pruritus, and a short course of corticosteroids in more severe cases. Simple observation may be adequate for mild cases and transient lesions of HSP/IgAV-related purpura. Nonsteroidal anti-inflammatory agents, colchicine, antihistamines, and dapsone may be used in chronic cutaneous vasculitis without recognizable cause and in selected patients prior to administration of corticosteroids and cytotoxic drugs. Rituximab has remission-induction efficacy equivalent to cyclophosphamide in AAV, each in conjunction with corticosteroids.¹⁵ Morphologic alternations of the vessel wall lumina and perivascular areas may be useful in treatment strategy. Healed arteritis with intimal thickening due to luminal occlusion should suggest the need for anticoagulation and vascular dilating agents, whereas pathologically confirmed acute and subacute arteritis generally warrants combination immunosuppressive therapy to suppress ongoing vascular inflammation and tissue damage.

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