A Clinical Overview of Vasculitis as Seen by the Dermatologist

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The clinical spectrum of vasculitis as seen by the dermatologist varies from conditions limited to the skin to those less frequently seen as a cutaneous manifestation of a systemic process. The dermatological entities may be divided into two groups: those with vascular damage and a predominantly lymphocytic infiltrate, and those with vascular damage with leukocytoclasia. Conditions to be reviewed briefly from the first group are progressive pigmented purpura, pityriasis lichenoides et varioliformis acuta (PLEVA), and lymphoid papulosis; conditions from the second group include granuloma faciale erythema elevatum diutinum and cutaneous polyarteritis. The clinical expression of these dermatological entities depends on the size of the involved vessel, the type and degree of damage, and the level in the dermis of the vascular insult.

The so-called purpuric pigmented dermatoses are a group of uncommon eruptions which present with non-palpable purpuric lesions. These lesions favour the lower extremities but may spread to involve other parts of the body except the face, are unassociated with systemic involvement or constitutional symptoms, and, on histopathologic study, have a lymphocytic non-necrotizing superficial small vessel vasculitis with haemorrhage into the dermal papillae and epidermis. The eruptions consist of usually asymptomatic purpuric lesions that appear as 'cayenne pepper' spots or erythematous or orange-brown inflammatory plaque lesions containing a purpuric component. Some may be eczematous and pruritic. The eruptions are chronic and persist for years and eventually clear up spontaneously. They respond to administration of topical or systemic corticosteroid agents but relapse when medication is discontinued.

Pityriasis lichenoides et varioliformis acuta (Mucha-Habermann disease) is an acute dermatitis affecting mainly young males. It is characterized clinically by crops of polymorphic lesions consisting of erythematous purpuric papules and crusted vesicles that heal with superficial scarring, affecting the trunk, thighs, and flexural areas of upper extremities. A rare severe febrile ulceronecrotic variant has been described. Rarely, constitutional symptoms, such as fever, malaise, and headache that may last a few days, and, in the more severe cases, arthralgia and arthritis can occur. The disease may be misdiagnosed as chicken pox. It may clear within 6 months, but can continue for years with continuous or intermittent acute recurrences. Histologic study reveals proliferation of the dermal capillaries and damage to their endothelium with papillary oedema and presence of red blood cells and lymphocytes in and about the
capillaries and into the epidermis. Therapy is unpredictable with an occasional response to oral antibiotics and a more predictable response to phototherapy (ultraviolet B or ultraviolet A with oral psoralen).

Lymphomatoid papulosis, which may resemble PLEVA, is a continuously self-healing papular eruption that is clinically benign but which, on histopathologic examination, has malignant features. The age of onset is usually in the second to the fifth decade; both sexes are equally susceptible. The recurrent self-healing papular lesions ulcerate and heal, leaving scars. The ulcers can be greater than 2 cm. The eruption is usually widespread and asymmetric with frequent facial and/or scalp involvement. Histopathologic study reveals a wedge-shaped dermal inflammatory process with a superficial lichenoid infiltrate and an upper and lower dermal perivascular infiltrate of small and large convoluted lymphocytes as well as plasma cells, eosinophils, and neutrophils. Vascular endothelial hypertrophy, degeneration, and sometimes necrosis and thrombosis are present. Also seen are Ki-1 Ag positive large atypical lymphoid cells. The disease can last for 8 or more years. No good therapy has been found. Ultraviolet A and oral psoralen (PUVA) therapy and methotrexate can be helpful. A 10% potential exists for a transformation to malignant lymphoma (Hodgkin's disease, mycosis fungoides, or Ki-1 lymphoma).

Granuloma faciale is a chronic localized persistent dermatosis of the face, especially of the nose, cheek, or forehead. It is clinically characterized by single or multiple purplish or 'plum' coloured plaques or nodules. Histopathologic study of the infiltrate reveals not only leucocytoclasia with a granulomatous component consisting of histiocytes, lymphocytes, plasma cells, and eosinophils sparing appendages with a subepidermal arentz zone and some vascular damage. The lesions have responded to treatment with intralesional corticosteroid agents, dapsone, cryosurgery, and the CO₂ laser.

Erythema elevatum diutinum is rare and can last for many years (as long as 20 years), but it can also clear spontaneously. The eruption is characterized by symmetrical erythematous or violaceous persistent papules, nodules, or plaques on the back of the hands and extensor surface of joints. The disease may be associated with an antecedent streptococcal infection. Atypical ulcerative or vegetative skin lesions resembling pyoderma gangrenosum have been described. Arthralgias and a polyarthritis may be present at the onset of the disease. Some patients may have a paraproteinemia such as IgA or mixed cryoglobulins, and multiple myeloma may develop as well. Administration of dapsone has been helpful in controlling the disease.

Isolated organ involvement with polyarteritis has been described, but not all of these cases have proved to be isolated when long-term follow-up studies, including angiographic studies, are performed. However, two entities, cutaneous polyarteritis nodosa (CPN) and the infantile polyarteritis of Kawasaki's disease (mucomutaneous lymph node syndrome), appear to merit classification as isolated phenomena. The so-called CPN has been described as a benign chronic relapsing form of polyarteritis nodosa without visceral manifestations. The skin lesions may present as livedo reticularis and nodules with or without ulceration or as a central erythematous nodule with a surrounding circle of small red nodules. Extracutaneous features are arthralgias, arthritis, and neuropathy and myopathy of the involved lower extremities. The patient may have moderate leukocytosis and an elevated sedimentation rate. The diagnosis is confirmed by a 'deep' biopsy of skin lesions which, on histopathologic study, will reveal a necrotizing arteriolitis of the lower dermis or arteritis of the subcutaneous tissue. To my knowledge, no clinical, laboratory, or angiographic evidence of visceral involvement has been reported. The presence and role of antineutrophilic antibodies in this disease has not been described. This entity has been described in association with Crohn's disease. Therapy consists of a trial of non-steroidal anti-inflammatory drugs (NSAIDs), dapsone, and oral prednisone, depending on the patient's response.

The systemic vasculitides are a group of rare diseases whose pathogenesis is not clearly and fully appreciated and which may have cutaneous involvement. The cutaneous lesions reflect the size, nature, degree of vessel damage, location, and character of the inflammatory infiltrate. The presence of palpable purpura, chronic urticaria, haemorrhagic vesicles and blisters, and non-specific erythematous macules or papular rash suggest a vasculitis of the postcapillary venule; the presence of a livedoid erythematous pattern with or without small ischaemic ulcers or purpuric nodules and 'atrophie blanche' suggest a small artery vasculitis (so-called livedo vasculitis) of the mid-dermis; the presence of erythematous deep nodules and supplicative plaques suggest small artery vasculitis involving the panniculus; and the presence of livedo reticularis with subcutaneous nodules, deep ulcers, peripheral gangrene, and deep ecchymosis suggest vasculitis involving medium-sized arteries (Table 1). When vasculitis is suspected, the physician should rule out conditions that simulate vasculitis, define the
Table 1
Dermal manifestations of vasculitis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Definition</th>
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<tr>
<td>Vasculitis of postcapillary venules</td>
<td>Palpable purpura, chronic urticaria, haemorrhagic vesicles and bullae, erythematous purpuric macules or papules</td>
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<tr>
<td>Small artery vasculitis of mid-dermis</td>
<td>Livedo vasculitis, atrophie blanche</td>
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<td>Vasculitis of small arteries and veins involving the panniculus</td>
<td>Vasculitis involving medium-size arteries</td>
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<tr>
<td>Vasculitis involving medium-size arteries</td>
<td>Livedo reticularis, subcutaneous nodules, ulceration, peripheral gangrene</td>
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<td>Deep ecchymosis</td>
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extent of involvement of vasculitis by history, physical examination, and appropriate laboratory tests, establish the nature of the vasculopathy by biopsy or angiography or both, and attempt to clarify the pathogenic mechanism. Among the diseases that simulate systemic vasculitis with skin manifestations are the presence of atrial myxoma, septicaemia, infective endocarditis, mycotic aneurysms and embolization, intravascular lymphomas or malignancies, cholesterol embolization, idiopathic arterial calcification, neutrophilic dermatitis (Sweet’s disease, pyoderma gangrenosum, bowel-bypass syndrome), ergotism, antinuclear lip syndrome, and primary and secondary thrombosis.

To help make a diagnosis to appreciate the nature of the underlying systemic vasculitis and to direct therapy, a workable classification should be available (Table 2). The factors to be considered in establishing a classification are organ involvement, the size of involvement of vessels, the nature of the inflammation present, the presence of immunoglobulin (i.e. IgA) in the vessel wall and circulating antineutrophilic cytoplasmic antibodies (ANCA), and the response to treatment.20-24

Antinuclear cytoplasmic antibodies (ANCA) are markers for vasculitis and are associated with a continuum of renal and extrarenal disease. Such vascular lesions are characterized by necrotizing inflammation and a paucity of immune deposits. Antinuclear cytoplasmic antibodies are specific for constituents of primary granules and monocytic lysosomes. Two types of cytoplasmic staining have been demonstrated by indirect immunofluorescence. A diffuse type (C-ANCA) results from staining for the cytoplasmic 29 KD molecules and serum proteinase, and a nuclear and a perinuclear pattern results from the staining of soluble nucleophilic granule constituents, such as myeloperoxidase, elastase, and other enzymes. In 1991, Goekop proposed a classification of ANCA-associated diseases that included Wegener’s granulomatosis, classic and microscopic polyarteritis, Churg-Strauss syndrome, small vessel vasculitis, and idiopathic crescentic glomerulonephritis. The various forms of necrotizing vascular inflammation from renal limited disease to widespread vasculitis, especially polyarteritis nodosa and Wegener’s disease, have a positive C-ANCA test. P-Antinuclear cytoplasmic antibodies have been demonstrated in patients with idiopathic pauci crescent necrotizing glomerulitis.

About 40-50% of the patients with small vessel vasculitis, as seen by dermatologists, do not have any systemic manifestations. Patients with systemic involvement most frequently have a rheumatic complaint, such as that which accompanies Schönlein-Henoch purpura, cryoglobulinemia, and the so-called collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis, and Sjögren’s disease).

Table 2
Classification of vasculitis

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Definition</th>
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<tr>
<td>Hypersensitivity vasculitis (postcapillary venule)</td>
<td>Serum sickness</td>
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<tr>
<td></td>
<td>Schönlein-Henoch purpura</td>
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<td></td>
<td>Mixed cryoglobulinemia</td>
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<td></td>
<td>Hypocomplementemic vasculitis</td>
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<td></td>
<td>Vasculitis associated with connective tissue disease (also small- and medium-size vessel involvement)</td>
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<td></td>
<td>Vasculitis associated with inflammatory bowel disease, chronic active hepatitis, primary biliary cirrhosis (also small- and medium-size vessel involvement)</td>
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<td>Vasculitis associated with malignancy</td>
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<td></td>
<td>Associated with other types of vasculitis, i.e. polyarteritis nodosa, Wegener’s granulomatosis</td>
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<tr>
<td>Polyarteritis nodosa (small- and medium-size vessel involvement)</td>
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<tr>
<td></td>
<td>Idiopathic</td>
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<tr>
<td></td>
<td>Associated with viruses (also small- and medium-size vessel involvement)</td>
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<td></td>
<td>Associated with rheumatic diseases (rheumatoid arthritis, Sjögren’s syndrome)</td>
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<tr>
<td></td>
<td>Associated with inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Associated with malignancies (especially hairy cell leukemia)</td>
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<td></td>
<td>Patheric and allergic granulomatosis and angiitis (small- and medium-size vessel involvement)</td>
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<tr>
<td></td>
<td>Wegener’s granulomatosis</td>
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<td></td>
<td>Churg-Strauss syndrome</td>
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<td>Necrotizing sarcoid granulomatosis</td>
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<td>Arteritis of large vessels</td>
<td>Giant cell arteritis (temporal arteritis)</td>
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<td></td>
<td>Takayasu’s arteritis</td>
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<td></td>
<td>Complicating diseases, such as ankylosing spondylitis, Reiter’s syndrome, relapsing polychondritis, Cogan’s syndrome</td>
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Schönlein-Henoch purpura (anaphylactoid or allergic purpura) is presumed to be associated with infections and is characterized by the classic clinical triad of palpable purpura, non-deforming arthritis, and the abdominal pain associated with colic. The palpable purpura favours the lower extremities but also can affect the buttocks. The patient can also present with an erythematous macular papular pruritic eruption. The feet, lower legs, and, less frequently, the hands, scalp, and periortibital areas can become edematous. Direct immunofluorescence has demonstrated the presence of immunoglobulins, especially IgA, even to the exclusion of the other immunoglobulins in the involved skin and kidney. 

Although renal disease occurs in approximately one half of the patients, fortunately it is usually mild and self-limited in the young; however, it is more severe and tends to be chronic in adults.

Hypocomplementemic vasculitis is a syndrome characterized by an urticarial vasculitis that on biopsy reveals a necrotizing venulitis, hypocomplementemia, and multisystem involvement of arthritis, abdominal pain, glomerulitis, and chronic obstructive pulmonary disease. The skin lesions are erythematous papules or plaques that may develop central clearing. The lesions persist for 24–72 hours, may be pruritic or burning, and clear with purpuric pigmentation, hyperpigmentation, or without residua. Bullae and erythema multiforme-like lesions have been associated with urticaria-like lesions. Patients most commonly exhibit depression of the early components of the classic pathway, namely C1q, C4 and C2.

In patients who have essential mixed cryoglobulinemia, a clinical syndrome can occur that is characterized by palpable purpura, acral necrosis of the skin, Raynaud’s phenomenon, arthralgias, non-deforming arthritis, peripheral neuropathy, and glomerulonephritis.

Of the medium-size vessel vasculitides, idiopathic periarteritis nodosa or polyarteritis nodosa, a multisystem disease, is the prototype of those cases associated with infections, i.e. viral hepatitis, collagen vascular diseases, amphetamine abuse, and inflammatory bowel disease. The diagnosis is usually triggered by a high index of clinical suspicion, corroborated by characteristic angiographic findings, and confirmed by tissue diagnosis. Cutaneous lesions are an unusual presentation that occur in about 30% of cases. The nature of the skin lesions depends on the size and degree of vessel involvement. Involvement of the medium-size vessel in the lower dermis and panniculus is responsible for the livedo reticularis and tender nodules with or without ulceration and large necrotic ulcers, and the small vessel involvement in the upper dermis is responsible for the urticarial and palpable purpuric lesions.

Among the granulomatous vasculitides that may show cutaneous lesions are Wegener’s granulomatosis and Churg-Strauss vasculitis, characterized histologically by small necrotizing vasculitis and palisading necrotizing granuloma; lymphomatoid granulomatosis, characterized histopathologically by angiocentric and angiodestructive lymphocytic infiltrate with a significant number of atypical lymphocytes and plasma cells involving small arteries and veins; and giant-cell arteritis and Takayasu’s arteritis, characterized histopathologically by giant-cell granulomatous inflammation of large arteries.

Wegener’s granulomatosis is a systemic disease of unknown cause with a destructive clinicopathologic presentation, characterized by the triad of aseptic necrotizing granulomatous lesions of the upper and lower respiratory tract, focal segmental glomerulonephritis, and necrotizing vasculitis of small arteries and veins. Although limited forms of this disease have been described, they could also represent either an early or protracted stage that will ultimately become generalized. Skin lesions occur in about half of the cases; the most frequent clinical presentation is palpable purpura, which occurs mainly on the lower extremities but can involve the trunk and upper arms. Erythematous nodules that may ulcerate are also seen. The characteristic gingival changes, granular magenta gingival and interdental papillary hypertrophy with diffuse petechial markings, the so-called ‘strawberry gums’, appear to be a diagnostic clinical sign. The disease can present as pyoderma gangrenosum. The antineutrophil cytoplasmic antibodies appear to be a useful serologic and diagnostic marker and their titre may be helpful in monitoring the course of the disease and response to treatment, as well.

Complete remission has been reported with cytotoxic and adrenocorticoid therapy or with cyclophosphamide. Limited disease or mild exacerbations reportedly have been controlled with trimethoprim sulphamethazole.

Churg-Strauss syndrome is a disorder characterized by history of asthma, systemic vasculitis, peripheral eosinophilia, and extravascular granulomas. Among the cutaneous findings are palpable purpura usually on the lower extremities, a macular-papular eruption or urticaria, livedo vascular pattern with or without infarcted areas, and subcutaneous tender nodules that appear on the scalp or extremities.

Lymphomatoid granulomatosis is presented briefly because it enters into the differential
diagnosis of systemic inflammatory destruction of small blood vessels especially of the lung, skin, and central nervous system. Unlike Wegener's granulomatosis and Churg-Strauss syndrome, which have been linked immunopathologically to circulating immune complexes, lymphomatoid granulomatosis appears to be a lymphomatoid angiocentric angiolytic clonal T-cell lymphoproliferative disorder with a clinicopathologic spectrum from an initial severe inflammatory process to a lymphoma in about 13% of patients. Most commonly involved organs are the lungs, skin, and central nervous system. The skin lesions can occur in about 60% of patients, and 10% may antedate the appearance of lung involvement. Usually, erythematous dermal nodules or plaques appear that can be painful and can become arcuated and ulcerated.71

Granulomatous involvement of medium and large arteries is responsible for Takayasu's arteritis and giant cell arteritis. Takayasu's disease is an inflammatory arteriopathy of unknown cause that affects large vessels, e.g. the aorta and its branches and the pulmonary artery.72 Among the dermatological lesions that are rare are ulcerations of digits, lips, and tip of nose, atrophy of skin of face, loss of hair and teeth, and lesions resembling pyoderma gangrenosum and erythema nodosum.73

Giant cell arteritis (temporal arteritis, cranial arteritis, and granulomatous arteritis) is not limited to the vessels that originate from the arch of the aorta, especially the temporal artery, but may involve the medium or large arteries anywhere in the body.74,75 Polymyalgia rheumatica has been seen in 40–60% of patients and was the initial symptom complex in 20–40% of patients. The diagnosis should be suspected when a patient over 50 years of age presents with headache, transient or sudden loss of vision, polymyalgia rheumatica, unexplained sustained fever or anaemia, and significantly elevated sedimentation rate. Patients who are suspected of having giant cell arteritis should undergo biopsy of the temporal artery and, less frequently, of the occipital or facial artery. Among the cutaneous manifestations are temporal or occipital tenderness and, rarely, gangrene and ulceration of the scalp, tongue, and extremities.76,77

Among the entities of mixed small and large vessel necrotizing vasculitis are those associated with hepatitis antigenaemia,78 seen with chronic rheumatoid disease, such as rheumatoid arthritis,79 systemic lupus erythematosus; relapsing polychondritis; mixed connective tissue disease, Sjögren's syndrome,80 and childhood and adult dermatomyositis;81 and with granulomatosis, such as that seen with Wegener's granulomatosis and allergic angiitis and granulomatosis (Churg-Strauss vasculitis).

The two connective diseases that are more apt to occur with mixed arterial vessel disease are rheumatoid arthritis and systemic lupus erythematosus. When vasculitis occurs at onset of rheumatoid arthritis, the prognosis is poor. Necrotizing vasculitis is more apt to occur in men and in those patients who have had severe rheumatoid arthritis, rheumatoid nodules, and a high titre of rheumatoid factor or in patients who have Felty's syndrome. Among the cutaneous lesions are not only the ungual infarcts and palpable purpura and an urticarial eruption caused by small vessel disease but also leg ulcers, livedo reticularis, and digital gangrene caused by medium-size vessel involvement.

Patients with systemic lupus erythematosus can experience cutaneous lesions similar to those seen in patients with rheumatoid arthritis except for the occurrence of urticarial vasculitis in systemic lupus erythematosus.82 The vasculitis usually parallels the activity of systemic lupus erythematosus and is associated with circulating immune complex, low levels of serum complement, and elevated levels of anti-DNA antibodies. Patients with Ro-positive subacute lupus erythematosus can develop vasculitis presenting as urticaria, palpable purpura, and nailfold infarcts. Cutaneous and systemic small vessel vasculitis can also develop in patients with Sjögren's disease who have high titres of anti-Ro antibodies.

Conclusion

Hopefully, an awareness of the necrotizing vasculitides and their heterogenous presentations will help to differentiate them from their clinical simulants and will lead to an early diagnosis and more effective therapy.

References