Review Article

CUTANEOUS VASCULITIS

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Introduction

Vasculitis is not unoften missed in clinical practice [1]. It may be the primary pathological feature of a disease or manifestation of an underlying disorder. The clinical manifestations reflect the size of affected blood vessels and extent of inflammation. The term cutaneous vasculitis implies involvement of skin and, frequently, other organs, histopathologically characterized by a polymorphonuclear infiltrate and fibrinoid change in the dermal vessels. The presenting features denote the predominant and not the only organ of involvement signifying that there is no sharp line of demarcation between cutaneous and systemic vasculitis. The clinical features are those of palpable purpura, mononeuritis multiplex, cerebrovascular accident, glomerulonephritis and ischaemia or infarction of an extremity or bowel.

Aetiopathogenesis

In many of these disorders, immune mechanisms are thought to be involved in the pathogenesis [2,3]. Deposits of immunoglobulins and complement components have been demonstrated in the walls of blood vessels, and immune complexes detected in the serum of patients with various types of vasculitis. The responsible antigen, however, usually has not been identified in these immune complexes. Evidence that immune complexes cause vasculitis comes from studies of acute and chronic serum sickness in experimental animals [4]. Immune deposits or circulating immune complexes have been

described in patients with hypersensitivity vasculitis, Henoch-Schonlein purpura, polyarteritis nodosa, Wegner's granulomatosis, giant cell arteritis, Takayasu arteritis, and Kawasaki disease [5-10]. The inability to demonstrate immune deposits in the wall of an affected blood vessel, however, does not exclude the possibility of an immune complex pathogenesis because immune reactants can be removed or altered by phagocytic cells within 24 hours after the appearance of a new lesion [11]. Deposits of immune complexes in the vessel wall result either from the deposition of circulating immune complexes or local formation of an antigen antibody complex. Many factors influence the pathogenicity of immune complexes. These include the properties of antigens and antibodies, the size of immune complexes, the Fc portion of IgG and the electrostatic charges on antigens and antibodies. Other factors are the structure of endothelium, blood flow characteristics and vascular permeability.

The deposition of immune complexes with activation of the complement system leads to accumulation of inflammatory cells and eventually, to damage of the endothelium and vessel wall leading to inflammation. Blood vessels dilate and become more permeable resulting in decreased blood flow leading leukocytes to move closer to vessel wall. The interaction of leukocyte integrins with their ligands on endothelial cells is of higher affinity which leads to emigration and localisation of leukocytes which is responsible for clinical manifestations of vasculitis.

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Classifications

Vasculitis can be classified based upon etiology [12] or pathology [16] (Tables 1 & 2). However, criteria for clinical classification were recently developed by a subcommittee of American College of Rheumatology [17]. Seven clinical forms viz. hypersensitivity vasculitis, Henoch-Schonlein purpura, polyarteritis nodosa, Wegener's granulomatosis, allergic angiitis, and granulomatosis, giant cell arteritis, Takayasu arteritis and Kawasaki disease, were distinguished by clinical features, laboratory studies, angiography and biopsy reports. The criteria identify and separate one disease from the other, permit comparison for research studies and also provide better information for establishing prognosis and defining treatment.

Leucocytoclastic vasculitis

Leukocytoclastic vasculitis is an acute dis-

TABLE 1
Etiological Classification of vasculitis [12]

a. Infections and Infestations		
<i>Bacterial</i>	<i>Viral</i>	<i>Protozoal</i>
Streptococci	Influenza	Malaria
Syphilis	Poliomyelitis	
Tuberculosis	Herpes simplex	
Leprosy	Hepatitis B,A,C	
	virus infection	
	HIV	
b. Drugs		
Serum injections, sulphonamides [13], penicillin, erythromycin, tetracycline, thiazides, aspirin, iodides, methicillin, gold, amphetamine, vasoactiveamines, herbicides and insecticides, penicillamine, TAB vaccine [14], and psoralens [15].		
c. Inflammatory diseases		
Rheumatoid arthritis		
Sjogren's syndrome		
Connective tissue diseases		
Ulcerative colitis		
Crohn's disease		
d. Malignant diseases		
Visceral carcinoma		
Hodgkins disease		
Lymphatic leukaemia		
Multiple myeloma		
Lymphosarcoma		

TABLE 2
Pathological Classification of vasculitis[16]

a. Small Vessels
<i>Polymorphonuclear</i>
Allergic vasculitis
Erythema elevatum diutinum
Henoch-Schonlein vasculitis
Acute febrile neutrophilic dermatosis (Sweet)
Hypersensitivity angiitis
In 'connective-tissue' disorders
Erythema nodosum (early)
Bowel associated dermatitis arthritis syndrome
Behcet's disease
Urticarial vasculitis
<i>Lymphocytic</i>
Drug eruption
Toxic erythemas
Erythema nodosum
Pityriasis lichenoides acuta
Dysproteinaemia
Malignant atrophic papulosis
Perniosis
<i>Granulomatous</i>
<i>Systemic</i>
Wegener's granulomatosis
Allergic granulomatosis
Infective forms (leprosy, syphilis, tuberculosis)
Lymphomatoid granulomatosis
<i>Focal</i>
Lethal midline granuloma
Eosinophilic and necrotizing focal granulomas
Facial granuloma
Nodular vasculitis
b. Large Vessels
<i>Polymorphonuclear</i>
Polyarteritis nodosa
Superficial migratory thrombophlebitis
Lymphangitis
<i>Lymphocytic</i>
Peripheral vascular disease
Lupus erythematosus
<i>Granulomatous</i>
Giant cell arteritis
Erythema induratum
Takayasu's syndrome

ease commonly caused by drugs and infections; and characterised by palpable purpura, haemorrhagic and necrotic lesions. Systemic

features include pain abdomen, joint pains, gastro intestinal bleeding, haematuria and proteinuria. Investigations include urinalysis, stool for occult blood, radiological examination of chest, cryoglobulins, antinuclear antibody and serum hepatitis B antigen testing. Skin biopsy reveals fibrinoid necrosis, leukocytoclasia and RBC extravasation. On immunofluorescence study, granular deposits of C3, IgM, IgG are seen within the vessel wall. Treatment consists of antibiotics, corticosteroids and cytotoxic drugs depending on the aetiological factors. American College of Rheumatology (ACR) laid down the criteria (1990) for leukocytoclastic vasculitis i.e., age less than 16 years, history of recent drug ingestion, presence of granulocytes around arterioles or venules on histopathological examination of skin biopsy. Presence of three or more criteria give a sensitivity of 71% and specificity of 84%.

Allergic angiitis

It is characterised by hypereosinophilia and a widespread necrotizing vasculitis in people who have pre-existing asthma. In 1951, Churg and Strauss [18] described 13 patients with fever, asthma, and systemic vasculitis, hence also called as Churg Strauss syndrome. It is a rare disorder. Allergic angiitis on the skin has subcutaneous nodules, palpable purpura and skin ulcers. The ACR criteria (1990) listed for allergic angiitis are asthma, eosinophils greater than 10% of differential leucocytic count, mono/polyneuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormality and skin biopsy evidence of vessels with extravascular eosinophils. The presence of four or more criteria indicate sensitivity of 85% and specificity of 98%.

Henoch-Schonlein purpura (HSP)

A distinct form of hypersensitivity vasculitis (HSV) characterised by acute purpura and arthritis in children was first described by Schonlein [19] in 1837 and later, in 1874, Henoch [20] added colicky abdominal pain and nephritis to the syndrome. It usually af-

fects children less than 16 years old and presents between 2 and 10 years. The syndrome also occurs in adults, who tend to have a more chronic intermittent course. An upper respiratory infection frequently precedes the onset of this syndrome, suggesting an association with an infectious agent. The finding of IgA deposits in affected blood vessels and in the glomerular mesangium distinguishes HSP from other HSVs.

Clinically HSP is characterised by palpable purpura, arthritis (transient, affects large joints, and is nondeforming), abdominal pain, gastrointestinal bleeding, and in some instances, bowel infarction, perforation, and intussusception. Approximately 50% have glomerulonephritis which usually is mild, but progressive renal insufficiency can develop in a few patients. HSP is usually self-limiting, subsiding in 6 to 16 weeks. About 5 to 10% continue to have recurrent episodes for variable periods of time, ranging from months to years.

Criteria developed by the ACR for identifying and distinguishing HSP from other forms of vasculitis are age less than or equal to 20 years, palpable purpura, acute abdominal pain, and biopsy results showing granulocytes in the walls of arterioles or venules. The diagnosis of HSP is based on the presence of two or more of these criteria.

Livedoid vasculitis

Livedoid vasculitis is a chronic, recurrent, focal, purpuric, infarctive endarteritis of the middle and deep dermal vessels of the feet, ankles, and lower legs. It commonly heals with stellate white scars and peripheral telangiectasia. Episodes of activity and healing produce a polymorphous, chronic picture. The term livedoid is used because the patchy hemosiderosis, scarring, and purpuric inflammation frequently produce a false appearance of livedo reticularis [21]. Clinically early lesions show multiple, focal, purpuric infarctions, which develop into small, punched-out ulcerations about the ankles and feet. Recurrent crops of lesions show both active and healing lesions. The ulcerations

may enlarge but usually heal with the stellate, dead-white scars of atrophic blanche with peripheral telangiectasias. Continued activity produces patchy, infarctive, and scarred lesions in skin with some hemosiderosis. Among the associated diseases, most characteristic is the presence of connective tissue disease - lupus erythematosus, scleroderma, Sjogren's syndrome, and dermatomyositis. The presence of periarteritis nodosa of deep muscular vessels of the extremity or of visceral tissue may rarely be associated. Ulcers must be treated by bed rest and astringent wet dressing. Sulfapyridine, guanethidine, nicotinic acid, phenformin, and estrogen have been tried. Corticosteroids are not useful. Many patients have undergone vein stripping, grafting of ulcers, and sympathectomy with no positive benefit. Therapy for associated diseases is necessary for continued improvement.

Polyarteritis nodosa

Polyarteritis nodosa is a necrotizing vasculitis affecting small to medium size arteries and involving several organ systems. The onset of disease most often is between the ages of 40 and 60 years. The male to female ratio is 2 : 1. Skin, joints, peripheral nerves, gastrointestinal tract, and kidneys most often are involved. Lung involvement is not considered a manifestation of classic polyarteritis. Histologically, the lesions are segmental, with a predilection for branching points and bifurcations of arteries, and various lesions may be at different stages of development. Lesions show fibrinoid necrosis that usually is accompanied by an intense mixed cell inflammatory infiltrate. The ACR subcommittee on vasculitis listed 10 criteria for the classification of polyarteritis [22]. These are weight loss of four or more kilograms, livedo reticularis, testicular pain or tenderness, myalgias, mono- or poly-neuropathy, systolic pressure equal to or greater than 90 mmHg, elevated blood urea nitrogen or serum creatinine levels, positive hepatitis B serology, arteriographic abnormalities by angiogram, and the presence of granulocytes or a mixed

leukocyte infiltration in an arterial wall on biopsy. Presence of three or more of these 10 criteria is almost diagnostic. The treatment of polyarteritis initially is with steroids. In progressive disease, cyclophosphamide, and other cytotoxic drugs, such as azathioprine or methotrexate, are found effective.

Kawasaki disease

The mucocutaneous lymphnode syndrome (MCLNS) was first described by Kawasaki in 1967 [23]. It characteristically affects infants and toddlers; however, adolescents and young adults can rarely be affected. Like many disorders of unknown etiology, a list of diagnostic clinical criteria defines this entity. The cutaneous eruption may be morbilliform, scarlatiniform, multiform, or a diffuse erythema. Striking edema of the hands and feet is followed by desquamation of the fingertips and toes after 5 to 6 days. Mucous membrane changes may include conjunctivitis, cheilitis, pharyngitis, or glossitis (strawberry tongue). The acute febrile phase of the illness lasts about 2 weeks, but the complications of coronary artery aneurysm rupture, and coronary thrombosis can occur months later. Investigations reveal decreased hemoglobin, increased white cell count, raised ESR, positive CRP, raised transaminase levels, pyuria and proteinuria. Treatment consists of aspirin, 80-100 mg/kg/day.

Urticarial vasculitis

Urticarial vasculitis represents a spectrum of diseases histologically characterised by swelling of the endothelial cells, a perivascular infiltrate, leukocytoclasia, extravasation of erythrocytes and fibrinoid deposits in and around blood vessels [24]. Clinically, these diseases are characterised by painful urticarial lesions that persist for more than 24 hours and leave a residual purpura and pigmentation. Patients may also experience arthralgias or arthritis or both, that effects small joints and is nondeforming. In addition, patients may have angioedema, abdominal pain and glomerulonephritis. Renal disease usually does not progress to renal failure. The

incidence of chronic obstructive lung disease is increased in patients with urticarial vasculitis who are cigarette smokers. Chronic obstructive pulmonary disease is the major cause of morbidity and mortality in patients with urticarial vasculitis.

Urticarial vasculitis has been associated with collagen vascular diseases, infections, other underlying diseases, exposure to sun and drugs. Decreased levels of complement are found in approximately one third of patients and may be low even when disease is quiescent. Immune complexes are found in approximately 15% of patients. Low complement levels may be caused by the binding of IgG autoantibodies to C1q, resulting in activation of complement. The course of urticarial vasculitis is variable, ranging from several weeks to as long as 7 years. Treatment depends on the aetiological factor.

Pyoderma gangrenosum

Pyoderma gangrenosum is a unique cutaneous ulceration characterised by its clinical presentation. Although frequently associated with inflammatory bowel disease, it may occur independently. The etiology of pyoderma gangrenosum remains unknown but it shares the features of other disorders of neutrophil accumulation. Pyoderma gangrenosum manifests as an ulceration with an irregular, purulent base, an elevated dusky purple undermined border and a surrounding red areola. The ulcer border is tender; spontaneous pain is often present. The lesion begins with a small, tender, inflammatory pustule or nodule which may enlarge rapidly. The ulcer may heal in the centre while spreading peripherally. The scar is typically atrophic and cribriform. Ulcers are most common on the trunk and legs, but any area may be affected. Although usually occurring in adults, the disease may appear in infants or children [25]. The disease has been associated with active or occult Crohn's disease, ulcerative colitis, chronic active hepatitis, rheumatoid and other arthritis, leukemia of several types, polycythemia vera, myeloid metaplasia, paraproteinemia and multiple

myeloma. Despite thorough evaluation, however, many patients show no associated disease. Treatment modalities are prednisolones, dapsones, sulphasalazines, azathioprine, cyclophosphamide and 6-mercaptopurines.

Erythema elevatum diutinum

This rare but chronic skin disease usually appears after the age of 30 years, attacks both sexes equally and demonstrates small vessel involvement in keeping with vasculitis. Certain clinical forms of erythema elevatum diutinum (EED) are now referred to as extracellular cholesterosis. Clinically EED is a rare skin disorder, consisting of persistent, slowly evolving nodules and plaques symmetrically located over bony prominences, knuckles, elbows and knees [26]. Lesions may appear on the pretibial surfaces, around the wrists or ankles and sometimes on the buttocks. Rarely the palms and soles are involved. At first the nodules and plaques are soft and may have vesicles on their surface. But later, as fibrosis occurs, they become firm and indurated. They are usually hyperpigmented and red-brown, wine or plum in colour. Skin biopsy reveals eosinophilic collagen and extracellular cholesterosis. Lesions of erythema elevatum diutinum and extracellular cholesterosis are notoriously resistant to therapy. Although there is a tendency for lesion to regress spontaneously, this may take years. Dapsone has been reported to make a dramatic improvement in a number of cases and is probably the treatment of choice at the present time, although a number of treatment failures have been reported. Intralesional corticosteroid is worth trying. Surgery of selected lesions might be contemplated.

Giant cell arteritis

Giant cell arteritis is a wide spread granulomatous arteritis of large, medium and small blood vessels especially of cranium. Cutaneous lesions include palpable purpura, bullae and necrotic ulcers on the scalp [27]. Other manifestations are constitutional symptoms, blindness, glossitis, polyarthritis, deafness,

peripheral neuritis and mental changes. The common complications are cerebral infarction, coronary occlusion, aneurysm and mesenteric thrombosis. Skin biopsy reveals necrotizing panarteritis and granuloma formation. Treatment consists of steroids for 6-12 months. The ACR classification criteria (1990) included age greater than 50 years, new localised headache, temporal artery tenderness or diminished temporal artery pulsation, ESR greater than 50 mm and a positive artery biopsy. The presence of three or more criteria gives a sensitivity of 95.3% and specificity of 90.7%.

Acute febrile neutrophilic dermatosis

Acute febrile neutrophilic dermatosis is a rare, unusual, self-limiting illness which is characterised by a high, persistent fever with no appreciable internal organ involvement and by painful nodules and plaques with a consistent histopathologic picture and a tendency to recur [28]. On histopathologic examination of skin lesions, there is vasodilation, endothelial swelling and focal or massive infiltration of polymorphonuclear leukocytes in the upper and mid-dermis. There may be numerous pyknotic polymorphonuclear leukocytes near the centre of the infiltrate, resembling the formation of an incipient abscess. The condition is probably a hypersensitivity reaction to agents as yet undiscovered. Usually an antecedent upper respiratory infection occurs about two weeks before the onset of the skin lesion. The disease predominates in middle-aged women, who constitute 90 per cent of the reported cases. They have a persistent fever of 100 to 102°F, no chills and malaise. On physical examination no systemic signs are appreciated. The cutaneous lesions are dull red, tender and painful edematous nodules which coalesce to form plaques. Vesicles or small sterile pustules may appear on the surface of the lesions. The plaques appear asymmetrically and centrifugally on the extremities, face and neck and vary in size from 0.5 to 4.0 cm, in diameter. The active disease, fever and skin lesions subside spontaneously, usually

in four to eight weeks, although it has been reported to persist for up to six months. No scarring is present. The only significant laboratory abnormalities are leukocytosis and an elevated erythrocyte sedimentation rate. The differential diagnosis includes atypical erythema multiforme, erythema nodosum, erythema elevatum diutinum, granuloma faciale and bromoderma. The disease responds to steroids. It recurs in one third of cases.

Midline granulomas

Midline lethal granuloma (Stewart) results from malignant reticulosis [29] and is characterised by indurated swelling of nose with necrosis and ulceration which extends to the orbit, pharynx, oral cavity and brain destroying soft tissue and bone. Skin biopsy reveals lymphocytes and bizarre reticulum cells. Death is usually due to secondary infection. Treatment consist of tumoricidal X-ray therapy and immunosuppressive drugs. Midline lethal granuloma (Wegener's) is of unknown aetiology and is characterised by papules, plaques, ulcers, vesicles, petechiae and cutaneous nodules. Constitutional symptoms may be associated. The systemic features are sinusitis, rhinitis, otitis media, laryngitis, hemoptysis, chest pain, pericarditis, mono/polyneuritis, conjunctivitis and iritis. Skin biopsy reveals polymorpho-nuclear infiltration, granulomatous vasculitis and fibrosis. ACR classification criteria (1990) [30] for Wegner's granulomatosis are nasal or oral infection, X-ray chest findings of nodules, infiltrates or cavities, microhaematuria and granulomatous infiltrate on biopsy. The presence of two or more criteria gives a sensitivity of 82% and specificity of 92%.

Laboratory Investigations

Investigations in vasculitis are done depending on the cause or effect of the underlying disease and for diagnostic and prognostic purposes i.e., haemoglobin estimation, total and differential white cell count, ESR, platelet count, urine examination and culture, throat swab culture, blood sugar, liver func-

tion tests, blood culture, rheumatoid factor, antinuclear antibody, autoantibody to neutrophilic cytoplasmic antigen, immunoglobulin profile, serum complement levels, ECG, skin biopsy, immunofluorescent studies, radiological examination of chest, angiography and other investigations depending on the merit of the case.

Treatment

The successful management of any potentially serious illness lies in making an early and accurate diagnosis recognizing prognosis, anticipating the effects of disease and treatment of concurrent illnesses. Meeting these goals is often a difficult task in patients with cutaneous vasculitis, for which clinical manifestations may mimic infection, malignancy, endocrinopathy, coagulopathy, atrial myxoma [31] with emboli, cholesterol emboli, antiphospholipid antibodies, Kohlmeier Dego's disease, drug toxicity and poisoning. Many of these competing diagnoses may be ruled out by a thorough history and physical examination and some others can be assessed within hours by appropriate laboratory studies. Suspicion of cutaneous vasculitis should be especially heightened when combination of the following features are present : rash with palpable purpura, glomerulonephritis, peripheral neuropathy, pre-existing features of autoimmunity, and evidence of regional ischemia. Still, situations may arise when one cannot be certain whether fever, rash, a heart murmur and/or pulmonary infiltrates are due to infection, multifocal emboli or vasculitis. Under pressing circumstances there may be a need to provide therapies that address more than one contingency pending the results of investigations and subsequently specific treatment should be instituted as and when definite diagnosis is established.

The use of immunosuppressive agents in vasculitis is a debatable issue. However, it is generally agreed that successful treatment of these patients may be extremely complex and that their care requires frequent scrutiny of disease activity and attention to complications of therapy. The cornerstone of success-

ful management lies in early diagnosis and successful treatment. Involvement of special organ systems often requires a multidisciplinary team approach.

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