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CONTINUING MEDICAL EDUCATION

Cutaneous small-vessel vasculitis

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Cutaneous small-vessel vasculitis (CSVV) refers to a group of disorders usually characterized by palpable purpura; it is caused by leukocytoclastic vasculitis of postcapillary venules. CSVV can be idiopathic or can be associated with a drug, infection, or underlying systemic disease. Initially, the pathogenesis of CSVV is immune complex related, but in its later stages different pathogenetic mechanisms may intensify the reaction and lymphocytes may predominate in the infiltrate. Cure requires elimination of the cause (ie, drugs, chemicals, infections, food allergens) when possible, as well as therapy with nonsteroidal antiinflammatory agents, corticosteroids, dapsone, potassium iodide, fibrinolytic agents, aminocaproic acid, immunosuppressive agents (ie, cyclophosphamide, azathioprine, methotrexate, cyclosporine) or even monoclonal antibodies, depending on disease severity. (J Am Acad Dermatol 1998;39:667-87.)

Learning objective: At the conclusion of this learning activity, participants should have a firm understanding of the cause, pathogenesis, clinical features, and treatment of CSVV.

Cutaneous small-vessel vasculitis (CSVV) is characterized by a spectrum of cutaneous lesions, but palpable purpura is most common. Biopsy specimens show angiocentric, segmental inflammation, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls.[1-4] The skin is often the only organ involved, but systemic involvement may occur. Skin lesions may represent the initial sign of a systemic vasculitis.[3-7]

Although blood vessels of any size may be affected in systemic vasculitis, CSVV usually affects small venules (postcapillary venules)[3-8]; the histopathologic pattern is that of a leukocytoclastic vasculitis with a presumed immune complex–mediated pathogenesis. In the later phases different pathogenetic mechanisms may become involved with the evolution of a lymphocytic infiltrate.[9-17] Recently recurrent cutaneous eosinophilic vasculitis has been described.[18-20]

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CLASSIFICATION

The marked variability in the clinical and histologic features of the vasculitides and the numerous causes for these disorders have created confusion and prevented the adoption of a universally accepted classification. After Zeek's article in the 1950s, the groundwork for many contemporary nosologic schemes was presented by Gilliam and Smiley[21] in 1976; since then many alternative classification systems have been proposed.[22-28] The most recent one proposed by the American College of Rheumatology (ACR) in 1990[28] classifies vasculitis as follows: polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, hypersensitivity vasculitis, Henoch-Schönlein purpura, giant cell (temporal) arteritis, Takayasu's arteritis, granulomatous angiitis of the central nervous system, Berger's disease, and Kawasaki disease. Table I illustrates the ACR criteria for the diagnosis of

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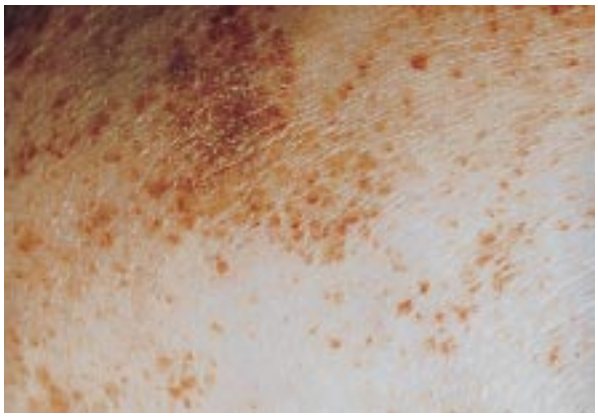

Fig 1. Cutaneous small-vessel vasculitis is manifested clinically by spectrum of cutaneous lesions, "palpable purpura" representing its clinical hallmark.

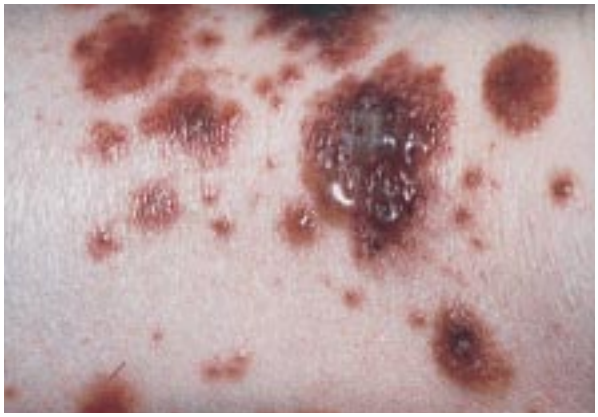

Fig 2. Cutaneous small-vessel vasculitis with palpable purpura, nodules and ulcers.

hypersensitivity vasculitis, which corresponds to CSVV. In this classification 3 particularly obvious problems are the attempt to codify the histologic findings of hypersensitivity vasculitis, the age limit, and the drug at onset category. Alternatively, some investigators have proposed a classification based on the histopathologic features; with this classification vasculitis can be divided into neutrophilic, lymphocytic, and granulomatous subtypes that involve either small or large vessels.[27] Neutrophilic vasculitis is known histologically as leukocytoclastic vasculitis, which, when affecting small venules of the dermis, is the characteristic feature of CSVV. This is the most common type of vasculitis affecting the skin.

However, the development of a classification that is clinically relevant, is workable by various specialists, and addresses clinical features, laboratory features, and underlying causes of vasculitis is a goal that remains elusive. An attempt to present a working classification has been previously presented by us[29,30] and is discussed here (Table II).

Table I. American College of Rheumatology criteria for hypersensitivity vasculitis (1990)[28]

1. Age at disease onset > 16 y
2. Medication at disease onset
3. Palpable purpura
4. Maculopapular rash
5. Biopsy including arteriole and venule with histologic changes showing granulocytes in a perivascular or extravascular location

At least 3 of 5 criteria must be present. The presence of 3 of 5 criteria was associated with a specificity of 83.9% and a sensitivity of 71%.

Table II. Proposed working classification of vasculitis[30]

I. Cutaneous small-vessel vasculitis
A. Idiopathic cutaneous small-vessel vasculitis
B. Henoch-Schönlein purpura
C. Essential mixed cryoglobulinemia
D. Waldenström's hypergammaglobulinemic purpura
E. Associated with collagen vascular disease
F. Urticarial vasculitis
G. Erythema elevatum diutinum
H. Rheumatoid nodules
I. Reactive leprosy
J. Septic vasculitis
II. Large-vessel necrotizing vasculitis
A. Polyarteritis nodosa
1. Benign cutaneous form
2. Systemic form
B. Granulomatous vasculitis
1. Wegener's granulomatosis
2. Allergic granulomatosis
3. Lymphomatoid granulomatosis
C. Giant cell arteritis
1. Temporal arteritis
2. Takayasu's disease
D. Large-vessel vasculitis with collagen vascular disease
E. Nodular vasculitis

INCIDENCE

CSVV occurs equally in both sexes and at all ages,[3,4] and approximately 10% of affected patients are children.[31,32] Confusion is created by the ACR criteria that label patients younger than 16 years of age with CSVV as having Henoch-

Table III. Cutaneous small-vessel vasculitis: Precipitating agents

A. Infections
1. Bacterial infections (β-hemolytic *Streptococcus* group A, *Staphylococcus aureus, Mycobacterium leprae)*
2. Viral infections (hepatitis A, B, C virus; herpes simplex virus; influenza virus)
3. Fungal infections *(Candida albicans)*
4. Protozoan infections *(Plasmodium malariae)*
5. Helminthic infections *(Schistosoma haematobium, Schistosoma mansoni, Onchocerca volvulus)*
B. Drugs (insulin, penicillin, hydantoins, streptomycin, aminosalicylic acid, sulfonamides, thiazides, phenothiazines, vitamins, phenylbutazone, quinine, streptokinase, tamoxifen, anti-influenza vaccines, oral contraceptives, serum)
C. Chemicals (insecticides, petroleum products)
D. Foodstuff allergens (milk proteins, gluten)

Table IV. Cutaneous small-vessel vasculitis: Association with coexistent diseases

Chronic diseases
Systemic lupus erythematosus
Sjögren's syndrome
Rheumatoid arthritis
Behçet's disease
Hyperglobulinemic states
Cryoglobulinemia
Bowel bypass syndrome
Ulcerative colitis
Cystic fibrosis
Primary biliary cirrhosis
HIV seropositivity and AIDS
Malignant neoplasms
Lymphoproliferative disorders
Hodgkin's disease
Mycosis fungoides
Lymphosarcoma
Adult T-cell leukemia
Multiple myeloma
Solid tumors
Lung cancer
Colon carcinoma
Renal cancer
Prostate cancer
Head and neck cancer
Breast cancer

Schönlein purpura and patients older than 16 years of age as having hypersensitivity vasculitis. We consider Henoch-Schönlein purpura to be a subset of CSVV mediated mainly by IgA immune complexes, which affects both children and adults.

CLINICAL FEATURES

CSVV (Figs 1 and 2) is manifested clinically by a spectrum of cutaneous lesions, although "palpable purpura" is its clinical hallmark.[1-4] At the onset, the lesions might not be palpable, but almost all patients have purpura. As the process continues, the lesions, which range in size from pinpoint to several centimeters, may become papulonodular, vesicular, bullous, pustular, or ulcerated as superficial infarctions occur.[1-8,33,34] Occasionally, subcutaneous edema in the area of the vascular lesions can be observed. Lesions, usually at the same stage, occur in crops, and they appear first and predominate on the legs and ankles. Other dependent areas or areas under local pressure are also affected.[3-5] Lesions may also occur on other areas, but they are uncommon on the face, palms, soles, and mucous membranes. Lesions may be mildly pruritic or painful and subside within 3 or 4 weeks, leaving residual hyperpigmentation or an atrophic scar.[3,4,8] The disease may be self-limiting, but can recur or become chronic and intermittent, with new crops of lesions appearing for months or years. Every episode of eruptive cutaneous vascular lesions may be associated with fever, malaise, arthralgia, and/or myalgia.[3-5,7] Unusual manifestations of CSVV may occur on dependent areas of the body or areas under local pressure or otherwise traumatized (Koebner phenomenon).[35]

ETIOLOGY

There are no recognized genetic factors.[8-36] Many factors, especially infections (eg, viral, bacterial, fungal, protozoan, helminths), drugs (eg, insulin, penicillin, sulfonamides), chemicals (eg, insecticides, petroleum products), and food (eg, milk proteins) should be considered as a possible cause of CSVV[3-5,6,8,32,37] (Table III). The frequency of viral or bacterial infections is probably underestimated.[32]

CSVV has been reported in association with coexistent diseases (ie, collagen-vascular diseases, hypergammaglobulinemic purpura, cryoglobulinemia, inflammatory bowel disease, malignant neoplasm, cystic fibrosis)[3-8,32,33] (Table IV).

In many patients the cause of CSVV remains unknown.[3-6,8,32,36] The factors to which a clear etiologic role can be attributed in CSVV are limited, and no cause is identified in up to 60% of patients.

Infections, drugs, foods, as well as constitutional and local factors may play some part in the initiation or perpetuation of the disease.[3,4,7,9,38] Most of the etiologic factors have been incriminated by association rather than by direct demonstration. Only the streptococcal M protein, *Mycobacterium tuberculosis,* and the hepatitis B surface antigens have been found in the same pattern and in the same affected vessels as the corresponding antibodies.[38-40] Acral pustular lesions are the hallmark of chronic gonococcal vasculitis. The bowel bypass syndrome is another pustular vasculitis. It is associated with bacterial overgrowth in blind loops of bowel and in inflammatory bowel disease.[33] Papulonecrotic tuberculids with necrotizing papules, which heal with varioliform scars, are considered the extreme form of hypersensitivity to *M tuberculosis.* In addition, erythema induratum (Bazin), with inflammatory deep nodules leading to ulceration on the calves of women, has been recognized as a hyperergic reaction to mycobacteria.[3,4,33] Nodular vasculitis (subcutaneous inflammation) may be a reaction to deposits or inadequate clearance of bacterial antigens with various local factors affecting individual vulnerability.[3,4,33]

Purpura and ischemic necrotic lesions have been described with infections caused by mycoplasma and rickettsiae. Recently CSVV has been described in association with chronic hepatitis caused by hepatitis C or A virus during treatment with oral contraceptives (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg), intravenous streptokinase, intravenous tamoxifen, and after anti-influenza vaccination.[3,4,33]

Cold, stasis, previous injury, or constitutional defects may predispose patients to the development of vasculitis. In livedo vasculitis, which is probably not a true vasculitis, ulceration progresses in an irregular fashion and is painful; atrophie blanche is evident and the stellate appearance with involved surrounding skin is characteristic.[3,4,33]

CSVV has been demonstrated in some patients with chronic infections (eg, viral, bacterial, fungal, protozoan, helminthic),[6,8,38-44] serum sickness, and serum sickness–like reactions[8,36,45] (Table III). Usually the clinical presentation is that of urticarial vasculitis and, less commonly, palpable purpura.[8,36]

Serum sickness and serum sickness–like reactions may be produced by exposure to drugs (eg, penicillin, hydantoins, aminosalicylic acid, streptomycin, thiazides, sulfonamides, streptokinase, tamoxifen, oral contraceptives, anti-influenza vaccine, and serum) and are currently considered as immune-complex reactions. The symptoms (fever, malaise, urticaria, arthralgias, nausea, vomiting, lymphadenopathy) appear 7 to 10 days after primary exposure or 2 to 4 days after secondary exposure and last for 4 or more days. Usually these diseases resolve without sequelae.[8,45,46,47]

CSVV may occur in association with a variety of collagen vascular diseases,[8,36,48,49] most frequently systemic lupus erythematosus,[50-54] Sjögren's syndrome,[55-57] and rheumatoid arthritis,[58-61] as well as Behçet's disease.[62-64] In addition, patients with hyperglobulinemic states[65] and cryoglobulinemia[66-69] may have CSVV. CSVV is only occasionally associated with bowel bypass syndrome,[70,71] ulcerative colitis,[72] cystic fibrosis,[73] and primary biliary cirrhosis[72]; there have been reports of CSVV in patients with HIV seropositivity or AIDS.[74-76]

Sjögren's syndrome is typically characterized by the triad of keraconjunctivitis sicca, xerostomia, and positive rheumatoid factors, and it may be associated with CSVV in 20% to 30% of patients. Clinical lesions range from petechiae to palpable purpura to widespread ecchymoses. It has also been reported that cutaneous vasculitic manifestations are commonly associated with both the antibodies of Sjögren's syndrome A and B (SS-A and SS-B) and vasculitis of the peripheral nerves and muscles.[3,4,8,55-57]

In patients with rheumatoid arthritis, vasculitis more often develops when HLA-DR4 is present. Severe rheumatoid arthritis with high-titer rheumatoid factor and nodules is often characterized by small to medium-sized vessel involvement with associated signs and symptoms, such as peripheral neuropathy, digital gangrene, nailfold infarcts, palpable purpura, cutaneous ulceration, gastrointestinal bleeding, scleromalacia, and possibly heart, lung, and kidney involvement. Other patients may have cutaneous vasculitic lesions, such as nailfold telangiectases, minute digital ulcerations or petechiae, and digital pulp papules (Bywater's lesions). The early lesions of this mild type have been studied and substantiate that they are indeed a form of leukocytoclastic vasculitis.[3,4,8,33,58-61]

Behçet's disease consists of an association of oral aphthae, genital aphthae, and posterior uveitis.

The patients may also have cutaneous pustular vasculitis, other ocular manifestations, thrombophlebitis, seronegative arthritis, as well as neurologic, gastrointestinal, renal, and cardiovascular involvement. Histologically oral, genital, and cutaneous lesions show a neutrophilic vascular reaction that may be leukocytoclastic vasculitis or a neutrophilic reaction with late lymphocytes.[3,4,62-64]

In patients with hyperglobulinemic states, affecting predominantly younger women, CSVV is characterized by crops of petechial hemorrhages on the dependent parts of the body together with polyclonal hypergammaglobulinemia.[3,4,8,65]

In patients with cryoglobulinemia, CSVV usually presents as recurrent palpable purpura of the lower extremities. Cryoglobulins are immunoglobulins that precipitate at cold temperatures and redissolve on warming. Cryoglobulins belong mainly to the IgG or IgM (macroglobulin) fraction and rarely to the IgA fraction.[3,4,36,66,69,77,78] Type I cryoglobulins are single monoclonal immunoglobulins (usually IgM) that occur predominantly in patients with plasma cell myeloma or Waldenström's macroglobulinemia. Type II cryoglobulinemia include two or more immunoglobulin fractions (usually IgG and IgM); the IgG fraction is polyclonal, but the IgM fraction is always monoclonal and has rheumatoid activity. Both types of cryoglobulins can be present in patients with Waldenström's macroglobulinemia, connective tissue diseases, and chronic infections, but they are in most cases idiopathic (essential mixed cryoglobulinemia). Finally, type III cryoglobulins are immune complexes in which all the immunoglobulin fractions are polyclonal. In most patients cryoglobulins accompany infective, inflammatory, and autoimmune diseases; sometimes they are not associated with any disease and are classified as essential mixed cryoglobulinemia,[78] a disorder in which typical skin manifestations are dependent on the season. Cold purpura manifests as petechial hemorrhages on cold-exposed areas, especially the hands and feet, or as large ecchymoses. Moreover, cold urticaria, Raynaud's syndrome, ulcerations, and acrocyanosis can be present. Symmetric arthralgias may accompany cutaneous manifestations. In some patients the course of the disease is particularly aggressive with severe compromise of peripheral circulation characterized by progressive renal involvement, ocular symptoms, cerebrovascular accidents, and cardiac insufficiency.[79,80]

Various researchers have reported an association between CSVV and HIV seropositivity or AIDS. Palpable purpura or petechial hemorrhagic lesions are the major clinical manifestations. The legs and arms are the most commonly affected sites, but lesions may occur on other parts of the body. Not surprising, given the frequent follicular accentuation of skin disease in HIV-seropositive patients, is the report of an HIV-positive patient with CSVV in a follicular localization.[74-76]

CSVV can also be associated with malignancies[3,4,8,36,81,82] (Table IV), especially with lymphoproliferative disorders (Hodgkin's disease, mycosis fungoides, lymphosarcoma, adult T-cell leukemia, multiple myeloma).[72-87] Solid tumors (lung cancer, colon carcinoma, renal cancer, prostate cancer, head and neck cancer, and breast cancer) are less commonly associated with CSVV.[81,88,89] In some patients CSVV can occur 2 to 4 years before the clinical manifestation of the tumor,[81] and the major clinical feature is again palpable purpura of the lower extremities.[81] Less common presentations include urticarial vasculitis and erythema elevatum diutinum.[81,82] Some pathogenetic mechanisms have been postulated to explain the association between CSVV and malignant neoplasms.[65,66] Tumor cells might (1) cause immunologic reactions against vascular endothelium, (2) release various cytokines (provoking endothelial injury), (3) induce a delayed hypersensitivity reaction by deposition of cancer proteins on vessel walls, (4) overrun vessel walls, (5) induce critical levels of circulating immune complexes injuring the postcapillary venule endothelial cells, or (6) behave as sensitizing agents. Concomitant precipitating events (infections, drugs) might also provoke immune complex–mediated disease in the setting of neoplastic disease. No cause can be established in approximately 50% of patients with CSVV (idiopathic CSVV).[3,4,8]

SUBSETS OF CSVV AND RELATED DISORDERS

Henoch-Schönlein purpura is characterized clinically by skin lesions (in all cases, by definition), joint pains (74% to 84%), gastrointestinal symptoms (61% to 76%), and renal changes (44% to 47%).[90,91] This disorder occurs primarily in

children (mainly boys) with a peak incidence between 4 and 8 years of age.[91] Confusion exists because rheumatologists tend to label patients with CSVV younger than 16 years of age as having Henoch-Schönlein purpura, whereas dermatologists reserve this term for patients with IgA circulating immune complexes and CSVV. The disease often follows a streptococcal or upper respiratory tract infection with a latency of 1 to 3 weeks. In approximately 40% of patients, the cutaneous manifestations are preceded by mild fever, headache, joint symptoms, and abdominal pain for up to 2 weeks.[90] The most common skin manifestations are symmetric petechial hemorrhagic or palpable purpuric lesions on the lower extremities and buttocks; the trunk is usually spared. The skin lesions often regress after 10 to 14 days. Arthralgias and arthritis usually involve the knees and ankles. Gastrointestinal symptoms include colicky pain, vomiting, melena, and hematemesis. Acute focal or diffuse glomerulonephritis may occur; microscopic hematuria and proteinuria are a constant feature.[36] Progression to acute and chronic renal failure has been reported.[90] Central nervous system involvement may occur as headaches and diplopia.[92] Direct immunoflorescence studies show deposits of immunoglobulins (IgA),[93] complement components (C3, C5), and fibrin within vessel walls.[93]

Another possible variant of CSVV is acute hemorrhagic edema of infancy, characterized by the abrupt onset of edema and palpable purpura in infants (younger than 2 years of age) who are otherwise healthy. Biopsy specimens show leukocytoclastic vasculitis. The disease has a short benign course followed by spontaneous complete recovery.[94]

The chronic recurrent disorder urticarial vasculitis is a leukocytoclastic form of CSVV that usually affects young adult women. The clinical manifestations are pruritic red wheals or elevated erythema and occasionally petechiae.[95-100] The lesions persist for 2 to 3 days, unlike ordinary urticaria that clears within 24 hours.[95-100] The disease may present with atypical erythema multiforme or angioedema. This form of CSVV may be associated with low-grade fever, arthralgias, abdominal pain, uveitis, renal disease, polylymphadenopathy, and obstructive pulmonary disease. The course of the disease is chronic. Biopsy specimens show leukocytoclastic vasculitis. Laboratory findings from patients with active disease include elevated erythrocyte sedimentation rate; hypocomplementemia with depressed CH_{50}; C1q, C4, or C2; blood eosinophilia; and leukocytosis. Some patients have antinuclear antibodies, rheumatoid factor, or cryoglobulins. This form of CSVV can also occur in patients with infections, serum sickness, systemic lupus erythematosus, and Sjögren's syndrome.

Schnitzler's syndrome is characterized by urticarial vasculitis in association with monoclonal IgM and varying extracutaneous manifestations, including fever, arthralgia, bone pain, lymph node enlargement, hepatomegaly, and hyperostosis. Some patients may have an abnormal complement profile, rheumatoid factor, antibodies to nonidentified soluble nuclear antigens, and anticytoplasmic antibodies. The monoclonal protein has been regarded as "monoclonal gammopathy of unknown significance." Although the long-term course of the disease is usually benign, evolution to true lymphoplasmocytic malignancy has been reported.[33,101]

In a variant of the Muckle-Wells syndrome (chronic relapsing urticaria, fever, arthralgias, deafness, and renal amyloidosis) the urticarial lesion histologically was leukocytoclastic vasculitis. Amyloid deposits have been seen in eccrine sweat glands.[33,102]

Erythema elevatum diutinum is a rare disorder that is more frequent in female patients. Clinically the most prominent skin lesions are nonpurpuric, persistent, erythematous papules and plaques on the extensor surface of the extremities. The lesions are often accompanied by arthralgias (in approximately 40% of patients) and drug intolerance. The cause of this disorder might be an allergic reaction to streptococcal superantigens. Biopsy specimens reveal leukocytoclastic vasculitis. The disease is usually chronic, although sometimes lesions heal spontaneously.[3,4,8,32,33,103-105]

Livedo vasculitis is characterized by a flat network of intersecting blue-red lines. This is not a true vasculitis and should be distinguished from the necrosing livedo reticularis often present in larger vessel vasculitis and from cholesterol emboli or hyperviscosity states. There is a predilection for distribution on the legs, arms, and lower trunk. Ulceration is rare. Livedo vasculitis may be associated with systemic lupus erythematosus, cryoglobulinemia, and cerebrovascular disease. This last

association, called Sneddon's syndrome, is characterized by livedo vasculitis and hemiplegia, aphasia, and/or hemianopsia.[3,4,8,32,106,107]

Rheumatoid nodules develop in approximately 20% of patients with chronic rheumatoid arthritis. Sites of predilection are the ulnar region of the elbows, less often the hands (especially on the backs of the fingers), the ears, or mechanically stressed skin regions. The nodules are chronic, hard, flesh-colored projections; they vary in size from 5 to 15 mm and may ulcerate from pressure or trauma. Specimens from lesions reveal palisading granuloma formation with a central zone of altered collagen with fibrin deposits. The lesions usually persist indefinitely.[33,58,61]

Apart from the vascular changes in rheumatoid nodules, vasculitis is a common complication of seropositive rheumatoid arthritis, particularly of the "classic" or complicated variety. The following cutaneous manifestations are seen: nailfold and finger pulp lesions, small painless red-brown infarcts in the nailfolds, or as larger painful hemorrhagic papules on the fingertips; bullae of the tips of fingers and toes that progress to involve a wide area carry a poor prognosis; mononeuritis multiplex, resulting from involvement of the vasa nervorum and leg ulcers. Prognosis depends on the severity and extent of the changes.[33,58-61]

Nodular vasculitis affects chiefly women from 30 to 60 years of age. The legs are predominantly involved, particularly the posterolateral aspects, but lesions may occur on the thighs and arms. The evolution of the nodules is usually slow. Lesions that do not ulcerate may heal within 2 to 6 weeks with little atrophy or scarring. The nodules continue to erupt at irregular intervals for months or years.[3,4,8,32,33]

In HIV-seropositive patients palpable purpura may develop in a follicular localization. It is a symmetric eruption on the anterior aspects of the legs, thighs, and scrotum that consists primarily of well-circumscribed, 3 to 5 mm, perifollicular, purpuric papules. Because perifollicular hemorrhage is one of the earliest and most specific signs of scurvy, some investigators have suggested that HIV infection can reduce total body vitamin C stores enough to produce follicular accentuation of certain skin diseases.[74,77]

SYSTEMIC INVOLVEMENT IN CSVV

In addition to cutaneous involvement, which may be the only apparent manifestation of the disease and can cause significant symptoms and morbidity itself, any organ can be involved with associated specific clinical and pathologic manifestations. In addition, distinctive patterns of organ system involvement have led to the designation of separate identifiable syndromes.[3,4]

Table V. Cutaneous small-vessel vasculitis: Systemic manifestations*

Kidneys (nephritis with microscopic hematuria and proteinuria; acute and chronic renal failure)
Gastrointestinal tract (colicky pain, nausea, vomiting, diarrhea, melena, and hemathemesis)
Lungs (asymptomatic or cough and hemoptysis)
Heart (myocardial angiitis, pericarditis)
Nervous system (headache, diplopia, hypoesthesia, paresthesia)
Joints (arthralgia, arthritis)
Ear, nose, and throat (particularly in granulomatous vasculitis)
Eyes (retinal vasculitis, conjunctivitis, keratitis, pseudotumor cerebri)
Miscellaneous (fever, constitutional symptoms, pancreatitis)

*Immune complexes are deposited in the locations shown in the table.

Systemic vasculitis (Table V) often, but not always, has cutaneous manifestations (eg, CSVV), but the latter often occurs without any demonstrable systemic manifestation. It is best to consider that every patient with CSVV may have a systemic disease; other frequently affected sites include the synovia, pleura, pericardium, and gastrointestinal tract (which should be evaluated with stool guaiac tests). Thus a careful history and physical examination are mandatory. Attention must be given in particular to ear, nose, and throat (ENT) examination, especially in cases of large-vessel vasculitis, such as Wegener's granulomatosis, because those patients may also have CSVV lesions, and neurologic signs and symptoms. Every patient should be screened for renal involvement. In addition, a test for anti–neutrophil cytoplasmic antibodies (ANCA) may be advisable, and a positive result should be followed by investigation to discover a possible necrotizing systemic vasculitis if the antibodies are directed toward proteinase-3 or myeloperoxidase.[3,4,108,109]

ANCAs are autoantibodies that react with cytoplasmic structures of neutrophils or monocytes. With indirect immunofluorescence these antibod-

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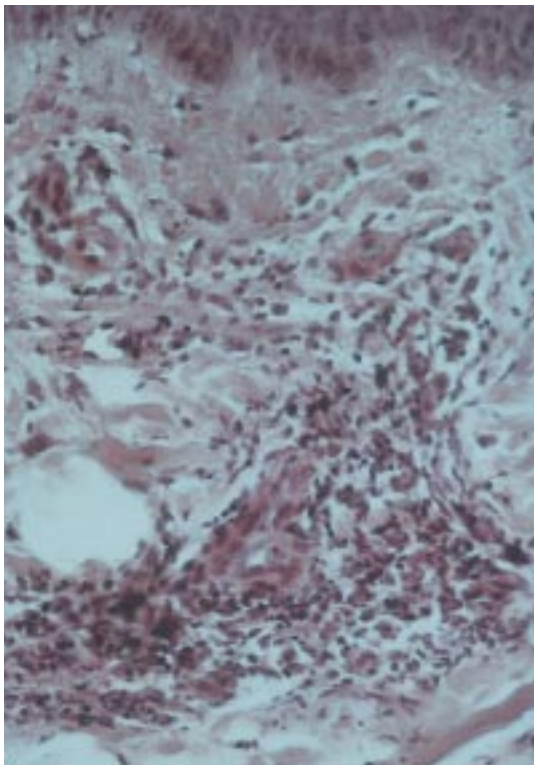

Fig 3. Photomicrograph of leukocytoclastic vasculitis reveals angiocentric segmental inflammation, endothelial cell swelling, fibrinoid necrosis of blood vessel walls, and cellular infiltrate around and within blood vessel wall composed largely of neutrophils showing fragmentation of nuclei (karyorrhexis or leukocytoclasia).

ies show two distinct patterns: a cytoplasmic pattern (c-ANCA) and a perinuclear pattern (p-ANCA). c-ANCA recognizes a 29-kd serine protease, known as proteinase-3, whereas p-ANCAs are directed against myeloperoxidase. The presence of c-ANCA is noted in diseases like extensive Wegener's granulomatosis (in > 90% of patients), limited Wegener's granulomatosis without renal involvement (75% of patients), and vasculitis overlap syndromes (40%-50%). Changes in c-ANCA titer can precede disease activity and may be used as a guideline for treatment. p-ANCAs are found more frequently in the other forms of CSVV.[108]

HISTOPATHOLOGY

The hallmark histopathologic pattern of CSVV is leukocytoclastic vasculitis. A lymphocytic form (in which lymphocytes predominate) has also been described.[9,109,110] However, there is still not enough evidence to prove that the lymphocytic pattern is truly relevant. Old lesions of CSVV may no longer demonstrate leukocytoclastic vasculitis and may contain mainly lymphocytes around blood vessels. Recently, an eosinophilic pattern has been described.[18-20] Leukocytoclastic vasculitis (Fig 3) is characterized by angiocentric segmental inflammation, endothelial cell swelling, fibrinoid necrosis of blood vessel walls (postcapillary venules), and a cellular infiltrate around and within dermal blood vessel walls composed largely of neutrophils showing fragmentation of nuclei (karyorrhexis or leukocytoclasia). Erythrocyte extravasation is another key feature. Thrombosis of the affected postcapillary venules and hyalinization of blood vessel walls may be observed in the late phase of the disease.[9,110,111] In the later phase lymphocytes and monocytes may predominate in the infiltrate.

PATHOGENESIS (Fig 4)

The histologic pattern of leukocytoclastic vasculitis, such as in the Arthus reaction, may result from the deposition of circulating immune complexes, in moderate antigen excess, which initiates the vasculitic process in patients with CSVV.[111,112] Immunofluorescence and ultrastructural studies have documented immunoglobulins (IgG, IgM, IgA), complement components (C1q, C3) and fibrin deposits within postcapillary venule walls.[3-6,8,113,114] The deposited immune complexes are postulated to activate the classical and alternative complement pathways.[32,115,116] The activation of the complement cascade by immune complexes results in the production of the C3a and C5a anaphylatoxins, which, in turn, degranulate mast cells.[7,32,115] In addition, these mediators attract neutrophils to the lesional area. During this process, circulating neutrophils adhere to the endothelial cells and subsequentely migrate into the surrounding connective tissue where they may phagocytize and degrade the immune complexes.[6,7] At the same time, neutrophils disintegrate and release different lysosomal enzymes (protease, collagenase, elastase) that may damage the vascular endothelium.[115] Another mechanism by which neutrophils damage endothelium is in the production of oxygen free radicals, which, in the presence of iron free radicals, become especially injurious products.[6]

Clinical experience indicates that immunoreactants are detectable only in the early lesions of

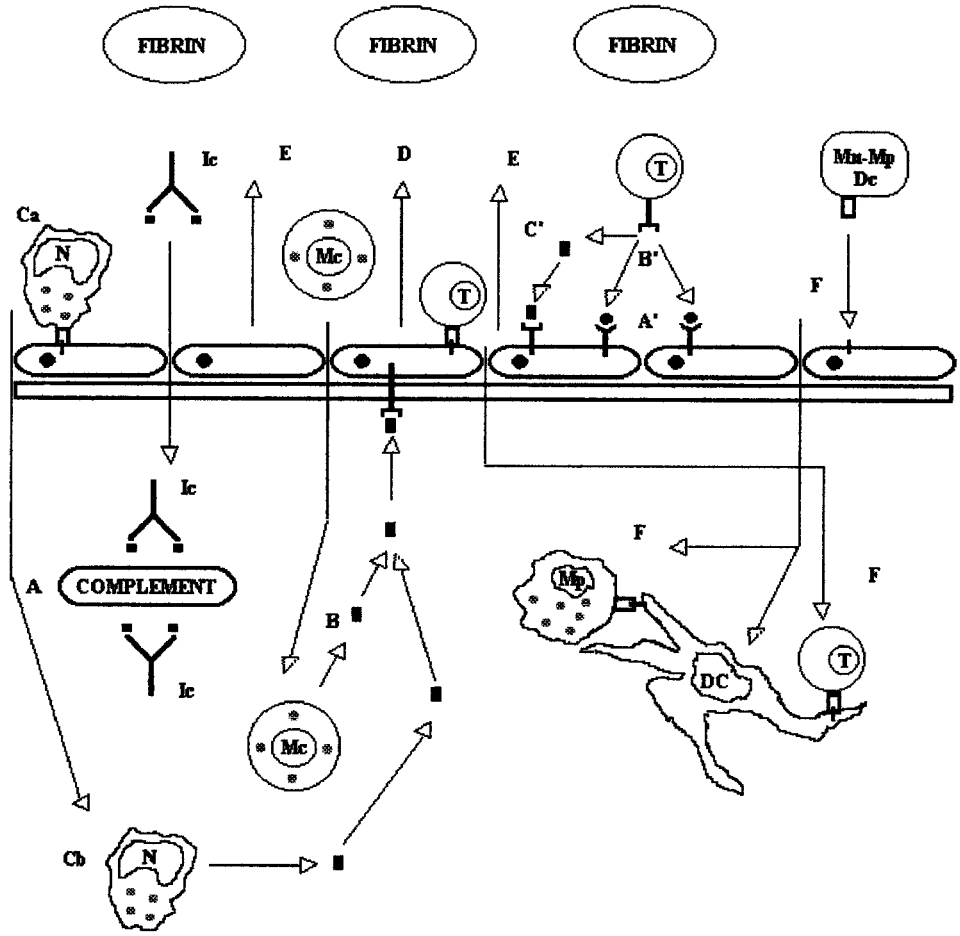

Fig 4. Pathogenesis of cutaneous small-vessel vasculitis. *N*, Neutrophils; *Ic*, immune complexes; *Mc*, mast cell; *T*, T lymphocyte; *Mp*, macrophage; *Dc*, dendritic cell; *Mn*, monocyte. **Cutaneous small-vessel vasculitis (early phase): *A,*** Intraperivascular deposition of circulating immune complexes and activation of the complement cascade; ***B,*** activation of mast cells and release of mediators; ***Ca,*** neutrophils become adherent to endothelial cells and migrate into the surrounding connective tissue; ***Cb,*** neutrophils phagocyte and degrade the immune complexes; at the same time these cells are disintegrated and release different lyzosomal enzymes; ***D,*** release of inflammatory mediators by activated endothelial cells; these cytokines could lead to a hypercoagulative state, leading to possible microvascular thrombosis; ***E,*** secretion of mediators by activated endothelial cells; ***F,*** mediators attract inflammatory cells to the lesional area. **Cutaneous small-vessel vasculitis (late phase): *A´,*** Expression of "non self" antigens by endothelial cells (consequent to release of lyzosomal proteolytic enzymes by neutrophils); ***B´,*** endothelial cells operating as "antigen presenting cell" may activate the T lymphocytes; ***C´,*** release of cytokines by activated T lymphocytes; ***D,*** as in early phase of cutaneous small-vessel vasculitis; ***E,*** as in early phase of cutaneous small-vessel vasculitis; ***F,*** as in early phase of cutaneous small-vessel vasculitis.

CSVV (3 to 12 hours).[113-116] The entire chain of events from initial immune complex and complement deposition to removal usually requires about 18 to 24 hours.[7,113-116] The production of various inflammatory agents (leukotriene B_4, histamine, thrombin, interleukin [IL]-1, IL-6, tumor necrosis factor [TNF]–α, interferons) increase the influx of neutrophils into the tissue and induce the synthesis and expression of a variety of surface adhesion molecules on the endothelial cells that mediate adhesion of these cells to endothelium.[6,113-122] Thus the "selectins," platelet activation–dependent

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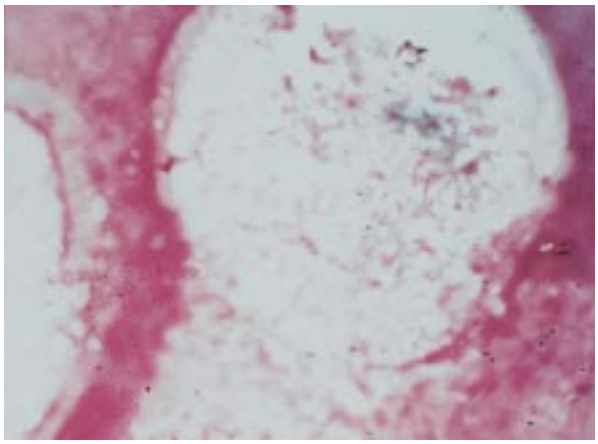

Fig 5. Cutaneous fibrinolytic activity results increased in early phase of cutaneous small-vessel vasculitis.

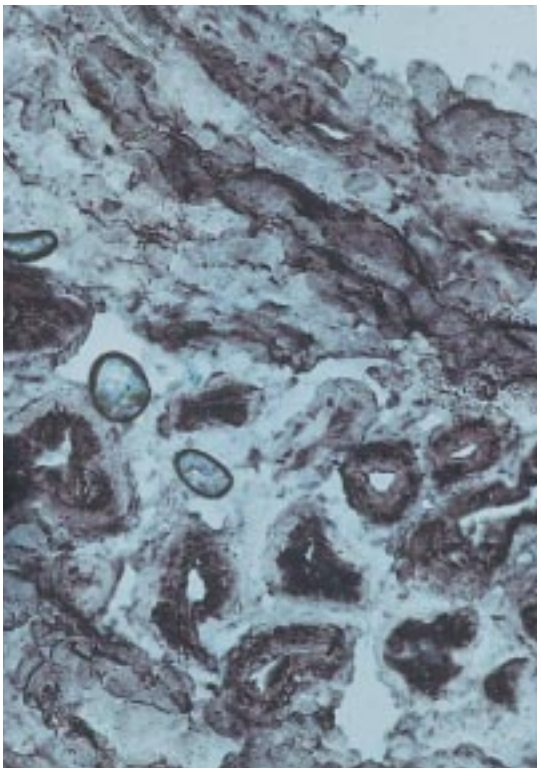

Fig 6. In situ hybridization: specific mRNA expression of adhesion molecules ICAM-1. (Original magnification ×25.)

granule external membrane protein (PADGEM or GMP 140), endothelial leukocyte adhesion molecule–1, and the mouse lymph node homing receptor (gp90, or Mel-14 antigen) mediate neutrophil migration at inflammatory sites.[122-126] The first is rapidly mobilized to the surface of endothelial cells after stimulation with thrombin, histamine, and complement components, whereas the others are expressed 2 to 8 hours after stimulation with inflammatory mediators, especially IL-1.[127-130] Immune complexes may also interact by means of their Fc receptor with lymphocytes, provoking the release of various cytokines.

Many factors appear to influence the deposition of circulating immune complexes and both amplify and maintain the tissue damage,[37] specifically (1) the ability of the erythrocytes to transport complement-related immune complexes to the fixed macrophage system (the red cells express receptors for the fragment C3b of complement)[37]; (2) hydrostatic pressure and turbulent flow[37,131]; (3) the functional state of the tissue macrophage system (that may be partially "blocked," such that the immune complexes are not efficiently removed)[37]; (4) platelet release of serotonin and histamine (which facilitates the initial immune complex deposition within postcapillary venules walls)[132,133]; and (5) the integrity of the fibrinolytic system. Cutaneous fibrinolytic activity varies depending on the stage of the disease; it is increased in the early phase (Fig 5) and reduced in the late phase. It has been hypothesized that immune complexes, interacting by means of their Fc receptor with endothelium, may activate the endothelial cells, thereby provoking release of high levels of tissue plasminogen activator (t-PA). This activation of the local fibrinolytic system influences both the vasopermeability and the tissue deposition of immune complexes.[122,134-142]

The vascular endothelium participates in the regulation of hemostasis, vascular permeability, and vascular tone and plays a key role in immunologic reactions and acute and chronic inflammation.[124] The imbalance between the procoagulant and anticoagulant properties of the endothelial cells may lead to thrombosis.[143] Many stimuli may influence the activation of endothelium, for example, histamine, immune complexes, anoxia, thrombin, and various cytokines (IL-1, IL-2, TNF-α, interferon gamma).[144-157] At basal conditions, the endothelial cell surface is anticoagulant.[115-122] Immunohistochemical, electron microscopic, and in situ hybridization studies have demonstrated that the infiltrate in lesions of CSVV is poor in $CD3^+$, $CD4^+$, $CD1a^+$, and $CD36^+$ cells in the early phase of the leukocytoclastic vasculitis, whereas it is rich in these cells in the later phase.[11-17] The

adhesion receptors intercellular adhesion molecule–1 (Fig 6) and LFA-1 are expressed in the late phase.[11-17] These data seem to suggest that in the late phase of leukocytoclastic vasculitis the deposition of immune complexes with activation of the complement cascade and the release of mediators, lysosomal enzymes, and oxygen free radicals could provoke the expression on the cell membrane of endothelial cells of "not self" antigens.[11-17] The dendritic cells and T cells could initiate a secondary cell-mediated immune response or contribute to self-perpetuation of the disease.[11-17] These very endothelial cells might participate as antigen-presenting cells, releasing inflammatory mediators (anaphylatoxin C and cytokines) that could provoke expression of class I and II major histocompatibility complex antigens (by interferon gamma) on the vascular surface endothelium. These cytokines could lead to a hypercoagulative state, with possible microvascular thrombosis.[11-17] According to this point of view we support the concept of the dynamic nature of CSVV, in which the infiltrate progressively changes from a preponderance of neutrophils over lymphocytes to a predominance of lymphocytes, as a continuum of a single disease process. On the basis of this hypothesis, the different histologic patterns could be caused mainly by differences in the age of the biopsy specimens.[19,111,158]

Antiphospholipid antibodies may be important in microvascular injury,[159] in systemic lupus erythematosus, Takayasu's arteritis, and Henoch-Schönlein purpura. Antiphospholipid antibodies (which are able to react with the sugar phosphate DNA, ie, the same epitope that is responsible for expression of lupus anticoagulant, provoking a biologically false-positive reaction for syphilis) might form immune complexes with phospholipids (which are present on the endothelial cells, such as phosphatidylserine or phosphatidylinositol) or cross-react with bacterial or viral antigenic substances.[159-163] In addition, these antibodies (through their effects on thromboxane production from platelets and prostaglandin production from vascular endothelial cells) might play some role in the development of microvascular lesions following pathways other than that of immune complex–mediated vascular injury.[159-163]

THE FIBRINOLYTIC SYSTEM IN CSVV

The fibrinolytic system is a physiologic process that involves the degradation of the insoluble polymer fibrin into the soluble fibrin degradation products.[136,140,142,164,165] This system is part of a complex mechanism that regulates the equilibrium between fibrinosynthesis and fibrinolysis.[140,142] This balance is a consequence of the activity of inhibitors (plasminogen activator inhibitor 1 and 2, and antiplasmins) and activators (tissue-type plasminogen activator [Mr 74000] and urokinase [Mr 55000]) of fibrinolysis.[136,140,142,164-167] The lysis of the insoluble polymer fibrin requires plasmin (an endopeptidase with powerful proteolytic activity).[140,142,168] This active enzyme derives from plasminogen by means of plasminogen activators.[169] The plasminogen activator inhibitors inhibit plasminogen activation, in contrast to the antiplasmins that specifically antagonize the proteolytic action of plasmin.[170]

Abnormal fibrinolysis has been demonstrated in patients with CSVV.[134-142] Circulating immune complexes interacting by means of their Fc receptor with venular endothelial cells may determine in the first stage of the disease (hyperfibrinolytic phase) a massive release of endothelial tissue-type plasminogen activator (t-PA) with subsequent activation of the local fibrinolytic system (Fig 5). This influences vasopermeability, facilitating the passage of serum and immune complexes and their tissue deposition.[122,134-142] All this provokes activation of the complement cascade, kinin, and prostaglandin synthetic systems.[171-173] This initial hyperfibrinolytic phase, characterized clinically by urticarial wheals, is followed by a late hypofibrinolytic phase, clinically manifestated by palpable purpura, which seems related to the reduction of endothelial t-PA release and high levels of plasminogen activator inhibitors. The reduction of fibrinolytic activity, leading to intravascular deposition of fibrin (with subsequent areas of necrosis) may activate the coagulative-fibrinolytic system with the transformation of new fibrinogen into fibrin. This leads to microvascular thrombosis and both amplification and maintenance of tissue damage.[122] The synthesis and release of plasminogen activators or plasminogen activator inhibitors can be modulated by various cytokines (IL-4, TNF-α).[142,174-176]

NEUROPEPTIDES, VASCULAR TONE, AND IMMUNE FACTORS IN CSVV

Neuropeptides are protein molecules present in the nerve cells of the central and peripheral ner-

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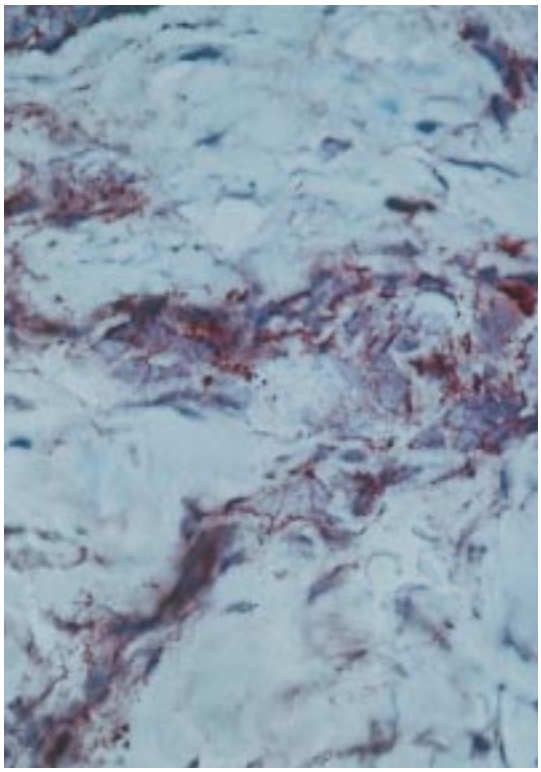

Fig 7. γ/δ T lymphocytes in infiltrate of late phase of leukocytoclastic vasculitis. (Original magnification ×25.)

vous system, where they function as neurotransmitters or immune modulators, or both.[177,178] Cutaneous neuropeptides are contained in myelinated fibers (A delta fibers) and unmyelinated fibers (C fibers).[178] The control of cutaneous circulation includes various mechanisms: the vasoconstrictor tone of blood vessels is mainly under the control of the sympathetic nerves that secrete noradrenaline and neuropeptide Y, whereas parasympathetic nerves containing acetylcholine and neuropeptides, such as vasoactive intestinal peptide and peptide histidine isoleucine, seem to play a role in vasodilatation. The cutaneous nervous fibers that release neuropeptides, such as substance P, neurokinin A, and calcitonin gene-related peptide (CGRP), also provoke vasodilatation.[179]

Substance P and neurokinin A are members of the tachykinin family; they develop vasodilator action and increase vascular permeability.[180] Substance P, in inducing the activation of mast cells and macrophages, stimulates the release of cytokines (IL-1, TNF-α, histamine, leukotrienes, prostaglandin D_2) with subsequent expression of adhesion molecules on the endothelium and chemotactic action for neutrophils and monocytes. Injection into the skin of substance P determines increased cutaneous fibrinolytic activity, mediated by t-PA.[177-180] In addition, substance P reduces the duration of action of CGRP. CGRP expands the plasma extravasation induced by substance P. In addition, CGRP induces the expression of endothelial leukocyte adhesion molecule–1 and GMP-140 at the level of endothelial cells, and it is also chemotactic for T cells.[177] The endothelial cells, borderline between blood and extravascular tissues, play an important role in the physiology and pathology of the skin, participating in the regulation of hemostasis, vascular permeability, and vascular tone. The endothelium modulates these mechanisms through interaction with other cells and release of a wide array of mediators. Molecules synthesized and released by the vascular endothelium include cytokines (IL-1, IL-6, IL-8, colony-stimulating factors) and chemotactic factors (gro-α and MCP). The endothelial cells regulate vascular tone through the production of endothelium-derived relaxation factor and endothelium-derived contracting factor. Little is known about the role of NPs in the vasculitic phenomemon. On the basis of the most recent data we can hypothesize the following:

- Neuropeptides modulate the fibrinolytic system.
- Neuropeptides modulate the local immune system.
- Neuropeptides activate macrophages and mast cells, which release cytokines.
- Neuropeptides provoke transitory vasodilatation and vasopermeabilization.
- Neuropeptides induce the expression of adhesion molecules on endothelial cells.

γ/δ T CELLS AND CSVV

γ/δ T cells are a small population of T lymphocytes that express a T-cell receptor characterized by the γ and δ polypeptide chains.[181-184] These cells are mainly localized at peripheral interfaces (skin, gut, lungs) where they function as a first line of defense against infections.[181-184] Recent experiments have shown that γ/δ T cells are able to recognize human heat shock proteins (HSPs, a family of proteins whose synthesis increases in response to various types of injury, including temperature changes, UV radiation, malignant transformation, and infection) as well as HSP-65 kd of *M tubercu-*

losis. This HSP-65 kd protein shares approximately 50% sequence identity with the corresponding human HSPs, such that a cross-reaction between pathogens and human HSPs could be hypothesized.[181,183-187] Thus γ/δ T cells might mediate surveillance of epithelia against transformed, infected, or otherwise stressed autologous cells.[187] The occasional presence of γ/δ T cells (Fig 7) has been observed in leukocytoclastic vasculitis in CSVV, in which these cells are widely represented in CSVV patients with a documented infectious cause.[14,16,188-190*] These patients express the HSP-72 kd (Fig 8) in endothelial cells and antigen-presenting cells. The observation that high levels of both γ/δ T cells and abnormal expression of HSP-72 kd were evident in the lesional skin in patients with CSVV with an infectious cause could suggest that the infectious agents lead to selective raised tissue levels of HSPs, which are preferentially recognized by T γ/δ cells.[189] This could explain the increased levels of γ/δ T cells in the infiltrate only in those patients with an infectious cause and might provide, if supported by further studies, a clue to the infectious cause of CSVV.[189]

LANGERHANS CELLS AND VASCULITIS

Langerhans cells are members of the dendritic cell system that reside in the skin.[191,192] The identification of these cells is based on demonstration of the expression of CD1a antigen, by light microscopy, and a characteristic inclusion, the Birbeck granule by electron microscopy.[193] Another less common marker of Langerhans cells is ATPase activity,[194,195] which has been used in conjunction with CD1a antigen. Langerhans cells that do not possess Birbeck granules should be labeled "indeterminate cells," but this term is being abandoned because (1) Birbeck granules may be relatively rare in a cell and serial sectioning of the whole cell would be required to exclude their presence (this is, as a rule, an unfeasible task), (2) there is no evidence that Birbeck granules are necessary for the function of Langerhans cells; therefore, the placement of cells without this inclusion body in a separate category among $CD1a^+$ cells is not justified.[196,197] Langerhans

*Ghersetich I, Campanile G, Comacchi C, Lotti T. Gamma/delta TCR lymphocytes: A marker of cutaneous necrotizing venulitis with infective etiology? Presented at the 52nd Annual Meeting of the American Academy of Dermatology, Washington, DC, Dec 4-9, 1993.

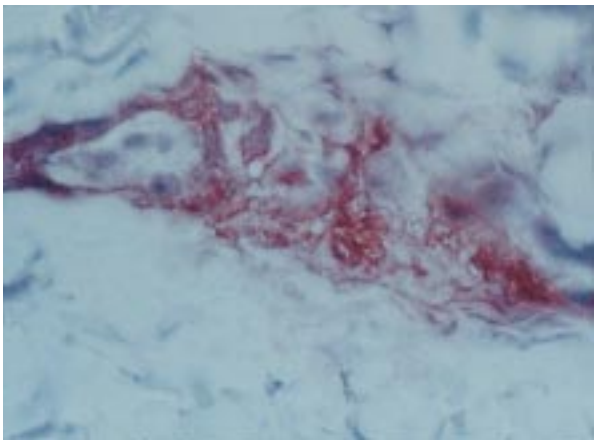

Fig 8. Heat shock protein 72 kd expression in late phase of leukocytoclastic vasculitis. (Original magnification ×40.)

cells contribute to the creation of a favorable microenvironment for T lymphocytes independent of antigen presentation.[198] Therefore they may be primarily responsible for the formation of T-helper lymphocyte infiltrates in the skin.[191]

We investigated the cellular infiltrate of patients with CSVV, both leukocytoclastic and lymphocytic dominant and, in cases of leukocytoclastic vasculitis, in early (within 2 to 3 hours after appearance of a new lesion) and late phases (more than 24 hours after appearance of a lesion). In the late phase of leukocytoclastic vasculitis we found many mononuclear cells, including lymphocytes, in addition to neutrophil remnants. Special attention was paid to the presence of dendritic cells in the infiltrate and their relation to lymphocytes, when present.[191,199-202] Electron microscopy revealed many oval or dendritic cells in the dermis in the late phase of leukocytoclastic vasculitis. They had a pale nucleus, with a thin peripheral rim of condensed chromatin, few cisternae of rough endoplasmic reticulum and primary lysosomes, a well-developed Golgi apparatus, and many smooth, sometimes coated, vesicles. These cells were in contact with each other and with pericytes, lymphocytes, and perivascular dendritic macrophages and were interpreted, on the basis of ultrastructure, as immature cells of dendritic lineage.[200-202]

The observed pattern of the cell infiltrate suggests that a cell-mediated immune response may play a major role in the pathogenesis of late lesions of vasculitis and that dendritic cells and lymphocytes contribute to the self-perpetuation of

leukocytoclastic vasculitis. Cell-mediated immunity may be activated in these cases in response to endogenous antigens that appear in lesional areas during the early phase of the disease, possibly as a consequence of the release of proteases and other active molecules from neutrophils.[191]

PSYCHOSOMATIC PURPURAS AND VASCULITIDES

Stress is a term that is readily recognized by everyone but defies rigorous scientific definition. It is widely interpreted as the emotional and biologic responses to novel or threatening situations. In humans, however, the term *distress* seems to be preferable, more clearly defining that it is the response that is being referred to, rather than the stimulus. Distress has been postulated to be capable of precipitating an overt illness, for example, when it occurs coincidentally with an incipient infection or neoplasm. Moreover, distress is able to provoke several disorders and symptoms in many tissues and organs, including the skin. Special consideration is given to a peculiar form of skin disease, psychogenic purpura, together with the stigmata of mystics that, in large part, seem to be conditioned or provoked (or provokable) by emotional stress or psychic reaction that influence cutaneous fibrinolytic activity.[203-206]

LABORATORY FINDINGS

Laboratory screening tests are always required in patients with CSVV both to confirm the diagnosis and to determine the exent of systemic vasculitis and/or the existence of underlying associated diseases. The necessary laboratory evaluations include histopathologic and occasionally immunofluorescent microscopic studies, blood tests, and urinalysis.[3-8,32,37]

Direct immunofluorescence microscopy may show immunoglobulins, complement components, and fibrin deposits in and around the blood vessels; IgG rather than IgM is more likely to be present when there is an underlying collagen vascular disease, and IgA may be indicative of Henoch-Schönlein purpura.[3-8,32-34] Decreased levels of complement components are more often present in CSVV associated with rheumatoid arthritis (C1, C4, C2), systemic lupus erythematosus (C1q, C4, C2, C3, factor B, C9), cryoglobulinemia, Sjögren's syndrome, or urticarial vasculitis. Circulating immune complexes, rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies, and cryoglobulins can be detected in association with antistreptolysin antibodies and hepatitis B (C and A) surface antigens. Urinalysis may reveal proteinuria, hematuria, and cylindruria caused by renal involvement.[3-9,37]

Because significant morbidity can result from systemic involvement in patients with CSVV, careful evaluation of the patient should be done to rule out or define the type and severity of systemic involvement.[109]

In addition, in patients suspected of having systemic vasculitis, tests such as c-ANCA for Wegener's granulomatosis may be helpful.[109] The recommended battery of laboratory studies, roentgenograms, serologic tests, and cutaneous biopsy is not specific for systemic involvement. Such studies serve only as a guide to rule out systemic vasculitis. In other words, if the laboratory results are normal, further invasive studies to identify systemic involvement are probably warranted.[109,207] Laboratory studies do not replace the need for a thorough history and physical examination. If a diagnosis of systemic disease is still being considered after the initial screening, 3 options are available. When large-vessel vasculitis is suspected, the following should be considered: (1) sural nerve electrophysiologic studies, followed by biopsy if abnormal; (2) muscle biopsy; and (3) open lung biopsy if pulmonary disease is evident. If the diagnosis remains unconfirmed after these studies and the patient has an abnormal "active" urinary sediment rate, percutaneous renal biopsy should be considered. If the urinary sediment rate is negative, other studies such as testicular biopsy or visceral angiography, or both, can be considered. In addition, in another recent study, the association of a variety of anutoantibodies and factors released by damaged endothelial cells were analyzed for their predictive value in the diagnosis of large-vessel vasculitis.[109,207,208] It was found that of the 4 tests employed (ANCA, anticardiolipin antibody, von Willebrand factor antigen, and fibronectin), only ANCA was specific. Although the other tests were often abnormal (highly sensitive), they were not specific.[109]

TREATMENT OF CSVV

When possible, identification and removal of the causative agent (eg, drugs, chemicals, infections, foods) are an effective approach to treat-

ment. This is occasionally followed by rapid clearance of the skin lesions, and no other treatment is necessary. Otherwise, local and systemic therapies are recommended.[3-8,32-37]

Local treatments

Topical therapy (corticosteroid creams, antibiotic creams) may be helpful in some patients.[3,4,6,209] Gradient support stockings may be useful for lesions on the legs.

Systemic treatments

These treatments include (1) systemic corticosteroids, (2) nonsteroidal anti-inflammatory drugs, (3) colchicine, (4) dapsone, (5) potassium iodide, (6) antihistamines, (7) fibrinolytic agents, (8) aminocaproic acid, (9) immunosuppressive agents, and (10) monoclonal antibodies.[3-8,32-34,210,211] Almost no double-blind, placebo-controlled, prospective trials exist.

Systemic treatment with corticosteroids (prednisone, 60-80 mg/d) is advised for patients with CSVV with significant systemic manifestations or those with significant cutaneous ulceration. Rebound is a serious problem with rapid reduction of dose; therefore, if this therapy is selected, it should be reduced slowly (3 to 6 weeks).[3-8,32,36,210]

Nonsteroidal anti-inflammatory drugs such as acetylsalicylic acid and indomethacin have been used for vasculitis with persistent or necrotic lesions. Some cases of urticarial vasculitis have responded to indomethacin[5,37] or phenylbutazone in cases of nodular vasculitis.[7,32,210,212] These therapies are probably more effective for myalgias, fever, and arthralgia than for actual lesions.

Oral colchicine, which inhibits neutrophil chemotaxis, in doses of 0.6 mg twice to three times daily, may be helpful in chronic forms of the disease, although a recent double-blind study failed to show benefit.[3-8,32,36]

Dapsone (50 to 200 mg/d) has also been used, usually in patients with skin involvement alone (especially in patients with erythema elevatum diutinum).[3-6,32,36,210,213]

Potassium iodide (0.3-1.5 g four times daily) is useful in nodular vasculitis.[210]

H_1 antihistamines alone or in combination with H_2 antihistamines are used to alleviate pruritus and to block histamine-induced endothelial gap formation with resultant trapping of immune complexes.[3-8]

Fibrinolytic agents can be used in patients who have decreased plasma and/or cutaneous fibrinolytic activity. Stanozolol (5 mg twice daily), phenformin hydrochloride (50 mg twice daily) plus ethyloestrenol (2 mg four times daily) can be used for about a year. Other fibrinolytic agents, such as heparin (5000 U twice daily), mesoglycans (50-100 mg/d), and intramuscular defibrotide (700 mg/d) have been beneficial in various types of hypofibrinolytic vasculitis.[210,214,215]

Low-molecular-weight dextran, given its fibrinolytic effect, is also indicated in the hypofibrinolytic phase of disease. This seems to produce beneficial effects both in livedo reticularis and livedoid vasculitis.[8,216]

Aminocaproic acid (8-16 g/d for many months) can be used to treat patients with hyperfibrinolytic states.[217]

Immunosuppressive agents, such as cyclophosphamide (2 mg/kg per day or as a monthly intravenous pulse), methotrexate (10-25 mg/wk), azathioprine (50-200 mg/d) and cyclosporine (3-5 mg/kg per day), are effective, especially in patients with CSVV with a rapidly progressing course and systemic involvement that is not controlled with corticosteroids or for patients with large-vessel vasculitis.[3,4,7,32,36,210,218]

Recently a patient with intractable systemic vasculitis was treated with two monoclonal antibodies, Campath-1H and rat CD4 228. Anti-idiotypic antibodies, cytokine inhibitors, or antagonists and monoclonal antibody treatment against leukocyte and endothelial cell adhesion molecules, such as ICAM-1 or VCAM-1, have been used in some pilot studies to prevent vascular and perivascular inflammatory reaction and necrotizing vasculitis connected with organ tranplantation and reconstructive surgery.[211,218,219*]

In the course of vasculitis induced by immune complexes with concomitant arterial disease drugs that reduce platelet aggregation (dypyridamole, acetylisalicylic acid, tiklid) and plasmapheresis can be used.[8]

The correction of local factors such as trauma, cold stasis, and lymphedema may be important.[209]

*Winn RK, Vedder NB, Paulson JC. Monoclonal antibodies (MAbs) to leukocyte adhesion molecules ameliorate tissue damage resulting from ischemia reperfusion injuries. Presented at the International Conference on The Vascular Endothelium and Inflammation, Schloss Elmau, Germany, 1992.

CONCLUSIONS

CSVV can manifest clinically with a large spectrum of cutaneous lesions; "palpable purpura" is the clinical hallmark. At the initial stage, and when still small, the lesions might not be palpable but almost all show purpura at onset. As the process continues, the lesions, ranging in size from pinpoint to several centimeters, may become papulonodular, vesicular, bullous, pustular, or ulcerative and superficial infarctions may occur. Lesions predominate on the legs and ankles. They may occur on other areas of the body, but are uncommon on the face, palms, soles, and mucous membranes. The skin is often the only organ apparently involved, but clinically relevant systemic involvement may occur and the changes in the skin may represent the initial signs of a systemic vasculitis and/or some other underlying diseases.

The hallmark histopathologic pattern of CSVV is leukocytoclastic vasculitis with a presumed immune complex–mediated pathogenesis. Leukocytoclastic vasculitis is characterized by angiocentric segmental inflammation, endothelial cell swelling, fibrinoid necrosis of blood vessel walls (postcapillary venules), and cellular infiltrate around and within dermal blood vessel walls composed largely of neutrophils showing fragmentation of nuclei (karyorrhexis or leukocytoclasia). In the later phase other pathogenetic mechanisms occur with evolution of the histopathologic pattern to a lymphocytic form. This may be caused by the expression of "nonself" antigens, consequent to the release of lysosomal proteolytic enzymes by neutrophils. Cutaneous fibrinolytic activity is increased in the early phase and reduced in the late phase of leukocytoclastic vasculitis, leading to intravascular and perivascular deposits of fibrin with subsequent tissue hypoxia and necrosis.

γ/δ T lymphocytes and HSP are strongly represented only in lesional skin of cases of leukocytoclastic vasculitis of documented infectious cause, suggesting that the investigation of γ/δ T cells and HSPs in CSVV might provide evidence of an infectious cause of CSVV.

Therapeutic approach requires elimination of the cause (drugs, chemicals, infections, food allergens) when possible. In other patients local and systemic anti-inflammatory or immunosuppressive therapy is recommended.

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CME examination

Identification No. 898-111

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-32, Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. J Am Acad Dermatol 1998;39:667-87.

Directions for questions 1-3: Give single best response.

1. Which sex is usually affected by cutaneous small-vessel vasculitis?
   a. Female
   b. Male
   c. No prevalence

2. What is the clinical presentation of cutaneous small-vessel vasculitis?
   a. Palpable purpura
   b. Wheals
   c. Ulcers
   d. Blisters
   e. Palpable purpura is the most typical aspect, but wheals, nodules, ulcers, and/or blisters may also be present.

3. Cutaneous small-vessel vasculitis is characterized by lesions mainly on the
   a. legs
   b. buttocks
   c. palms and soles
   d. upper trunk and arms
   e. neck

Directions for questions 4-6: For each numbered item, choose the appropriate lettered item.

   a. Erythema elevatum diutinum
   b. Henoch-Schönlein purpura
   c. Urticarial vasculitis

4. The most common skin finding is symmetric petechial hemorrhagic or palpable purpuric lesions on the lower extremities and buttocks; the trunk is usually spared.

5. The clinical presentation consists of pruritic reddish wheals or elevated erythema and occasionally petechiae.

6. The most prominent skin lesions are nonpurpuric persistent erythematous papules localized on the extensor surface of the extremities.

Directions for questions 7-9: For each numbered item, choose the appropriate lettered item.

   a. Nodular vasculitis
   b. Acute hemorrhagic edema of infancy
   c. Livedo vasculitis

7. The lesions are nodules found predominantly on the lower legs, particularly the posterolateral aspects.

8. This disorder is characterized by a flat network of intersecting blue-red lines.

9. It is characterized by sudden onset of acute edema and palpable purpuric skin lesions in infants (younger than 2 years of age) in good general condition.

Directions for questions 10-14: Give single best response.

10. Henoch-Schönlein purpura occurs most commonly in
    a. children
    b. young men
    c. young women
    d. middle-aged men
    e. middle-aged women

11. What are the histologic hallmarks of cutaneous small-vessel vasculitis?
    a. Angiocentric segmental inflammation, endothelial cell swelling and fibrinoid necrosis of the vessel wall (postcapillary venules), and cellular infiltrate around and within dermal blood vessel walls composed largely of neutrophils showing fragmentation of nuclei (karyorrhexis or leukocytoclasia)
    b. Perivascular inflammation, red blood cell extravasation, and endothelial cell swelling
    c. Edema of the papillary dermis with endothelial cell swelling and perivascular inflammation with exocytosis
    d. Red blood cell extravasation and elastosis
    e. Perivascular inflammation, mild spongiosis of the stratum malpighii, and patchy parakeratosis

12. Is fibrinolytic activity usually modified in vasculitis?
    a. Cutaneous fibrinolytic activity is usually increased in the early phase of cutaneous small-vessel vasculitis and reduced or absent in the late phase.
    b. Cutaneous fibrinolytic activity is not modified in cutaneous small-vessel vasculitis.
    c. Cutaneous fibrinolytic activity is always increased in cutaneous small-vessel vasculitis.
    d. Cutaneous fibrinolytic activity is always decreased in cutaneous small-vessel vasculitis.

13. In which patients are high levels of both γ/δ T cells and abnormal expression of HSP72 kd expected?
    a. In those with cutaneous small-vessel vasculitis caused by food allergens
    b. In those with cutaneous small-vessel vasculitis associated with malignant neoplasm

c. In those with drug-induced cutaneous small-vessel vasculitis
d. In those with cutaneous small-vessel vasculitis with documented infective origin
e. In those with livedo vasculitis

14. Substance P
    a. reduces cutaneous fibrinolytic activity
    b. increases the duration of action of calcitonin gene-related peptide
    c. provokes vasoconstriction
    d. provokes vasodilation, increases cutaneous fibrinolytic activity, and reduces the duration of action of calcitonin gene-related peptide

Directions for questions 15-19: For each numbered item, choose the appropriate lettered item.

a. Immunosuppressive agents
b. Anti-inflammatory drugs
c. Corticosteroids
d. Dapsone
e. Potassium iodide

15. Usually in patients with skin involvement only, especially in patients with erythema elevatum diutinum
16. In cases of nodular vasculitis
17. For patients with cutaneous small-vessel vasculitis who have significant systemic manifestations or for those with significant cutaneous ulceration
18. In patients with cutaneous small-vessel vasculitis with a rapidly progressing course and systemic involvement that is not controlled with corticosteroids
19. For patients with vasculitis who have more persistent or necrotic lesions

Questions 20-32: What are the recommended dosages of the following drugs in the treatment of cutaneous small-vessel vasculitis?

Directions for questions 20-23: For each numbered item (drugs), choose the appropriate lettered item (dosages).

a. 60 to 80 mg per day
b. 0.3 to 1.5 g four times a day
c. 0.6 mg twice daily to three times a day
d. 50 to 200 mg per day

20. Prednisone
21. Colchicine
22. Dapsone
23. Potassium iodide

Directions for questions 24-27: For each numbered item (drugs), choose the appropriate lettered item (dosages).

a. 700 mg/day given intramuscularly
b. 5 mg twice a day
c. 50 to 100 mg/day
d. 5000 U twice a day

24. Stanozolol
25. Heparin
26. Mesoglycans
27. Defibrotide

Directions for questions 28-32: For each numbered item (drugs), choose the appropriate lettered item (dosages).

a. 10 to 25 mg per week
b. 2 mg/kg per day
c. 50 to 200 mg per day
d. 8 to 16 g per day for many months
e. 3 to 5 mg/kg per day

28. Aminocaproic acid
29. Cyclophosphamide
30. Methotrexate
31. Azathioprine
32. Cyclosporine

Answers to CME examination

Identification No. 898-110

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Questions 1-31, Touart DM, Sau P. J Am Acad Dermatol 1998;39:527-44.

1. b
2. c
3. d
4. e
5. e
6. b
7. c
8. d
9. e
10. e
11. a
12. c
13. e
14. c
15. e
16. c
17. c
18. d
19. a
20. e
21. b
22. c
23. b
24. d
25. b
26. a
27. a
28. a
29. c
30. a
31. b