Cutaneous Vasculitis

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Abstract
Cutaneous vasculitis is a histopathologic entity characterized by neutrophilic transmural inflammation of the blood vessel wall associated with fibrinoid necrosis, termed leukocytoclastic vasculitis (LCV). Clinical manifestations of cutaneous vasculitis occur when small and/or medium vessels are involved. Small vessel vasculitis can present as palpable purpura, urticaria, pustules, vesicles, petechiae, or erythema multiforme-like lesions. Signs of medium vessel vasculitis include livedo reticularis, ulcers, subcutaneous nodules, and digital necrosis. The frequency of vasculitis with skin involvement is unknown. Vasculitis can involve any organ system in the body, ranging from skin-limited to systemic disease. Although vasculitis is idiopathic in 50% of cases, common associations include infections, inflammatory diseases, drugs, and malignancy. The management of cutaneous vasculitis is based on four sequential steps: confirming the diagnosis with a skin biopsy, evaluating for systemic disease, determining the cause or association, and treating based on the severity of disease.

Keywords
Cutaneous vasculitis, leukocytoclastic vasculitis

Definition

Vasculitis is inflammation of the blood vessel wall that leads to various clinical manifestations depending on which organ systems are involved. Cutaneous vasculitis is a histopathologic entity characterized by neutrophilic transmural inflammation of the vessel wall associated with fibrinoid necrosis, termed leukocytoclastic vasculitis (LCV). Other histologic findings that may be seen include extravasated erythrocytes, granulocytic debris (leukocytoclasis), granulomatous or lymphocytic inflammation, and deposition of immunoreactants in the vessel wall. Vasculitis has a wide spectrum of severity, ranging from skin-limited disease to life-threatening systemic involvement. Recognizing the symptoms and signs implicating systemic involvement is of paramount importance in the evaluation of patients with cutaneous vasculitis.

Classification / Etiology

The classification schemes for the vasculitides are based on several criteria, including the size of the vessel involved, clinical and histopathologic features, and etiology. Large vessels include the aorta and large arteries and veins; medium-sized vessels include the medium and small-sized arteries and veins; and small vessels refer to the arterioles, venules, and capillaries.

The American College of Rheumatology (ACR) criteria of 1990 includes clinical, historical, and histologic data to classify the vasculitides (Table 1) (1). In 1994, the Chapel Hill Consensus Conference (CHCC) defined 10 types of vasculitis based primarily on histopathologic criteria (Table 2) (2). Although together these classification schemes include most forms of cutaneous vasculitis, they were developed as

research tools to define vasculitic syndromes and not as diagnostic criteria for the clinician.
A clinically useful classification scheme for cutaneous vasculitis could be based on etiology, differentiating between primary (idiopathic) and secondary disease. Approximately 50% of cases are idiopathic, while infection (15-20%), inflammatory diseases (15-20%), drugs (10-15%), and malignancy (<5%) are the predominant secondary causes of cutaneous vasculitis (Figure 1) (3-5). Multiple infectious agents including viruses (hepatitis B and C, HIV), bacteria, parasites, and fungi can be associated with vasculitis (6). Various inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and inflammatory bowel disease (IBD), can present with associated cutaneous vasculitis. These patients typically have severe symptoms related to their underlying inflammatory disease and have increased morbidity and mortality (7-10). Several drugs, including penicillins, sulfonamides, thiazides, and oral contraceptives, as well as chemicals (insecticides, petroleum) and foodstuff allergens (milk products, gluten) have been associated with cutaneous vasculitis (11). The diagnosis of drug-induced vasculitis is a diagnosis of exclusion and is based on the temporal relationship between exposure to the offending agent and the development of disease. Lastly, cutaneous vasculitis may be associated with malignancy, typically a paraproteinemia or lymphoproliferative disorder, and abates with treatment of the underlying cancer (12, 13).
Because multiple causes may contribute to the development of cutaneous vasculitis, a classification scheme based on the diseased vessel size is perhaps most useful to the clinician. Dermatologic signs of vasculitis are present only when small and medium-sized vessels are involved. Therefore the diseases can be divided into those with predominantly small vessel involvement, predominantly medium vessel involvement, both small and medium vessel involvement and other diseases that can show cutaneous LCV as a secondary finding (Figure 2). The predominantly small vessel vasculitides (SVV) include cutaneous small vessel vasculitis (CSVV), urticarial vasculitis (UV), and Henoch-Schonlein purpura (HSP). Polyarteritis nodosa (PAN) is the only cutaneous vasculitis involving predominantly medium-sized vessels (MVV). Vasculitis associated with cryoglobulinemia, connective tissue diseases (CTD), and anti-neutrophil cytoplasmic antibodies (ANCA) involve small and medium-sized vessels. Neutrophilic dermatoses including Behcet's disease and pyoderma gangrenosum, and other skin diseases such as erythema elevatum diutinum (EED), a rare condition affecting the extensor surface of the extremities, can show evidence of SVV with LCV on biopsy (11).

Clinical Manifestations
The cutaneous findings of vasculitis depend upon which vessels are primarily involved. SVV most frequently presents as palpable purpura (Figure 3) but can also manifest as urticaria, pustules, vesicles, petechiae, or erythema multiforme-like lesions. Cutaneous signs in MVV include livedo reticularis, ulcers, subcutaneous nodules, and digital necrosis (Figure 4).

Predominantly Small Vessel Vasculitides

Cutaneous Small Vessel Vasculitis (CSVV)
CSVV is a diagnosis of exclusion used to describe a SVV confined only to the skin. New medications or infectious agents are frequently associated with the onset of CSVV. The typical clinical presentation is the development of a single crop of lesions that resolves spontaneously within several weeks or a few months (14). The lesions may present as purpura, papules, vesicles or urticaria, and tend to occur in dependent areas, in areas of trauma, or under tight-fitting clothing (15). A chronic, recurrent form of CSVV can occur in up to 10% of patients (16).

Urticarial Vasculitis (UV)
Approximately 5-10% of patients who present with chronic urticaria have UV (17, 18). Features that differentiate UV from chronic urticaria include the duration of lesions for greater than 24 hours, symptoms of burning rather than itching, and the presence of purpura and hyperpigmentation from lesions that have resolved (19). Most cases of UV are idiopathic, but frequent associations include connective tissue diseases (SS, SLE), serum sickness, infections (HCV), malignancy, or physical exposures (cold, UV light) (17). UV can be divided into two subsets, those with normal complement levels (NUV) and those with low complement levels (hypocomplementemic urticarial vasculitis (HUV)). The latter type is associated with a higher risk of systemic disease such as arthritis, obstructive airways disease, or gastrointestinal symptoms (17, 20). Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare form of UV characterized by the presence of anti-C1q antibodies, with clinical features similar to SLE, such as glomerulonephritis and pleuritis (21).

Henoch-Schonlein Purpura (HSP)
HSP typically presents in children (especially boys aged 4 to 8 years) and is characterized by palpable purpura affecting the lower extremities

and buttocks, arthritis, nephritis, and colicky abdominal pain (22). The disease often presents acutely following an upper respiratory tract infection (23). Histologically HSP is characterized by the presence of IgA immune deposits in and around small vessels on direct immunofluorescence (DIF) (2). HSP is usually self-limited, but chronic renal disease can occur in 20-30% of patients with an increased incidence in adults compared to children (24).

Predominantly Medium Vessel Vasculitides

Polyarteritis nodosa (PAN) can be classified as classic or cutaneous. Classic PAN is defined by the CHCC as a necrotizing vasculitis of the medium-sized arteries that spares the arterioles, venules, and capillaries, and is not associated with glomerulonephritis (2). Classic PAN usually presents with constitutional symptoms, arthralgias, and myalgias, followed by more overt signs of vasculitis. PAN has a predilection for certain organ systems including the skin, peripheral nerves (mononeuritis multiplex), gastrointestinal tract, and kidneys, but some patients can also have genitourinary (orchitis) or cardiovascular (congestive heart failure) involvement. Vasculitis of the medium-sized intrarenal arteries results in renovascular hypertension and renal failure, but not glomerulonephritis (25). Cutaneous lesions include palpable purpura, livedo reticularis, ulcers, subcutaneous nodules, and rarely digital gangrene (26, 27). PAN is associated with hepatitis B infection in 5-7% of cases, with more frequent orchitis occurring in those patients (28). The diagnosis of PAN requires either a tissue biopsy demonstrating MVV, or an angiogram demonstrating microaneurysms in a clinically appropriate setting (29).
Cutaneous PAN (c-PAN), a primarily skin-limited disease, represents about 10% of PAN cases (30). It is the most common form of PAN in children, and skin lesions are usually accompanied by fever, myalgias, and arthralgias. Peripheral neuropathy, usually manifesting as mononeuritis multiplex of the lower extremities, occurs in 20% of patients (31). Cutaneous lesions are frequently painful dermal or subcutaneous nodules that may ulcerate, although livedo reticularis and digital gangrene can also occur (32). Cutaneous PAN has been associated with various infections, including streptococcal, parvovirus B19, HIV, and hepatitis B, as well as IBD (31). Although c-PAN usually resolves spontaneously, the disease typically follows a chronic course with frequent relapses (33).

Small and Medium Vessel Vasculitides

Cryoglobulinemic Vasculitis (CV)
Cryoglobulins are cold-precipitable immunoglobulins that can be divided into three subtypes. Type I consists of monoclonal IgM and is always associated with a hematologic disorder. Type I cryoglobulins lead to vessel obstruction and can result in Raynaud's phenomenon or acrocyanosis of the limbs (34). Types II and III, termed mixed cryoglobulins, consist of monoclonal IgM directed against IgG and polyclonal IgM directed against IgG respectively (35). CV develops in approximately 15% of patients with mixed cryoglobulinemia and is thought to result from immune complex deposition and complement activation (35).
Infections, primarily HCV, are responsible for approximately 75% of cases of CV. Other less frequent associations include autoimmune diseases and lymphoproliferative disorders (36). Cutaneous involvement of CV usually presents as palpable purpura of the lower extremities, though Raynaud's phenomenon, ecchymoses, and dermal nodules can occur (34, 37). Common features of systemic involvement in CV include arthralgias, nephritis, and peripheral neuropathy (36). Frequent serologic abnormalities seen in patients with CV include hypocomplementemia (90%), positive rheumatoid factor (70%), transaminitis (25-40%), and positive anti-nuclear antibodies (20%) (38).

Vasculitis due to Connective Tissue Diseases
Vasculitis can occur in patients with various autoimmune diseases, including RA, SLE, and SS (15). Rheumatoid vasculitis (RV) occurs in 5-15% of patients with RA, typically those with end-stage disease and high RF titers (7, 8). Common sites of involvement in RV include the skin and peripheral nerves. Cutaneous manifestations most commonly present as lesions of SVV with palpable purpura and nailfold infarctions, termed Bywaters lesions (39). Vasculitis associated with SLE can affect essentially any organ system in the body and usually represents a flare of disease (5, 15). Skin lesions usually present as SVV, but livedo reticularis, cutaneous infarction, and superficial ulcerations can occur (9). Vasculitis in patients with SS commonly affects the skin and central nervous system, with cutaneous vasculitis present in 9-32% of patients (40). Systemic involvement with life-threatening vasculitis correlates with the presence of cryoglobulinemia (10).

ANCA-associated Vasculitides
Anti-neutrophil cytoplasmic antibodies (ANCA) are antibodies directed against various antigens

and produce one of three patterns on immunofluorescence: cytoplasmic (C-ANCA), perinuclear (P-ANCA), or atypical. C-ANCAs are primarily directed against the antigen proteinase 3 (PR-3) (41), whereas the perinuclear pattern can be seen with antibodies against various antigens, including myeloperoxidase (MPO), lactoferrin, and elastase (42, 43). Although ANCAs may be present in various disease processes, anti-PR-3 and anti-MPO antibodies are frequently associated with three cutaneous vasculitic syndromes, Wegener's Granulomatosus (WG), Churg-Strauss Syndrome (CSS), and Microscopic Polyangiitis (MPA). ANCAs are useful in the diagnosis of ANCA-associated vasculitides with a sensitivity of 85% and specificity of 98% when immunofluorescence and enzyme-linked immunosorbent assays are used in combination (44, 45). ANCAs are thought to be pathogenic in these diseases and may have a role in predicting relapses (46, 47).

Although the ANCA-associated vasculitides are responsible for 60% of all patients presenting with a pulmonary-renal syndrome, these diseases can affect any organ system (48). The ANCA-associated vasculitides all follow a chronic course with frequent relapses, but they differ in clinical and laboratory features as delineated in Table 3.

Approach to the Patient

Confirm Diagnosis

The first step in evaluating a patient with cutaneous findings suggestive of vasculitis is to rule out other disease processes that can mimic LCV, and this can only be done with a skin biopsy (Table 4).

Skin biopsies with direct immunofluorescence (DIF) are often necessary to confirm the diagnosis of cutaneous vasculitis. The optimal lesions to sample are between 12-24 hours of age, as lesions less than 12 hours or greater than 24 hours old can have a predominantly mononuclear rather than neutrophilic infiltrate (19). If medium vessel involvement is suspected, a wedge biopsy may be required. In addition, diagnostic yield of MVV is site dependent. Biopsies taken from nodules generally have a higher yield than samples taken from an ulcer edge or livedo. DIF demonstrating perivascular IgA immune deposits may be useful in confirming a diagnosis of HSP, however, this finding is not 100% specific for this disease. In contrast, ANCA-associated vasculitides have little or no deposition of complement or immune complexes in and around the vessels ("pauci-immune").

Evaluation for Systemic Disease

After confirming the diagnosis of cutaneous vasculitis, the clinician must determine the extent and severity of organ involvement. A complete history frequently reveals symptoms of systemic involvement, such as constitutional symptoms, sinus congestion, hemoptysis, shortness of breath, hematuria, abdominal pain, or paresthesias. The physical examination is helpful in determining whether the vasculitis primarily involves small or medium vessels. Vital signs indicating fevers or weight loss suggest systemic involvement; while hypertension may be secondary to MVV involving intrarenal vessels, such as in PAN. A complete cardiopulmonary, abdominal, and neurologic examination should be performed in any patient in whom systemic vasculitis is suspected.

All patients with cutaneous vasculitis should have a urinalysis to ensure that there is no occult renal involvement. If the clinician suspects systemic involvement, or the cutaneous signs have persisted beyond 6 weeks, the following additional laboratory studies to evaluate for systemic disease should be obtained: complete blood cell count with differential, blood urea nitrogen, creatinine, liver function tests, stool guaiac, hepatitis B and C serologies, HIV, complement levels, RF, ANA (if suspect CTD), and serum and urine protein electrophoresis. If a patient presents with significant pulmonary or renal involvement, ANCAs should be obtained, as well as imaging studies of the chest and, if indicated, the sinuses. If classic PAN is suspected, a visceral angiogram should be done to evaluate for microaneurysms.

Through the initial history and laboratory work-up, causal associations may become evident, including exposures to drugs, infectious agents, history of inflammatory diseases, or likelihood of malignancy. The symptoms, signs, and laboratory findings may be consistent with a particular systemic vasculitic syndrome, but a tissue biopsy (ie. lung or kidney) is often necessary to confirm the diagnosis.

Treatment

Approximately 50% of patients with cutaneous vasculitis will have a treatable associated condition, such as infection, inflammatory disease, or malignancy. Anti-viral therapy is warranted for patients with known viral-associated vasculitides, such as HCV-associated CV and HBV-associated PAN.

A general algorithm for the treatment of idiopathic cutaneous vasculitis can be proposed based on the extent of systemic involvement. For skin-limited disease, general measures include eliminating causal exposures, rest, leg elevation, avoiding tight-clothing, and keeping warm. For chronic or persistent skin-limited

vasculitis, dapsone and/or colchicine may be effective (49, 50). These agents have also been reported to be helpful in the treatment of UV and HSP (23, 51-53). Second-line agents for severe or recalcitrant cutaneous vasculitis include traditional immunosuppressive agents. A brief period of high dose oral corticosteroid therapy may be required for initial control of severe cutaneous disease (14). Recalcitrant cases may respond to alternate immunosuppressive therapies, such as low-dose methotrexate (<25 mg/wk), azathioprine (2 mg/kg/d), or cyclosporine (3 mg/kg/d) (54-58).

For patients with systemic involvement, such as in the ANCA-associated vasculitides, induction therapy includes high dose corticosteroids in combination with cyclophosphamide. For WG, this regimen induces remission in 75% of patients (59). Azathioprine, methotrexate, and mycophenolate mofetil are currently being studied as alternative agents to cyclophosphamide for induction, maintenance, and relapse therapy (60-62).

Intravenous immunoglobulin or plasmapheresis may be useful in the treatment of severe, refractory vasculitis, or in patients who have contraindications to traditional immunosuppressive therapy (63-65).

Future Directions

Cutaneous vasculitis describes a spectrum of diseases with various etiologic, clinical, and laboratory associations. Although the ACR and CHCC classification schemes include most forms of cutaneous vasculitis, the development of a new all-encompassing classification system needs to be developed. Such a system, as well as further studies to elucidate the pathogenesis of these diseases, will lead to a better understanding of vasculitis and allow the development of more targeted therapies.

Biologic agents are currently under investigation for use in the treatment of systemic vasculitides, such as CV and the ANCA-associated vasculitides. Preliminary studies using the tumor necrosis factor (TNF)-α inhibitors, etanercept and infliximab, in the treatment of ANCA-associated vasculitides have produced mixed results. The first report of etanercept therapy in WG was an open label study in 20 patients with persistently active disease which demonstrated a mean improvement in Birmingham Vasculitis Activity Scores (BVAS) after 6 months of treatment (66). A subsequent 12-month double blind randomized controlled trial of etanercept in 180 patients with WG revealed no difference in flare rate between the etanercept and placebo groups (Stone et al., unpublished observations). Preliminary studies using infliximab in addition to corticosteroids and cyclophosphamide suggest that this combination may be more effective in inducing remission than standard therapy; however, there is an increased risk for severe infection (67, 68). A recent open-label study using rituximab, an anti-B cell therapy, in 11 patients with ANCA-associated vasculitis refractory to conventional therapy demonstrated sustained remission in all patients while B lymphocytes were absent (69). Currently available agents targeting cytokines, B cells, T cells, neutrophils, or complement activation require further investigation in clinical trials.

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Table 1.

The ACR Classification Criteria for Vasculitis

Polyarteritis nodosa (PAN)

1. Weight loss >4 kg
2. Livedo reticularis
3. Testicular pain or tenderness
4. Myalgias, myopathy or tenderness
5. Neuropathy
6. Hypertension (diastolic BP>90 mm Hg)
7. Renal impairment (elevated BUN or creatinine)
8. Hepatitis B virus
9. Abnormal arteriography
10. Biopsy of artery showing PMN

Three criteria classify PAN with sensitivity of 82.2% and specificity of 86.6%

Wegener's granulomatosis (WG)

1. Nasal or oral inflammation
2. Chest X-ray showing nodules, infiltrates (fixed) or cavities
3. Microscopic hematuria or red cell casts in urine
4. Granulomatous inflammation on biopsy (within vessel wall or perivascular)

Two criteria classify WG with a sensitivity of 88.2% and specificity of 92.0%

Churg-Strauss syndrome (CSS)

1. Asthma
2. Eosinophilia (>10%)
3. Neuropathy
4. Pulmonary infiltrates (non-fixed)
5. Sinusitis
6. Extravascular eosinophils on biopsy

Four criteria classify CSS with a sensitivity of 85% and specificity of 99.7%

Hypersensitivity vasculitis

1. Age >16 yr at onset
2. Medications which may have precipitated event
3. Palpable purpura
4. Rash
5. Positive biopsy

Three criteria classify HSV with a sensitivity of 71.0% and specificity of 83.9%

Henoch-Schonlein purupura (HSP)

1. Palpable purpura
2. Age at onset <20 yr
3. Bowel angina
4. Vessel wall granulocytes on biopsy

Two criteria classify HSP with sensitivity of 87% and specificity of 88%

Table 2.

The CHCC Definitions of Vasculitis

	Medium-sized Vessel Vasculitis
Polyarteritis nodosa (classic PAN)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
	Small-Vessel Vasculitis
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g. capillaries, venules, arterioles, and arteries); *necrotizing glomerulonephritis is common*
Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles); *necrotizing arteritis involving small and medium-sized arteries may be present; necrotizing glomerulonephritis is very common; pulmonary capillaritis often occurs*
Henoch-Schonlein purpura	Vasculitis, with IgA-dominant immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles); *typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis*
Essential cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles), and associated with cryoglobulins in serum; *skin and glomeruli are often involved*
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis

Table 3. Comparison of the ANCA-associated vasculitides

	Wegener's Granulomatosis	Microscopic Polyangiitis	Churg-Stauss Syndrome
ANCA	***C-ANCA 80%*** P-ANCA 10%	C-ANCA 30% ***P-ANCA 55%***	C-ANCA 10% ***P-ANCA 55%***
Necrotizing granulomas	+	-	+
Asthma/eosinophilia	-	-	+
Pulmonary	+++	++	+++
Renal	+++	+++	++
Cutaneous	++	++	++
ENT	+++	+	++
Musculoskeletal	++	++	++
Neurologic	++	+	+++
Gastrointestinal	++	++	++

Table 4. Clinical mimics of LCV

- Vascular disorders
  - lymphocytic vasculitis
    - Pityriasis lichenoides
    - Perniosis
  - "vasculopathy"
  - livedoid "vasculitis"
  - other vascular occlusive diseases
    - Factor V Leiden
    - Protein C/S deficiency
    - Homocysteinemia
    - DIC
    - TTP
    - Thrombocythemia
    - Cryofibrinogenemia
  - Embolic states
    - Cholesterol embolism
    - Left atrial myxoma
    - Sneddon's syndrome
  - Purpura
    - Actinic
    - Medication-related
    - Secondary to platelet dysfunction
    - Secondary to coagulopathy
- Dermatoses
  - Interface dermatoses (i.e. SLE)
  - Pigmented purpuric eruptions
- Other
  - Arthropod bites
  - Amyloidosis
  - Cutaneous lymphoma
  - Factitial/traumatic

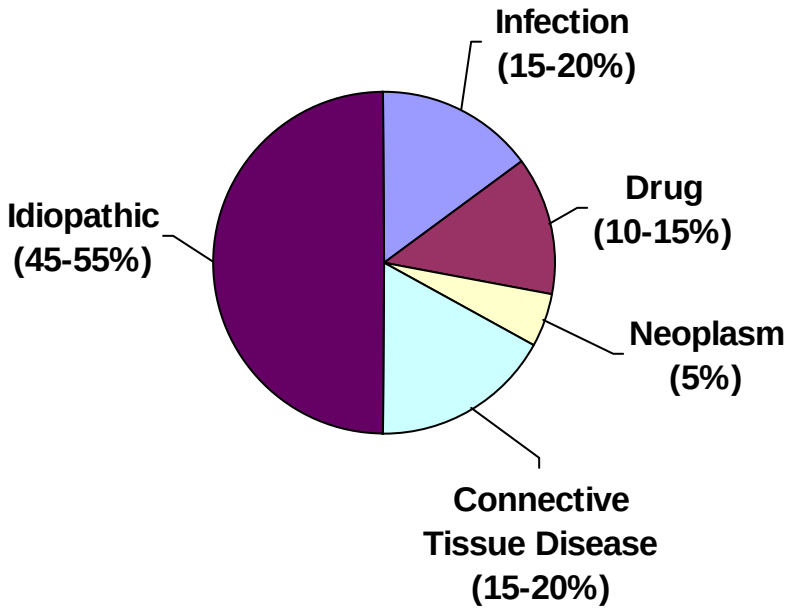

Figure 1. Etiologies of Cutaneous Vasculitis

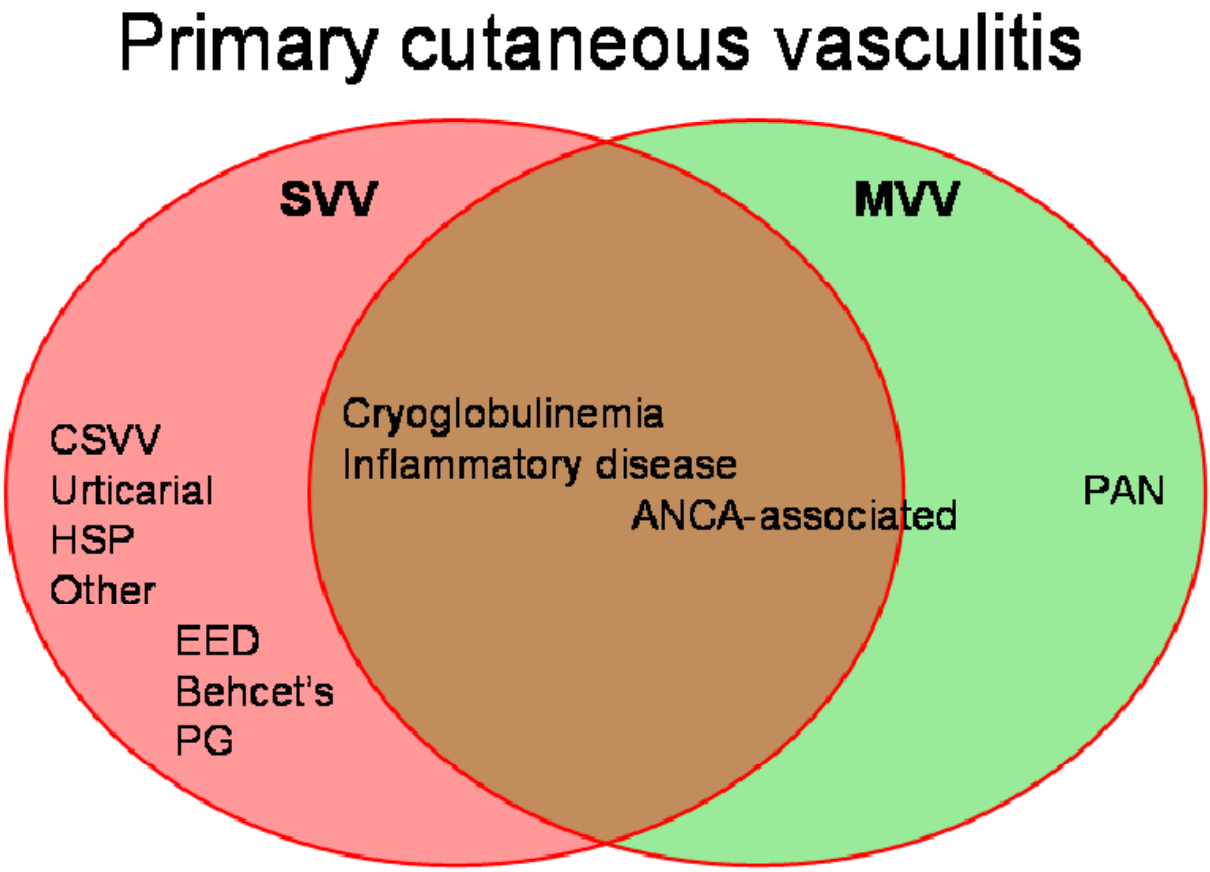

Figure 2. Classification of Primary Cutaneous Vasculitis based on diseased vessel size

Abbreviations in legend:
SVV=small vessel vasculitis
MVV=medium vessel vasculitis
CSVV=cutaneous small vessel vasculitis
HSP=Henoch-Schonlein Purpura
EED=erythema elevatum diutinum
PG=pyoderma gangrenosum
PAN=polyarteritis nodosa
ANCA=anti-neutrophil cytoplasmic antibody

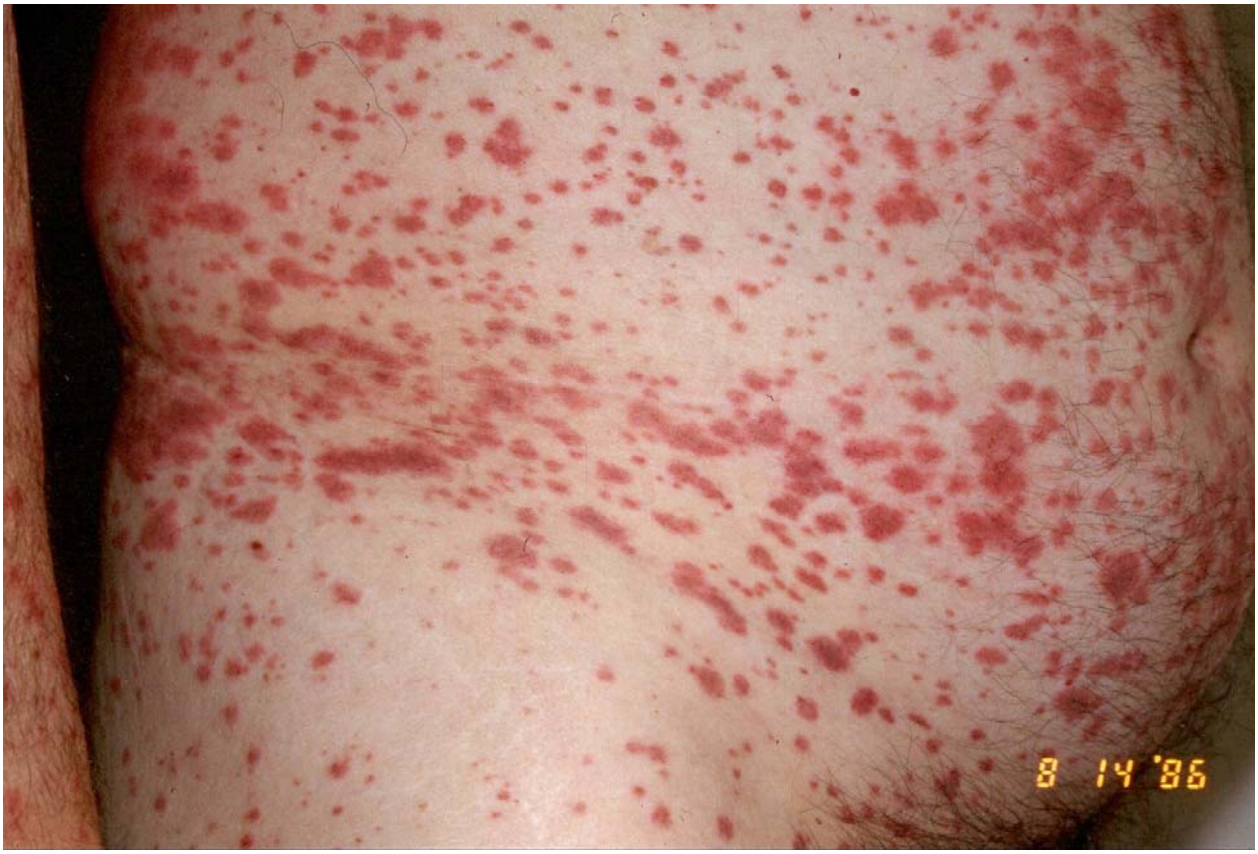

Figure 3. Palpable purpura: a manifestation of small vessel vasculitis

Figures 4. Cutaneous manifestations of medium vessel vasculitis

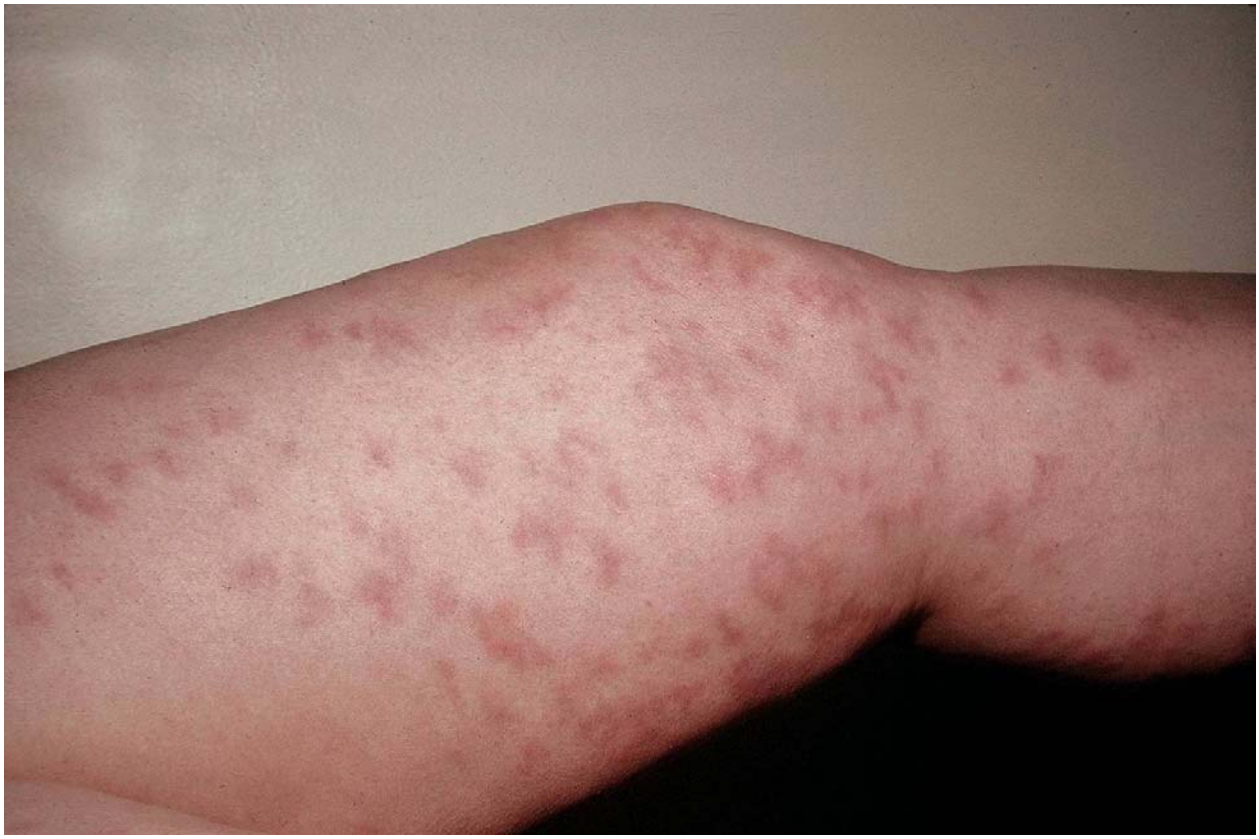

Fig 4a : Livedo reticularis

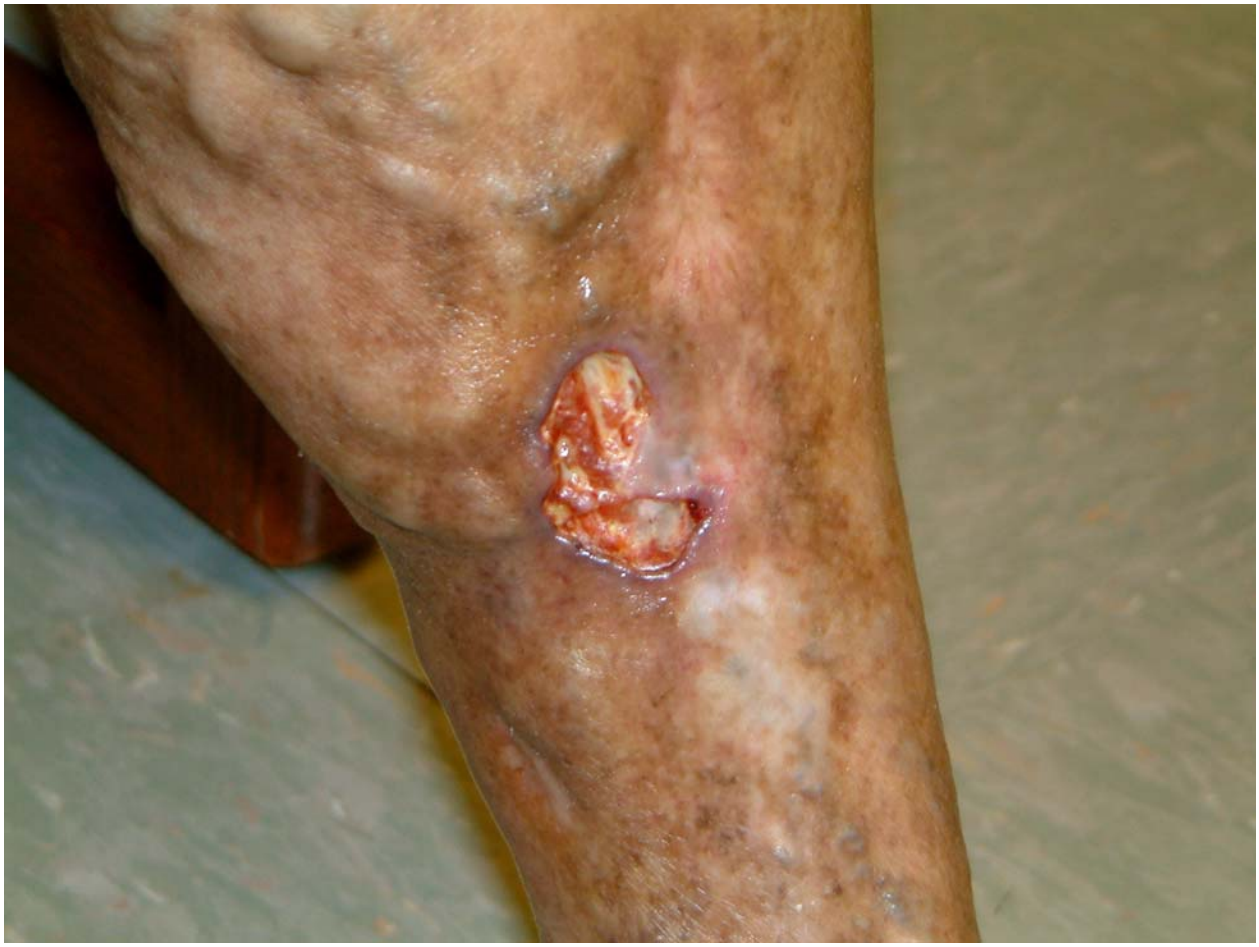

Fig 4b: Ulcer

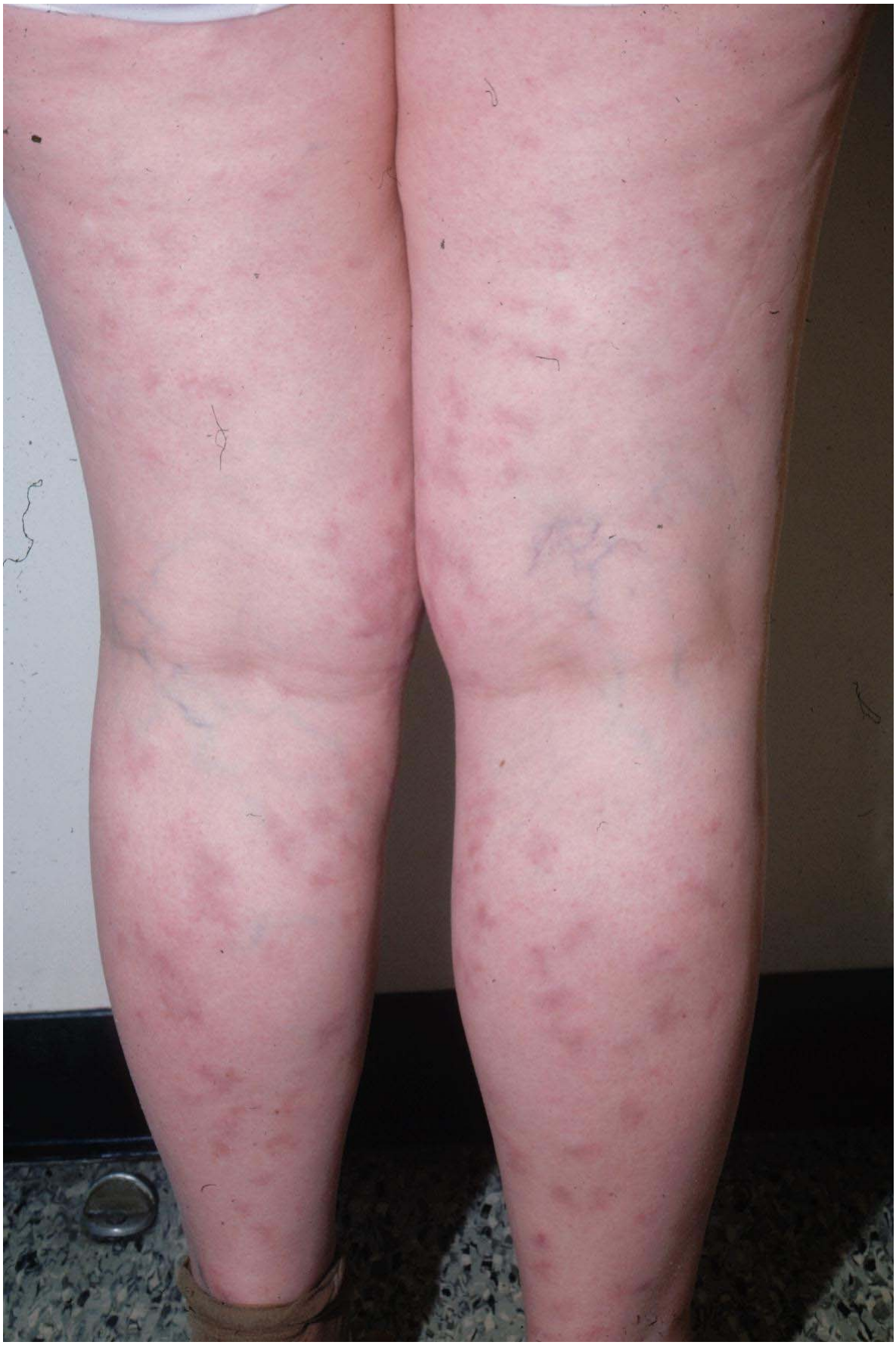

Fig 4c: Subcutaneous nodules

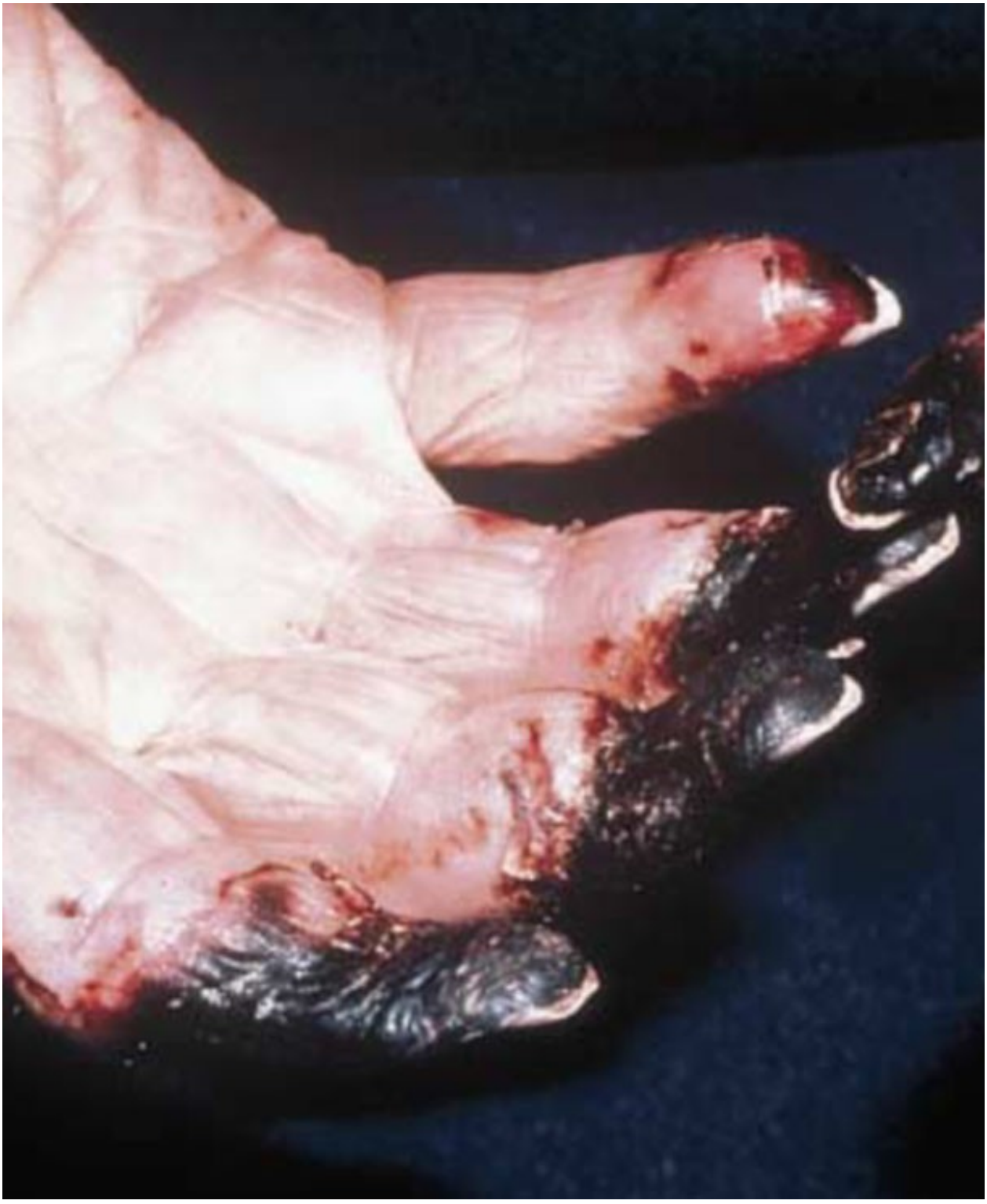

Fig 4d: Digital necrosis (from "Vasculitis", by David B. Hellmann, MD, Thomas Provost, MD. Page 186 in: "Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease". Thomas Provost, John Flynn. 2001. BC Decker, Inc. Hamilton, Ontario.)