

Importance of Cutaneous Vasculitis in Rheumatology

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Abstract

Cutaneous vasculitis may present as a significant component of many systemic vasculitic syndromes such as rheumatoid vasculitis or anti-neutrophil cytoplasmic antibody (ANCA) associated primary vasculitic syndromes like microscopic polyangiitis. Cutaneous vasculitis manifested most often as palpable purpura or infiltrated erythema indicating dermal small vessel vasculitis and less commonly as nodular erythema, livedo reticularis, deep ulcers or digital gangrene suggesting subcutaneous muscular vessel vasculitis. Coexistence of dermal small vessel vasculitis and subcutaneous muscular vessel vasculitis usually indicated systemic vasculitis such as connective tissue disease (CTD)-associated vasculitis, ANCA associated vasculitis, Behcet's disease, polyarteritis nodosa, Cogan's syndrome, and malignancy associated. An appropriate lesional skin biopsy is the key to obtaining the diagnosis. Treatment for cutaneous vasculitis should include devoid of the triggers (excessive standing, infection, drugs) and exclusion of vasculitis-like syndromes (psudovasculitis). In most instances, cutaneous vasculitis represents a self-limited condition and will be relieved by leg elevation, avoidance of standing and therapy with non-steroidal anti-inflammatory drugs. For mild recurrent or persistent disease, colchicine and dapsone are first-choice agents. Severe cutaneous and systemic disease requires more potent immunosuppression (prednisone plus azathioprine, methotrexate, cyclophosphamide). The new biologic therapies that work via cytokine blockade or lymphocyte depletion such as tissue necrosis factor-inhibitor infliximab and the anti-B cell antibody rituximab, respectively, are showing benefit in certain settings such as CTD and ANCA associated vasculitis.

Rheumatologists who are familiar with the complicated clinical and histopathological spectrum of cutaneous vasculitis and correlation of systemic vasculitis as well as the technique of skin biopsy will make the diagnosis earlier in vasculitis syndromes with skin involvement.

Keywords: Cutaneous vasculitis; Vasculitis syndromes; Behcet's disease; Skin

Introduction

Vasculitis is an inflammatory process primarily occurring on the vessel wall leading to vessel wall destruction and subsequent hemorrhagic and ischemic events. Any organs rich in blood vessels could have lesions of vasculitis which may result in a fatal life-threatening condition when occurring in the major organs such as kidney, lung, gastrointestinal tract and central nervous system or follow a persistent morbidity with permanent sensory/motor disturbance of the extremities as well as refractory leg ulcers and toes gangrenes followed by a miserable outcome of amputation of extremities later.

Skin is the most common target organs for small vessel vasculitis found in either primary systemic vasculitis (ANCA-associated vasculitis, polyarteritis nodosa) or secondary systemic vasculitis (CTD-associated, drug-related, infection-related and neoplasm-related vasculitis) [1,2]. Vasculitis in skin (dermis to subcutis) could reflect a self-limited benign disease restricted to skin such as cutaneous leukocytoclastic angiitis and cutaneous polyarteritis nodosa (cutaneous arteritis) [1,3] or present as a significant component or even the first sign of many systemic vasculitic syndromes such as ANCA-associated primary vasculitic syndromes [1,2].

As clinical presentations of vasculitis in skin can be easily and accurately identified by naked eyes observation and palpable examination followed by a subsequently easier and relatively non-invasive skin biopsy for histopathological examination, the crucial diagnostic evidence for vasculitis, skin lesions with suspected vasculitis presentations provide an extremely valuable clue for making diagnosis of vasculitis easily and precisely when comparing to those vasculitis in either internal organs (kidney, lung, gastrointestinal tract, etc.) or peripheral nerves and muscles, an invasive and blind biopsy is usually needed for histopathological confirmation.

Cutaneous Manifestations and Histopathological Findings of Cutaneous Vasculitis

As vessels affected in cutaneous vasculitis ranging from dermal small vessels to subcutaneous muscular vessels, cutaneous vasculitis presents as a mosaic of clinical findings [1,2] (Figure 1-5).

Cutaneous vasculitis of dermal small vessels clinically manifests most frequently as palpable purpura (Figures 1A-3A), and less often infiltrated or swollen/elevated erythema, characterized by feature of leukocytoclastic vasculitis with a prominent infiltrate of neutrophils and nuclear debris (Figures 1C, 2B and 3B), while vasculitis of subcutaneous small muscular vessels (arteritis (Figure 4B) or phlebitis (Figure 5B)) is less commonly and clinically presents as nodular erythema (Figures 4A and 5A), livedo reticularis (Figures 4A), deep ulcers, or subcutaneous nodules.

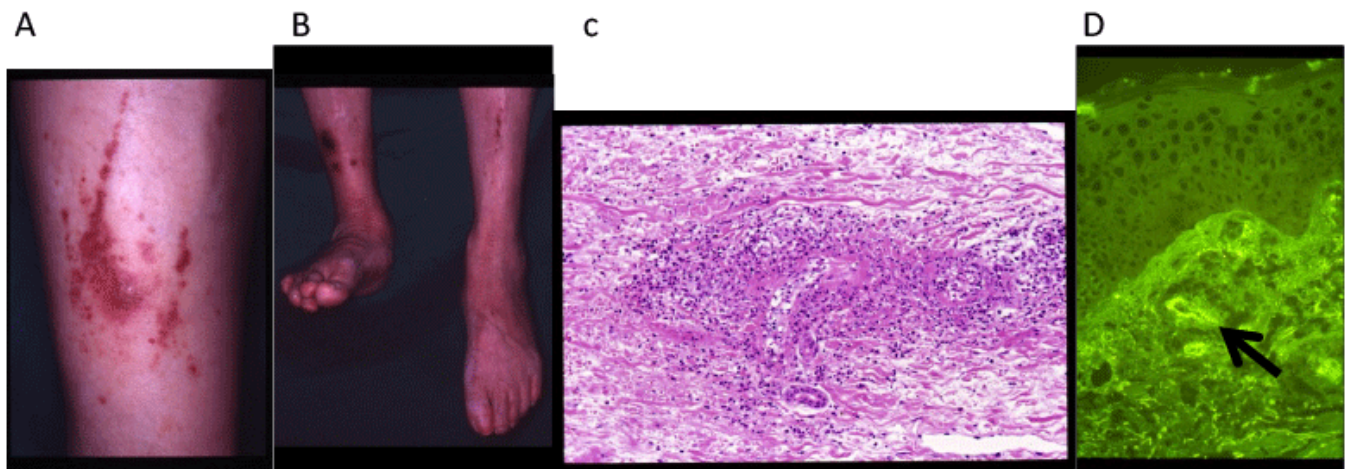


Figure 1: Rheumatoid vasculitis with hypocomplementemia and circulating immune-complexes. (A) Palpable purpura of the right leg with Köbner phenomenon (arrow), a sign of immune complex-mediated vasculitis. (B) Occurrence of left foot drop thereafter. (C) Histopathology of palpable purpura showing leukocytoclastic vasculitis of dermal small vessels. (D) Direct immunofluorescence showing IgM (arrow) vascular deposit.

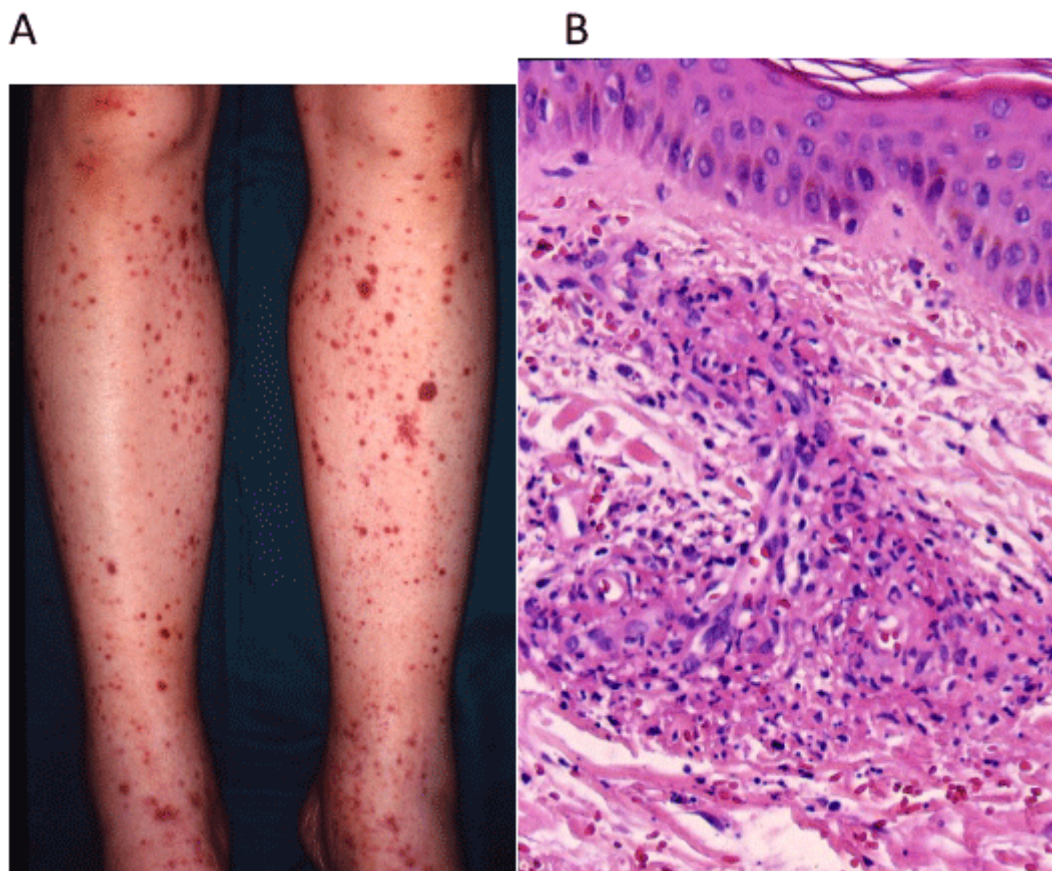


Figure 2: Dermal-renal vasculitis in a case with a history of ventricular septal defect that was complicated by *Streptococcal septicemia* with glomerulonephritis and persistent palpable purpura. Palpable purpura of the lower legs (A) Leukocytoclastic vasculitis of dermal vessels.

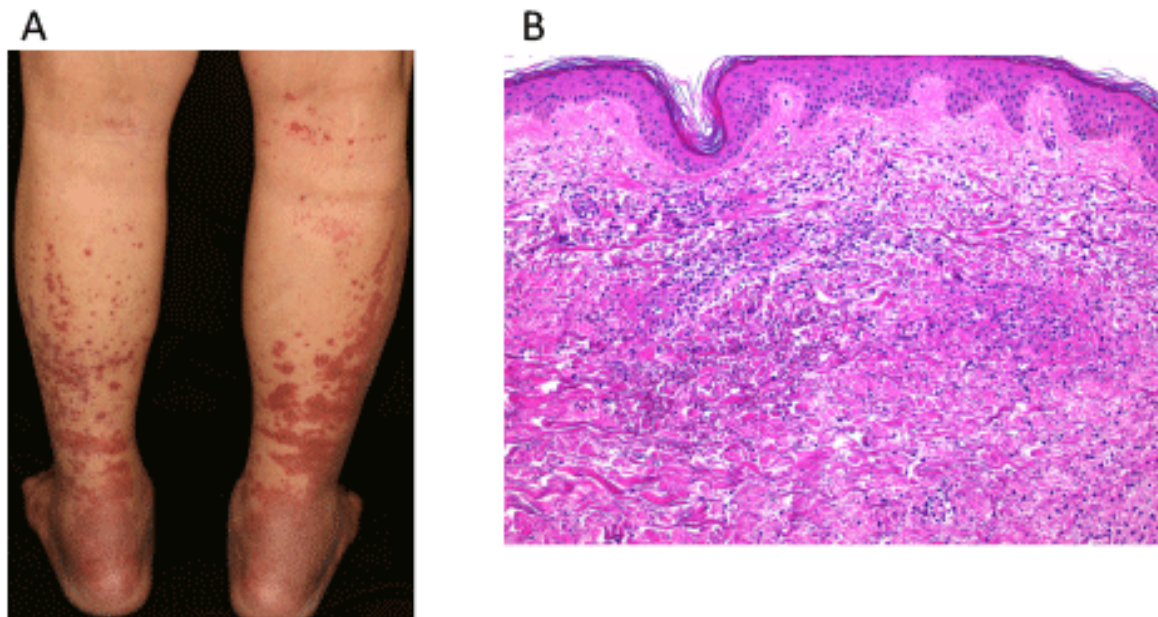


Figure 3: Dermal-renal vasculitis in a chronic hepatitis patient presenting as recurrent purpura of lower legs with cryoglobulinemia, hypocomplementemia and hematuria/ proteinuria. Palpable purpura of the lower legs (A) Histopathology of palpable purpura: Leukocytoclastic vasculitis of dermal vessels.

Dermal Small Vessel Vasculitis and their Related Disorders

Dermal small vessels vasculitis, the most common presentation of cutaneous vasculitis, can be found in both primary vasculitis syndromes including ANCA-associated vasculitis (microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis) [2,3] polyarteritis nodosa, Behçet disease and Cogan's syndrome being listed in the category of variable vasculitis in 2013 updated definition of vasculitis [3] , IgA-vasculitis [4] and skin-limited cutaneous leukocytoclastic angiitis [3] and also secondary vasculitis syndromes including collagen-associated vasculitis (rheumatoid vasculitis (Figure 2) [5], lupus vasculitis, relapsing polyarthritis and Sjögren's syndrome), drug-induced vasculitis, infection-induced vasculitis (streptococcal/ staphylococcal infection, (Figure 3) hepatitis C/B viral infection, (Figure 4) most often) , and relatively rare in paraneoplastic vasculitis.

Dermal small vessel vasculitis predominately affecting venules (venulitis) rather than the arterioles, is the most common histopathologic feature of cutaneous vasculitis. However, in systemic vasculitis such as ANCA-associated vasculitis not only venules but arterioles may be affected. Palpable purpura on the lower legs is the most common clinical feature. (Figures 2-4) Because many vasculitic disorders including both primary and secondary ones such as collagen disease-associated vasculitis (Figure 1) and infection-induced vasculitis (Figures 2,3) share the same histopathologic feature of dermal small vessel vasculitis and the similar cutaneous manifestations. A constellation of the clinical and laboratory evaluation is often needed to make the final diagnosis [1,3] (Table 1) (Figures 5 and 6).

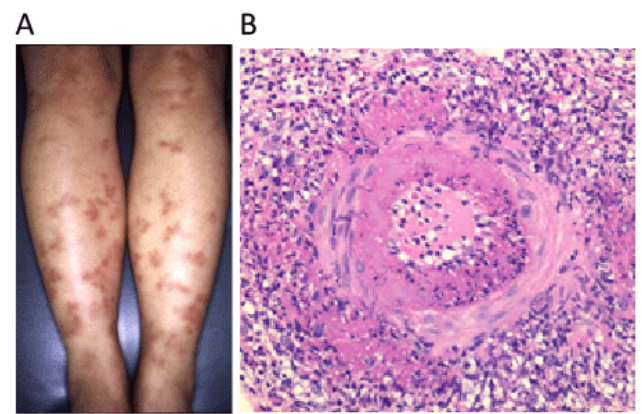


Figure 4: Cutaneous polyarteritis nodosa. Tender nodular/ infiltrated erythema ranging from 5-10mm in size mixed with livedo reticularis of the lower legs. Histopathology showing coronal-like sub-intimal fibrinoid necrosis of the vessel wall with a marked mixed infiltrate of neutrophils , lymphocytes and histiocytes.

Disorders with Coexistent Dermal Small Vessel Vasculitis and Subcutaneous Muscular Vessel Vasculitis

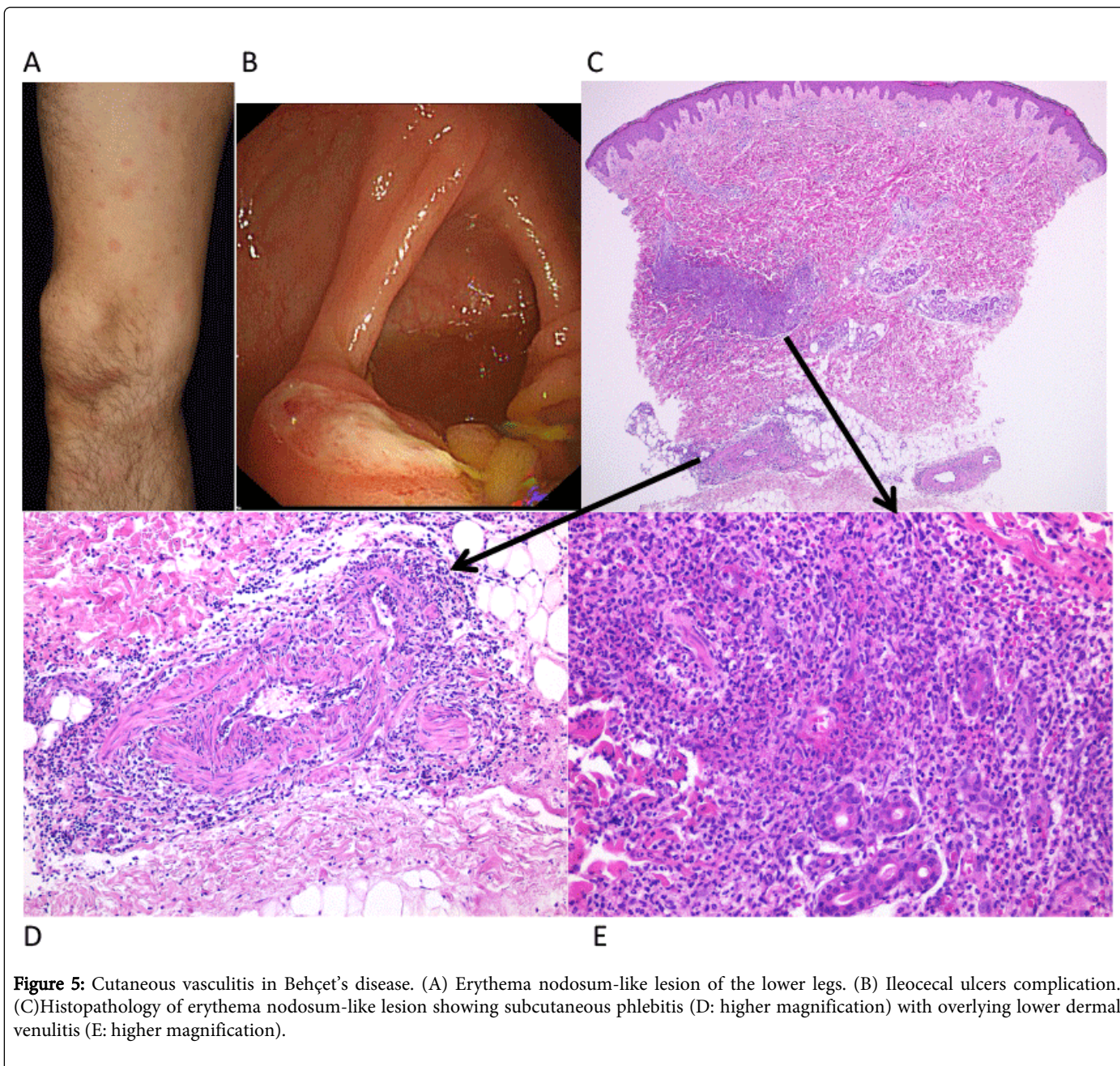
Coexistent dermal small vessel vasculitis and the overlying subcutaneous muscular vessel vasculitis is the characteristic features of systemic vasculitis such as ANCA-associated vasculitis [1,2], collagen

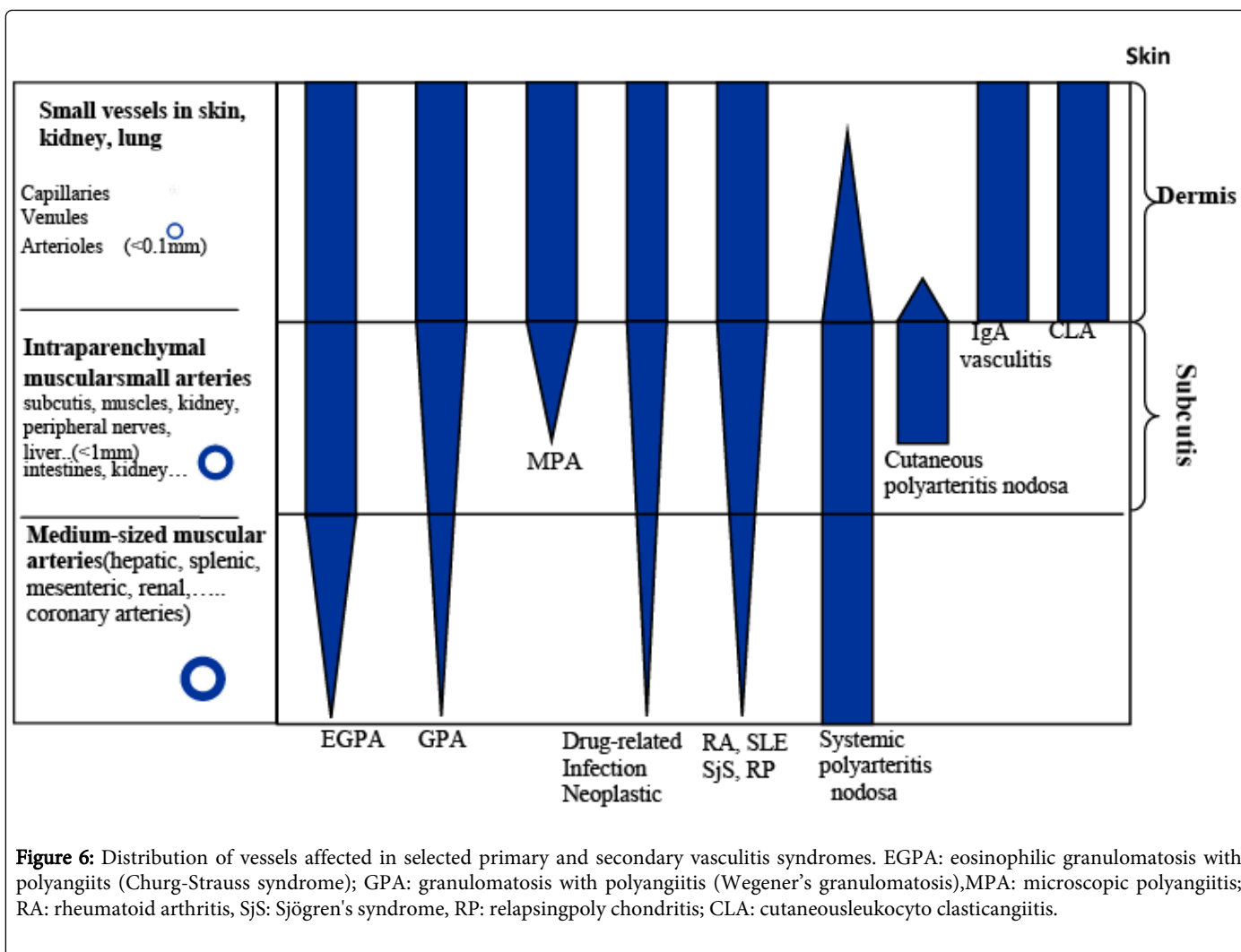
disease [5] and Behçet's disease [6,7](Figure 5) Cogan's syndrome, or infection, bowel inflammatory disease, drug and neoplasm-related vasculitis [4] (Figure 6).

Muscular Vessel Vasculitis and their Related Disorders

Muscular vessels are those vessels with caliber larger than 100um of small to medium-sized muscular vessels (arteries and veins) found in

lower dermis to subcutis. Small arteries or veins at dermo-subcutaneous junction ranging from 200um to 400um are the common vessels affected in either cutaneous polyarteritis nodosa (also known as cutaneous arteritis) [3], (Figure 4) a rather chronic disease limited to skin of the lower legs most often[1] or superficial (thrombo)phlebitis in either idiopathic ones or Behçet's disease [6] (Figure 5)





Importance of Skin Biopsy

As the crucial diagnosis of vasculitis is based on the histopathological findings, an appropriate skin biopsy is the key to obtaining a significant result for cutaneous vasculitis. Timing for a skin biopsy should not be performed after 48 hours for the appearance of the purpuric or infiltrated lesions and 72 hours for the appearance of the deep nodular erythematous lesions as the biopsy is poorly timed, the pathologic features of vasculitis may be absent. A biopsy extending to the subcutis should be taken from the most palpable purpuric lesions or the most tender, reddish nodular or infiltrated lesions. For purpuric lesions or infiltrated erythematous lesion smaller than 5mm in size, a 3 to 4 mm large punch biopsy extending to the subcutis will enable the histopathologic confirmation, while lesions of nodular erythema or infiltrated erythema larger than 5 mm in size, a spindle-shaped incisional biopsy extending to the subcutis with a 5 to 8 mm

large tissue sample in size should be performed on the central lesions [1,4].

In Summary

Cutaneous vasculitis could reflect a self-limited benign disease restricted to skin or present as a significant component or even the initial sign of many systemic vasculitic syndromes. As the merit of easy and precise diagnosis of vasculitis via skin biopsy, physicians who are familiar with the cutaneous manifestations of cutaneous vasculitis such as palpable purpura indicating dermal small vessel vasculitis while nodular lesions and livedo reticularis implicating deep dermal to subcutaneous arteritis/ phlebitis and the technique of skin biopsy, coupled with extra cutaneous clinical and laboratory evaluations (Table 1) will make the final diagnosis earlier for either systemic vasculitis with skin involvement or skin-limited vasculitis.

Findings	Suspected systemic vasculitis syndrome
Clinical signs or symptoms	
High fever	Infection, systemic vasculitis disorders

Paresthesias, foot drop Asthma, eosinophilia	EGPA, PAN, RV EGPA
Abdominal pain	IgA vasculitis, EGPA, MPA, PAN, RV, LV, BD
Frank arthritis	RV, infection, PAN, EGPA, LV, BD
Hypertension	PAN
Purpura above waist, upper extremities, face	IgA vasculitis, MPA, GPA, EGPA, RV, LV
> 1 type of vasculitic lesion*	MPA, GPA, EGPA, RV, LV, BD
Punctate palmar lesions	IgA vasculitis, MPA, GPA, EGPA, RV, LV
Laboratory evaluation Eosinophilia, elevated IgE, elevated RF	EGPA
Elevated RF, cryoglobulins, low complement, C hepatitis Elevated anti-CCP antibodies, elevated RF, low complement	CV (Figure 3) RV (Figure 1)
Chest x-ray: infiltrates or cavities	GPA (fixed infiltrates), EGPA (non-fixed infiltrates), MPA, malignancy
Hematuria and/or proteinuria and/or abnormal Creatinine Hypocomplementemia	Dermal-renal vasculitis syndrome: WG, MPA, IgA vasculitis, SLE, CV infective endocarditis (Figure 2) UV associated SLE, LV, RV(Figure 1), CV, infective endocarditis
cANCA (PR3)	GPA
pANCA (MPO)	MPA, EGPA
Histopathologic Findings	
Dermal small vessel vasculitis	IgA-vasculitis skin-limited cutaneous leukocyte clasticangiitis (CLA) ANCA-associated vasculitis (MPA, GPA, EGPA) PAN BD Cogan's syndrome Collagen –associated vasculitis (RV, LV, RP, Sjögren's syndrome) drug-induced vasculitis infection-induced vasculitis paraneoplastic vasculitis
Subcutaneous muscular vessel vasculitis	ANCA-associated vasculitis (MPA, GPA, EGPA) PAN BD Cogan's syndrome Collagen –associated vasculitis (RV, LV, RP and Sjögren's syndrome) drug-induced vasculitis (rare) infection-induced vasculitis (rare) paraneoplastic vasculitis (rare)
Vasculitis with tissue eosinophilia	EGPA and drug induced vasculitis
Direct immunofluorescence	
Isolated or predominate IgA vascular deposits	IgA vasculitis
IgM/G vascular deposits	RV, LV, CV, CLA

Lupus band (IgG, IgM, and/or C3 at the BMZ)	LV, UV associated with SLE
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Table 1: Clinical, pathologic, and laboratory findings indicating a high probability of systemic disease

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