Review

Cutaneous vasculitis: A diagnostic approach

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Cutaneous vasculitis (CV) comprises a wide spectrum of diseases that involve predominantly the blood vessels and surrounding tissues of the skin (1). All of them share the presence of vascular inflammation and blood vessel damage with inflammation of the small blood vessels including arterioles, capillaries and post-capillary venules of the skin. However, a variable grade of visceral involvement and vascular inflammation involving the medium-sized arteries is often observed (2, 3).

Cutaneous vasculitides are generally characterized by leukocytoclastic changes (2,4). Their histology shows infiltration of neutrophils within and around blood vessel walls, leukocytoclasia (degranulation and fragmentation of neutrophils leading to the production of nuclear "dust"), fibrinoid necrosis of the damaged vessel walls, and necrosis, swelling and proliferation of the endothelial cells (Fig. 1).

Several points can be made about the diagnosis of a patient with cutaneous vasculitis:

(1) The vasculitis may be limited to skin and, in this case, the outcome is good. In this regard, although occasionally associated with synovitis, other signs of systemic involvement are absent. Thus, the morbidity of a vasculitis limited to skin is low. However, cutaneous vasculitis may be the clinical expression of a vasculitis involving arterioles, capillaries and post-capillary venules not restricted to the skin, e.g. Henoch-Schönlein purpura (5), with variable grades of systemic manifestations. Also, histopathologic findings in a skin lesion may not be representative of that found elsewhere (e.g. the lung). Patients with Churg-Strauss syndrome or Wegener's granulomatosis may present with leukocytoclastic vasculitis and not have granulomatous changes in the skin.

(2) Cutaneous vasculitis may be the presenting manifestation of a vasculitides with frequent overlap of small and medium-sized blood vessel involvement, e.g. microscopic polyangiitis, Churg-Strauss or Wegener's granulomatosis (6). In these cases the outcome depends on the type and severity of visceral involvement.

(3) Since the etiology of most vasculitides is not understood, classification systems have been developed which are based on vessel size. In some cases, when the disease presentation is typical, agreement in classification of vasculitides occurs (4). This is the case of children with Henoch-Schönlein purpura presenting with palpable purpura in the lower extremities, joint and gastrointestinal manifestations, and/or hematuria (7). Problems may occur when the vasculitides are not typical, in particular in adults.

(4) In the presence of typical palpable purpura, a diagnosis of cutaneous vasculitis can be made in a straightforward fashion by clinicians that often see this condition. However, a skin biopsy to confirm the presence of leukocytoclastic vasculitis is always required as other conditions, e.g. scurvy (8), pigmented purpuric eruptions or severe thrombocytopenic purpura may mimic a cutaneous vasculitis. Since cutaneous vasculitis is a dynamic process, it is more convenient to do biopsy of a lesion of 18-24 hours'duration, as this will show the most diagnostic features.

(5) Cutaneous vasculitis limited to skin, often precipitated by the use of drugs, is remarkably predictable in its rapid and sometimes complete improvement after bed-rest (9, 10) and in some cases with low-dose prednisone therapy. The therapeutic efficacy of non-steroidal antiinflammatory drugs, dapsone or colchicine in cutaneous vasculitis is inconsistent and remains controversial.

(6) In most cases there is a lack of specific diagnostic tests. In view of this, the clinician should remain alert to the possibility that another disease different from a primary vasculitis may be present [e.g., a hematological disorder

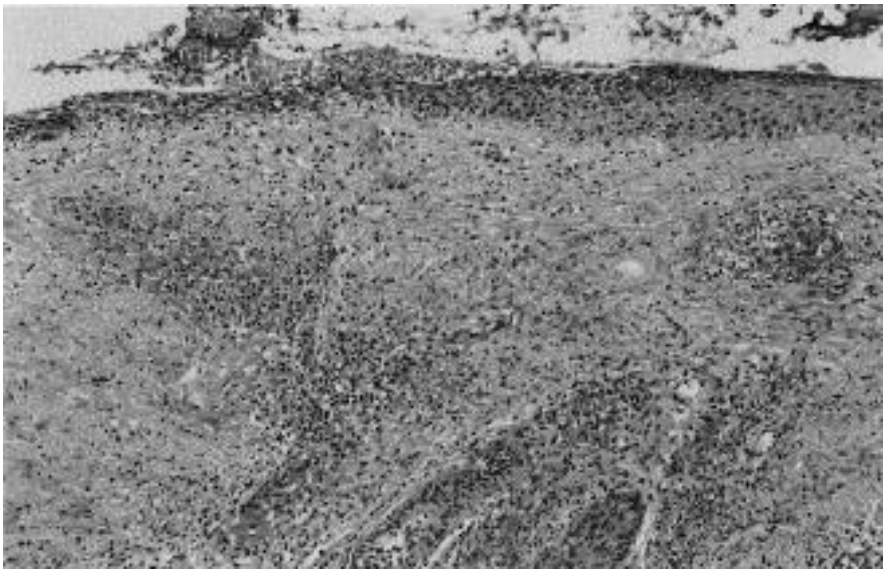

Fig. 1. Perivascular dermal neutrophilic inflammatory infiltrate, leukocytoclasia and vessel wall fibrinoid necrosis (H-E x 100).

or severe infection (11-13)], and follow up clues to the presence of another disease when present.

(7) Due to the considerations discussed above, a diagnostic work-up of the patient with cutaneous vasculitis should be performed (Fig. 2A and 2B).

Skin involvement in cutaneous vasculitis manifests initially as a maculopapular rash that may be followed by other skin lesions, in particular by palpable purpura. The term "palpable purpura" has frequently been considered to be synonymous with small sized cutaneous leukocytoclastic vasculitis (Fig. 3). It is caused by extra-vasation of erythrocytes through damaged blood vessel walls into the tissues. In contrast to simple purpura, these lesions do not blanch when pressure is applied to the skin. The increased hydrostatic pressure predisposes to certain areas of involvement. This fact explains why skin lesions are more common on the legs and buttocks (1).

However, the presence of purpura does not always indicate the diagnosis of small-sized blood vessel vasculitis, as a heterogeneous group of conditions (atheroembolic disease, thrombotic disorders such as the antiphospholipid antibody syndrome, thromboembolism, neoplasms such as cardiac myxoma or scurvy) may also cause purpuric cutaneous lesions and mimic vasculitis (Fig. 2A).

Cholesterol embolization is the best example of atheroembolic disease. It constitutes an important condition to be differentiated from cutaneous vasculitis. At least one-third of patients with atheroembolic disease have cutaneous features. In these patients, livedo reticularis involving the lower body is the most common cutaneous manifestation. In addition, infarction, ulceration, nodules and purpura may be observed. The antiphospholipid syndrome often mimics vasculitis. In this syndrome as well, livedo reticularis with or without acrocyanosis is the most common cutaneous manifestation. However, erythematous or cyanotic areas on the hands and feet, hemorrhages, ulcers or even gangrene may be observed. Embolic diseases can cause purple discoloration on the foot and toes. Macules, papules, telangiectasies or ulcerations may be present in patients with cardiac myxoma. Ischemic cutaneous lesions may occasionally be observed in patients with pheochromocytoma.

In the management of a patient with palpable purpura or with cutaneous lesions suggestive of vasculitis skin biopsy, specimens for routine microscopy and direct immunofluorescence are recommended, in particular in adult patients. Of note, other skin lesions such as non-palpable macules, urticaria or non-specific changes may also be observed in patients with cutaneous leukocytoclastic vasculitis (1, 3).

An important point to be considered is the difference between chronic urticaria and urticarial vasculitis (in which the skin biopsy also yields a leukocytoclastic angiitis). Unlike chronic urticaria, lesions in urticarial vasculitis last from 24-72 hours. They tend to have a burning quality. In contrast, chronic urticaria lesions generally last less than 24 hours and are more pruritic than those of urticarial vasculitis (1,14). Urticarial vasculitis lesions often evolve to purpura (1, 14).

Clinical decisions, however, should not be delayed until the biopsy result is available. A careful clinical history should search for data regarding the ingestion of drugs, the presence of preexisting symptoms suggestive of chronic or acute disorders, autoimmune diseases and a history of recent or a chronic infection (Fig. 2B).

Infections can cause vasculitis in small dermal vessels, either by direct invasion (septic vasculitis) or by generating pathogenic immune complexes. *Neisseria meningitidis* is the most common infection leading to septic cutaneous leukocytoclastic vasculitis. Other gram-negative and gram-positive bacteria and rickettsia may be responsible for cutaneous leukocytoclastic vasculitis (13).

Physical examination, routine laboratory tests (blood and urine) and chest radiograph should be performed in all cases.

If specific symptoms or signs of an underlying systemic disorder are present, further studies (e.g. colonoscopy in patients with gastrointestinal manifestations or renal biopsy in patients with severe glomerular manifestations) should be considered. Furthermore, in these cases specific laboratory tests should be performed. These tests should include the following:

ANCA determinations in cases with pulmonary and/or kidney involvement (microscopic polyangiitis or Wegener's granulomatosis) (15).

Cryoglobulin tests, C4 and C3 complement serum levels and rheumatoid factor, in cases of recurrent purpuric epi-

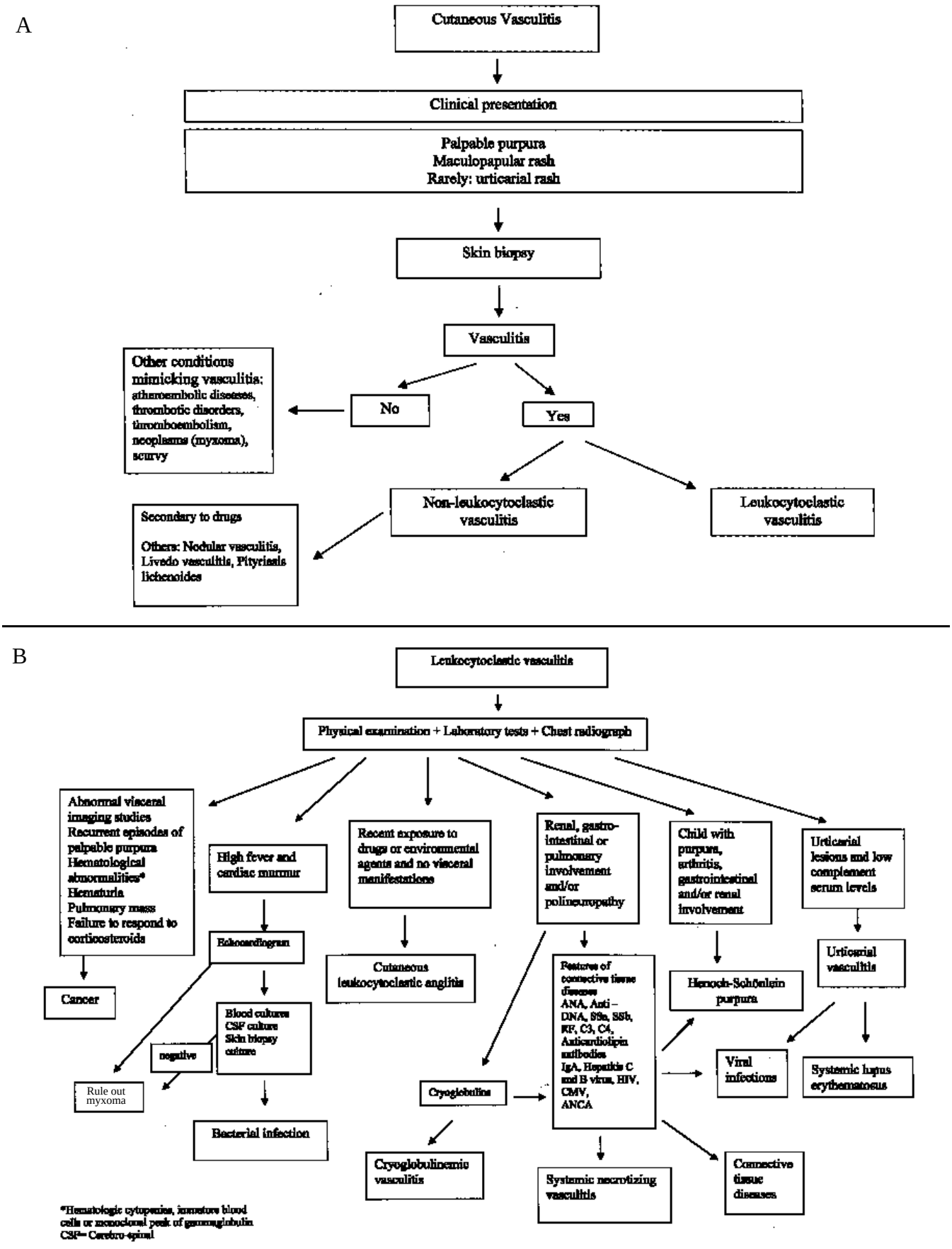

Fig. 2. (**A**) Diagnostic approach in a patient presenting with cutaneous vasculitis. (**B**) Work-up in a patient with leukocytoclastic vasculitis.

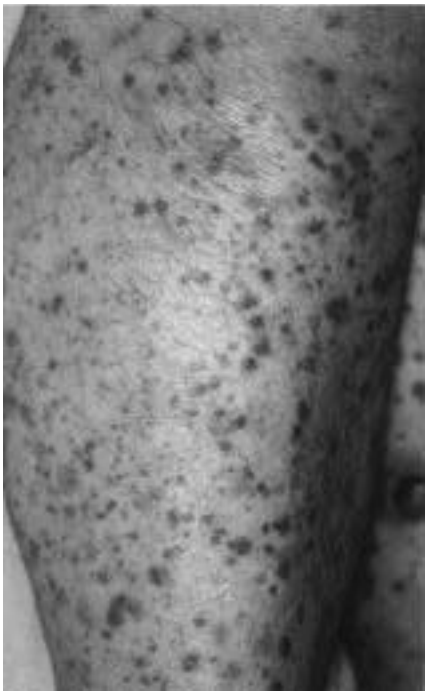

Fig. 3. Palpable purpura in the leg in a patient with biopsy-proven cutaneous leukocytoclastic vasculitis.

sodes of vasculitis, frequently associated with visceral involvement, e.g. glomerulonephritis and neuropathy. In these cases determinations for hepatitis C and B virus should also be performed (16-18).

Antinuclear antibody and anticardiolipin tests in patients with features of connective tissue diseases (19).

Besides immunofluorescence studies for the presence of IgA immune deposits in the skin or kidney, an IgAdetermination in serum should be carried out in patients with suspected Henoch-Schönlein purpura (6).

In patients with urticarial vasculitis a determination of complement serum levels should be performed, as hypocomplementemic urticarial vasculitis is often associated with systemic manifestations and conditions such as systemic lupus erythematosus, viral infections and sometimes with hematologic diseases (14).

It is important to consider that a cutaneous vasculitis may be the presenting manifestation of a non-vasculitic disease. In cases like this, the presence of abnormalities on physical examination, e.g. high fever and cardiac murmur or lymphadenopathies or abnormalities in laboratory tests, e.g. hematologic cytopenias, monoclonal peak of gammaglobulin or unexplained hematuria, may lead to the search for infection or cancer (1). Imaging studies may help to reveal defects in visceral organs and echocardiogram may disclose a myxoma (a typical condition mimicking vasculitis). Finally, non-responsiveness to corticosteroids may indicate an underlying neoplasm in patients with cutaneous vasculitis.

References

1. GONZALEZ-GAY MA, GARCIA-PORRUA C: Other vasculitides including small vessel vasculitis. *In* ISENBERG DA, MADDISON P, WOO P, GLASS D and BREEDVELD F (Eds.): *Oxford Textbook of Rheumatology*, 3rd ed., Oxford University Press (in press).
2. LIE JT and MEMBERS AND CONSULTANTS OF THE AMERICAN COLLEGE OF RHEUMATOLOGY SUBCOMMITTEE ON CLASSIFICATION OF VASCULITIS: Illustrated histopathologic classification criteria for selected vasculitis syndromes. *Arthritis Rheum* 1990; 33: 1074-87.
3. STONE JH, NOUSARI HC: "Essential" cutaneous vasculitis: What every rheumatologist should know about vasculitis of the skin. *Curr Opin Rheumatol* 2001; 13: 23-34.
4. LIE JT: Nomenclature and classification of vasculitis: plus ça change, plus c'est la meme chose. *Arthritis Rheum* 1994; 37: 181-6.
5. GONZALEZ-GAY MA, GARCIA-PORRUA C: Henoch-Schönlein purpura. *In* BALLGV and BRIDGESSL JR (Eds.): *Vasculitis*, New York, Oxford University Press 2002; chapter 35: 476-94.
6. JENNETTE JC, FALK RJ, ANDRASSY K *et al*.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
7. CALVINO MC, LLORCA J, GARCIA-PORRUA C, FERNANDEZ-IGLESIAS JL, RODRIGUEZ-LEDO P, GONZALEZ-GAY MA: Henoch-Schonlein purpura in children from northwestern Spain: A 20-year epidemiologic and clinical study. *Medicine (Baltimore)* 2001; 80: 279-90.
8. GONZALEZ-GAY MA, GARCIA-PORRUA C, LUEIRO M *et al*.: Scurvy can mimic cutaneous vasculitis. Three case reports. *Rev Rhum (Engl. ed.)* 1999; 66: 360-1.
9. GARCIA-PORRUA C, GONZALEZ-GAY MA: Comparative clinical and epidemiological study of hypersensitivity vasculitis versus Henoch-Schonlein purpura in adults. *Semin Arthritis Rheum* 1999; 28: 404-12.
10. GARCIA-PORRUA C, LLORCA J, GONZALEZ-LOUZAO C, GONZALEZ-GAY MA: Hypersensitivity vasculitis in adults: A benign disease usually limited to skin. *Clin Exp Rheumatol* 2001; 19: 85-8.
11. GARCIA-PORRUA C, GONZALEZ-GAY MA: Cutaneous vasculitis as a paraneoplastic syndrome in adults. *Arthritis Rheum* 1998; 41: 1133-5.
12. GONZALEZ-GAY MA, GARCIA-PORRUA C, SALVARANI C, HUNDER GG: Cutaneous vasculitis and cancer: A clinical approach. *Clin Exp Rheumatol* 2000; 18: 305-7.
13. GARCIA-PORRUA C, GONZALEZ-GAY MA: Bacterial infection presenting as cutaneous vasculitis in adults. *Clin Exp Rheumatol* 1999; 17: 471-3.
14. MEHREGAN DR, HALL MJ, GIBSON LE: Urticarial vasculitis: A histopathologic and clinical review of 72 cases. *J Am Acad Der - matol* 1992; 26: 441-8.
15. GROSS WL: Antineutrophil cytoplasmic autoantibody testing in vasculitides. *Rheum Dis Clin North Am* 1995; 21: 987-1011.
16. LACIVITA L, ZIGNEGO AL, LOMBARDINI F *et al*.: Exacerbation of peripheral neuropathy during alpha-interferon therapy in a patient with mixed cryoglobulinemia and hepatitis B virus infection. *J Rheumatol* 1996; 23: 1641-3.
17. FERRI C, LONGOMBARDO G, LA CIVITA L *et al*.: Hepatitis C virus chronic infection as a common cause of mixed cryoglobulinaemia and autoimmune liver disease. *J Intern Med* 1994; 236: 31-6.
18. FERRI C, ZIGNEGO AL, GIUGGIOLI D *et al*.: HCVand cryoglobulinemic vasculitis. *Cleve Clin J Med* 2002; 69 (Suppl. 2): SII20-3.
19. GONZALEZ-GAY MA, GARCIA-PORRUA C: Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. *Medicine (Baltimore)* 1999; 78: 292-308.