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Bacterial infection presenting as cutaneous vasculitis in adults

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Cutaneous vasculitis, leukocytoclastic vasculitis, hypersensitivity vasculitis, mixed cryoglobulinemia, bacterial infection, systemic vasculitis.

ABSTRACT

Objective.
To examine the frequency and clinical features of patients with bacterial infection presenting with biopsy-proven leukocytoclastic cutaneous vasculitis (CV) in a well-defined area of southern Europe (northwestern Spain).

Methods.
A retrospective study of an unselected population of adult patients (age > 20 years) with biopsy-proven leukocytoclastic CV diagnosed at the Hospital Xeral-Calde (Lugo, Spain) was carried out from January 1988 through December 1997. Cutaneous vasculitis related to bacterial infection was considered if the vasculitis was confirmed by a skin biopsy showing leukocytoclastic vasculitis, if no drug intake was registered prior to the development of CV, and if bacteriologic evidence of infection was obtained.

Results.
Four of 138 patients (2.9%) presenting with biopsy-proved CV were diagnosed with leukocytoclastic CV related to bacterial infection. Three patients (2 with bacterial endocarditis and 1 with meningococcemia) met the ACR criteria for the classification of hypersensitivity vasculitis. Another patient with bacterial endocarditis met the criteria for mixed cryoglobulinemia. All of them presented with palpable purpura, high or low grade fever, an elevated erythrocyte sedimentation rate and leukocytosis.

Conclusion.
Cutaneous vasculitis may be the presenting manifestation of bacterial infection. In this respect, rheumatologists should be aware of possible infectious causes of vasculitis, even though they are not common.

Introduction

Cutaneous vasculitis (CV) comprises a broad and diverse group of diseases characterized by predominant involvement of the skin with histopathologic findings that have in common vascular inflammation and blood vessel damage (1). Cutaneous vasculitis may be confined exclusively to the skin (2). However, it may be also associated with systemic necrotizing vasculitis or other entities such as malignant disorders or connective tissue diseases. Cutaneous vasculitis may also be associated with infections (3, 4). Viruses, parasites and bacteria have been reported as being responsible for CV development.

The aim of our study was to examine the frequency and clinical features of patients with CV associated with bacterial infection in a large series of unselected patients with biopsy-proven leukocytoclastic CV in adults.

Patients and methods

We retrospectively studied the case records of all adult patients (age > 20 years) diagnosed with biopsy-proven CV at the Rheumatology Division of the Hospital Xeral-Calde (Lugo, Spain) from January 1988 to December 1997, inclusive. From this group, the case histories of the subset of patients with CV and bacterial infection were reviewed.

Because of the organization of the Public Health System in our area, this series reflects the actual spectrum of patients receiving medical care. Our hospital is the only referral center for a mixed rural and urban (40%) population of almost 250,000 people living in central Galicia, Spain (5). All patients with suspected CV are sent to the hospital by general practitioners or are self-referred to the emergency unit (5). Only our Rheumatology Division diagnoses and treats CV in this area. However, consultation, advice and examination by dermatology staff physicians is requested in all cases presenting with skin lesions (5).

As previously described (5), patients more than 20 years of age were considered as adults. The cut-off value of 20 years was chosen because this age has been proposed as a criterion for Henoch-Schönlein purpura (HSP) by the American College of Rheumatology (ACR) (6) and because this age best discriminated HSP from hypersensitivity vasculitis (HV) in previous studies (7).

In all patients presenting with CV, routine laboratory studies including a full blood count, coagulation studies, and

liver and renal function tests were performed at the time of diagnosis. As previously reported (5), immunologic testing including rheumatoid factor (RF) (by nephelometry), antinuclear antibodies (ANA) (by indirect immunofluorescence using Hep2 cells as substrate), anti-native DNA (by indirect immunofluorescence using Crithidia luciliae as substrate), and C3 and C4 serum determinations were performed in most patients. Testing for anti-neutrophil cytoplasmic antibodies (by indirect immunofluorescence on alcohol fixed neutrophils) was performed in those cases diagnosed after 1990.

Cutaneous vasculitis was diagnosed by characteristic histological findings on skin biopsy, such as neutrophilic infiltration, leukocytoclasis, and fibrinoid necrosis into the vessel wall of arterioles, capillaries, and post-capillary venules.

Cutaneous vasculitis relating to bacterial infection was considered if CV was confirmed by a skin biopsy showing leukocytoclastic vasculitis, if no drug intake was registered prior to the development of CV, and if bacteriologic evidence of infection was obtained.

Results

Four of the 138 biopsy-proven cases of CV (2.9%) were found to be related to bacterial infection (Table I). In these four adults a skin biopsy revealed a leukocytoclastic vasculitis. Three of them were diagnosed with bacterial endocarditis and another with meningococcemia. At their time of admission, the three patients with bacterial endocarditis presented with palpable purpura, low-grade fever (≤ 37.7°C) and heart murmur. Despite treatment with corticosteroids starting ten days before due to a clinical picture of CV consisting of palpable purpura along with maculopapular lesions, the patient with meningococcemia had high fever (> 39.5°) on admission. During their stay at the hospital, the patients with endocarditis developed fever (> 37.7°C). Blood cultures were positive in all four patients. However, tissue biopsy cultures performed in 3 of the 4 cases (cases 1, 2 and 4) were negative. In all 3 cases with endocarditis an echocardiography yielded positive results. The mitral valve was involved in two cases, while the aortic valve was involved in the other.

The treatment and outcome of cases 1, 2 and 3 were as follows: Case 1 was started on ceftriaxone with progressive improvement of his symptoms. Cases 2 and 3 were treated with penicillin plus tobramycin and with ampicillin plus gentamicin, respectively. However, despite progressive improvement of the symptoms, a prosthetic mitral valve replacement was required in both patients. In the patient with meningococcemia (case 4) skin lesions disappeared rapidly within 24 hours after treatment with ceftriaxone had been started. Finally, 3 of the 4 patients met the ACR classification criteria for HV (8). The other patient (case 2) was diagnosed as having mixed cryoglobulinemia (MC) according to previously reported criteria (9) (Table I).

Discussion

In this report we have focused on the spectrum of CV occurring in the setting of severe bacterial infections in a series of unselected adult patients with biopsy-proven CV. As expected (10), meningitis and endocarditis accounted for the cases of CV associated with bacterial infection. However, in addition to *Neisseria meningitidis*, we also found unusual

Table I. Main features of four patients with cutaneous leukocytoclastic vasculitis (CV) related to bacterial infection.

Case	Age/ sex*	Type of CV	Predisposing conditions	Main clinical features on admission	Main laboratory tests	Onset of episode of CV in relation to the diagnosis of infection	Causal bacteria	Final diagnosis
1	72/M	HV	Diabetes mellitus prosthetic aortic valve	Low-grade fever** murmur and palpable purpura	Leukocytosis*** elevated ESR****	4 days before	*Acinetobacter*	Bacterial endocarditis
2	64/M	MC	Corticosteroid therapy for chronic bronchopathy	Low-grade fever murmur and palpable purpura	Leukocytosis, RF(+), C4 low, cryoglobulins(+), raised serum creatinine, elevated ESR	1 month before	*Fusobacterium avium*	Bacterial endocarditis
3	21/M	HV	Mitral prolapse	Low-grade fever murmur and palpable purpura	Leukocytosis elevated ESR	5 days before	*Enterococcus faecalis*	Bacterial endocarditis
4	38/M	HV	None#	Persistent high fever (>39.5ºC), palpable purpura and maculopapular skin lesions	Leukocytosis, elevated ESR	10 days before	*Neisseria meningitidis*	Meningococcemia

* M: male; **low-grade fever: 37.1° and 37.7° C; *** leukocytosis: > 11,000 leukocytes/mm^3.
****Elevated ESR: erythrocyte sedimentation rate > 40 mm/1st hour.
No abnormalities of the late components of complement were found.
HV: hypersensitivity vasculitis; MC: mixed cryoglobulinemia; RF: rheumatoid factor.

bacteria such as *Fusobacterium avium* to be associated with biopsy-proven CV. Also, although drug therapy prior the onset of the CV has been implicated in the etiology of CV, especially in patients with HV (7, 8), and in some cases CV may occur following antibiotic therapy for bacterial infections, none of our patients had received any drug prior to the onset of their skin lesions.

McCluskey and Fienberg described bacterial infections as specific etiologic factors included in a subgroup of diseases with known causative agents in which vasculitis sometimes occurs (11). However, many classification systems for the vasculitides do not make a well-differentiated separation between primary and secondary vasculitis (2, 12). In contrast, Lie (12) and Scott and Watts (13) have underlined the relationship between primary and secondary vasculitis which is of special relevance to rheumatologists who often study patients with secondary vasculitides. Indeed, although the largest group of small-vessel vasculitides includes the "isolated" cutaneous vasculitis which is in general a benign process, CV can be also associated with either systemic necrotizing vasculitis or other entities such as infections (14), malignancies (5), or connective tissue diseases (15).

Hypersensitivity vasculitis, HSP and MC have been associated with bacterial infections (14). In most series gram-positive cocci (*Staphylococcus* and *Streptococcus*) and *Neisseria meningitidis* and *gonorrhoeae* were the most common bacteria implicated in this process. However, gram-negative bacteria, anaerobes, mycobacteria and brucella have also been implicated in the development of CV (14).

Several possible mechanisms for the development of CV related to bacterial infection have been suggested (3, 14). Indeed, it is important to differentiate between a direct infectious cause for CV with bacteria or other microorganisms present in the biopsy tissue as documented by tissue cultures or special stains for micro-organisms or by PCR or other laboratory techniques versus those patients who have infectious etiologies for vasculitis and a sterile cutaneous biopsy with no evidence for direct infection of the blood vessels and the skin.

A direct infectious cause would be most likely in cases of bacterial endocarditis or disseminated bacterial infections, while the latter cases would represent a true hypersensitivity type of CV based purely on a immune complex-mediated process initiated by antigens of the bacteria responsible for the acute or chronic infection. Thus, leukocytoclastic vasculitis may result from abnormal immunoregulation related to the infectious disease. In our cases, where they were carried out tissue biopsy cultures were sterile. However, PCR procedures were not performed, and for this reason we cannot exclude completely a direct infectious cause for CV.

In summary, CV may be the presenting manifestation of bacterial infection. Indeed, although in most cases the vasculitis is obviously related to the bacterial infection, in some patients CV may be the herald of a concealed life-threatening bacterial infection. In patients presenting with palpable purpura and leukocytosis with either low-grade or high fever, the possibility of bacterial infection should be considered. In these cases blood cultures should be taken and an echocardiogram should be performed, especially if a cardiac murmur is present.

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