Vasculitis mimicking bacterial endocarditis

Marco Calachanis, Paolo Ferrero, Fulvio Orzan, Filippo Marchisio*, Giampaolo Trevi

*Cardiology Unit, *Radiology Unit, Molinette Hospital, Turin, Italy*

Key words:
Endocarditis; Mitral valve prolapse; Transesophageal echocardiography; Vasculitis.

Fever of unknown origin is one of the most intriguing issues in clinical practice. One of the most feared diagnoses, especially in patients with known valvular disease, is endocarditis. The differential diagnosis of fever is often complicated by the clinical-pathological overlap between the systemic inflammatory response in different types of pathologies such as infectious, autoimmune or neoplastic disorders. We report a case of a patient presenting with fever, cutaneous nodules and malaise, with a known mitral valve prolapse and moderate regurgitation, in which the diagnosis of Wegener's granulomatosis was finally made.

(Ital Heart J 2003; 4 (11): 816-818)

Received January 7, 2003; revision received April 29, 2003; accepted July 2, 2003.

Address:

Dr. Marco Calachanis

U.O. di Cardiologia
Ospedale Molinette
Corso Bramante, 88
10126 Torino
E-mail:
marcocalachanis@hotmail.com

Introduction

Fever of unknown origin is one of the most intriguing clinical problems that the physician has to manage in clinical practice. The classic definition of this syndrome requires the presence of an external body temperature of at least 38.3°C lasting for at least 3 weeks, in the absence of a certain cause, despite 1 week of hospital diagnostic work-up[1]. Because of the optimization of the health resources, the turnover of patients in hospitals has become more and more rapid, and most of the diagnostic work-up in the management of fever of unknown origin is done on an ambulatory basis so that the second part of the definition (1 week of hospital assessment) is no longer required.

The differential diagnosis of the fever of unknown origin includes a wide spectrum of possibilities ranging from infectious diseases to neoplasia to rheumatic and collagen disorders.

In case of a patient with fever it is essential to assess his risk profile according to his clinical history. One of the most important diagnoses to consider in a patient with fever and organic valvular disease is endocarditis. The diagnosis of endocarditis is based on the presence of the histopathological, clinical-cultural and echocardiographic findings stated by the Duke criteria[2]. Often, its clinical diagnosis is complicated by the presence of the so-called "fastidious pathogens" that are responsible for culture-negative endocarditis. Moreover, the presence of valvular heart disease with a grossly altered valvular apparatus (calcifications, mitral valve prolapse with redundancy of the leaflets) may render the echocardiographic diagnosis more difficult. In such patients, even though this possibility must always be borne in mind due to the ominous prognosis of a missed diagnosis, alternative diagnoses should still be taken into consideration. In fact, many of the systemic consequences of infective endocarditis, or other visceral infective foci, are also present in pure inflammatory diseases such as autoimmune disorders. On the other hand, an infective process such as endocarditis, can herald a systemic and immunological activation that may be very similar to an autoimmune disease.

We report a case of a man with malaise and fever preceded by chills, known valvular heart disease, and cutaneous nodular lesions.

Case report

On August 14, 2002 a 61-year-old patient with fever, malaise, weight loss and known mitral valve prolapse with moderate regurgitation was admitted to our unit with suspected infective endocarditis. At the time of admission, the patient appeared asthenic and pale. He had bouts of intermittent fever (max 39°C) sometimes preceded by chills, during which, samples of blood for aerobic and anaerobic bacteria cultures were drawn. There were no petechiae nor cutaneous nodules. The apical impulse was on the fifth intercostal space on the hemiclavicular line and a grade 3/6 pansystolic murmur irradiating to the axilla was audi-

ble at the apex. The lung fields were clear and the liver and spleen could be palpated under the subcostal margin during deep inspiration. The leukocyte and erythrocyte counts were normal, with a marked elevation of the erythrosedimentation rate (83 mm/hour), C-reactive protein (5.4 mg/l) and fibrinogen (744 mg/dl). Urea and liver enzymes were within normal limits. The urinary sediment was positive for mild albuminuria and hematuria. A transthoracic echocardiography documented a mitral valve prolapse with worsened regurgitation that was now severe and with a possible detachment of a tendinous cord and volume overload of the left ventricle. Overall, the systolic function was satisfactory. Transesophageal echocardiography confirmed these findings, and in particular the rupture of a first order cord, responsible for a large eccentric regurgitant jet (Fig. 1). Thoracic roentgenography was normal as was the abdomen echography.

Thereafter, empirical antibiotic therapy with amoxycillin and clavulanic acid (2.2 g 3 times daily), netilmicin 300 mg and clarithromycin 500 mg twice daily was started. Two days later the patient felt better and his temperature had decreased to within normal limits. At this time, however, two nodules were detected on the thenar eminence of both hands. They were raised, slightly purpuric and not tender; they disappeared almost completely the day after. At the same time, the patient began to complain of migratory arthralgia without swelling or any inflammatory changes of the joints. Blood cultures were all normal, and alternative diagnoses were hence taken into consideration. The clinical presentation of the patient is a common finding in the "vasculitis syndrome"[3] (malaise, fever, flu-like syndrome) and the nodules, first interpreted as Osler's nodes, could be regarded as a sign of cutaneous vasculitic involvement. Second level laboratory tests to confirm this hypothesis were performed. The serum levels of antinuclear antibodies, anti-DNA, lupus anticoagulant, extractable nuclear antigens, the cryoglobulin test, rheumatoid factor and perinuclear antineutrophil cytoplasmic antibodies (anti-myeloperoxidase) were all within normal limits but the antineutrophil cytoplasmic antibody titer (antiproteinase 3) was markedly positive. In order to exclude the possibility of a false positive result that may be seen in the course of an unknown infectious disease, we submitted the patient to complete serologic evaluation (Widal-Wright, anti-*Borrelia, Brucella, Mycobacterium* antibodies) that was negative, and to a contrast-enhanced abdominal and thoracic computed tomographic scan. The latter revealed the presence of areas of hypoperfusion in both lungs, possibly an expression of vasculitic involvement (Fig. 2). Urography revealed the presence of an inhomogeneity of the left renal parenchyma, and of some hyperdense streaks likely due to contrast tubular trapping. A few days following the computed tomographic scan and with the patient still on full antibiotic treatment, there were new bouts of fever and arthralgia, followed by a purpuric nodular eruption around his ankles. A biopsy was promptly taken, and the nodules disappeared within 2 days. The histopathological appearance of these cutaneous lesions was that of a leukocytoclastic vasculitis. Having consulted an urologist, a rheumatologist and a specialist in infectious diseases, the antibiotic therapy was interrupted and the patient was started on high dose (1 mg/kg) steroid treatment. The fever and arthralgia resolved completely and the patient felt much better. The erythrosedimentation rate returned within normal ranges, while mild abnormalities of the urinary sediment persisted during the patient's hospital stay. Unfortunately we do not know if they later disappeared because the urologic follow-up was done in another center. The patient returned to his job after 1 week, and the surgical indication to mitral valve repair will be later re-evaluated, once he has stabilized from the autoimmune point of view.

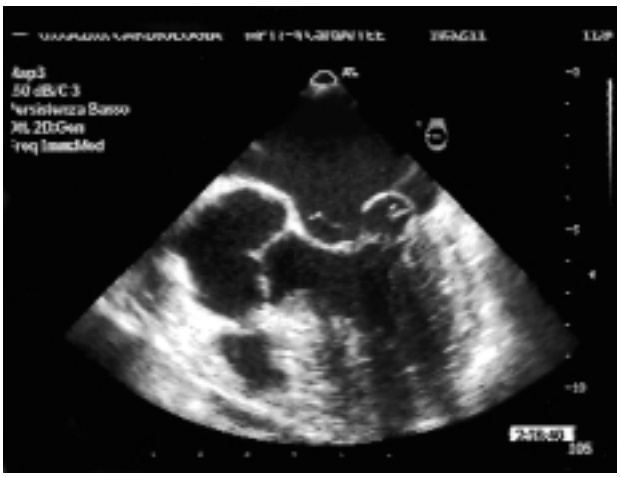

Figure 1. *Transesophageal echocardiographic image showing prolapse of the posterior mitral leaflet associated with rupture of the cord and a flail valve.*

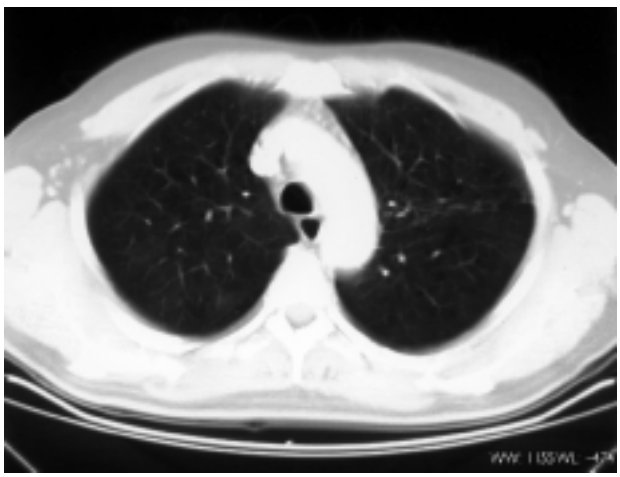

Figure 2. *Thoracic computed tomographic scan showing widespread areas of hypoperfusion suggesting vasculitic involvement of the lungs.*

Discussion

The imaging, pathological and serologic findings at presentation, together with the clinical evolution, strongly suggested the diagnosis of Wegener's granulomatosis, which, in particular, may explain the arthralgias, the cutaneous nodules and, finally, the mildly pathological sediment, as they are common sites involved by the disease. Different presentations of this syndrome were first described by McBride (1897) and Klinger (1931) but it was recognized as a definite clinical-pathological syndrome in 1936 by Wegener. The typical presentation of this disorder is characterized by the involvement of the upper and lower airways with the presence of granulomata in the affected organs[4]. The diagnosis is based upon clinical and histopathological findings, but, unfortunately, the presentation is usually far less typical. In particular, it may be complicated by the existence of the so-called "overlap syndrome", where the clinical and pathological characteristics of the different types of vasculitis, such as polyarteritis nodosa, Wegener's granulomatosis, cutaneous vasculitis, etc., may be similar mixed[5]. Moreover, it is usually difficult to obtain adequate material for histological examination by tissue biopsy, and even in optimal conditions of the sample, the pathognomonic granulomata of Wegener's disease may be absent. Our patient presented some challenging features; in fact, his clinical picture was quite unspecific. There was not the typical lung and kidney involvement and the pathological features of the cutaneous biopsy were those of a generally described leukocytoclastic vasculitis. Because of these difficulties in obtaining a more precise pathological diagnosis, many serologic tests, such as the detection of antineutrophil antibodies, have been developed. These tests are both sensitive and specific and may be useful to distinguish between different patterns of cytoplasmic staining[4]. The treatment of choice in Wegener's disease is immunosuppression (high-dose corticosteroids and cyclophosphamide). If promptly treated the disease usually has a benign course. If left untreated, the prognosis of Wegener's syndrome is very poor due to the rapid loss of function of the affected organs[6]. In the present case, we were intrigued by the possibility of an atypical presentation of a septic disease, for which corticosteroid treatment would have been detrimental. Pancardiac involvement in Wegener's syndrome has been described in the literature but is quite rare[5]. In particular, some cases of Wegener's granulomatosis simulating bacterial endocarditis have been reported[7]. These diagnostic challenges were raised by the finding of an acute aortic insufficiency due to a granulomatous involvement of the aortic root[8,9]. There are no complete literature reviews of the echocardiographic characterization and presentation of the valve involvement in Wegener's disease. In particular, there is only one article in which the authors describe the presence of aortic valvular vegetations; in all the other cases, aortic regurgitation was mainly due to aortic root dilation or thickening of the aortic leaflets[7]. Pathological examination of the valve in surgical or autoptic series revealed the presence of myxoid and collagenous degeneration of the excised valve tissue[6].

To our knowledge, there are no such detailed literature reports of a similar involvement of the mitral apparatus, probably because in normal hearts granulomatous changes of the papillary muscles and subvalvular apparatus remain clinically silent. In our case, the worsening of mitral regurgitation, more or less simultaneously to the onset of the symptoms of vasculitis, may be a pure coincidence; indeed, the natural history of mitral valve prolapse is sometimes unpredictable, especially when, as in this case, there is evident myxomatous degeneration of the valve. An alternative, more speculative explanation could be that of a cardiac involvement of the subvalvular apparatus or even the valvular leaflets themselves, already weakened by the myxomatous degeneration, leading to the detachment of the cord and hence to the sudden worsening of the insufficiency.

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