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CASE REPORT

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Severe rheumatoid valvular heart disease

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Abstract Rheumatoid arthritis (RA) is a systemic inflammatory disease in which extra-articular involvement is not uncommon. Cardiac compromise may be frequent, although most often, it is clinically silent. Herein, two cases of RA-related endocarditis, one of which required valve replacement, are described. Etanercept was useful in controlling the articular and extra-articular RA compromise in both cases.

Keywords Cardiovascular disease · Colombians · Endocarditis · Etanercept · Nodulosis · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an articular inflammatory disease of unknown etiology, with a worldwide prevalence of about 1% [1]. Cardiac involvement in RA is common and occurs in up to 50% of the affected patients [2]. It has been recognized since 1881 when Charcot described RA-associated pericarditis and later, in 1941, when Baggenstoss and Rosenberg described cardiac nodules associated with this disease [2]. It has different presentations, including pericarditis (30–50%), endocarditis (9–70%) and myocarditis, but the overt clinical manifestations are rare [3]. Clearly, it has a higher prevalence among male patients who have active RA with a positive rheumatoid factor [3].

RA has been related to an increased mortality due to cardiovascular events secondary to inflammatory mediators, increased homocystein seric levels and decreased high-density lipoproteins [4]. It has also been suggested that therapy with methotrexate is associated with increased cardiovascular events in the presence of established atherosclerotic disease [4].

Herein, valvular involvement in two patients with RA is described, and the general characteristics of this common but usually clinically silent disease complication are discussed.

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Case 1

A 45-year-old woman with a past medical history of positive rheumatoid factor RA diagnosed 20 years ago was admitted to our Rheumatology Unit in March 1997. She complained of symmetric polyarticular pain compromising metacarpophalangeal and interphalangeal joints along with morning stiffness lasting for 2 h. Upon being physically examined, she was found to have an articular index of 6, diminished grip strength and interosseous muscle atrophy. The cardiopulmonary system was normal. She was started on meloxicam at 15 mg/day p.o. and methylprednisolone at 4 mg/day p.o. The following month, she came for follow-up with a poor response, and methotrexate was started; later, the dose was increased to 20 mg p.o. weekly. She had multiple exacerbations that required local infiltrations with steroids. During follow-up in November 1997, she was found to have a systolic murmur grade II/VI in the aortic area which radiated up to the neck and other foci. An echocardiogram disclosed thickening of the aortic valve and mild prolapse of non-coronary and right coronary leaflets. The mitral valve showed prolapse in the meso- and telesystolic septal leaflets. Aortic valve insufficiency grade I/IV with deceleration of more than 3.0 m/s^2 and a maximal systolic transvalvular gradient of 20 mmHg was diagnosed as well as diminution in the mitral valve deceleration time and venocapillary pulmonary hypertension. Captopril at 25 mg t.i.d. was prescribed.

In March 1999, her pretibial edema had progressed to grade II/IV, and she described paroxysmal nocturnal dyspnea, orthopnea and dyspnea at rest. She was started on beta-methyldigoxin at 0.25 mg/day and aspirin at 100 mg/day. A

new echocardiogram was performed revealing significant cardiomegaly with left side dilation, increased myocardial max index and systolic stress, an ejection fraction of 55%, massive aortic valve insufficiency, mitral insufficiency grade III/IV, tricuspid valve insufficiency grade II/IV, pulmonary artery pressure of 64 mmHg and diminution of global motility. Cardiac catheterization showed normal coronary arteries. Otherwise, the results were coincident with the echocardiogram. HLA class II typing disclosed the haplotypes DRB1*0404/*0302, DQB1*0401/02 and DQB1*06.

During April 1999, the patient's functional capacity was declining, and she was taken to surgery for mitral and aortic valve replacement. The pathological analysis of valvular tissue disclosed rheumatoid nodules in the aortic valve and degenerative changes in the mitral valve. After surgery, she was discharged with methylprednisolone at 4 mg/day, celecoxib at 200 mg b.i.d., aspirin at 100 mg q.i.d., beta-methyldigoxin at 0.25 mg/day and ranitidine at 150 mg/day. It was suspected that cardiac nodulosis was induced by methotrexate, thus therapy was switched initially to cyclophosphamide at 1 g i.v. monthly and, later, to etanercept at 25 mg s.c. two times a week. She responded well to therapy and is now on clinical remission.

Case 2

A 42-year-old male was sent for evaluation and treatment in January 1999. He had a 3-year history of inflammatory articular pain that had started in his right shoulder and was followed by symmetric articular tenderness and effusions in his knees, proximal interphalangeal and metacarpophalangeal joints and morning stiffness lasting for 1 h. The rheumatoid factor was positive (128 IU/ml). Otherwise, levels of testosterone, uric acid and thyroid-stimulating hormone were within the normal range as were the tests for total blood count, liver and renal function. He had been diagnosed as having RA 2 years earlier and had been treated with methotrexate at 7.5 mg/week and diclofenac at 50 mg t.i.d. On physical examination, his functional status was poor, with an articular index of 19 and diminished grip strength, and the decision was made to admit him to the clinic. He was treated with intra-articular injections of steroids, methylprednisolone i.v. bolus (500 mg/day for 3 days) and started on methotrexate at 12.5 mg/week p.o. He was found to have bilateral episcleritis and a mild left pleural effusion that was related to the active RA. A thoracic computed tomography was performed confirming the pleural effusion. In addition, he had a small left apical fibrotic area with no evidence of pulmonary infiltrates. He was screened for HIV and tuberculosis, including bronchoalveolar lavage and smears, but all tests were negative. For his episcleritis, he was started on topical flurbiprofen and, later, topical steroids.

He improved moderately and was discharged, but he came again a couple of months later with an articular index of 7. Because of the modest response and the functional decline, cyclophosphamide pulses (1 g i.v. monthly for 6 months) were started along with methylprednisolone. Later, azathioprine at 100 mg/day was added, but he required admission several times for pain control and new steroid pulses. Methotrexate was increased to 20 mg/week with no adequate response.

He came for follow-up in September 2000, and a grade III/VI diastolic cardiac murmur in the aortic and mitral areas was found. An echocardiogram was performed showing no alteration in cardiac chamber size, an ejection fraction of 60%, aortic sclerosis and aortic valve insufficiency grade II/IV with mild mitral insufficiency. No pericardial or vessel involvement was found. He had a cardiac output of 5.952 l/min. Given the persistent articular and extra-articular involvement, the patient was placed on etanercept at 25 mg s.c. two times a week, prednisone at 10 mg q.i.d., captopril at 25 mg b.i.d., calcium at 600 mg b.i.d., calcitriol at 0.25 μg q.i.d. and naproxen at 500 mg b.i.d. He experienced marked improvement and was in complete remission during his follow-up.

Discussion

The extra-articular manifestations (EAMs) of RA are variable and include sicca syndrome, rheumatoid nodules and pulmonary and cardiac involvement. EAMs have been associated with an increased mortality having an incidence of about 40% in some studies [5].

Concerning heart valve disease, a screening using transthoracic and transesophageal echocardiography performed by Guedes et al. [6] showed an increased incidence of mitral, aortic and tricuspid valve dysfunction, involving up to 83% of RA patients compared with 40% of the controls, although there were usually no clinical symptoms in either group. The mitral valve is the one most commonly compromised by valvular heart disease in RA, and it is followed in frequency by the aortic, tricuspid and pulmonary valves. This pattern of involvement is mainly related to the pressure load faced by the valves, with more pressure leading to more damage [2]. The cardiac nodulosis associated with RA has a variable clinical presentation, including intracardiac masses mimicking atrial mixomas and other masses obliterating the right ventricular cavity, but valvular compromise with classic cardiac nodules is rare [2, 7].

Iveson et al. [8] reviewed 22 cases of rheumatoid nodules in the aortic valve. They found an association between the aortic and mitral involvement by RA nodules in 66% of the cases; 78% of the patients had severe RA with subcutaneous nodulosis, but some had mild symptoms, and epiescleritis was found in 66% of the cases. The rheumatoid nodules were found mainly on the valve ring or cusps [8]. Other researchers have described valvular thickening as one of the classical patterns of heart involvement in RA [9]. It is noteworthy that our case 2 had epiescleritis associated with valvular cardiac involvement.

In our cases, the patients developed signs and symptoms of cardiac failure secondary to the valve incompetence caused by inflammation and secondary deformity. We

observed that the time of onset was variable, and evolution after clinical diagnosis was followed by a continuing loss of myocardial function. This suggests that although overt clinical valvular disease in RA is rare, the prognosis after it appears is related to the specificity and readiness of therapy. However, currently, there is no evidence that classical disease-modifying antirheumatic drugs are efficient in these cases [3]. There are some reports suggesting that cardiac involvement can be attributed to methotrexate-induced accelerated rheumatoid nodulosis (MIARN), a syndrome which is characterized by the appearance of rheumatoid nodules in patients treated with methotrexate and with no previous history of nodulosis [10]. It can compromise mitral, aortic and tricuspid valves leading to cardiac murmurs and valvular regurgitation and has been associated with the *HLA-DRB1*0401* allele [10], a rare variant among Colombian patients with RA [11]. The RA activity is not related to MIARN. The location of rheumatoid nodules is usually in the fingers [12]. In case 1, it was suspected that methotrexate was the possible cause of, or at least had some influence on, the development of valvular nodulosis.

Combe et al. [12] explained that EAMs of RA may be aggravated by methotrexate in up to 23% of those patients with previous nodulosis. Accelerated nodulosis, mainly located in the fingers, developed in 11% of the patients that were started on methotrexate and had no previous EAMs. Therapy with hydroxychloroquine actually decreased the incidence of nodulosis related to methotrexate in these patients [12]. A small group of ten patients with MIARN studied by Kerstens et al. [13] showed that this syndrome only appeared in patients during therapy with methotrexate (MTX) but not in patients treated with azathioprine. Interestingly, one patient developed a mitral valve nodule [13]. Dash et al. [14] described a significant improvement in vasculitic lesions and the disappearance of pulmonary MIARN with D-penicillamine.

MIARN should be considered as a possible cause in those cases in which nodulosis appears after an initial trial of methotrexate. This is usually limited to fingers but may involve multiple organ systems, including the cardiac valvular system. When this occurs, treatment includes a multidisciplinary assessment but remains limited and non-specific.

We observed that, in the case of our patients, etanercept, the soluble p75 tumor necrosis alpha receptor, had as much of a benefit on the articular disease as on the EAMs, including nodulosis. While some have observed that etanercept seems to induce nodulosis [15], others have not registered an increase of this manifestation in any significant number of patients treated with etanercept [16]. Controlled studies will be needed to further elucidate this.

Valve replacement offers clinical and prognostic improvement for patients with reversible left ventricular dysfunction but requires weighing the operative risk against the clinical benefit. Captopril prescription and cardiology referral are suggested in all cases of clinically apparent cardiac RA [3]. When valve replacement is indicated, some researchers have suggested that prosthetic valves should be avoided as much as possible because these patients are usually involved in multiple drug therapy and have an increased risk of peptic ulcer disease. Therefore, long-term anticoagulation therapy may be relatively contraindicated [17]. Further studies should be carried out to find the optimal management of cardiac valvular nodulosis.

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