Case Report

Libman-Sacks Endocarditis and Oral Anticoagulation

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The patient is a 34-year-old female with systemic lupus erythematosus and secondary antiphospholipid antibody syndrome, who evolved with convulsive crises, partially controlled with an anticonvulsant, and auscultation of a cardiac murmur, whose investigation showed the presence of a mitral valve vegetation. Once the diagnosis of Libman-Sacks endocarditis was established, therapy with warfarin sodium was initiated, and, after 6 months of oral anticoagulation, the patient had total control of the convulsive crises and the valvular vegetation disappeared on echocardiography. This study discusses the occurrence of Libman-Sacks endocarditis in systemic lupus erythematosus, its association with antiphospholipid antibody syndrome, and the anticoagulant therapy. A literature review is also provided.

Libman-Sacks endocarditis was initially reported in 1924 as the presence of bacterium-free valvular vegetations[1], and later as a manifestation of systemic lupus erythematosus[2]. Its incidence varies and may even reach 60% in postmortem studies [3]. It is usually asymptomatic, but fragmentation of the vegetations may occur with systemic embolization and a predisposition to infective endocarditis [4]. The simultaneous presence of antiphospholipid antibodies has been reported in a small number of studies, and this association is still controversial [5,6]. Corticosteroids and immunosuppressants are known not to have an effect on the valvular lesions of Libman-Sacks endocarditis. On the other hand, anticoagulation may be used in the treatment of antiphospholipid antibody syndrome, and some authors have suggested the use of this therapeutic modality when the association of antiphospholipid syndrome and Libman-Sacks endocarditis occurs.

We report the case of a patient with systemic lupus erythematosus, secondary antiphospholipid antibody syndrome, and Libman-Sacks endocarditis, whose vegetations disappeared after anticoagulation therapy.

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Case report

The patient is a 34-year-old female being followed up at the Rheumatology Service of the Hospital das Clínicas of the University of Minas Gerais since May 1994 due to the diagnosis of systemic lupus erythematosus, according to the criteria of the American College of Rheumatology [5]. The patient had malar erythema, photosensitivity, discoid cutaneous lesions, symmetric polyarthritis, oral ulcers, and positive antinuclear factor titers (1:1024). She also had renal impairment, confirmed on biopsy, which revealed diffuse proliferative glomerulonephritis (class IV of the World Health Organization). Prednisone (1 mg/kg/day) and monthly pulse therapy with cyclophosphamide (1 g/month) were initiated with progressive improvement in clinical findings and later a reduction in medications.

The patient evolved stably until March 1998, when she began to experience generalized tonicoclonic convulsive crises. Computerized tomography of the brain and examination of the cerebrospinal fluid were normal, and the investigation of anticardiolipin antibodies revealed an IgG of 12.2 GPL (< 10) and an IgM of 0.5 MPL (< 10). However, the search for lupus anticoagulant with the techniques of the kaolin coagulation test and the tissue thromboplastin inhibition test was positive. The patient had a previous history of 3 abortions in the second gestational trimester, therefore confirming the diagnosis of secondary antiphospholipid antibody syndrome. An anticonvulsant (diphenylhydantoin) at a dosage of 300 mg per day and acetylsalicylic acid at a dosage of 200 mg per day were initiated, and partial control of the convulsive crises was obtained. In January 2000, the physical examination showed a regurgitation cardiac murmur in the inferior left sternal border, and the transthoracic echocardiography showed vegetation in the mitral valve. Blood cultures were negative (fig. 1). The presence of Libman-Sacks endocarditis was hypothesized, an oral anticoagulant (10 mg of warfarin per day) was initiated, and an INR above 2.0 was maintained. In July 2000, the patient was asymptomatic, with no convulsive crises, and a new control echocardiography (transesophageal and transthoracic) showed no vegetation in the mitral valve (fig. 2). Currently, the patient is using prednisone, azathioprine, and warfarin, in maintenance doses, and her disease is inactive.

Discussion

Valvular heart diseases are the most frequent and important cardiac manifestations of systemic lupus erythematosus [4,8]. The

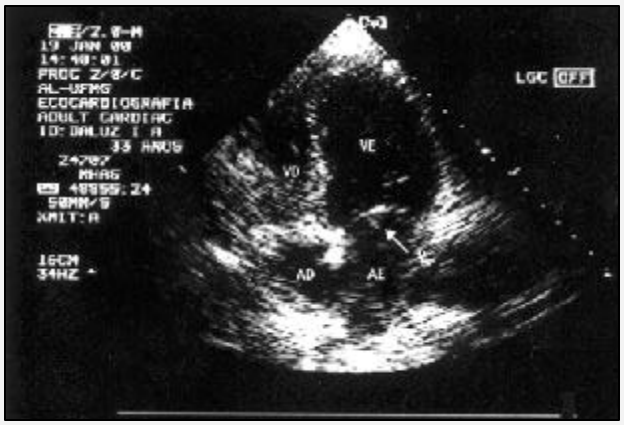

Fig. 1 - Initial transthoracic echocardiogram, showing a vegetation in the mitral valve.

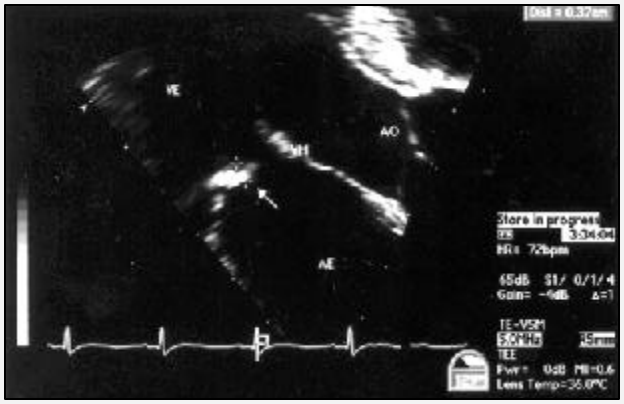

Fig. 2 - Transesophageal echocardiogram, showing thickening of the mitral valve and absence of vegetation.

valvular alterations may manifest as Libman-Sacks masses or vegetations, valvular thickening, regurgitation, and, rarely, stenosis. The mitral valve is the most frequently affected, followed by the aortic valve. Impairment of the tricuspid and pulmonary valves is rarely reported [5-8].

More than half of the patients with systemic lupus erythematosus, when assessed through transesophageal echocardiography, have clinically silent valvular alterations with few anatomic and functional repercussions [9]. Despite this, these patients have a greater incidence of stroke, peripheral embolism, heart failure, infective endocarditis, and death as compared with patients with no valvular heart disease [9]. No temporal relation seems to exist between valvular impairment and activity, duration, and therapy for systemic lupus erythematosus, although one study related the presence of valvular alterations to the duration of the disease [9].

The Libman-Sacks vegetations are a sterile build-up of immune complexes, mononuclear cells, hematoxylin bodies, and fibrin and platelet thrombi. They may develop at any site on the endocardial surface, but are more commonly found on the left heart valves, particularly on the atrial surface of the mitral valve. Their healing leads to fibrosis, and, in some cases, to calcification. If the vegetations are large, the scarring process may cause valvular deformity, possibly leading to mitral or aortic regurgitation [6-10].

On echocardiography, these masses are usually less than 1 square centimeter in size and have irregular margins, heterogeneous echodensity, and do not move. Most valves with masses have associated thickening or regurgitation [6,9].

The pathogenesis of Libman-Sacks endocarditis has not yet been completely elucidated. The major mechanisms proposed are as follows: 1) formation of fibrin and platelet thrombi on the impaired valves, whose organization leads to fibrosis, distortion, and subsequent valvular dysfunction. The thrombotic phenomena may result from the following biological effects of antiphospholipid antibodies: an increase in platelet activity, a reduction in antithrombin III levels, inhibition of prostacyclin release by endothelial cells, inhibition of thrombomodulin protein C-protein S system, and decreased activity of the tissue plasminogen activator released by endothelial cells; 2) immunologic injury as an initial insult to the valvular apparatus, triggering the sequence of pathogenetic events. Deposits of immunoglobulins and complement were shown in the subendothelial layer of the valves in patients with antiphospholipid antibodies [6,11].

Some studies have suggested an association between valvular heart disease and the presence of antiphospholipid antibodies, although other studies have not confirmed this relation [5,6]. These divergencies partially result from the different methods used for detecting antiphospholipid antibodies, as well as from variations in the echocardiographic technique used and in the interpretation of the results [6]. A correlation between the type and the titer of anticardiolipin antibodies and the probability of developing valvular heart disease seems to occur: patients with moderate to high IgG anticardiolipin antibody titers have a higher incidence of valvular alterations when compared with patients whose IgG and IgM anticardiolipin antibody titers are low. However, in some patients with valvular disease, the lupus anticoagulant may be the only antiphospholipid antibody detected [6].

The ideal treatment for patients with antiphospholipid syndrome has not yet been defined, partially due to the scarcity of information on the natural history of the disease in untreated patients. Most authors recommend high-intensity (INR>3) anticoagulation as secondary prevention for thromboembolic phenomena. Due to the high risk of recurrence of thrombotic episodes, especially in the first 6 months after the interruption of anticoagulant therapy, indefinite anticoagulation is indicated in patients with persistently high titers of antiphospholipid antibodies [12]. Primary prevention of thrombotic episodes in patients with moderate to high titers of antiphospholipid or anticardiolipin antibodies is controversial. These patients usually receive low doses of acetylsalicylic acid, although no evidence exists about the efficacy of this approach. Corticosteroids and immunosuppressants are not used in patients with antiphospholipid syndrome because they do not influence the hypercoagulable state [11-16]. Our patient had antiphospholipid syndrome secondary to systemic lupus erythematosus, the use of the immunosuppressant being justified for controlling the clinical manifestations of the primary disease not related to the syndrome.

Five cases have been reported about patients with primary antiphospholipid antibody syndrome manifested as stroke or acute myocardial infarction, who underwent oral anticoagulation. These patients had vegetations in the mitral valve and no evidence of infection, as in our case. After approximately 6 weeks to 4 months of treatment, all patients evolved with resolution of the vegetations [17-19].

A recent study described the echocardiographic characteristics of 29 patients with primary antiphospholipid antibody syndrome [20]. Transesophageal echocardiography was performed in all patients in the beginning of the study, and 22 had valvular lesions consisting of the presence of irregular nodules on the atrial face of the mitral

valve and on the vascular face of the aortic valve. In addition to valvular abnormalities, 2 patients had evidence of myocardial infarction and a defect in the atrial septum. All patients used an oral anticoagulant or antiplatelet agent for 1 year, and 13 patients ended up undergoing a new transesophageal echocardiogram. The second examination showed unchanged lesions in 6 patients and new lesions in the other 7. The authors concluded that treatment with an oral anticoagulant or antiplatelet agent does not contribute to the disappearance of noninfectious valvular vegetations, despite the sporadic reports on the resolution of vegetations with the use of high-intensity oral anticoagulation for less than 1 year. Our patient evolved with disappearance of the vegetations with oral anticoagulation for 6 months, and, in addition, control of the convulsive crises, which was partial up to then.

One complication of systemic lupus erythematosus is the thromboembolic phenomenon, the brain being the most affected site [8,21]. In most cases, the embolic episodes are known to be subclinical, but sometimes they may manifest as signs and symptoms of ischemia of the affected organ[8,21]. Convulsive crises may be a sign of cerebral ischemia [22]. In our patient, the control of convulsive crises coincided with the beginning of oral anticoagulation, and one may infer that the medication may have acted on one of the pathophysiological processes (hypercoagulable state) involved in the formation and release of thrombi from the vegetation [21]. However, epilepsy is one of the most common neuropsychiatric manifestations of lupus and is associated with a high prevalence of antiphospholipid antibodies, in whose pathogenesis the occlusion of small vessels of the cerebral circulation is implicated, as a result of the hypercoagulable state [23]. Therefore, in our case, more than 1 etiology for the convulsive crises may have existed, all of which related to the presence of antiphospholipid antibodies and to a hypercoagulable state, upon which oral anticoagulation may have therapeutically acted, controlling the convulsive crises.

Considering the ease of transthoracic and transesophageal Doppler echocardiography and the current difficulty of indicating long-term anticoagulation for patients with systemic lupus erythematosus, this case is worth reporting. In our patient, anticoagulation may have played an efficient therapeutic role, especially considering the presence of lupus anticoagulant. Our efforts should be directed to the study of the prevalence of the disease, its association with antiphospholipid antibodies and their manifestations, as well as to more adequate therapy and duration of treatment.

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