Association between Immunological Diseases and their Similar Clinical Manifestations

Alexandre de Matos Soeiro, Maria Carolina Feres de Almeida, Tarso Augusto Duenhas Accorsi, Guilherme Sobreira Spina, Carlos Vicente Serrano Jr., Flávio Tarasoutchi

Instituto do Coração (InCor) – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP)[1]; Liga de Combate à Febre Reumática[2], São Paulo, SP, Brazil

We report on a 30-year-old female patient, with biological mitral valve prosthesis due to symptomatic mitral stenosis and a history of acute myocardial infarction and generalized tonic-clonic seizure episodes, visual hallucinations, cerebral thromboembolic events and, at present, chorea and acute carditis. The patient was diagnosed with active rheumatic fever (RF), systemic lupus erythematosus (SLE) and Antiphospholipid syndrome (APS). The combination of three unusual diagnoses in the same patient makes this a unique case, modifying patient treatment and prognosis.

Introduction

The prevalence of autoimmune diseases has increased in recent decades, especially due to the greater medical knowledge on the subject and the development of specific diagnostic methods. Therefore, such diseases have acquired an extremely relevant importance, as the early and accurate diagnosis can reduce morbidity and mortality in most patients[1]. However, little is known about the association between several autoimmune diseases. The present describes the assumption that the same immune mechanism would be responsible for distinct clinical manifestations, albeit with no pathophysiological proof of the phenomenon, particularly due to the rarity of cases[1].

Case Report

This is case report of a 30-year-old Brazilian mulatto female patient, born and raised in São Paulo, with difficulty to speak and involuntary finger, hand, mouth and tongue movements for 18 months. She reported dyspnea with moderate effort (New York Heart Association [NYHA] functional class II). She also reported surgical replacement of the mitral valve for a biological prosthesis due to symptomatic mitral stenosis 18 months before. She was a smoker (three pack-year history), with a history of four pregnancies with normal deliveries without complications (last pregnancy six years before).

In 2005, the patient had angina at rest and remained in the hospital for 14 days in the intensive care unit; she was discharged with a diagnosis of acute myocardial infarction and mitral valve stenosis. At that time, she began to present dyspnea with moderate effort, with three exacerbation episodes, and in 2008, cardiac surgery for mitral valve replacement by a biological prosthesis was indicated. She underwent preoperative myocardial perfusion scintigraphy, which showed persistent hypo-uptake in the left ventricular (LV) anterior wall. The surgery had no complications and a postoperative transthoracic echocardiogram showed a left atrium (LA) with a 45-mm diameter, LV of 68 x 56 mm associated with moderate diffuse hypokinesis (ejection fraction [EF] of 44%) and mitral bioprosthesis with no structural changes with minimal regurgitation. She was discharged on the 5th day of hospitalization receiving aspirin, carvedilol, digoxin, captopril, furosemide and aldactone.

In 2008, she developed headaches accompanied by paresthesia in the left arm and involuntary movements of hands, mouth, tongue and fingers. She then presented tonic-clonic seizures and episodes of visual hallucinations, delirium and severe emotional lability. The neurological symptoms lasted approximately for thirty days and only the involuntary movements remain to date. The patient received cyclobenzaprine, but there was no improvement.

At physical examination, she was in good general health, had tachycardia (heart rate = 130 beats per minute), blood pressure was 120x70 mmHg, visible and palpable *ictus* in the fifth intercostal space over the left midclavicular line, presence of rhythmic heart sounds with loud B1 and pericardial friction rub audible in midsystole and proto and telediastole and fine crackling rales in both pulmonary bases. The involuntary movements of extremities remained. At this point, the diagnosis of active rheumatic fever was achieved due to the presence of acute carditis and chorea.

The electrocardiogram showed sinus rhythm with a PR of 0.28 s and right bundle branch block with inactive antero-septal area. The chest X-ray showed a double contour in the left atrium and bulging pulmonary arc.

Keywords

Mitral valve stenosis; immune system diseases; rheumatic fever; lupus erythematosus, systemic; myocarditis.

Mailing Address: Alexandre de Matos Soeiro •
Rua Maranhão, 680 / 81 - Santa Paula - 09530-440 – São Caetano do Sul, SP - Brazil
E-mail: alexandre.soeiro@bol.com.br
Manuscript received December 08, 2010; revised manuscript received December 18, 2010; accepted April 15, 2011.

A transthoracic echocardiogram was requested, which showed LA of 48mm, left ventricular ejection fraction (LVEF) of 32% with diffuse hypokinesis, mitral bioprosthesis with no structural alterations and slight pericardial effusion. Cardiac MRI was performed, which showed diffuse hypokinesis and akinesis with subepicardial late enhancement in mid-apical anterior LV wall (Figure 1). Laboratory tests showed 76,000 platelets/mm^3, erythrocyte sedimentation rate of 20 mm, C-reactive protein of 1.37 mg/L and APTT (R) of 1.42 (suggestive of inhibitor presence). Gallium scintigraphy performed for suspected acute myocarditis showed positive result for active inflammatory process (Figure 2). Due to the presence of chorea, a head MRI was requested, showing multiple areas in the cerebral hemispheres and cerebellum that were suggestive of previous embolism. The hypothesis of rheumatologic disease was considered and tests showed ASO of 786 IU / mL, positive antinuclear factor > 1/320 (homogeneous), positive anti-SM, positive anticardiolipin IgM (14 IU) and negative IgG antibodies and negative lupus anticoagulant test.

These findings allowed the simultaneous diagnosis of active rheumatic fever, systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome (APS). Due to the picture of acute myocarditis and pericarditis the patient was started on steroids with prednisone 1 mg/kg/day and benzathine penicillin every 15 days. Because of the clinical manifestation of heart failure, the patient received carvedilol, enalapril and furosemide. Additionally, the patient was started on warfarin due to the diagnosis of APS with the presence of previous thromboembolic events, as well as haloperidol for the chorea.

After six months, the patient reported dyspnea to great efforts (NYHA functional class I), and complete disappearance of the neurological symptoms when haloperidol was started. At physical examination she showed no pericardial friction rub and the electrocardiogram showed a PR interval of 0.20 s.

Discussion

The diagnosis of rheumatic fever was established by the Jones criteria of the American Heart Association. The presence of chorea alone confirms the diagnosis[2]. In addition, the patient still had acute carditis, valvular lesion and PR interval increase (highly suggestive of myocarditis).

The rheumatic carditis, in 15% of cases, may present with acute myocarditis associated with LV dysfunction, as in the described case[2]. The presence of acute myocarditis can be confirmed by myocardial scintigraphy with gallium, even when it has not been demonstrated at the MRI[2]. Pericarditis, characterized by the presence of pericardial friction and effusion does not differ from other etiological presentations[2]. It should be noted that the use of benzathine penicillin as prophylaxis for new outbreaks of rheumatic fever should have been maintained even after the valve replacement surgery, which could prevent the new aggravation in the form of pancarditis and chorea.

As for the chorea associated with rheumatic fever (Sydenham), it has been described in patients between 8 and 12 years old, with duration of 3 to 4 months[3]. Although uncommon, the occurrence in adults with its longer-lasting

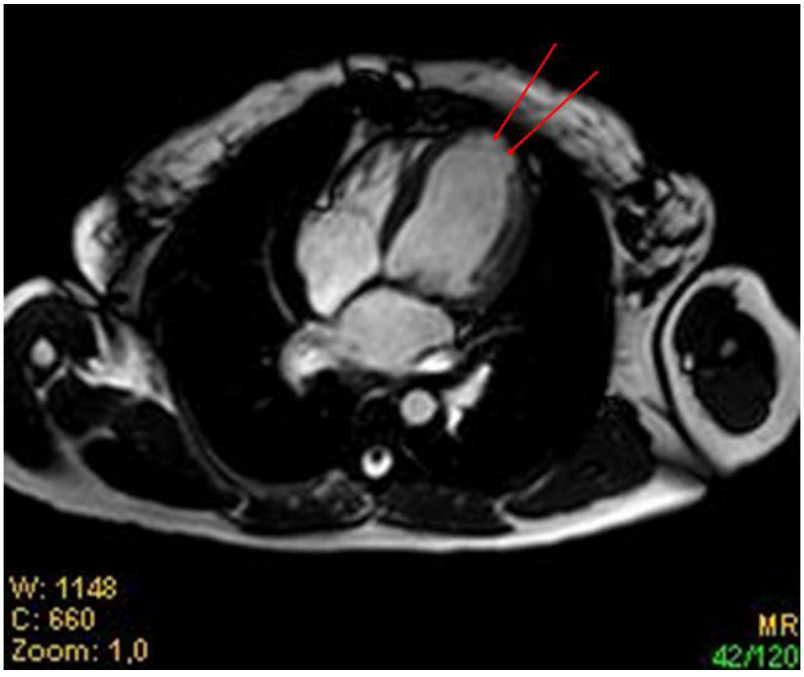

Figure 1 – *Cardiac magnetic resonance in the horizontal plane disclosing subepicardial late enhancement in the mid-apical anterior wall and left ventricular mid-portion antero-septal segment (red arrows).*

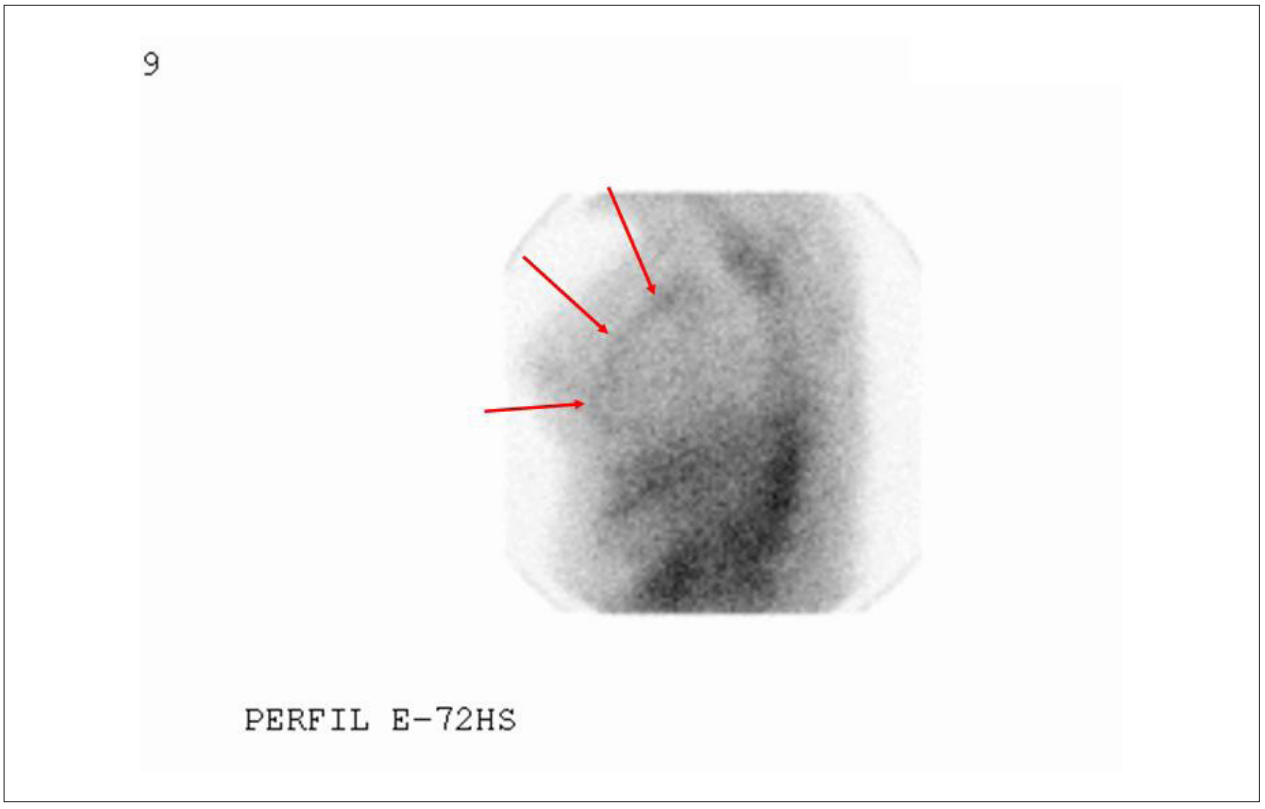

Figure 2 – *Myocardial scintigraphy with gallium disclosing myocardial uptake area outlining the cardiac silhouette (red arrows).*

form is possible[3]. Recurrences of chorea in adults can occur especially in women during pregnancy or associated with oral contraceptive use.

The diagnosis of SLE was made based on the criteria of the American College of Rheumatology of 1997, by the presence of serositis (pericardial effusion), positive anti-SM, positive antinuclear factor, thrombocytopenia and neurological manifestations (seizures and hallucinations)[4].

Some form of heart disease is found in 30% to 89% of patients with SLE, probably due to the deposition of immune complexes and complement activation[4]. The aggression by the disease may occur as pericarditis (20% to 30% of cases), myocarditis (10%), Libman-Sacks endocarditis, and coronary artery disease and should be quickly recognized for immunosuppression establishment together with specific cardiology therapy. Both acute myocarditis and pericarditis are clinically different from other etiologies[4]. Moreover, Libman-Sacks endocarditis can lead to a degenerative form of the disease, but rarely requires surgical valve correction[4].

Lupic chorea is uncommon, being observed in 2% of cases of SLE[3]. As in rheumatic fever, it occurs in children aged around 11 years, especially females and it may be indistinguishable from Sydenham's chorea[3,5].

Finally, we characterized the presence of APS due to the presence of anticardiolipin antibody, associated with previous thrombotic events and thrombocytopenia[4,6,7].

The presence of acute myocardial infarction is evident due to the description of persistent hypo-uptake area at the myocardial scintigraphy and late enhancement images obtained at the cardiac MRI. Pictures like this can be present in 4% to 20% of patients with APS[6]. Furthermore, APS may present with mitral valve vegetations or thickening in up to 33% of patients, with most of them being asymptomatic and rarely showing valvular degeneration[6,7].

Different studies have reported APS as the primary cause of chorea[3,5,8]. It is rare manifestation and occurs especially in females. A prospective cohort study in patients with APS and chorea showed that in most cases the symptoms were bilateral, involving particularly the extremities and head, with mild to moderate presentation. The mean age was 44 years, which differs from SLE and rheumatic fever cases. Additionally, episode duration varied from 1 to 84 months (mean 14 months). Of all the immunological markers, the one that appears to be more strongly associated is the presence of positive anticardiolipin antibody IgM[8].

As observed, in some cases, more than one concurrent autoimmune disease can be diagnosed in the same individual. This situation can be interpreted as two or more rare diseases that are simultaneously present or the same disease displaying characteristics that belong to another disease. It is believed that similar immunological mechanisms between different autoimmune diseases can cross-over and display similar manifestations in a particular

individual[1]. Up to 24% of patients with rheumatic fever can have ß2 glycoprotein-1 antibodies, which are characteristic of APS and, conversely, around 14% of patients with APS have anti-streptococcal M-protein antibodies, which are typical of rheumatic fever[1,9]. It is suggested that streptococcal infection may be a trigger for the production of anticardiolipin antibodies, which would help clarify the association between APS, SLE and rheumatic fever[9,10].

Moreover, endothelial activation present in SLE valve lesion is similar to that of rheumatic fever, once again suggesting the presence of the same involved immune mechanism[9]. Regarding any of the three diseases reported in the patient, it is known that both humoral and cell immune response mechanisms may be involved, very often with the same manifestation involving a balance between the different mechanisms. Specifically regarding the link between the diseases, it is unclear what would be the main mechanism involved, once again assuming the presence of both, although they should be further investigated[9].

In Latin American countries such as Brazil, where the prevalence of rheumatic fever is significant, the chance of occurrence of multiple immune disorders in the same patient is higher, and must always be investigated[9].

Conclusion

The combination of three unusual diagnoses in the same patient makes this case unique, reinforcing the occurrence of similar immunological mechanisms. The patient who develops rheumatic fever has a genetic and immunological substrate that predisposes to the occurrence of other autoimmune diseases. Therefore, one should be alert to the emergence of other autoimmune diseases in rheumatic patients, which may also have important cardiac manifestations.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

References

1. Blank M, Krause I, Magrini L, Spina G, Kalil J, Jacobsen S, et al. Overlapping humoral autoimmunity links rheumatic fever and the antiphospholipid syndrome. Rheumatology (Oxford). 2006;45(7):833-41.
2. Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. Lancet. 2005;366(9480):155-68.
3. Wild EJ, Tabrizi SJ. The differential diagnosis of chorea. Pract Neurol. 2007;7(6):360-73.
4. Doria A, Iaccarino L, Sarzi-Puttini P, Atzeni F, Turriel M, Petri M. Cardiac involvement in systemic lupus erythematosus. Lupus. 2005;14(9):683-6.
5. Avcin T, Benseller SM, Tyrrell PN, Cucnik S, Silverman ED. A followup study of antiphospholipid antibodies and associated neuropsychiatric manifestations in 137 children with systemic lupus erythematosus. Arthritis Rheum. 2008;59(2):206-13.
6. Cohen D, Berger SP, Steup-Beekman GM, Bloemenkamp KW, Bajema IM. Diagnosis and management of the antiphospholipid syndrome. BMJ. 2010;340:c2541.
7. Roldan CA. Valvular and coronary heart disease in systemic inflammatory diseases: Systemic Disorders in heart disease. Heart. 2008;94(8):1089-101.
8. Orzechowski NM, Wolanskyj AP, Ahlskog E, Kumar N, Moder KG. Antiphospholipid antibody-associated chorea. J Rheumatol. 2008;35(11):2165-70.
9. Blank M, Aron-Maor A, Shoenfeld Y. From rheumatic fever to Libman-Sacks endocarditis: is there any possible pathogenetic link? Lupus. 2005;14(9):697-701.
10. Dzhuzenova BS, Nasonov EL, Kovalev VIu, Lopaeva OV, Speranskiĭ AI, Nasonova VA. [Cardiolipin antibodies in acute rheumatic fever]. Klin Med (Mosk).1992;70(2):66-71.