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Case Report

Myocarditis of Mixed Connective Tissue Disease: Favourable Outcome after Intravenous Pulsed Cyclophosphamide

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Abstract: A 30-year-old woman with mixed connective tissue disease was admitted with Wernicke's aphasia and progressive dyspnoea with chest pain. Multiple brain infarcts on a computed tomographic scan were compatible with a thromboembolic aetiology. Echocardiography showed marked hypokinesia of the posterior wall, biventricular dilatation and a decreased left-ventricle ejection fraction (40%). A diagnosis of myocarditis was made on myocardial biopsies disclosing interstitial lymphocytic infiltrates and myocardial fibre necrosis. A treatment with steroids and monthly pulsed cyclophosphamide was introduced. The heart function rapidly improved as assessed by a left-ventricle ejection fraction of 55% and remained stable 17 months thereafter.

Keywords: Cyclophosphamide; Heart failure; Mixed connective tissue disease; Myocarditis

Introduction

Mixed connective tissue disease (MCTD) is characterised by Raynaud's phenomenon, arthritis, myositis, swollen fingers and high antibody titres against nuclear ribonucleoprotein (RNP) [1]. Originally, undifferentiated connective tissue disease (UCTD) or Sharp's syndrome was considered to have a good prognosis. It was later recognised that a more severe evolution of the disease could be observed when other vital organs were involved, such as the heart or lungs (interstitial fibrosis and subsequent pulmonary hypertension). In order of frequency, pericarditis is the most common clinical manifestation of cardiac involvement, followed by mitral prolapse, right heart failure secondary to pulmonary hypertension, intimal hyperplasia of the coronary arteries and myocarditis.

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Case Report

A 25-year-old woman developed Raynaud's phenomenon and arthritis of the knees. Three years later, she experienced polyarthritis of the hands, wrist and knees. Her erythrocyte sedimentation rate was 27 mm/h, C-reactive protein was 11 mg/ml and rheumatoid factor 182 U (<30 U); a speckled pattern of antinuclear antibodies (titre 1:20480) was identified by enzyme-linked immunosorbant assay (ELISA) as anti-RNP antibodies (titre: 1:1024). Anti-nDNA and anti-Sm antibodies were negative. A diagnosis of MCTD was made, based on the clinical and serological parameters mentioned above. The patient remained stable for 2 years until she suddenly developed slurred speech, word-finding difficulty and dizziness. She had no joint complains or cutaneous lesions but, for the first time, she reported an exertional dyspnoea, apparently present for at least 3 years, and, more recently, chest pains. Neurological examination showed Wernicke's aphasia, and increased tendon reflexes on the right. No signs of heart failure were found, but a fourth cardiac sound was present. Creatine phosphokinase (CPK) and muscle brain (MB) fraction levels were normal. Antinuclear antibodies were 1/5120 and there were no changes in the other serological parameters. Complement fragments C3

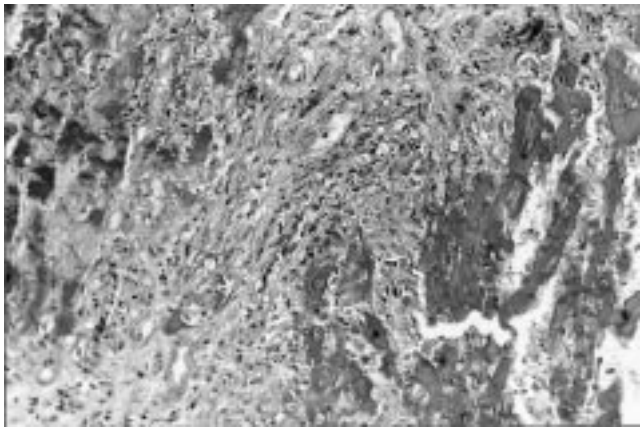

Fig. 1. Endomyocardial biopsy: myocardial cell necrosis, granulation tissue expansion with lympho-monocytic infiltration and the beginning of fibrosis (H&E, $\times 140$).

and C4 were within the normal range. A computed tomographic (CT) scan of the brain showed multiple infarcts in the left parietal and posterior frontal lobes and internal capsule. These lesions suggested a potential thromboembolic aetiology, which led to an extensive search for a coagulopathy or cardiovascular abnormalities: anticardiolipin antibodies, anti-ß$_2$-glycoprotein-1, serum level of protein C, antithrombin III, factor V Leiden and activated partial thromboplastin time (aPTT). These were either negative or within the normal range. Protein S activity, in contrast, was decreased to 60% (normal range 70–140%) and the free fraction to 47% (normal range 70–130%). Doppler imaging of the cervical arteries revealed no abnormalities. Her electrocardiogram was unremarkable except for T-wave inversion in lead II and rare premature ventricular contractions. An echocardiographic examination showed a marked hypokinesia of the posterior wall, a biventricular dilatation, a decreased left-ventricle ejection fraction (40%) and a small pericardial effusion, but excluded a foramen ovale. Myocardial biopsies at four different sites demonstrated an interstitial lympho-monocytic infiltrate, with necrosis of the myocardial fibres and a slight interstitial fibrosis (Fig. 1). Viral serologies for echovirus and coxsackie virus were negative.

In addition to treatment with angiotensin converting enzyme inhibitors and anticoagulation by warfarine (INR 2,5), an immunosuppressive therapy was introduced including pulsed methylprednisolone for 3 days (125 mg/pulse), followed by oral prednisone 80 mg/day, slowly tapered over 1 year. Cyclophosphamide was immediately started as monthly pulses (750 mg/m^2). By 4 weeks later, an echocardiogram already showed an improvement of the left-ventricle ejection fraction (55%) and, during the next 3 months, the patient noticed a subjective improvement of dyspnoea which disappeared 8 months later as well as the chest pains. After 8 months, myocardial biopsies at five different sites showed no signs of inflammation. Myocardial scintigraphy using antimyosin antibodies, which was not performed at the initial visit, revealed a myocardial activity slightly above background. The left-ventricle ejection fraction and myocardial uptake of ^{111}In-labelled antimyosin antibodies were unchanged 12 months later at the end of steroid and pulsed cyclophosphamide treatment.

Discussion

Myocardial dysfunction appears to be common in MCTD, as suggested by an abnormal left ventricular diastolic filling in 100% of 18 asymptomatic MCTD patients [2–4]. Nevertheless, myocarditis, as a possible cause of heart failure, has been rarely reported: three cases in children and six in adults [5–10]. Since even severe MCTD cases, with myocardial involvement, including myocardial necrosis, interstitial inflammation and fibrosis at necropsy, may be asymptomatic, the frequency of myocarditis in MCTD is probably underestimated [5]. Similar observations were made in active systemic lupus erythematosus (SLE), where myocarditis was symptomatic in about 10% of patients, compared with an incidence of 40% in autopsy series [11,12]. The endomyocardial biopsy is of considerable help in confirming the clinical suspicion of myocarditis, although it is invasive and of variable sensitivity because of the focal nature of the disease [13]. Recently, several studies underlined the interest in myocardial scintigraphy with ^{111}In-labelled antimyosin antibodies [14,15]. The sensitivity of this technique is high (83–100%) but its specificity is low (53–58%) compared with endomyocardial biopsy. The negative predictive value of normal antimyosin imaging is 92–100%. Thus, this technique appears to be particularly useful in establishing the diagnosis of myocarditis when there is strong clinical suspicion and a negative endomyocardial biopsy. However, this approach has its limitations in the follow-up of patient's. Indeed, in a subgroup of patients with biopsy-proven myocarditis, Dec et al. [15] described a persistence of abnormal uptake of ^{111}In-labelled antimyosin antibody even 6 months after immunosuppressive therapy, despite clinical improvement and an increase in the left ventricular ejection fraction. The significance of this persistent antimyosin uptake is unclear and has also been observed in the present case report.

By exclusion, the aetiology of the thromboembolic event in the present case is most probably related to myocarditis and associated myocardial incompetence, because no other embolic sources were detected. However, a moderate decrease in protein S, which was still present at the end of therapy, may have played a contributary role. In contrast, neither antiphospholipid, anticardiolipine, lupus anticoagulant nor anti-ß$_2$-glycoprotein-1 antibodies were detected.

Optimal treatment of myocarditis in MCTD remains undefined and includes glucocorticoids and azathioprine, but little has been reported on their respective efficacy.

Recently, Frustaci et al. [16] described a case of myocarditis and left ventricular aneurysm in SLE, with rapid clinical improvement and complete mechanical and histological resolution after steroid treatment. Most patients initially improved, but later the evolution of the disease was often rapidly poor despite an increase in steroid doses [7]. Addition of azathioprine has been reported in very few cases and did not allow any conclusion about its efficacy.

There is, so far, no report on the efficacy of cyclophosphamide in the treatment of myocarditis in MCTD. In a recent report, a young woman with SLE and cardiogenic shock with myocarditis responded to a combination of steroids, cyclophosphamide and intravenous immunoglobulin, whereas treatment with steroids and cyclophosphamide appeared to be ineffective [17]. Nevertheless, the evaluation was conducted only 10 days after the first pulse of cyclophosphamide, which may be too early to confirm the inefficacy of the drug in this case.

In this present report, moderate to severe myocarditis rapidly improved with steroids and cyclophosphamide without the adjunct of intravenous immunoglobulins. More importantly, the evolution of the disease was free of long-term relapse, in contrast to other reported cases treated with steroids alone. This is reminiscent of vasculitis where cyclophosphamide was shown to decrease significantly the relapse rate [18]. Despite early improvement under steroids, a combination of prednisone and immunosuppressive drugs, such as cyclophosphamide, may be more effective in this potentially life-threatening complication of connective tissue disease.

References

1. Sharp GS, Irvin WS, Tan EM et al. Mixed connective tissue disease. An apparently distinct rheumatic disease syndrome with a specific antibody to extractable nuclear antigen. Am J Med 1972;52:148–59.
2. Alpert MA, Goldberg SH, Singsen BH et al. Cardiovascular manifestations of mixed connective tissue disease in adults. Circulation 1983;68:1182–93.
3. Oetgen WJ, Mutter ML, Lawless OJ, Davia JE. Cardiac abnormalities in mixed connective tissue disease. Chest 1983;83:185–8.
4. Leung WH, Wong KL, Lau CP, Wong CK, Cheng CH, Tai YT. Doppler-echo evaluation of left ventricular diastolic filling in patients with mixed connective tissue disease. Cardiology 1990;77:93–100.
5. Singsen BH, Bernstein BH, Kornreich HK, King KK, Hanson V, Tan EM. Mixed connective tissue disease in childhood: a clinical and serologic survey. J Pediatr 1977;90:893–900.
6. Howard JP. Mixed connective tissue disease in a child. J Ky Med Assoc 1980;87:601–3.
7. Lash AD, Wittman AL, Quismorio FP. Myocarditis in mixed connective tissue disease: clinical and pathologic study of three cases and review of the literature. Semin Arthritis Rheum 1986;15:288–96.
8. Whitlow PL, Gilliam JN, Chubick A, Ziff M. Myocarditis in mixed connective tissue disease. Arthritis Rheum 1980;23:808–15.
9. Grossman LA, Li JKH. Myocardial involvement in mixed connective tissue disease. NY State J Med 1981;81:379–81.
10. Braun J, Sieper J, Schwarz A et al. Widespread vasculopathy with hemolytic uremic syndrome, perimyocarditis and cystic pancreatitis in a young woman with mixed connective tissue disease. Rheumatol Int 1993;13:31–6.
11. Doherty NE, Siegel RJ. Cardiovascular manifestations of systemic lupus erythematosus. Am Heart J 1985;110:1257–65.
12. Badui E, Garcia-Rubi D, Robles E et al. Cardiovascular manifestations in systemic lupus erythematosus. Prospective study of 100 patients. Angiology 1985;36:431–41.
13. Lie JT. Myocarditis and endomyocardial biopsy in unexplained heart failure: a diagnosis in search of disease. Ann Intern Med 1988;109:525–8.
14. Yasuda T, Palacios IF, Dec W et al. Indium 111-monoclonal antimyosin antibody imaging in the diagnosis of acute myocarditis. Circulation 1987;76:306–11.
15. Dec GW, Palacios I, Yasuda T et al. Antimyosin antibody cardiac imaging: its role in the diagnosis of myocarditis. J Am Coll Cardiol 1990;16:97–104.
16. Frustaci A, Gentiloni N, Caldarulo M. Acute myocarditis and left ventricular aneurysm as presentations of systemic lupus erythematosus. Chest 1996;109:282–4.
17. Disla E, Rhim HR, Reddy A, Ramaprasad S, Taranta A. Reversible cardiogenic shock in a patient with lupus myocarditis. J Rheumatol 1993;20:2174.
18. Guillevin L, Jarrousse B, Lok C et al. Longterm followup after treatment of polyarteritis nodosa and Churg–Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. J Rheumatol 1991;18:567–74.

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