



CASE STUDY

MYOCARDITIS AS A FORM OF RELAPSE IN PATIENT WITH ADULT ONSET STILL'S DISEASE

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ABSTRACT

Still's disease is a subset of juvenile idiopathic arthritis (JIA) that usually presents with intermittent fever, rash, and arthritis. It represents 10–20% of all the cases of JIA. This disorder may be called adult-onset Still's disease when it occurs in patients over the age of 16. Extra-articular flares can occur several years after disease onset (Javier Alberto Cavallasca *et al.*, 2010). We report a case of adult Still's disease with myocarditis after several years of being in remission. A 22-year-old man with history of systemic juvenile arthritis in remission since age 15 was admitted in hospital with 7 days history of fever, odynophagia, and arthralgias. Chest X-ray and cardiac ultrasound showed cardiac enlargement and impairment in ejection fraction. A cardiac MRI revealed acute myocarditis. He was treated with high dose of methylprednisolone with improvement of his general condition and cardiac parameters.

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INTRODUCTION

First described in 1971 by EG Bywaters, adult-onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology (Bywaters, 1971). Its main features are high spiking fever, evanescent rash, sore throat, polyarthralgia or arthritis, serositis, lymphadenopathy, hepatosplenomegaly, leukocytosis, elevated polymorphonuclear neutrophils (PMNs), high erythrocyte sedimentation rate, high serum ferritin (SF), and elevated liver enzymes. Despite the high diagnostic value attributed to high SF associated with low SF glycosylated fraction (<20%), the diagnosis of AOSD is difficult to establish, and the spectrum of differential diagnoses is wide (Fautrel *et al.*, 2002). The clinical course of the disease may follow 1 of 3 patterns: a monocyclic systemic course, an intermittent or polycyclic systemic course, and a chronic course that mimics chronic arthritis (Wouters *et al.*, 1986). The treatment of AOSD remains empirical. It includes nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, methotrexate, and intravenous immune globulins (IVIGs) (Efthimiou *et al.*, 2006). Biological agents such as tumor necrosis factor α (TNF- α) blockers, interleukin-1 (IL-1) receptor antagonists, and IL-6 inhibitors were recently used in refractory cases (Pouchot and Arlet, 2012). The most frequent cardiac involvement during AOSD is pericarditis. It occurs in

nearly 20% of the patients. Its outcome is most often favorable though some cases involved cardiac tamponade (Gerfaud-Valentin *et al.*, 2014). Conversely, myocarditis in AOSD is rare. To the best of our knowledge, none of the major AOSD cohort studies have mentioned myocarditis; only isolated cases have been reported. Myocarditis can be a form of relapse in patient with AOSD, which corresponds to the case of our patient.

Observation

A 22-year-old man with a history of systemic onset juvenile arthritis was in remission since age 15. He was admitted in hospital with 7 days history of febrile syndrome, odynophagia, arthralgias and effort dyspnea. On examination he had fever (38°C), heart rate of 110/min, blood pressure of 120/60 mmHg, and wrists and ankles arthritis. Laboratory tests revealed: white blood cell count 32250/mm³ (Neutrophils 90%), erythrocyte sedimentation rate (ESR) 35 mm/h, c-reactive protein rate 160mg/l, high serum ferritin rate 2374 μ g/ml, low glycosylated SF fraction (10%), high cardiac troponin rate 1,1 ng/ml. Blood and urine cultures were negative. Antineutrophil cytoplasmic antibodies, antinuclear antibodies (ANA), rheumatoid factor (RF), serological test for Human immunodeficiency virus, hepatitis B virus, hepatitis C virus, were negative. Chest X-ray showed enlarged cardiac silhouette. Cardiac ultrasound showed global hypokinesia, left ventricular dilatation, impairment of ventricular ejection

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(36%) and normal pericardium (Figure 1). The electrocardiogram (EKG) showed sinus tachycardia. Cardiac magnetic resonance imaging (MRI) showed high signal intensity at the basal to middle portion of the left ventricle with short-TI inversion recovery and at the medial layer with gadolinium-delayed enhancement (Figure 2). The diagnosis of myocarditis were established. He started treatment with intravenous methylprednisolone 240mg/day for 3 days. Fever resolved and he had improvement of his general condition and his left ventricle ejection fraction (LVEF=51%) (Figure 3). The patient was discharged on meprednisone 80 mg/day, the dose was gradually reduced.

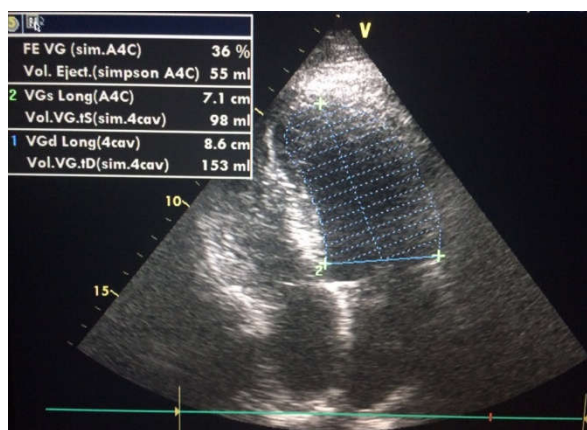


Figure 1. Transthoracic echocardiography: an apical four-chamber view showing an impairment of LVEF

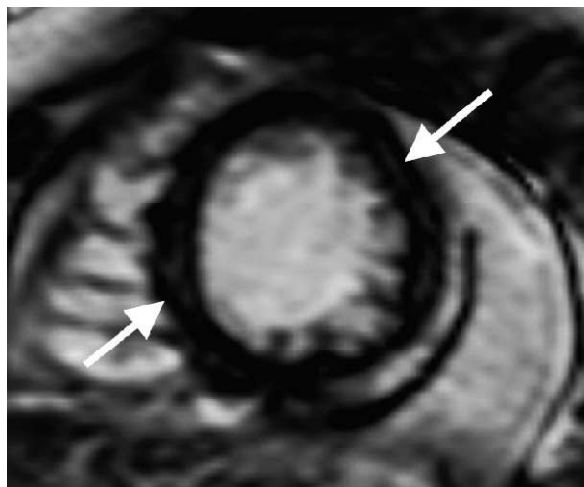


Figure 2. Medial layer of cardiac muscle was delayed-enhanced in gadolinium cardiac-magnetic resonance imaging (white arrow).

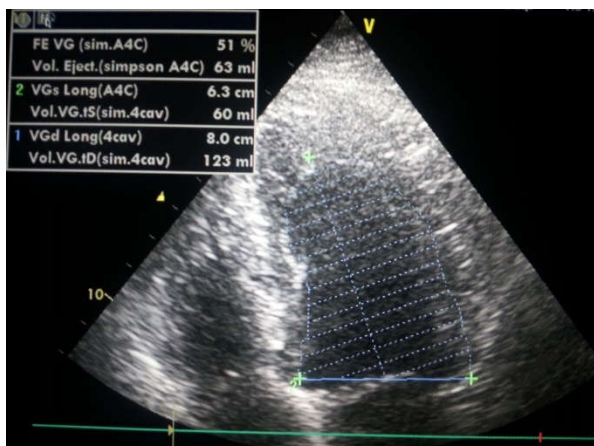


Figure 3. Transthoracic echocardiography: an apical four-chamber view showing an improvement of LVEF

DISCUSSION

Despite being a life-threatening condition (Colina *et al.*, 2009) myocarditis is probably the least described visceral involvement in AOSD (Yamaguchi *et al.*, 1992); its prevalence is rarely reported even in the largest case series. The prevalence of AOSD has been estimated at less than 1 case per 100,000 persons (Magadur-Joly *et al.*, 1995) and pericarditis is seen in about 20% of AOSD cases (Colina *et al.*, 2011). Myocarditis is less common; its prevalence in AOSD is about 7% (Mathieu Gerfaud-Valentin *et al.*, 2014). The pathophysiology of myocarditis in AOSD remains unclear. However, 2 mechanisms could be involved: an AOSD-specific myocarditis and a non specific myocardial involvement during a cytokine storm. On the one hand, Zhao *et al.* (2011) showed an active lymphocytic myocarditis at the acute phase, which may lead, in the chronic phase, to irregular fibrosis and atrophy. This argues for an inflammatory mechanism linked to the AOSD. On the other hand, cardiac failure occurring mostly in reactive hemophagocytic syndrome complicated AOSD may be secondary to a myocardial stunning in the context of a severe systemic inflammatory response syndrome as described in severe sepsis. The clinical picture of myocarditis in AOSD does not seem to differ from that of myocarditis of other origins. The presence of a majority of male patients has been already noted in myocarditis of different origins (Caforio *et al.*, 2007; Magnani *et al.*, 2006) but seems much more marked in AOSD, as seemed to occur in our case. In comparison with other myocarditis cases, myocarditis in AOSD may be equally asymptomatic (8%) but chest pain seems more frequent (58% vs 32%) (Hufnagel *et al.*, 2000); this is probably due to the high prevalence of associated pericarditis. Our patient had no pericarditis which explain the absence of chest pain. As in other myocarditis cases, the most common findings on ECG were sinus tachycardia and nonspecific STsegment and T-wave abnormalities; however, in AOSD with myocarditis (AOSD+M), 29% of ECGs were normal (Cooper, 2009) None of the AOSD patients exhibited severe arrhythmia as reported in other immune myocarditis cases such as giant-cell or sarcoidosis myocarditis, which joined the case of our patient who had a sinus tachycardia with a stable hemodynamics. Cardiac troponin was assessed in a few literature cases; it cannot thus be reliably analyzed. Nevertheless, Smith *et al.* (1997) have found that troponin I has a very limited sensitivity (34%) in the diagnosis of myocarditis; it only helps to confirm the diagnosis (specificity, 89%). The findings on transthoracic ultrasonography (TTU) were consistent with acute myocarditis but not with fulminant myocarditis because smaller left ventricular chamber size and increased wall thickness were never reported (Felker *et al.*, 2000). Moreover, TTU was shown to have a prognostic value in non-AOSD myocarditis; the loss of right ventricular function was shown to be the most powerful predictor of adverse outcome (Mendes *et al.*, 1994). Cardiac MRI as an alternative non-invasive tool to evaluate myocarditis has been reported. Currently, its place is growing because a combination of T2-weighted MRI and post gadolinium early and late T1-weighted MRI have shown good sensitivity (67%) and specificity (91%) in diagnosing myocarditis (Friedrich *et al.*, 2009) as well as myocardial involvement in rheumatic and autoimmune diseases (Mavrogeni and Vassilopoulos, 2011). In this study, cardiac-MRI showed high signal intensity at the basal to middle portion of the left ventricle with short-TI inversion recovery and at the medial layer with gadolinium-delayed enhancement. Cardiac-MRI may be a useful diagnostic tool in myocarditis associated

with AOSD. However, EMB is the gold standard. Data from an AOSD patient with myocarditis showed that EMB had been performed six weeks after onset, and results showed mononuclear cell infiltration and fibrosis (Masahiro Yamazoe *et al.*, 2014) it may not always be feasible or advisable. In our case, it was not performed.

As half of myocarditis cases occurred at the onset of AOSD, AOSD diagnosis may be suggested in case of feverish myocarditis or heart failure after ruling out infectious diseases, toxic causes (alcohol, radiation, antineoplastic drugs such as anthracyclines), and immunologic conditions (drug-induced hypersensitivity, eosinophilia, giant-cell myocarditis, sarcoidosis myocarditis, or myocarditis in connective tissue disease) (Cooper, 2009). In such cases, systemic symptoms, high WBC and PMN counts, high SF with collapsed glycosylated fraction, and steroid sensitivity should enhance the diagnostic probability. The nonspecific treatment of acute myocarditis in AOSD should not differ from that recommended by the current guidelines. A neurohormonal blockade with an ACE-I or angiotensin-receptor blockers, a β -adrenergic blocker, and refraining from intensive physical activities for a few months after the disease onset are recommended until ventricular recovery has been documented by noninvasive imaging (Sagar *et al.*, 2012). Studies suggested high-dose intravenous corticosteroids for treatment of myocarditis with AOSD as the first line specific treatment, and intravenous immunoglobulin, tumor necrosis factor- α antagonist (infliximab (IFX), etanercept (ETA), and adalimumab), anti-interleukin-1 inhibitor (anakinra, canakinumab, and rilonacept) and anti-interleukin-6 inhibitor (tocilizumab (TCZ)) for relapsing or resistant cases (Masahiro Yamazoe *et al.*, 2014; Casta-neda *et al.*, 2016). However, there were no clinical studies on the treatment appropriate for management of myocarditis in AOSD. Our patient received β adrenergic blockers, angiotensin-receptor blockers, corticosteroid therapy to produce a dramatic positive response. Due to the excellent response to steroids, further definitive treatment was not considered.

Conclusion

Cardiac involvement in patients with systemic JIA can be the first symptom of disease reactivation, even after many years of disease remission. In patients with clinical symptoms and signs suggestive of myocarditis, further investigation must be performed to confirm this severe complication.

Conflict of interest

None declared

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