Recurrent myocarditis in a patient with active ulcerative colitis: a case report and review of the literature

Giacomo Caio, Lisa Lungaro, Fabio Caputo, Maria Muccinelli, Maria Caterina Marcello, Eleonora Zoli, Umberto Volta, Roberto De Giorgio, Giorgio Zoli

ABSTRACT

Inflammatory bowel diseases such as ulcerative colitis (UC) may be complicated by several extraintestinal manifestations. These involve joints, skin, eyes and less commonly lungs and heart. Myocarditis may be triggered from the toxic effect of drugs (ie, mesalazine) commonly used for the treatment of UC or due to infections (eg, Coxsackieviruses, enteroviruses, adenovirus). Here, we report a case of a 26-year-old man affected by UC and complicated by two episodes of myocarditis. Both episodes occurred during two severe exacerbations of UC. However, in both cases the aetiology of myocarditis remains uncertain being ascribable to extraintestinal manifestation, drug toxicity or both.

INTRODUCTION

Inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn’s disease, are chronic inflammatory intestinal disorders, characterised by alternating periods of remission and relapse. It is well known that many factors including genetics, immune system, environment and gut microbiome may contribute to the onset of IBD. The incidence of IBD is increasing worldwide with 6.8 million cases in 2017.

Moreover, IBD can be associated with several extra-intestinal manifestations, mainly during acute exacerbations, in up to 30% of patients. Extraintestinal complications of IBD include joints (ankylosing spondylitis and spondyloarthropathies), eyes (uveitis), skin (psoriasis), and less commonly lungs (pleuritis) and heart (pericarditis and myocarditis) disorders. Myocarditis is a rare extraintestinal complication of IBD with a reported incidence of 6 cases over 15 000 patients. Interestingly, the incidence of myocarditis was slightly higher among patients with IBD compared with the general population. Despite rare, cardiac extraintestinal manifestations, such as pericarditis and myocarditis, are more commonly reported to occur in UC than Crohn’s disease patients. In addition, in patients with IBD myocarditis could be triggered by drugs currently used to treat this condition such as mesalazine (MSZ) or biological agents, and in newly diagnosed IBD. Last but not least, Coxsackie viruses, Parvovirus B19, Adenoviruses and enteroviruses can be aetiological agents for myocarditis.

Here, we report a clinical case of a young man affected by UC who had two episodes of myocarditis.

CASE REPORT

A 26-year-old male patient was admitted to our Internal Medicine Unit of SS Annunziata Hospital in Cento (Ferrara, Italy) in July 2018 because of fever, bloody diarrhoea (up to 10 bowel movements per day) and abdominal pain. His medical history reported a previous diagnosis of pancolitis in July 2017 successfully treated with oral MSZ (4.8 g/day) and beclomethasone (5 mg/kg). During the hospitalisation, the patient reported several episodes of severe chest pain associated with dyspnoea with no ECG abnormalities. Due to the persistence of these episodes, the patient was tested for troponin I (TnI) that turned to be positive (0.24 ng/mL; n.v.: <0.04 ng/mL). Echocardiography showed a hypokinetic area of the apical anterior aspect of the myocardium with a reduced ejection fraction (50%). Thus, a cardiac MRI was performed. According to Lake Louis Criteria, cardiac MRI, with at least 2 (oedema and necrosis) positive criteria, confirmed a diagnosis of myocarditis (figure 1A). The patient was tested for common infective causes of
myocarditis.

Stool examination for Adenovirus and bacteria (Shigella, Salmonella, Campylobacter, Escherichia coli O157h7, and Yersinia enterocolitica) resulted negative. Specific viral serological antibodies resulted negative: IgG anti-Coxackie virus was 2.4 U/mL (n.v.: <11 U/mL; positive >15 U/mL), and IgM anti-Coxsackie B virus 6.3 U/mL (n.v.: <10 U/mL; positive >15 U/mL), IgM anti-Herpes simplex 1 and 2 was 0.53 (n.v.: <0.9; positive >1.1), and IgM anti-Herpes zoster 0.26 (n.v.: <0.9; positive >1.1). Thus, these data led us to think that myocarditis was attributed to MSZ and the treatment was shifted to azathioprine (AZA) 150 mg/day associated with methylprednisolone 1 mg/kg/day for 7 days, tapered down until discontinuation. This therapeutic approach promoted remission of UC and troponin I (TnI) normalisation within 7 days. The clinical picture and the lab tests improved (WCC: 16.98×10^3/µL; CRP: 0.21 mg/dL; TnI: 0.01 ng/L; faecal calprotectin: 3213 mg/kg) and the patient was discharged. One month later (September 2018), a colonoscopy revealed a subacute ulcerative pancolitis with Mayo score 1.5. In December 2018, a follow-up cardiac MRI documented the resolution of myocarditis (figure 1B), and the echocardiography revealed the normalisation of the ventricular ejection fraction (68%).

In July 2019, due to a new exacerbation (acute proctosigmoiditis; Mayo 3) AZA treatment was discontinued, and vedolizumab was started (300 mg intravenous every 8 weeks). A month later (August 2019), the patient was re-hospitalised because of the occurrence of symptom relapse characterised by bloody diarrhoea, tachycardia and chest pain with an increase of high-sensitive TnI (358 ng/L) without ECG abnormalities. The patient was investigated for the third time with a cardiac MRI showing a new inflammatory lesion suggestive of myocarditis (figure 1C). A second diagnosis of myocarditis was established, certainly unrelated to MSZ since this drug was discontinued 1 year before. During the hospitalisation the patient was treated with intravenous methylprednisolone 1 mg/kg/day for 7 days associated with vedolizumab. Intestinal symptoms improved along with a reduction of the inflammatory markers: WBC from 15.19 to 9.36×10^3/µL; CRP from 3.21 to 0.83 mg/dL; TnI from 358 to 27 ng/L. At discharge, the treatment regimen included intravenous vedolizumab 300 mg every 8 weeks, methylprednisolone 32 mg/day (tapered down until complete discontinuation), topical beclometasone 3 mg/day, bisoprolol 2.5 mg/day and ramipril 5 mg/day. Intestinal symptoms improved along with a reduction of the inflammatory markers: WBC from 15.19 to 9.36×10^3/µL; CRP from 3.21 to 0.83 mg/dL; TnI from 358 to 27 ng/L. At discharge, the treatment regimen included intravenous vedolizumab 300 mg every 8 weeks, methylprednisolone 32 mg/day (tapered down until complete discontinuation), topical beclometasone 3 mg/day, bisoprolol 2.5 mg/day and ramipril 5 mg/day. A follow-up endoscopy (January 2020) showed ulcerative proctosigmoiditis with mild endoscopic activity, Mayo score 1. The patient is currently well and follows a therapy with intravenous vedolizumab 300 mg every 8 weeks, bisoprolol 2.5 mg and ramipril 5 mg, both on a daily basis.

**DISCUSSION**

UC is often accompanied by extra-intestinal manifestations as anaemia, arthropathy, metabolic bone abnormalities, cutaneous diseases (erythema nodosum and pyoderma gangrenosum), ocular (episcleritis and uveitis), hepatobiliary diseases (primary sclerosing cholangitis, pericholangitis, steatosis, chronic hepatitis, cirrhosis and gallstone formation), and less commonly, cardiovascular complications. However, cardiac manifestations can occur with a higher frequency than what it is clinically documented, as they may remain undiagnosed. Up to one-third of patients with IBD, particularly those with UC, can develop myocarditis or pericarditis with a higher rate of complications, and fatal outcomes in comparison with patients affected by Crohn’s disease. The patient presented in this report had myocarditis during UC exacerbation and required different therapeutic approaches to control both the inflammatory bowel disease and the cardiac abnormalities.

**Figure 1** (A) Cardiac MRI showing myocardial oedema of the apical anterior and septal site compatible with myocarditis (red arrow); (B) the oedema previously reported in the left ventricle was no longer detectable. Some interstitial/myocellular abnormalities, compatible with myocarditis, are present in the apical lateral site; (C) picture illustrating a small and nuanced area of oedema in the apical lateral site with subepicardial localisation (red arrow), compatible with a recent inflammation.
MSZ is a 5-aminosalicylic acid agent usually prescribed as a first-line therapy in the treatment of UC. MSZ mechanism of action has not been completely understood. However, it is thought that it reduces inflammation by inhibiting the cyclooxygenase enzyme and the peroxisome proliferator-activated receptor gamma cascade, thus reducing the proinflammatory signalling pathway of the nuclear factor κB. Along with the most common MSZ-evoked side effects (e.g., dyspepsia, pancreatitis, blood dyscrasias, nausea and headache), this drug can trigger the onset of cardiac inflammation, such as pericarditis, myocarditis and coronary vasculitis. The mechanisms leading to cardiotoxicity have not been elucidated yet; however, different theories have been proposed: (1) MSZ may increase the eosinophil-stimulating cytokines, promoting a hypersensitivity reaction; (2) a hypersensitivity reaction triggered by antibodies directed against the drug and a cross-reacting with the cardiac tissue; (3) an immunoglobulin E-mediated allergic reaction promoted by its toxicity on the myopericardium. MSZ induced myocarditis usually appears within 4 weeks from the beginning of the treatment, but concomitant corticosteroid use could delay the onset of the cardiotoxicity. MSZ-induced myocarditis has been reported in literature both in the treatment of UC, Crohn’s disease and in newly diagnosed IBD. Up to now, more than 51 cases of MSZ induced myocarditis have been reported.

The Food and Drug Administration has approved tumour necrosis factor-alpha (TNF-α) blockers (such as infliximab, adalimumab and golimumab) for the treatment of UC, and the use of these drugs has been associated with worsening of congestive heart failure. Namely, cardiomyopathy has been reported as a severe adverse reaction of adalimumab, golimumab and a cross-reactive with the cardiac tissue; (3) an immunoglobulin E-mediated allergic reaction promoted by its toxicity on the myopericardium. MSZ induced myocarditis usually appears within 4 weeks from the beginning of the treatment, but concomitant corticosteroid use could delay the onset of the cardiotoxicity. MSZ-induced myocarditis has been reported in literature both in the treatment of UC, Crohn’s disease and in newly diagnosed IBD. Up to now, more than 51 cases of MSZ induced myocarditis have been reported.

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