

Case Report

Myocarditis due to mesalamine treatment in a patient with ulcerative colitis: Favorable outcome after Infliximab treatment

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SUMMARY

Cardiac involvement is a rare extraintestinal manifestation of inflammatory bowel disease. When it occurs, the most frequent presentation is acute pericarditis, followed by myocarditis, myopericarditis, pericardial and pleural effusion, conduction defects, and cardiac tamponade. We describe a patient with ulcerative colitis, who developed acute myocarditis while receiving per-os mesalamine (5-aminosalicylic acid). The cardiac complication responded well to interruption of mesalamine, while the underlying bowel disease responded favourably to Infliximab administration during both the active phase and the maintenance treatment as well. Acute and maintenance treatment of patients with severe ulcerative colitis and myocarditis could be succeeded with Infliximab, which can be safely administered in the absence of signs of cardiac failure. Clinicians should not only be aware of this potential cardiac complication in patients with ulcerative colitis but also of options for therapy.

Key words: Mesalamine, ulcerative colitis, myopericarditis, cardiac involvement, extraintestinal manifestations, Inflammatory bowel disease, Infliximab.

festation of inflammatory bowel disease (IBD). When it occurs, the most frequent presentation is acute pericarditis, followed by myocarditis, myopericarditis, pericardial and pleural effusion, conduction defects, and cardiac tamponade.¹⁻⁸ All these clinical situations can arise as a true extraintestinal manifestation² or as a secondary effect of drugs containing mainly mesalamine, or azathioprine. Myocarditis could also be manifested in patients with Ulcerative Colitis (UC) or Crohn's disease (CD) children with IBD included.

Compared to other extraintestinal manifestations it seems that cardiac involvement in IBD has been rather inadequately studied and characterized. Infliximab (Remicade) is a chimeric anti-tumor necrosis factor-alpha antibody (TNF- α) recently approved for the treatment of UC not responding to intensive medical treatment.⁹

The aim of this presentation is to describe a patient with UC, who developed acute myocarditis while receiving per-os mesalamine (5-aminosalicylic acid). The cardiac complication responded well to interruption of mesalamine, while the underlying bowel disease responded favourably to Infliximab administration during both the active phase of UC and the maintenance treatment as well.

INTRODUCTION

Cardiac involvement is a rare extraintestinal mani-

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CASE REPORT

A male patient, aged 21, presented to the emergency department of our hospital, complaining of chest pain accompanied by high fever (39°C) and bloody diarrhoea. The bloody diarrhea was attributed to exacerbation of UC which was diagnosed and confirmed both endoscopically and histologically, ten months previously. The first attack of UC was of mild severity and settled promptly with a moderate dose of steroids peros and mesalamine enemas.

No other treatment was applied. Because of the appearance of some symptoms suggestive of recurrence of UC, the patient started on treatment with mesalamine (Salofalk granules 1000mg X 3/d, and Salofalk enema: 1X1/d) for four weeks prior to his present admission to the hospital. The patient did not have other side-effects that could be attributed to mesalamine treatment. Physical examination revealed marked tachycardia and tachypnoea. No other significant physical findings were recorded.

During his stay in the cardiology department a diagnosis of acute myocarditis was made based on the relevant clinical picture and laboratory results (cardiac ultrasound and electrocardiogram). Table 1 shows the serum levels of cardiac enzymes in different time periods. Other determinations such as renal and liver function tests, urine, and stool cultures, rheumatoid factor, antinuclear and anti-DNA antibodies, complement, and serology for Chlamydia, Mycoplasma pneumoniae, Epstein-Barr virus, Enterovirus, Herpes Simple Virus and Cytomegalovirus, were negative.

On his admission to the cardiology department the underlying UC was quite severe according to the criteria of Truelove and Witts. Six days after his admission and following improvement of the cardiac symptoms and laboratory indices related to myocarditis, the patient was transferred to our department for investigation and treatment of the underlying IBD. Laboratory investigation showed significant anaemia (hematocrite 24%), elevated ESR (85mm), and high levels of a1-acid-glycoprotein [1.83 (N.V. 0.5-1.2mg/dl)] and [retinol binding protein] [0.02 (n.v. 0.03-0.06mg/dl)]. Stools were negative for parasites, ova and pathogenic bacteria. Colonoscopy revealed extensive active UC which was confirmed histologically. Transdermal abdominal ultrasound revealed a 4mm bowel thickness in the sigmoid colon and 7mm in the transverse colon (N.V.<3mm). There was no pericardial effusion. Abdominal computed tomography scan revealed thickness in the area of transverse and sigmoid colon. Based on the fact that no other cause of myocarditis could be found except for the use of mesalamine, we decided to interrupt its use permanently.

Treatment with corticosteroid (50mg prednisolone IV) resulted in a gradual clinical improvement. Azathioprine was added in order to continue its use after stopping the

administration of corticosteroids. Unfortunately, the administration of azathioprine resulted in abnormal liver function tests and thus it was definitely stopped. However, because of the relative slowness of clinical and laboratory response to corticosteroids and bearing in mind the fact that practically we did not have any other kind of maintenance treatment to use, we decided to administer infliximab in order to succeed in both targets; treatment of the acute attack of UC and to keep it as a maintenance treatment as well. Infliximab was administered at a dose of 5mg/Kg at 0, 2 and 6th week. Fortunately, the patient responded very well to this treatment. At the end of week 2 the patient was already in clinical remission.

Nevertheless, in order to see if mesalamine was actually the cause of myocarditis, we decided to reintroduce the drug, starting with very small doses. After two weeks the dose of mesalamine was increased to 1.6 g/d. However, using this increased dose the patient again developed clinical and laboratory signs of recurrence of myocarditis after short duration of treatment with mesalamine. Administration of mesalamine was stopped immediately.

The administration of Infliximab was continued. Now, after almost three years of treatment with Infliximab at a dose of 5mg/Kg every 8 weeks, no signs of recurrence of either cardiac or large bowel disease could be noticed.

DISCUSSION

Cardiac involvement is a rare extraintestinal manifestation of patients with IBD appearing mainly in patients with UC. Cardiac involvement includes pericarditis, myocarditis, myopericarditis, pericardial and pleural effusion, conduction defects, and cardiac tamponade.¹⁻⁸ Most of the published reports describe cardiac involvement during an active phase of previously diagnosed IBD, sometimes years after initial intestinal symptoms. Similarly, in our patient, myocarditis appeared ten months after diagnosis of UC.

Myocarditis is included among the most frequent cardiac manifestations in patients with UC and can be either idiopathic or related to certain drugs such as mesalamine. Among 86 patients with idiopathic giant-cell myocarditis, five of the patients had IBD, and this was the most common associated disorder.¹ However, to distinguish myocarditis

Table 1. Cardiac enzyme levels at different time periods.

	9/12/2005	10/12/2005	11/12/2005	12/12/05	13/12/05
Troponin I (ng/ml N.V.<0.1)	3.89	2.51	1.45	0.55	0.37
CKMB(mass) (ng/ml N.V.<3.6)	4.8	1.6	0.6	<0.5	<0.5
CK: (IU/L N.V.35-240)	142				

as a true extraintestinal manifestation of IBD from that of a secondary effect of the treatment is not easy. In all cases identified as being the result of treatment toxicity, there was a clear improvement following the suspension of medication. In our patient the relationship between consumption of mesalamine and the appearance of myocarditis was well documented because symptoms of myocarditis reappeared after reintroduction of the drug. Thus the underlying inflammatory bowel disease was probably not involved in the pathogenesis of myocarditis in our patient.

The main clinicoepidemiological characteristics of our patient were the male sex, the young age, the short duration of the underlying UC, and finally the appearance of myocarditis which was linked to the consumption of 5-aminosalicylic acid.

The mechanisms of mesalamine-induced myocarditis are largely unknown. However, they may be attributed to a direct cardiotoxic effect, appearance of cell-mediated hypersensitivity, as an IgE-mediated allergic reaction and possibly as a humoral antibody response.²

Treatment of drug-related myocarditis includes the immediate interruption of the responsible drug as well as treatment of the underlying IBD. In our patient we faced the question of what could be the most suitable treatment after cessation of corticosteroids. Mesalamine, the drug of choice for maintenance treatment of patients with UC, obviously was not a candidate drug. Azathioprine also was not continued because of the appearance of side-effects. We decided to consider infliximab as the most suitable drug bearing in mind its documented efficacy in patients with acute UC not responding to conventional treatment⁹. The advantage of infliximab was the possibility that, in the case of good response, it could also be continued as a maintenance treatment. Fortunately, the patient responded very well both in the acute phase and in the maintenance scheme in the suggested dose of 5mg/Kg every 8 weeks. To the best of our knowledge infliximab has never been previously administered in patients with UC and acute myocarditis due to mesalamine treatment. The patient is now in excellent condition after treatment with infliximab for almost three years without recurrence of either myocarditis or UC.

In conclusion, the possibility of cardiac involvement although rare, needs to be considered in patients with UC who present with cardiac symptoms and are being treated with mesalamine. Clinicians should not only be aware of this potential cardiac complication of IBD but also of options for therapy. In those cases in which the symptoms can be attributed to treatment with mesalamine, a favourable clinical evolution could be obtained when the drugs are withdrawn. Obviously, these drugs are contraindicated for future use. Acute and maintenance treatment of patients with severe UC and myocarditis could be achieved with Infliximab, a drug which can be safely administered, in the absence of signs of cardiac failure.

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