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MESALAZINE-INDUCED MYOCARDITIS FOLLOWING DOSE ESCALATION IN ULCERATIVE COLITIS: A DIAGNOSTIC CHALLENGE

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ABSTRACT

Introduction: Mesalazine (5-aminosalicylic acid, 5-ASA) is the cornerstone treatment for mild-to-moderate ulcerative colitis. Although generally well tolerated, rare cases of drug-induced myocarditis have been reported. Distinguishing mesalazine-induced myocarditis from myocarditis related to inflammatory bowel disease is essential, as management differs substantially.

Case description: A 43-year-old man with recently diagnosed ulcerative colitis presented with acute chest pain, fever and elevated cardiac biomarkers eight days after initiation of oral mesalazine (3 g/day). Electrocardiography demonstrated diffuse ST-segment elevation, while echocardiography showed preserved left ventricular systolic function; coronary angiography excluded obstructive coronary artery disease. During hospitalisation, worsening gastrointestinal symptoms prompted escalation of mesalazine to 4.8 g/day. Within 24 hours, the patient developed recurrent chest pain, fever and a marked increase in troponin, inflammatory markers and NT-proBNP. Viral and autoimmune investigations were negative. The close temporal relationship between symptom recurrence and dose escalation raised suspicion of mesalazine-induced myocarditis. Following discontinuation of mesalazine, rapid clinical and biochemical improvement was observed. A cardiac magnetic resonance imaging (MRI) performed on day 7 demonstrated myocardial oedema on T2-weighted sequences and non-ischaemic epicardial late gadolinium enhancement involving the apical and inferolateral segments. This fulfilled both T2-based and T1-based criteria of the 2018 modified Lake Louise criteria for acute myocarditis. At follow-up, the patient remained asymptomatic with complete recovery of ventricular function.

Conclusion: Mesalazine-induced myocarditis is an uncommon but potentially serious adverse reaction that may mimic an extraintestinal manifestation of ulcerative colitis. Early recognition, careful assessment of drug exposure chronology and prompt withdrawal of mesalazine are crucial to prevent complications. Cardiac MRI plays a central role in confirming the diagnosis.

KEYWORDS

Mesalazine, myocarditis, ulcerative colitis, drug-induced myocarditis, cardiac MRI

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LEARNING POINTS

- Mesalazine-induced myocarditis is a rare but potentially life-threatening adverse effect that should be suspected in any patient with inflammatory bowel disease presenting with chest pain shortly after treatment initiation or dose escalation.
- Differentiating drug-induced myocarditis from myocarditis related to inflammatory bowel disease is crucial, as continuation of mesalazine may worsen cardiac injury.
- Prompt withdrawal of mesalazine usually leads to complete clinical recovery, while cardiac MRI plays a key role in confirming the diagnosis.

INTRODUCTION

Drug involvement is one of the potential causes of myocarditis[1]. Among pharmacological causes, mesalazine (5-aminosalicylic acid), widely used for mild-to-moderate ulcerative colitis, has been associated with rare but serious cases of myocarditis. The true incidence is unknown but appears to be very low. Delayed recognition may lead to dilated cardiomyopathy or sudden cardiac death. We report a case of mesalazine-induced myocarditis (MIM), emphasising the diagnostic challenge, particularly in patients with inflammatory comorbidities, where symptoms may overlap, and the importance of early suspicion, prompt discontinuation and cardiac magnetic resonance imaging (MRI) confirmation.

CASE DESCRIPTION

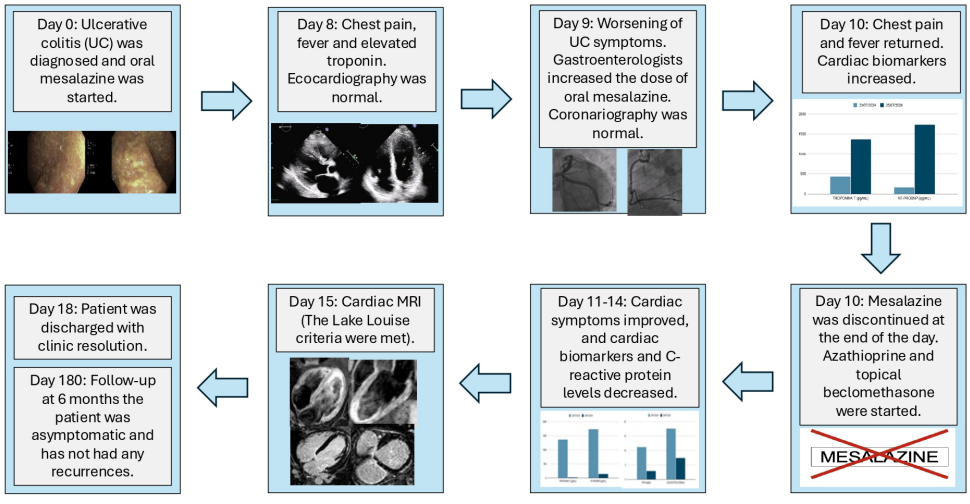
A 43-year-old man presented to the Emergency Department (ED) with acute chest pain, fever up to 39°C and diaphoresis. The timeline of the clinical course is summarized in *Figure 1*. He had a history of ulcerative colitis, diagnosed via colonoscopy two months prior and treated with topical mesalazine (1 g/day) since then. Oral mesalazine (3 g/day) had been initiated eight days before presentation because of persistent gastrointestinal symptoms, despite topical therapy. He also had a history of idiopathic thyroiditis.

On arrival, the electrocardiogram (ECG) *(Fig. 2)* showed diffuse ST-segment abnormalities suggestive of acute myocardial inflammation. Blood pressure was 118/72 mmHg, heart rate 95 bpm, oxygen saturation 98% and eupnoeic. Initial laboratory tests revealed troponin T at 485 pg/ml, C-reactive protein (CRP) 2.56 mg/dl and leucocytosis. Bedside echocardiography showed preserved left ventricular ejection fraction without regional wall motion abnormalities or pericardial effusion. Coronary angiography revealed normal coronary arteries.

The patient was admitted with a preliminary diagnosis of acute myocarditis. While admitted, his ulcerative colitis worsened with more than five bloody stools per day. The gastroenterology department was consulted and mesalazine was increased to 4.8 g/day. Twenty-four hours later, recurrent chest pain and a new onset of fever occurred, with sharp elevations in biomarkers (troponin T 1,200 pg/ml, N-terminal pro-B-type natriuretic peptide (NT-proBNP) 1,700 pg/ml, CRP 12 mg/dl, leucocytosis). A follow-up echocardiography remained normal.

Viral testing and the autoimmunity screening panel were negative. Due to the worsening situation after mesalazine escalation, MIM was suspected, and the drug was discontinued. Oral beclomethasone was started to control the ulcerative colitis flare. Over the next few days, clinical improvement and laboratory tests showed normalisation of biomarkers *(Fig. 3)*.

A cardiac MRI *(Fig. 4)* performed on day 7 showed mild biventricular systolic dysfunction (left ventricular ejection fraction 49%) and patchy epicardial hyperenhancement in apical and inferolateral walls, consistent with acute myocarditis. A colonoscopy was performed and confirmed



| ***Figure 1.*** *Timeline of case.*

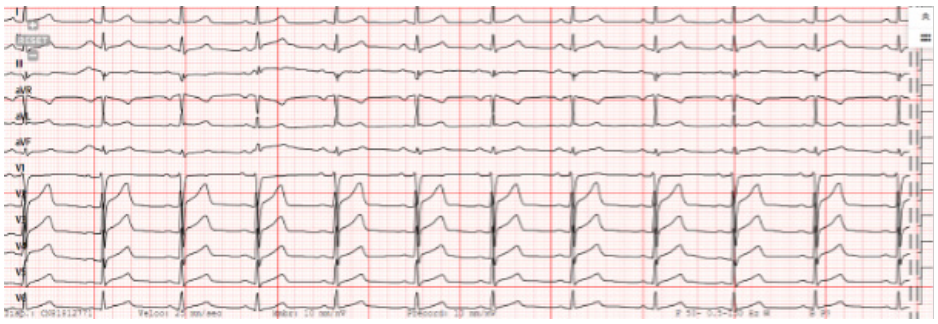


Figure 2. First ECG at ED arrival. Sinus rhythm with diffuse ST-segment abnormalities suggestive of acute myocardial inflammation.

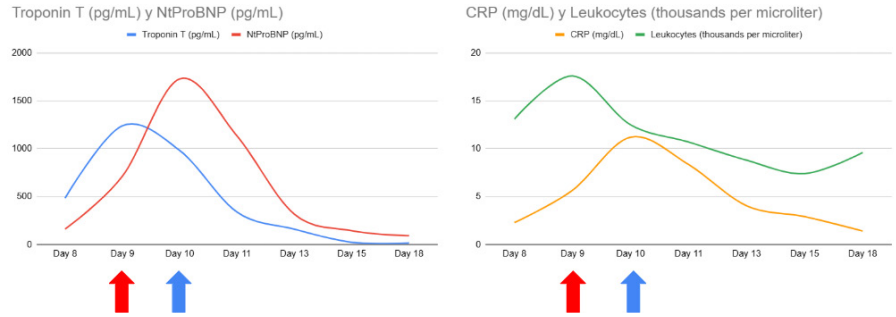


Figure 3. Evolution of cardiological (left graph) and inflammatory markers (right) during admission. On day 9 (red arrow), 5-ASA dosage was increased, while it was discontinued on day 10 (blue arrow). After discontinuation, both cardiac and inflammatory markers return to normal values.

active ulcerative colitis; azathioprine (150 mg/day) and topical beclomethasone were initiated.

At discharge, ECG abnormalities had improved *(Fig. 5)*. The patient remained asymptomatic with normal biomarkers at six months; echocardiography showed full recovery of function.

DISCUSSION

Patients with inflammatory bowel disease (IBD) have a higher risk of developing myocarditis compared to healthy controls. A Danish cohort establishes an 8.3-fold risk in the case of Crohn's disease and a 2.6-fold risk in the case of ulcerative colitis[2]. Patients being treated with mesalazine have a 48-fold risk of developing myocarditis compared to a control population[3,4]. However, in the case of ulcerative colitis the origin may come from either the disease or an adverse effect of mesalazine. Patients with ulcerative colitis-linked myocarditis do not improve after discontinuation of mesalazine and may even improve while the drug is still being administered[5]. MIM might be caused by a type IV hypersensitivity reaction leading to lymphocytic and eosinophilic myocardial infiltration. Reported latency from drug exposure to onset of cardiac symptoms ranges from a few days to four weeks, and recurrence upon re-challenge has been documented, supporting causality[6].

Recognition of this entity is critical and difficult, since MIM can be confused with an extraintestinal manifestation of IBD or either mimics viral or autoimmune myocarditis, leading to underdiagnosis. A thorough temporal analysis and early consideration of drug causality are essential steps in the diagnostic algorithm.

Although causality cannot be definitively established in the absence of endomyocardial biopsy or drug re-challenge, the close temporal relationship between mesalazine exposure, symptom recurrence after dose escalation, exclusion of alternative causes and rapid recovery following drug withdrawal strongly supports MIM. Such diagnosis was confirmed non-invasively by cardiac MRI according to the 2018 Modified Lake Louise Criteria *(Fig. 4)*[7].

Cardiac MRI is the cornerstone non-invasive imaging modality for the diagnosis of myocarditis[1], allowing characterisation of myocardial inflammation and fibrosis, often obviating the need for endomyocardial biopsy, as it happened in our case.

In line with the 2025 ESC Guidelines for the management of myocarditis and pericarditis, our case provides

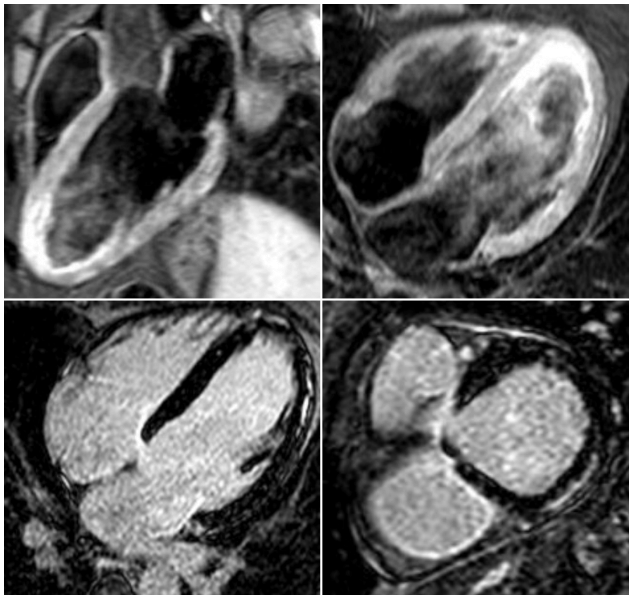


Figure 4. Cardiac MRI demonstrating acute myocarditis: T2-weighted images (2-chamber and 4-chamber views) showing myocardial oedema, and late gadolinium enhancement (4-chamber and short-axis views) confirming non-ischaemic epicardial injury in accordance with the 2018 modified Lake Louise criteria.

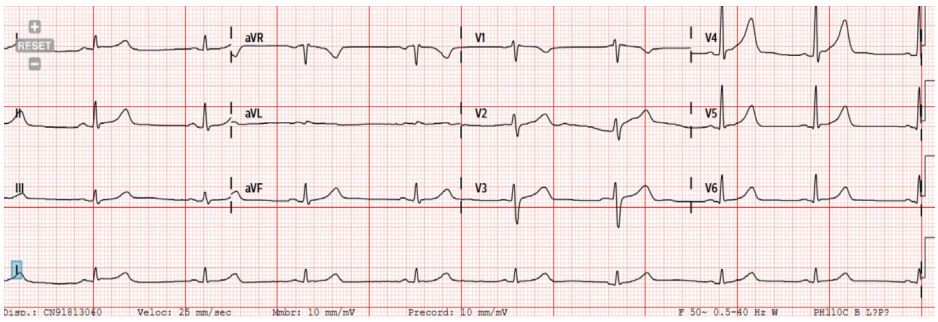


Figure 5. Normalisation of the ECG at discharge.

Naranjo scale question	Response	Score
Are there previous conclusive reports on this reaction?	Yes	+1
Did the adverse event appear after the suspected drug was administered?	Yes	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes	+1
Did the adverse reaction reappear when the drug was re-administered?	Not assessed (no formal re-challenge performed)	0
Are there alternative causes that could have caused the reaction?	No reasonably demonstrated alternative causes (viral and autoimmune work-up negative)	+2
Did the reaction reappear when a placebo was given?	Not assessed	0
Was the drug detected in blood or other fluids at concentrations known to be toxic?	No	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Yes, clear exacerbation after dose escalation	+1
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0
Was the adverse event confirmed by objective evidence?	Yes (elevated troponin levels, ECG abnormalities and cardiac magnetic resonance findings)	+1

Table 1. Naranjo adverse drug reaction probability scale.

clinically relevant insight. Notably, the guidelines include mesalazine among the drugs as a potential cause of drug-induced myocarditis. Recognising mesalazine as a causal agent supports prompt drug withdrawal and justifies the use of cardiac MRI, consistent with ESC guidance, to avoid misdiagnosis and potentially life-threatening complications[8].

Published cases suggest that MIM typically occurs within the first weeks after treatment initiation and usually resolves after drug withdrawal. Most reported patients present with chest pain, elevated cardiac biomarkers and ECG abnormalities, while prognosis is generally favourable when the diagnosis is recognised early and mesalazine is discontinued promptly. Additional contemporary case reports further support the association between mesalazine exposure and acute myocarditis. Kyriakou et al. described a patient who developed myocarditis shortly after mesalazine initiation and experienced complete clinical recovery following drug withdrawal, reinforcing the importance of early recognition and prompt discontinuation of the offending agent[9].

Application of the Naranjo Adverse Drug Reaction Probability Scale *(Table 1)* yielded a score of 8, indicating a probable causal relationship between mesalazine exposure and the development of myocarditis. The rapid recurrence of symptoms after dose escalation and prompt recovery following drug withdrawal strongly support this association.

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