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CASE SERIES
Cardiovascular imaging

Mesalazine-induced myopericarditis: a case series

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Background Inflammatory bowel diseases (IBD) are characterized by chronic inflammation of the gastrointestinal tract but can have multiorgan involvement. Mesalazine (5-ASA) is a key therapeutic agent in IBD. Mesalazine has rare but potentially life-threatening side effects such as cardiac injury.

Case summary We present two cases of myopericarditis, documented also with cardiac magnetic resonance, that we attributed to 5-ASA hypersensitivity: the first is a young woman with ulcerative colitis who developed myopericarditis after the initiation of 5-ASA, with a good clinical response after discontinuation; the second is a 79-year-old man who developed symptoms of heart failure after the diagnosis of IBD and the introduction of 5-ASA.

Discussion Mesalazine may cause rare but potentially life-threatening cardiac injury, which can be difficult to distinguish from acute IBD-induced cardiac inflammation.

Keywords Myopericarditis • Mesalazine • 5-ASA • Cardiotoxicity • Inflammatory bowel diseases • Case series

ESC curriculum 6.1 Symptoms and signs of heart failure • 9.9 Cardiological consultations

Learning points

- To understand the potential role of mesalazine in inducing myocardial injury.
- To be able to make a differential diagnosis between mesalazine-induced myopericarditis and other causes of cardiac inflammation, particularly those induced by inflammatory bowel diseases.
- To learn more about the management of mesalazine-induced myopericarditis.

Introduction

Inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), are intestinal diseases, but 25–30% of patients develop several extraintestinal manifestations involving joints, skin, eyes, and, less commonly, heart and lungs.[1] Inflammatory bowel disease has emerged in newly industrialized countries in Asia, South America, and Middle East and evolved into a global disease, with a stabilized incidence in Western countries (the prevalence exceeds 0.3%).[2,3]

Mesalazine (5-ASA) is the first-line treatment for many patients with mild-to-moderate UC (used in over 88% of all UC patients). It is also frequently used as first-line therapy for CD, despite the absence of robust evidence in this context.[4] Mesalazine has usually limited and mild side effects (nausea, nasopharyngitis, diarrhoea and constipation are the most common), which are dose related and usually improve with slow tapering of the drug.[5] However, 5-ASA and its derivatives can cause rare but potentially life-threatening side effects (cardiac inflammation, pneumonia and kidney failure), which are not dose related.[6,7,8]

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Due to the increasing number of patients treated with 5-ASA, physicians should be aware of these rare side effects, which require discontinuation of therapy to avoid life-threatening events. We present two case reports of 5-ASA-related cardiac injury.

Summary figure

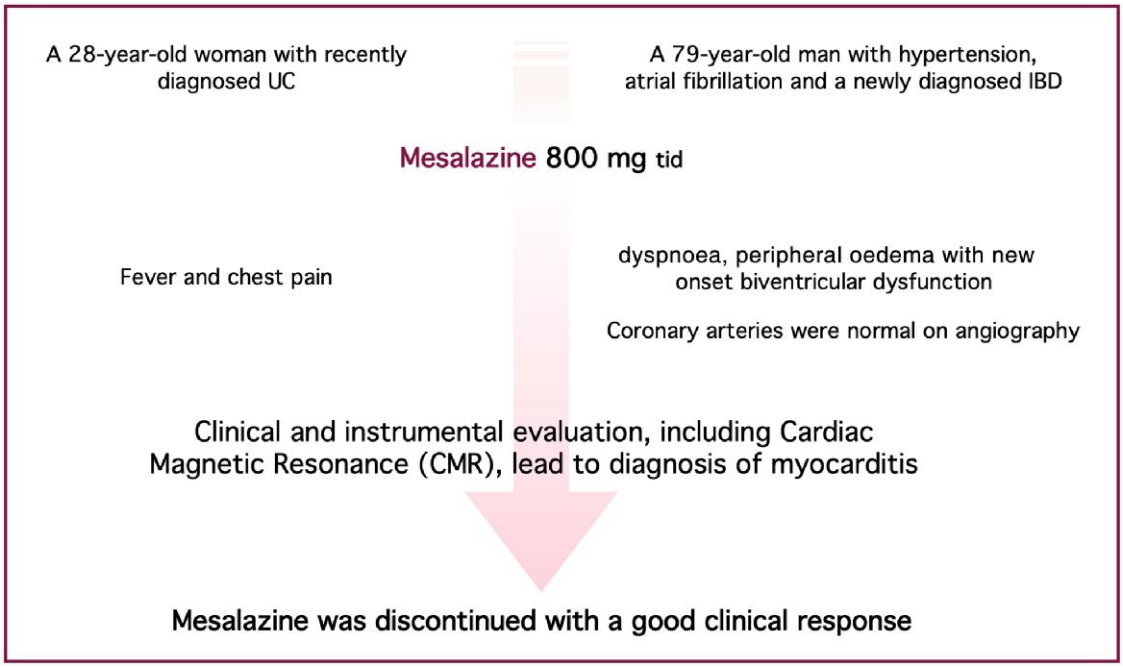


Table 1 Updated recommendations of cardiac magnetic resonance criteria of myocardial inflammation (modified by Ferreira *et al.*)

Updated Lake Louise criteria (2018)	
At least one criterion in each category is positive or only one criterion is positive in an appropriate clinical scenario	
Diagnostic targets	
T_2-based imaging: global or regional increase of myocardial T_2 relaxation time or an increased signal intensity in T_2-weighted images	Increased T_2: myocardial oedema
T_1-based imaging: global or regional increase of native myocardial T_1 relaxation time or extracellular volume (ECV) or area with high signal intensity in a non-ischaemic distribution pattern in late gadolinium enhancement (LGE) images	Increased T_1: oedema (intra- or extracellular), hyperaemia/capillary leak, necrosis, fibrosis LGE: necrosis, fibrosis, extracellular acute oedema Increased ECV: oedema (extracellular), hyperaemia/capillary leak, necrosis, fibrosis
Supportive criteria	
Pericardial effusion or high signal intensity of the pericardium in LGE images, T1-mapping or T2-mapping	
Left ventricular dysfunction	

Case presentation

Patient 1

A 28-year-old woman with UC, diagnosed about 1 month earlier, presented to our hospital with fever and chest pain. Eighteen days before admission, she had started 5-ASA 800 mg ter in die (t.i.d). Past medical history was unremarkable. Physical examination at the presentation revealed no signs of heart failure. Initial 12-lead electrocardiogram (EKG) showed a heart rate of 104 b.p.m. and an incomplete right bundle branch block. Labs revealed leucocytosis [12.5×10^3/μL; normal value (n.v.) 4.0-10-0 $\times 10^3$/μL], C-reactive protein concentration of 101 mg/L (n.v. < 5 mL/L), peak cardiac troponin T high-sensitivity of 218 pg/mL (n.v. < 14 pg/mL) and NT-proBNP of 4403 pg/mL (n.v. 1–125 pg/mL). An echocardiogram showed a normal left ventricular (LV) size and systolic function without LV wall motion abnormalities and minimal pericardial effusion. Given the high clinical suspicion of myocarditis and the warning about side effects of 5-ASA, the drug

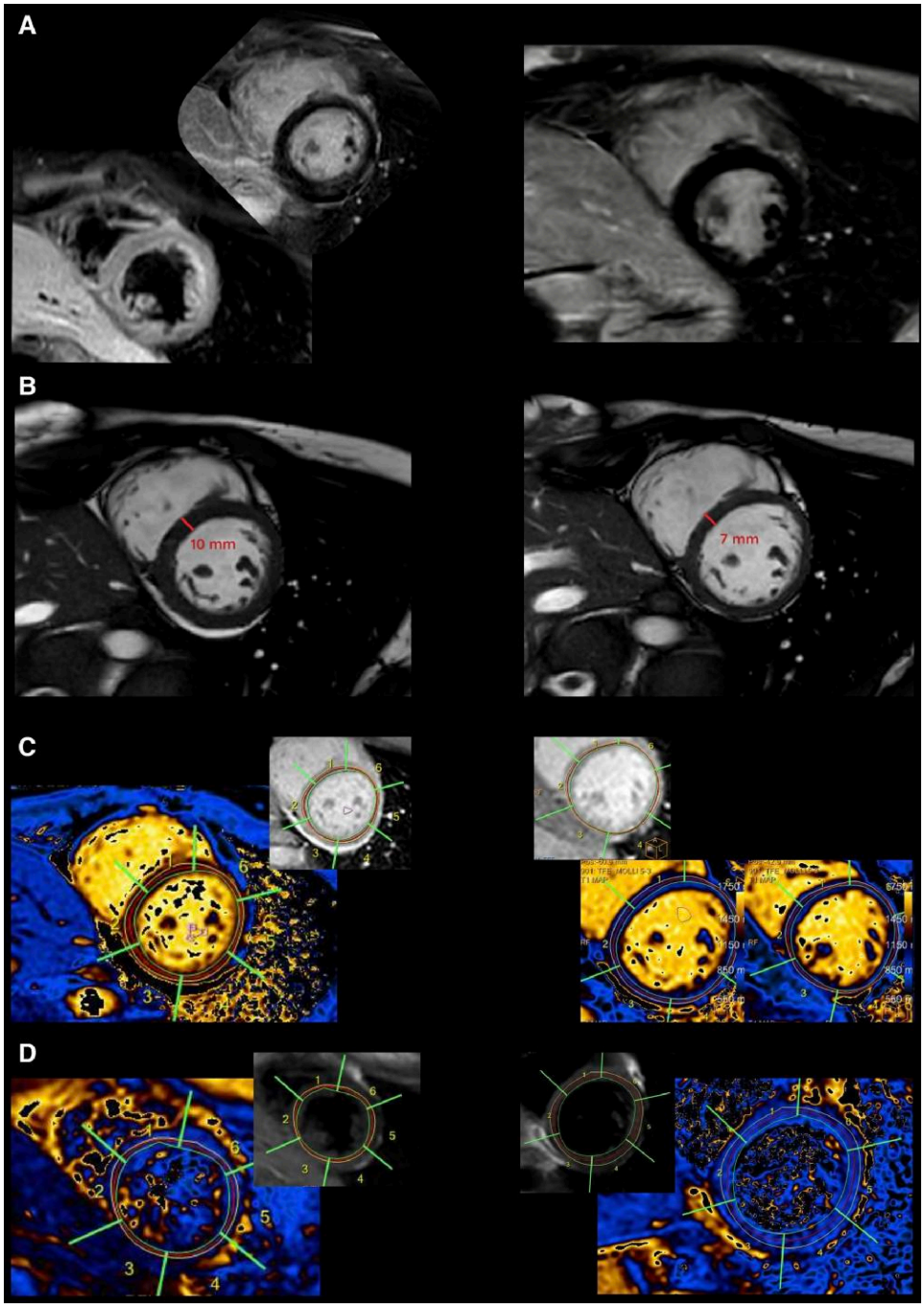


Figure 1 Patient 1 cardiac magnetic resonance. (*A*) During acute phase (on the left), T_2-weighted imaging showed a significant and diffuse increase of myocardial signal intensity, compared with skeletal muscle, reflecting oedema; nuanced late gadolinium enhancement is detectable in epi–mesocardial infero–lateral region of acute phase imaging but not in follow-up MRI (on the right). (*B–D*) Balanced steady-state free precession imaging (Cine imaging), T_1 and T_2 mapping during acute phase (on the left) and after 6 months (on the right): mild pericardial effusion was noted during acute phase, and no pericardial effusion at follow-up; it was associated with myocardial thickening: interventricular septum 10 mm vs. 7 mm (diastolic phase; on the left: heart rate (HR) 90 b.p.m., trigger delay 624 ms; on the right: HR 70 b.p.m., trigger delay 603 ms) (*B*) and significant acute increase of T_1 (*C*) and T_2 (*D*) relaxation time, respectively: T_1 mapping summary values 1185 ± 22.1 vs. 1037 ± 21; T_2 mapping summary values 60.4 ± 2.6 vs. 51 ± 3.

was initially discontinued, and rifaximin was introduced with a good clinical response. We did not perform coronary assessment because patient characteristics, clinical presentation, laboratory tests and echocardiographic images were not suggestive for coronary artery disease. After 3 days, 5-ASA was reintroduced after a gastroenterology consulting, and we assisted a relapse of the fever in the following

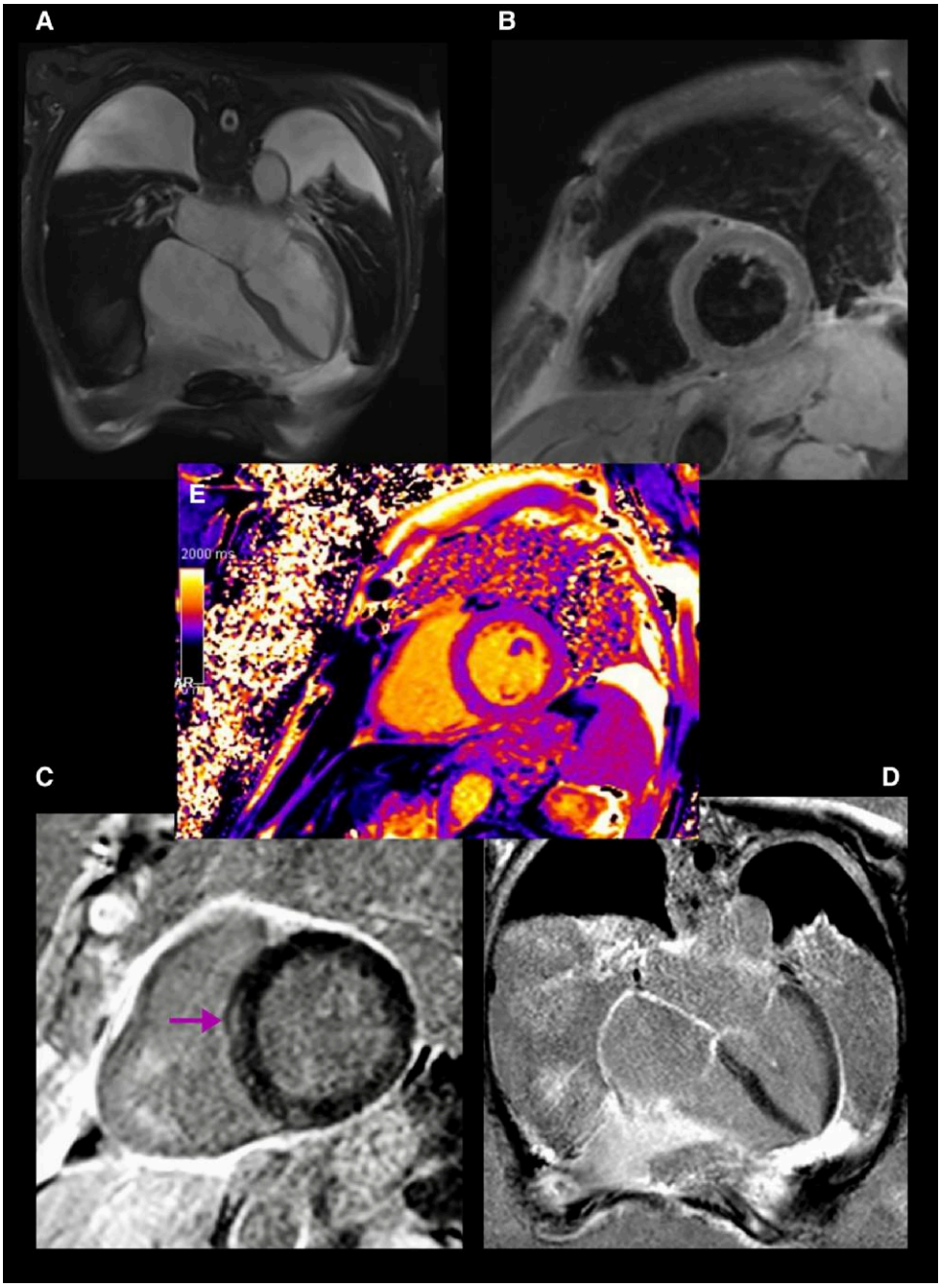


Figure 2 Patient 2 cardiac magnetic resonance. (*A*) Balanced steady-state free precession imaging showed dilated left ventricle with reduced ejection fraction and pleuro–pericardial effusion. (*B*) No significant oedema in T_2-weighted sequences, but non-ischaemic myocardial injury was seen as focal epi–mesocardial late gadolinium enhancement pattern in septum and, less specific, in junctional regions (*C*, *D*). (*E*) No signal abnormalities in T_1 mapping sequences.

days, with a new episode of chest pain. Mesalazine was then discontinued, with rapid resolution of symptoms. Despite the low diagnostic accuracy of peripheral blood serological and virological tests, the patient was tested for infectious causes of myocarditis with peripheral blood tests (Borrelia burgdorferi, Human Immunodeficiency Virus, Hepatitis B virus, Hepatitis C virus, Human Herpesvirus 6, *Legionella*, *Leptospira*, parvovirus B19, coxsackievirus, echovirus, adenovirus, *Enterovirus*, Citomegalovirus, *Toxoplasma*, *Mycoplasma pneumoniae*, *Treponema pallidum*, Severe acute respiratory sindrome-CoronaVirus2, rubella and *Chlamydia pneumoniae*), which were negative; we did not perform endomyocardial biopsy (EMB) given the low-risk clinical status of the patient. Cardiac magnetic resonance (CMR) was performed and showed the typical pattern of myocarditis according to 2018 updated Lake Louise criteria (*Table 1*): increased T_2 relaxation time (caused by myocardial oedema) and increased T_1 relaxation time (sign of non-ischaemic myocardial injury) (*Figure 1*).[7]

After 8 days, the patient was discharged asymptomatic and with a downward trend in biochemical markers of myocardial damage and

inflammation. Subsequently, the patient was reevaluated during the outpatient follow-up, which confirmed the good clinical status. Cardiac magnetic resonance was repeated after 6 months, showing complete recovery (*Figure 1*).

Patient 2

A 79-year-old man with hypertension, paroxysmal atrial fibrillation, Raynaud's disease and a new suspected IBD (diarrhoea and weight loss), on 5-ASA 800 mg t.i.d. for about 35 days previously, presented for exertional dyspnoea and peripheral oedema with a new finding of biventricular dysfunction (LV ejection fraction of 20%). Therapy with bisoprolol, ramipril, eplerenone and furosemide was started, and he was admitted to our ward for the necessary checks. Physical examination at presentation revealed an arterial blood pressure of 135/60 mmHg, mild systolic heart murmur for mitral regurgitation, decreased breath sounds at lung bases and swollen ankles. Electrocardiogram showed sinus rhythm 88 b.p.m. and diffuse alterations of the repolarization phase. Labs demonstrated NT-proBNP 10 427 pg/mL, C-reactive protein 34 mg/L and normal troponin values. Coronary arteries were normal on angiography. A CMR was performed: no oedema was found in T_2-weighted sequences, but positive epi–mesocardial late gadolinium enhancement (LGE) was observed; as supportive criteria, there were both pleural and pericardial effusion and global LV hypokinesis (*Figure 2*). It should be emphasized that in myocarditis presenting with a cardiomyopathic pattern, T_2-weighted images have low sensitivity—perhaps due to prolonged myocardial inflammation with progressive water reabsorption—and that LGE techniques are more accurate for this type of clinical presentation of myocarditis.[8]

Principal virus and other microbiological agents that mediated perimyocarditis were excluded by peripheral blood serological tests. The patient was screened for myocarditis-associated autoimmune disorders too: autoantibodies and other related blood tests were not significant. Contrast-enhanced computed tomography (CT) scan of the abdomen was performed and revealed low-density nodular lesions of the spleen with some enlarged mesenteric lymph nodes.

Immunophenotype of plasma cells, detected by flow cytometry, identified a small B cell subpopulation. The patient was evaluated with a positron emission tomography (PET): high glucose metabolism was detected in the spleen in correspondence with the nodule showed by the CT, suggestive for a neoplastic cause. Subsequential haematological investigations led to make diagnosis of splenic lymphoma.

Heart failure therapy was implemented, and since the diagnosis of IBD was only hypothetical, 5-ASA was discontinued after consultation with the gastroenterologist, given the possibility of 5-ASA-induced myocardial damage. After 1 month, an echocardiography was repeated showing mild LV dysfunction [ejection fraction (EF) 40%] and complete recovery of right ventricular function.

Discussion

Although UC and CD primarily involve the bowel, they are considered systemic diseases due to several extraintestinal manifestations. Cardiac inflammation is rare and mainly occurs during acute disease exacerbation,[6,9] especially in UC patients.

Mesalazine is a widely used first-line therapy in the context of IBD with a favourable safety profile. However, it can cause rare but potentially fatal cardiac side effects (frequency of 0–0.3%)[4] including myocarditis, pericarditis and coronary vasculitis.[2,5] These complications occur with both oral and topical preparations.[4]

Some case reports of myocarditis induced by 5-ASA have been described in the literature, the first published by Agnholt *et al.*[10] on *Lancet* in 1989. Patients typically present with chest pain, shortness of breath and fever within the first 28 days of starting therapy.[9,11] Physical examination, EKG and imaging are compatible with myocarditis, with or without associated pericarditis.[7] Only in a few cases CMR images are reported.[6,12]

The pathophysiology of 5-ASA-related cardiac manifestations is not well understood. Proposed theories include: hypersensitivity reaction (eosinophilic infiltration was described on EMB[5]); humoral-mediated hypersensitivity triggered by antibodies directed against 5-ASA cross-reacting with myocardium; allergic reaction mediated by immunoglobulin E; and direct toxicity.[2,9]

Unfortunately, there are not any pathognomonic features of 5-ASA-induced cardiac injury beyond the temporal relationship. The distinction between IBD- and 5-ASA-induced myocarditis remains a diagnostic challenge. Moreover, the diagnosis is essentially of exclusion: infection, malignancy and connective tissue disorders should be ruled out.[2,5] The clinical syndrome usually occurs within 1–2 weeks of starting treatment and up to 4 weeks, although the onset of the symptoms may be delayed due to concomitant use of steroids.[13] After discontinuation of therapy, there is a rapid resolution of symptoms with a recurrence of clinical presentation by rechallenge with 5-ASA.[5,9] Indeed, discontinuation of therapy is the only effective therapeutic intervention and should be performed as soon as possible.[11] Some authors suggest the use of steroids, which are resolutive in IBD-induced myocarditis but remain controversial in the 5-ASA cardiomyopathy.[9,11,13] Importantly, severe cardiac, renal, and pulmonary side effects are not dose related, and a dose reduction is not safe to minimize the risk of adverse events.[4]

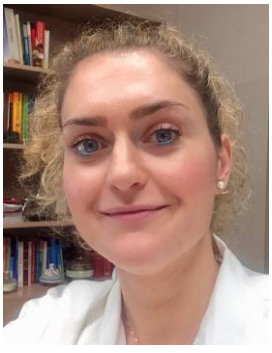
In our Patient 1, myocarditis was induced by 5-ASA, as confirmed by the temporal relationship between cardiac involvement, the rapid clinical response to the therapy discontinuation, and the relapse following drug reintroduction.

In Patient 2, the scenario is more ambiguous: he had signs of heart failure with biventricular dysfunction 4 weeks after the initiation of 5-ASA. Therapy was discontinued and heart failure therapy was implemented. After 1 month, we observed an improvement in LV function and a significant recovery of right ventricular one. In our opinion, the temporal relationship is suggestive of 5-ASA-induced myocardial damage.

Conclusion

Mesalazine derivates are widely used in IBD patients with a good safety profile. They can cause rare but potentially life-threatening side effects, such as myocarditis, and diagnosis remains a clinical challenge. If 5-ASA-induced myocardial damage is suspected, therapy should be discontinued immediately and not reintroduced if the suspicion is confirmed. Close liaison with the gastroenterology team is required for IBD management.

Lead author biography



Valentina Andrei, Italy, on 15 September 1988. She studied medicine at the University of Siena, where she completed her Master's degree in 2013. Since 2014–2017, she has completed the specialty in general practice. With a particular interest in cardiovascular diseases, she has been a cardiology resident at the University of Florence since 2017.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

References

1. Caio G, Lungaro L, Caputo F, Muccinelli M, Marcello MC, Zoli E, *et al.* Recurrent myocarditis in a patient with active ulcerative colitis: a case report and review of the literature. *BMJ Open Gastroenterol* 2021;**8**:e000587.
2. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017;**390**:2769–2778.
3. Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015;**12**:720–727.
4. Sehgal P, Colombel J-F, Aboubakr A, Narula N. Systematic review: safety of mesalazine in ulcerative colitis. *Aliment Pharmacol Ther* 2018;**47**:1597–1609.
5. Coman RM, Glover SC, Gjymishka A. Febrile pleuropericarditis, a potentially life-threatening adverse event of balsazide—case report and literature review of the side effects of 5-aminosalicylates. *Expert Rev Clin Immunol* 2014;**10**:667–675.
6. Shergill S. Mesalazine-induced myopericarditis: a case report. *Eur Heart J Case Rep* 2020;**5**:ytaa508.
7. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, *et al.* Management of acute myocarditis and chronic inflammatory cardiomyopathy, an expert consensus document. *Circ Heart Fail* 2020;**13**:e007405.
8. Francone M, Chimenti C, Galea N, Scopelliti F, Verardo R, Galea R, *et al.* CMR sensitivity varies with clinical presentation and extent of cell necrosis in biopsy-proven acute myocarditis. *JACC Cardiovasc Imaging* 2014;**7**:254–263.
9. Okoro KU, Roby MD, Bankole AA. Myocarditis secondary to mesalamine-induced cardiotoxicity in a patient with ulcerative colitis. *Case Rep Med* 2018;**2018**:9813893.
10. Agnholt J, Sørensen HT, Rasmussen SN, Gøtzsche CO, Halkier P. Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989;**1**:1135.
11. Brown G. 5-Aminosalicylic acid–associated myocarditis and pericarditis: a narrative review. *Can J Hosp Pharm* 2016;**69**:466–472.
12. Garcia-Ferrer L, Estornell J, Palanca V. Myocarditis by mesalazine with cardiac magnetic resonance imaging. *Eur Heart J* 2009;**30**:1015.
13. Taha ME, Abdalla A, Al-Khafaji J, Malik S. Mesalamine-induced myopericarditis: a case report and literature review. *Cardiol Res* 2019;**10**:59–62.