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Myocarditis as an extraintestinal manifestation of ulcerative colitis: A case report and review of literature

Wang YY *et al*. Myocarditis in UC

Abstract

BACKGROUND

Although extraintestinal manifestations of inflammatory bowel disease (IBD) are well documented, myocarditis has only rarely been reported as an extraintestinal manifestation, and it can be fatal. The various clinical presentations and causes of myocarditis in IBD patients complicate making a correct and timely diagnosis.

CASE SUMMARY

Here we report a 15-year-old boy who presented with myocarditis as the initial presentation of a relapse of ulcerative colitis. In reviewing the literature for cases of myocarditis complicating IBD, we found twenty-one other cases, allowing us to expand our understanding of the clinical presentation, diagnosis, management, and outcomes of this rare condition. The most frequent diagnostic clues for myocarditis in IBD patients are dyspnea, chest pain, tachycardia, raised cardiac biomarkers, and abnormalities on trans-thoracic echocardiography. Additionally, we discuss the etiology of myocarditis in IBD patients, which include an extraintestinal manifestation, the adverse effects of mesalamine and infliximab, selenium deficiency, and infection to help provide a framework for diagnosis and management.

CONCLUSION

Myocarditis as an extraintestinal manifestation of IBD can be life-threatening. Trans-thoracic echocardiogram and cardiac magnetic resonance may assist its diagnosis.

Key Words: Inflammatory bowel disease; Myocarditis; Ulcerative colitis; Crohn's disease; Extraintestinal manifestation; Case report

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Core Tip: While the extraintestinal manifestations (EIM) of inflammatory bowel disease (IBD) are well documented, myocarditis as an EIM of IBD is rare. Here we present a case of a 15-year-old boy who presented with myocarditis as the initial presentation of a relapse of ulcerative colitis. The case was unusual in that: (1) While the gastrointestinal symptoms were mild, the endoscopic severity was severe; and (2) He only had mild cardiac symptoms and minimal ventricular dysfunction except for acute chest pain. We therefore propose that cardiovascular manifestations of IBD may be more common than clinically documented, since they may remain undiagnosed.

INTRODUCTION

The inflammatory bowel diseases (IBD) Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing, inflammatory intestinal disorders. The prevalence of IBD is predicted to reach 0.12%-0.26% in Asia and Latin America and 1% in western countries over the next 30 years[1]. IBD mainly affects the gastrointestinal tract but is also associated with various extraintestinal manifestations (EIMs), most commonly of the skin, eyes, joints, biliary tract, and lungs[2]. Cardiovascular EIMs, especially myocarditis, are uncommon[3]. Nevertheless, IBD patients are at higher risk of myocarditis than the general population *via* three different mechanisms[4,5]: EIMs, infection, and the side-effects of therapies such as 5-aminosalicylic acid (5-ASA), biological agents, total parenteral nutrition (TPN), and colectomy. Although therapy-related side effects are well-documented[6], myocarditis as an EIM has received little attention even though its diagnosis can be challenging.

Here we present a case of an adolescent boy who developed myocarditis as an EIM of IBD. To provide a framework for the diagnosis and management of myocarditis occurring in this setting, we searched the PubMed database with the keywords "((inflammatory bowel diseases) OR (Crohn's disease) OR (ulcerative colitis)) AND myocarditis". We found twenty-one similar cases and summarized the clinical features of myocarditis as an EIM.

CASE PRESENTATION

Chief complaints

A 15-year-old boy presented to our department with a five-day history of fever (37.8-38.6 °C) and chest pain.

History of present illness

The boy had a two-year history of histologically-proven extensive UC, for which mesalamine was effective to achieve remission without adverse reactions. Two weeks prior to presentation, he experienced 7-8 bloody stools per day after eating ice cream, at which time he had been taking mesalamine (3 g/d) as maintenance therapy for a year. Given a likely gastrointestinal infection, cefixime (0.2 g/d) was added. His diarrhea and bloody stools improved quickly from 7-8 times a day to twice a day, which confirmed our diagnosis of infection. However, without any antibiotic changes, he developed modest fever, progressive pleuritic chest pain, and shortness of breath after activity.

History of past illness

He had not received any coronavirus disease 2019 vaccinations.

Personal and family history

There was no personal nor familial history of cardiac abnormality or dysfunction.

Physical examination

On admission, the patient's vital signs were stable and general examination was unremarkable.

Laboratory examinations

A 12-lead electrocardiogram (ECG) demonstrated sinus tachycardia of 102 bpm without other abnormalities. Laboratory tests revealed raised cardiac biomarkers (cardiac

troponin I (cTnI) 1.27 ng/mL, N-terminal (NT)-pro hormone brain natriuretic peptide (BNP) 303pg/mL and acute phase reactants [high-sensitivity C-reactive protein (hsCRP) 64.7 mg/L, erythrocyte sedimentation rate (ESR) 67 mm/h]. Other myocardial enzymes, including lactate dehydrogenase 121 U/L and creatine kinase MB (CKMB) isoenzyme 0.8 μg/L were normal. Complete cell counts were roughly normal, except for slight leukocytosis and anemia (white blood cells 10.9 × 10^9/L, neutrophils 9.1 × 10^9/L, hemoglobin 113 g/L).

Imaging examinations

Trans-thoracic echocardiogram (echo) revealed only trace pericardial effusion and a left ventricular ejection fraction of 66%. No hypokinesia or ventricular dilation was seen. Given the clinical presentation in the absence of cardiovascular risk factors, a diagnosis of acute myocarditis was suspected, and the etiology was initially considered to be an infection. He was treated with trimetazidine and potassium and magnesium supplementation. His clinical condition gradually improved, with cTnI decreasing to 0.84 ng/mL over the next five days. Cardiac magnetic resonance (CMR) imaging was performed. T1 mapping showed diffuse, slightly elevated T1 values (Figure 1) consistent with probable myocarditis[7].

Further diagnostic work-up

To identify the cause of myocyte injury, stool examination, blood cultures, and extensive viral serology for cytomegalovirus, coxsackie virus, and Epstein-Barr virus were checked and were negative. Endoscopic evaluation of the colon with biopsies revealed active UC (Mayo score 3) involving the colon from the hepatic flexure distally (Figure 2A), although the patient did not describe any worsening of gastrointestinal symptoms.

FINAL DIAGNOSIS

This evidence suggested that the myocarditis was attributable to an EIM of UC.

TREATMENT

The patient was treated with mesalamine (4 g/d) and hydrocortisone (100 mg/12 h), taking the mesalamine continuously during recovery from myocarditis.

OUTCOME AND FOLLOW-UP

His stools became more formed, the chest pain completely resolved, and both cTnI and CRP normalized within seven days, supporting the diagnosis of inflammatory myocarditis. The patient was referred to the Department of Gastroenterology on oral prednisolone. Then, the prednisolone was tapered down and he was further treated with vedolizumab. His dyspnea and chest pain continued to improve gradually, and his heart rate remained at 70-80 bpm and cTnI returned to normal levels. Three months later, follow-up endoscopy (including biopsies) showed remission of the UC (Mayo score 0-1; Figure 2B).

DISCUSSION

Literature review

Here we present a case of myocarditis as an EIM of IBD. Searching the literature using the PubMed database, we found twenty-one similar cases (Table 1). Overall, eight of these patients were female and 13 were male and they ranged in age from 11 to 56 years, with an average age of 29 years. Of patients with IBD, ten had CD and eleven UC. The most common symptoms were shortness of breath (12/21), chest pain (10/21), and fever (8/21); tachycardia (11/21) was also frequently noted by patients or clinicians. In ten cases, myocarditis was considered due to the presence of heart failure (HF). Seven developed rapidly progressive symptoms and/or signs of HF within several days, often with cardiogenic shock on admission. The other three reported fatigue and dyspnea at presentation, and two gradually developed further symptoms. In six cases, the initial manifestation of myocarditis was acute coronary syndrome-like, with sudden or worsening chest pain and elevated cardiac biomarkers (*e.g.*, troponin I) with or without

ST-segment elevation on ECG. In the absence of angiographic evidence of coronary artery disease and cardiovascular risk factors, myocarditis was suspected based on echocardiographic or CMR findings. Myocarditis presented with unexplained severe arrhythmia and cardiac arrest in three cases, and two had previously had dyspnea.

Myocarditis can also mimic other noninflammatory cardiac disorders. Two cases were initially suspected to be infective endocarditis and pulmonary embolism, but myocarditis was then considered due to serial negative blood cultures and pulmonary artery pressure examination by right cardiac catheterization, respectively. The majority of patients (19/21) did not report cardiovascular co-morbidities; only one patient had a history of stress cardiomyopathy and the other had deep venous thrombosis. Six cases reported recurrent myo(peri)carditis, with the recurrence rate in IBD patients significantly higher than in other myocarditis patients[8].

Myocarditis often occurred during the active stage of IBD in most patients (15/21), but it also preceded the gastrointestinal symptoms (3/21) or occurred during the asymptomatic stage (3/21) in others. Cases that were relatively free from gastrointestinal symptoms (5/6) usually had mild symptoms and did not need ventilatory or inotropic support. Of the twenty-one myocarditis patients, eleven were confirmed by histopathological examination or CMR features fulfilling the updated Lake Louise criteria[9]. The remaining ten patients were possible cases where the authors reported a diagnosis of myocarditis through supporting laboratory test results, 12-lead ECG, or echocardiographic features. Laboratory investigations were remarkable for elevated white cell count, acute phase reactants (*e.g.,* CRP and ESR), and cardiac biomarkers (*e.g.,* cTnI, BNP, CKMB, *etc.*) in most (though not all) cases.

In nineteen reported ECGs, except for sinus tachycardia, ST-T changes in the form of ST-segment elevation (4), depression (1), or flattening (1); non-specific ST-T wave changes (3); and T-wave inversion (4) were frequently noted. Arrhythmias and conduction block (4) were also observed. Three cases reported roughly normal ECGs. Fourteen cases reported echo findings which were all abnormal, mainly focal or global hypokinesia (11), low ejection fraction (10), ventricular dilation or enlargement (6), and

accumulation of pericardial fluid (4). Abnormal findings on chest radiograph were reported in ten cases and included pleural effusion (5), pulmonary edema (4), and cardiomegaly (4).

Endomyocardial biopsies (EMB) were reported in four cases. Together with the autopsy results in two other cases, myocarditis as an EIM presented with three histopathological patterns: (1) Giant cell myocarditis (2); (2) Lymphocytic myocarditis (2); and (3) Eosinophilic myocarditis (1). No abnormalities were found in one patient. In ten cases published after 2010, seven patients were assessed by CMR. Six showed both edema and delayed gadolinium enhancement on CMR, verifying the diagnosis of myocarditis; only one reported tissue edema. Pericardial effusion and hypokinesia were also mentioned. Myocardial lesions in IBD patients mainly involved the lateral free wall (5), consistent with the general characteristics of myocarditis[10], and two cases reported injury of the interventricular septum.

All cases reported treatment and outcomes. The treatment of myocarditis as an EIM can be divided into two main approaches: Immunosuppressive therapy and guideline-directed HF (and/or arrhythmia) therapy. Fifteen cases were given corticosteroids, and four were also prescribed a tumor necrosis factor-alpha inhibitor; two cases only used mesalamine. Nine patients were treated with advanced cardiopulmonary support, including mechanical ventilation, inotropic support, intra-aortic balloon pump, and extracorporeal membrane oxygenation, mainly due to rapidly progressive HF. Two cases received cardiac implantable electronic devices. Eighteen cases reported symptomatic improvement at subsequent follow-up visits. Histopathological examination of three deaths showed giant cell myocarditis (2) and lymphocytic myocarditis (1). The former is associated with a worse prognosis, as suggested previously[11]. Contrary to the histological deterioration, two patients showed symptom remission before death, suggesting that repeat EMB to monitor responses to therapy is necessary.

Discussion

Myocarditis is a heterogenous and insidious disease that can mimic other cardiovascular disorders. The incidence rate ratio for developing myocarditis is 8.3-times for CD and 2.6-times for UC compared with the background population[4]. Therefore, early diagnosis and treatment of myocarditis to avoid potentially life-threatening outcomes in IBD patients are essential. Myocarditis as an EIM of IBD is associated with various clinical patterns ranging from subclinical symptoms to sudden death. The initial symptoms of myocarditis are easily overlooked, including shortness of breath, palpitations, chest pain, and fever. When seeking medical advice, most of the cases presented in this review developed critical cardiac symptoms such as aggregated symptoms of HF, acute myocardial infarction-like syndrome, or severe arrhythmia.

As for auxiliary examinations, 12-lead ECG, routine laboratory studies, and trans-thoracic echocardiography are all used in the initial assessment of suspected cardiac diseases. There was no uniform pattern found on ECG in IBD patients with myocarditis, with the abnormalities reported including sinus tachycardia, ST-T changes, and arrhythmias. Myocarditis also causes non-specific elevation of inflammatory markers and cardiac troponins. Given that the former are often increased during episodes of IBD, the dynamics of biomarker changes are more important in these patients. Since patients with myocarditis were more likely to present with a syndrome of HF, echocardiography has sufficiently high sensitivity to evaluate ventricular function and diagnose HF and it should be performed in all patients with suspected myocarditis. The presence of hypokinesia, a low ejection fraction, ventricular enlargement or dilation, and pericardial effusion raise the likelihood of myo(peri)carditis. Endomyocardial biopsy (EMB) is the gold standard diagnostic test for myocarditis. However, due to its invasive nature, EMB is rarely applied in clinical practice and usually only performed in critically ill patients. CMR provides non-invasive characterization of the myocardium as an alternative and is recommended in clinically stable patients prior to EMB[12].

In our case, the patient initially only had mild chest discomfort, fever, and dyspnea during exercise, but this worsened over only a few days without treatment. Thus, health education is important in IBD patients and should include a recommendation to seek

medical intervention actively if they experience dyspnea, chest pain, or tachycardia. Our patient presented with acute coronary syndrome-like symptoms of chest pain and raised cardiac troponins and BNP. Sinus tachycardia and pericardial effusion on ECG and echo, respectively, led to the suspicion of myocarditis. The patient did not undergo coronary imaging due to a lack of typical cardiovascular risk factors, similar to other cases in young people presented in this review. Diffuse elevation of T1 values on CMR T1 mapping confirmed myocardial injury, although isolated elevated T1 cannot discriminate between the acute and healed stages of myocarditis[13].

Another challenge in the treatment of myocarditis is identifying the etiology. IBD patients may develop myocarditis due to an EIM of IBD, infection, or the adverse effects of medications. Myocarditis can occur as an EIM in both UC and CD. The pathogenesis of EIMs is incompletely understood, but a popular hypothesis is that they are caused by extension of antigen-specific immune responses from the intestine to extraintestinal sites. Ectopic expression of gut-specific chemokines and adhesion molecules, gastrointestinal effector T cell trafficking, microbial antigen translocation or cross-reaction, and circulating antibodies may contribute to the process[14]. Infections, especially enteroviruses, are also a non-negligible cause of myocarditis. Patients with IBD are at increased risk of acquiring infections compared to age-matched patients without IBD. The risk is higher when patients are treated with corticosteroids, immunomodulators, and biologic agents, in particular when treatments are combined[15]. Adverse side effects of medications must also be considered. Mesalamine, a 5-ASA derivative, is recommended as first-line treatment to induce remission in patients with mild-to-moderate IBD, especially those with ulcerative proctitis[16]. Mesalamine-induced cardiotoxicity can manifest as myocarditis, pericarditis, and pericardial effusion, perhaps *via* an immunoglobulin E-mediated allergic reaction, direct cardiac toxicity, a cell-mediated hypersensitivity reaction, or cross-reaction between antibodies against mesalamine and heart muscle[6]. Myocarditis induced by other treatments such as tumor necrosis factor-α inhibitors, TPN, and colectomy have

also been reported[17-19]. The latter two may trigger the disease by reducing selenium concentrations[20].

Our patient developed myocarditis after recovery from a gastrointestinal infection, and the bowel symptoms were under control. While infectious myocarditis was considered at first, blood and stool examinations and viral serology were all negative. Although the correlation between viral serology and myocardial infection is controversial and EMB is the only approach to diagnose viral myocarditis[21], these negative test results did turn our attention to other possible etiologies. There are no specific physical findings, clinical presentations, or laboratory tests that can help confirm the causative role of drugs in myocarditis. The diagnosis of mesalamine-induced myocarditis relies on symptom onset within 2-4 wk of starting the drugs and resolution of symptoms within several days of withdrawal. Presentation may be delayed due to concurrent administration of steroids[6]. In our patient, mesalamine-induced myocarditis was unlikely, since mesalamine was administered over a long duration without steroids and there were no notable previous adverse cardiac events. Subsequent colonoscopy revealed active UC, and myocarditis in association with relapsed UC was diagnosed. Treatment with steroids led to rapid resolution of both cardiac and colonic symptoms, further supporting the diagnosis.

During the improvement in gastrointestinal symptoms, our patient developed acute chest pain, which implied a UC flare as confirmed by colonoscopy. The bloody diarrhea was under control at that time, leading to difficulties in early diagnosis. Furthermore, compared with other cases in this review, he had less myocardial damage. If the chest pain had not deteriorated, the patient would not have seen a doctor. This leads us to suspect that cardiovascular manifestations of IBD may be more common than clinically documented, since they may remain undiagnosed.

CONCLUSION

In conclusion, though rarely reported, myocarditis as an extraintestinal manifestation of IBD can be life-threatening without timely diagnosis. Here we reported a 15-year-old

boy who developed myocarditis as an initial presentation of relapsing UC. We reviewed other reports of myocarditis complicating IBD. Shortness of breath, chest pain, and tachycardia in IBD patients, even without gastrointestinal manifestations, should raise clinical suspicion of this uncommon association. Our case and the literature review also highlight the utility of trans-thoracic echo and CMR in diagnosing myocarditis.

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