EJCRIM
European Journal
of Case Reports
in Internal Medicine

ACUTE SEVERE ULCERATIVE COLITIS FLARE COMPLICATED BY MYOPERICARDITIS AND INFLIXIMAB-INDUCED HEPATITIS

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Received: 14/02/2024 **Accepted:** 19/02/2024 **Published:** 04/03/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written consent has been provided by the patient for the publication of this case report, including all displayed images.

How to cite this article: Manti M, Kamperidis N, Toskas A, Martin H, Misra R. Acute severe ulcerative colitis flare complicated by myopericarditis and infliximab-induced hepatitis. *EJCRIM* 2024;**11**:doi:10.12890/2024_004383.

ABSTRACT

Ulcerative colitis (UC) is an autoimmune disease associated with both intestinal and extraintestinal manifestations. The latter may include heart complications, such as myopericarditis leading to life-threatening arrythmias. Nowadays, UC is commonly treated with biologic medications and infliximab is the first line therapy in an outpatient setting, while it is also used as rescue therapy in acute severe UC. However, it has been associated with severe immunosuppression, cytomegalovirus (CMV) reactivation and drug-induced hepatitis. We report a case of UC flare in a biologic naïve patient admitted with myopericarditis, which was further complicated by positive CMV biopsies and infliximab-induced transaminitis.

KEYWORDS

IBD, myopericarditis, CMV, infliximab, transaminitis

LEARNING POINTS

- In acute inflammatory bowel disease (IBD) flare presentation with tachycardia and chest pain, an underlying myocardial injury should be investigated.
- Mucosal healing should be evaluated endoscopically in cases of partial response to biologics.
- Both cytomegalovirus (CMV) infection and infliximab-induced liver injury may lead to acute hepatitis.

INTRODUCTION

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD). Its pathogenesis involves genetic and environmental factors that impact on the intestinal microbiota and the immune response. Its presentation and treatment can be complex.

Extraintestinal manifestations (EIMs) may occur in 6%–47% of patients with IBD and in 25% of cases they may even precede the diagnosis of IBD. Commonly, EIMs involve the skin and the joints. An EIM from the cardiovascular system is rare, with pericarditis being the most common (70%) and it periodically presents as myopericarditis[1]. The latter, if left untreated, could lead to fatal complications including heart failure, arrhythmias, cardiogenic shock, or sudden death.

Immunomodulators, small molecules and biologics have revolutionised the treatment of IBD, however the challenges

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of treatment complications and opportunistic infection remain. Cytomegalovirus (CMV)-reactivation is associated with a high risk of colectomy and may cause acute liver injury. However, hepatitis is often multifactorial and drug-induced liver injury should be always considered.

CASE DESCRIPTION

A 25-year-old man was admitted to a tertiary hospital with a three-week-history of bloody diarrhoea and abdominal pain, and a two-day history of chest pain. He was diagnosed with UC one year previously and was under no treatment. His body mass index was normal. At the time of admission, his ECG identified sinus tachycardia (110 beats per minute). His troponin was raised (457, upper limit: 14 ng/l), his liver function tests were normal and his septic screen was negative albeit with positive C-reactive protein (CRP) of 193 (upper limit: 5 mg/l). Subsequently, he underwent a transthoracic echocardiogram and a cardiac MRI scan, which were consistent with acute myopericarditis *(Fig. 1)*. His computed tomographic pulmonary angiography (CTPA) was negative for pulmonary embolism, while his abdominal CT scan showed acute pancolitis. A flexible sigmoidoscopy showed severe inflammation with friability and deep ulcers in the rectum. The UC endoscopic index of severity (UCEIS) was 7. His therapeutic regime included intravenous hydrocortisone for acute severe colitis, an empirical course of antibiotics (amoxicillin-clavulanic acid and metronidazole) and colchicine, along with ibuprofen for the myopericarditis injury.

Despite the treatment with intravenous corticosteroids, his colonic symptoms persisted with daily bloody diarrhoea. The troponin and inflammatory marker levels gradually normalised; therefore, ibuprofen and antibiotics were discontinued, and he received rescue therapy with infliximab (IFX) at a dose of 5 mg/kg. Treatment with colchicine was continued. At day 8 post infliximab infusion, his alanine aminotransferase (ALT) levels increased to 105 (upper normal limit is 50I U/l), with mild elevation of the alkaline phosphatase (ALP) as well, while his bilirubin, INR, CRP and the rest of the non-invasive liver screen tests were within normal range. The colonic symptoms remained uncontrolled, and a repeat flexible sigmoidoscopy showed a UCEIS score of 6 *(Fig. 2)*. Therefore, a decision for medical treatment intensification was reached.

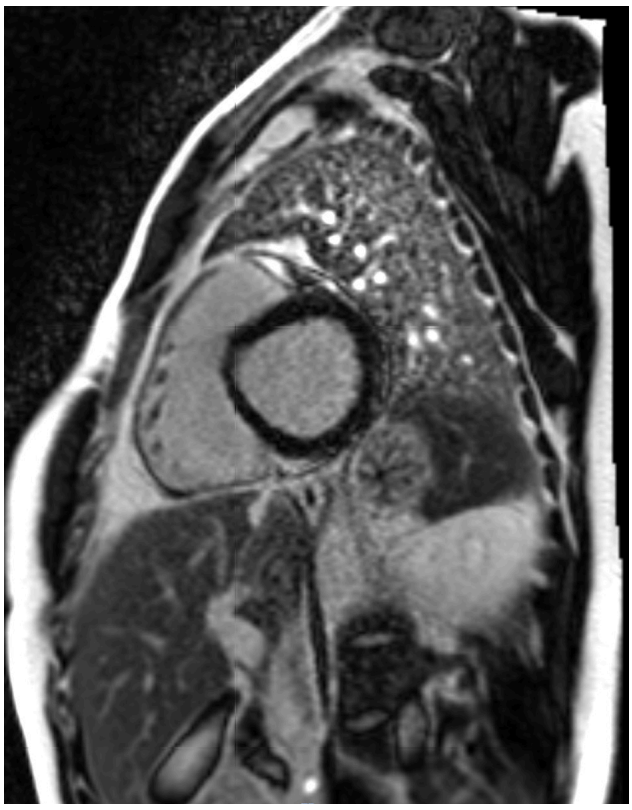

Figure 1. Limited epicardial late gadolinium enhancement in the basal inferolateral wall on cardiac MRI scan.

The second dose of IFX was given after a 10-day interval and at a dose of 10 mg/kg, but his ALT levels gradually started rising with a peak value of 592. Cross-sectional imaging was repeated and showed a normal liver parenchyma and a patent portal vein. However, a few days later his second sigmoidoscopy biopsy results revealed CMV-infected cells, while he also had high CMV serum viral load, necessitating the initiation of anti-viral treatment (ganciclovir). The patient

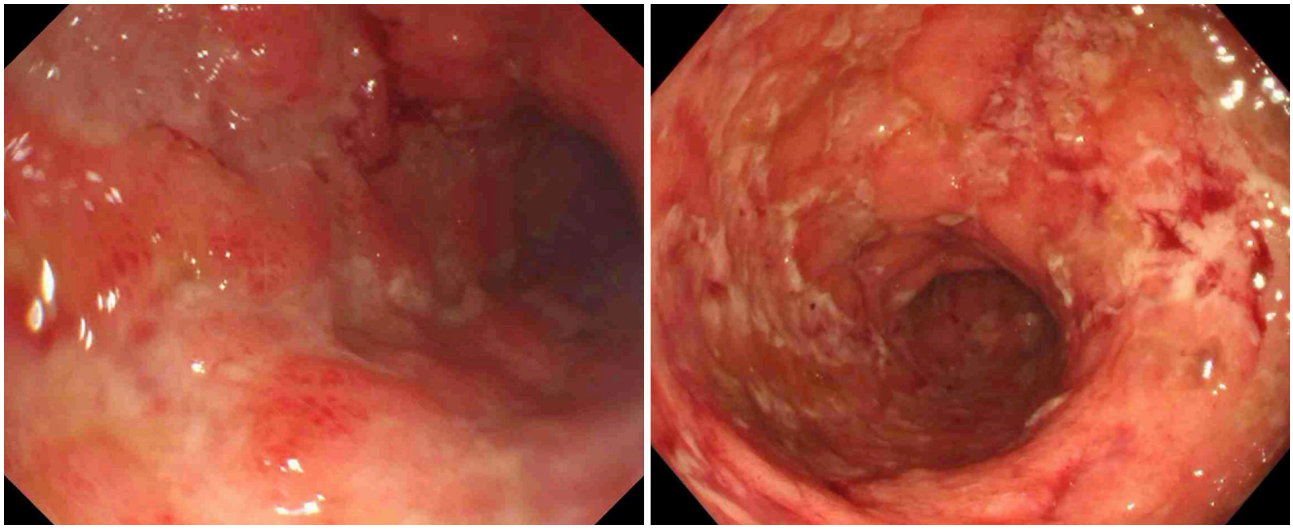

Figure 2. Flexible sigmoidoscopy images at admission (A) and after the first dose of infliximab (B).

remained afebrile with no systemic features of viraemia, and ganciclovir treatment was withheld due to the established liver injury. However, it was administered a few days later, along with a weaning dose of oral steroids, as diarrhoea continued to improve. Liver biopsy was withheld due to normal INR and bilirubin levels, while ALT levels had reached a plateau (480). During his last review, his blood tests showed persistent transaminasaemia (ALT 403), even though most of his clinical symptoms had subsided. At the time of writing, the patient is on oral steroids, oral valganciclovir and colchicine, while he is under close monitoring by the IBD and cardiology teams.

DISCUSSION

Pericarditis has been correlated in the literature with active UC, especially among male patients, while myocarditis is mostly described in Crohn's disease[2]. This was also described in a recent systematic review among 104 IBD patients, where myocarditis affected mostly young male patients with a median age of 31 years, and it was correlated with acute IBD flare[3]. Myopericarditis was mostly associated with underlying infection, immune-mediated process or drug-induced toxicity, especially in cases when mesalamine had been used[3]. In our case, the initial septic screen tests ruled out the presence of active inflammation, while the patient was biologic-factor naïve, under no recent treatment. Therefore it is likely that the underlying pathophysiology for myopericarditis is immune-mediated, representing a rare extraintestinal manifestation and relates to the overall immune activation in the context of active UC[4].

Once sepsis is excluded, myopericarditis treatment typically involves NSAIDs and colchicine; however, both of these drugs should be generally avoided in a concomitant acute IBD flare due to being associated with deterioration of colonic inflammation and diarrhoea[1]. Alternatively, systemic corticosteroids, already used in IBD flare, could aid in the management of inflammation[2].

Besides myopericarditis, our patient was affected by another uncommon complication: new onset hepatocellular liver injury a few days following the first IFX dose. The differential diagnosis could include autoimmune hepatitis – possibly drug induced, active inflammation and drug-induced liver injury (DILI). The former is less likely given that the patient had already received corticosteroids, which are considered the main therapeutic tools of autoimmune hepatitis.

Among IBD patients, while CMV infection is not uncommon, it comes with diagnostic challenges. In our patient, CMV inclusion bodies were identified at low density when a sigmoidoscopy was repeated, while his serum viral load was also detectable a few days later. It is described in the literature that 40%–100% of adults are CMV carriers[5]; thus, CMV reactivation should be taken into account. The European Crohn's and Colitis Organization guidelines recommend tissue immunochemistry methods or polymerase chain reaction (PCR) for CMV detection[7] instead of serum viral load, especially when specimens come from the ulcer base rather than the edge[5]. The importance of accurate CMV infection in IBD patients was highlighted in a study published by the Mayo Clinic. The authors showed that one-year colectomy-free survival is comparable between CMV positive and negative patients, however among CMV biopsy positive patients, high-grade density of inclusion bodies related to higher rates of colectomy[6].

CMV viraemia and infliximab could both be aetiological factors of our patient's acute liver injury. As the liver biochemistry had plateaued prior to treatment with ganciclovir, it was perceived that infliximab was the most likely offending agent.

The reactivation of CMV infection with viraemia and inclusion bodies in the colon could also relate to the development of myopericarditis; however, this would not be possible to prove clinically.

CONCLUSION

The medical management of acute severe colitis could be impeded by systemic complications even in young biologic naïve patients. Multi-disciplinary collaboration and extensive work-up is essential in these cases, while further studies are needed to clarify the time interval between CMV colitis and systemic viraemia manifestations, as well as the natural history of the infliximab-induced liver injury.

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