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Case Report

Mycophenolate-associated colitis in an orthotopic heart transplant patient- an unusual case presentation ☆,☆☆

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ABSTRACT

Mycophenolate mofetil (MMF), an immunosuppressive, is a pharmacologically inactive compound of mycophenolic acid, which has been widely used in solid organ transplant and autoimmune conditions. It mostly exerts gastrointestinal (GI) adverse effects, which include diarrhea, abdominal pain, nausea, and vomiting. It can lead to MMF-colitis, a challenging condition to diagnose due to its similarity with other GI-related conditions and infections. This case report discusses a heart transplant recipient who developed severe MMF-induced colitis. It adds significantly to the limited literature available for this difficult-to-diagnose condition. It also highlights the severity of the condition and underscores the importance of vigilant monitoring and the need for future cohort studies to set guidelines for diagnosing and treating MMF-associated colitis due to its widespread use.

Introduction

Mycophenolate mofetil (MMF) is an immunosuppressive drug with mycophenolic acid (MPA) as its active component. MPA acts as a selective, non-competitive, and reversible inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH) [1]. IMPDH is a rate-limiting enzyme in the de novo synthesis of guanine nucleotides. By inhibiting purine synthesis, MMF reduces the proliferation of T and B lymphocytes, thereby lowering immunoglobulin (Ig) production [2]. MMF is approved for preventing allograft rejection following renal, cardiac, or liver transplants, with recent research showing promising outcomes in lung and simultaneous pancreas-kidney trans-

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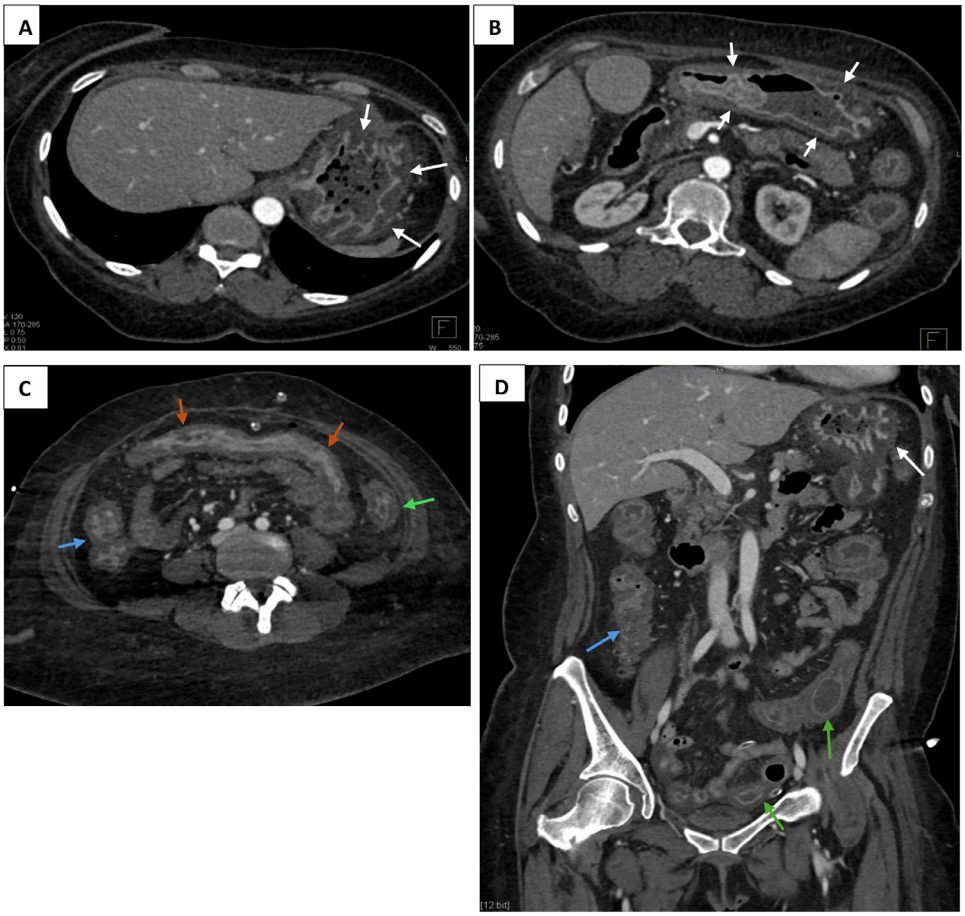

Fig. 1 – A 52-year-old female presenting with recurrent watery diarrhea. Contrast-enhanced axial CT scans show prominent thickening of the gastric folds in the gastric body (A- white arrows) and the antrum (B – white arrows). The patient has prominent enhancement of folds of the transverse colon (C – orange arrow), ascending colon (C – blue arrow) and descending colon (C – green arrow), in a pattern consistent with pancolitis. The small bowel shows no obstruction. Contrast-enhanced venous phase coronal CT scan demonstrates diffuse bowel wall thickening involving the stomach (D – white arrow), ascending colon (D – blue arrow), and descending colon down to the sigmoid (D – green arrow), depicting worsening pancolitis. No intraluminal contrast extravasation is seen to suggest an acute GI bleed.

plants, with an oral dosage of 1.0 to 1.5 g per day taken in two doses. It also shows potential benefits in treating autoimmune diseases, including lupus, myasthenia gravis, and glomerular disorders [1]. Nonspecific adverse effects include the increased risk of common infections due to increased immunosuppression [3]. Specifically, it leads to diarrhea, abdominal pain, nausea, and vomiting, as described by several clinical trials with diarrhea being the most common 1 [4–6]. To our knowledge, only a few cases of mycophenolate mofetil-induced colitis have been reported in orthotopic heart transplant patients [7,8].

Case presentation

Our patient was a 52-year-old female with a medical history of biopsy confirmed Amyloid Light-chain (AL) amyloidosis, complicated by restrictive cardiomyopathy resulting in an ejection fraction of 20–25%, who underwent orthotopic heart transplantation (OHT) two years ago at an outside institution. In addition, she had biopsy-proven amyloidosis of the colon and breast. Her post-OHT course was complicated by acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) with progression to end-stage renal disease (ESRD) thus shifting to peritoneal dialysis. After complication management, she was discharged on oral immunosuppressive therapy including Tacrolimus 4 mg every 12 hours, Mycophenolate mofetil 1000 mg every 12 hours, and Prednisone 7.5 mg daily.

The patient's medical history included an arterial thrombus in 2020, bilateral femoral-popliteal artery bypass complicated by compartment syndrome requiring thrombectomy and fasciotomy, recurrent thrombi while on apixaban (subsequently shifted to warfarin), a remote cerebrovascular accident (CVA), and a history of multiple myeloma.

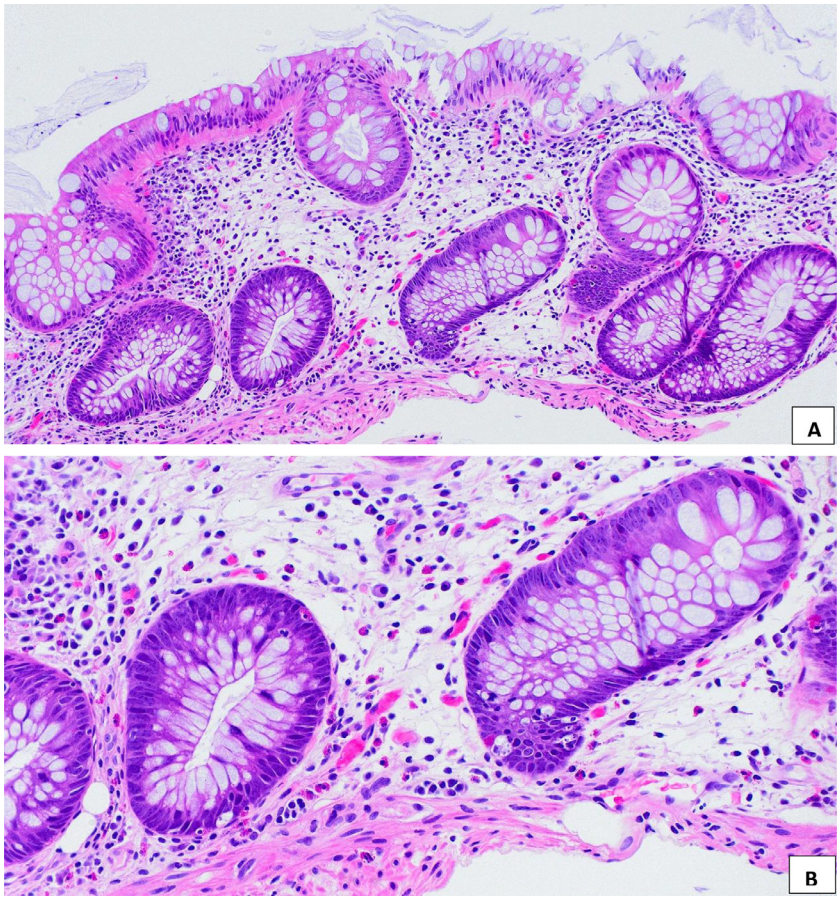

Fig. 2 – Colonic biopsy shows crypt architectural distortion (A, H&E, 200X) with scattered lamina propria eosinophils and crypt apoptosis (B, H&E, 400X), compatible with mycophenolate-associated injury.

The patient was hospitalized twice at our institution, during the middle of the year, for recurrent watery diarrhea. The differentials included infectious colitis, medication colitis, or possibly due to a complication of amyloidosis. Extensive workup was performed with multiple biopsies and a Computed Tomography (CT) scan (Fig. 1). Infectious disease workup was negative for Clostridium difficile, stool NAT panels for viral, protozoal, and bacterial pathogens, stool cultures, Microsporidium, and ova and parasites. Cytomegalovirus (CMV) and adenovirus immunostaining were also negative on biopsies. Multiple biopsies reported architectural distortion, increased lamina propria eosinophils, and increased apoptosis (Fig. 2). After excluding other potential causes, diarrhea was attributed to mycophenolate mofetil (MMF). MMF was then switched to sirolimus and tacrolimus, which improved patient symptoms.

She presented again later in the year with acute-on-chronic worsening of diarrhea, low oral intake, and a syncopal episode with a fall resulting in a head strike. This was her first syncopal episode involving a fall from a standing position, which was unwitnessed, and she reported no recollection of symptoms before and after the fall. She has been unable to tolerate solid foods due to postprandial nausea, poor appetite, and the sensation that solids exacerbate her diarrhea, leading her to switch to a liquid-only diet of water and juice. She reported rectal pain that improved after bowel movements. No fever, chills, melena, hematochezia, or vomiting were reported by the patient.

A push enteroscopy was attempted during this admission but aborted without biopsies taken due to retained solid food in the stomach. Two days later, it was re-attempted successfully, showing jejunal enteropathy. The jejunal biopsy showed lamina propria hemosiderin-laden histiocytes, interpreted as a non-specific finding. PAS was negative for fungal organisms, and Congo red stain was negative for amyloidosis. Abdominal CT scan with intravenous (IV) contrast reported increased mucosal edema involving the colon, distal ileum, and stomach, which raised suspicion for worsening pancolitis and gastritis (Fig. 1). A repeat CT scan, a month later, reported similar diffuse bowel wall thickening with submucosal enhancement possibly due to colitis.

She remained admitted for poor oral and calorie count and later developed rapidly progressive altered mental status, initially suspected to be delirium. However, due to persistent worsening, a noncontrast CT head was performed, which was unremarkable. A lumbar puncture (LP) revealed negative cerebrospinal fluid (CSF) studies for infectious causes.

The patient was admitted to the critical care unit (CCU) due to poor clinical status and developed severe septic shock

from Extended-Spectrum Beta-Lactamase (ESBL)–producing Escherichia coli, leading to persistent hypotension despite aggressive fluid resuscitation and maximum doses of norepinephrine, epinephrine, and vasopressin. On the same day, around evening, she remained hypotensive with mean arterial pressure (MAPs) in the 40s. She entered an accelerated junctional rhythm, subsequently lost her pulse, and required chest compressions as the code team was activated. Despite five rounds of CPR, she continued to exhibit pulseless electrical activity (PEA), and after consensus among the team, resuscitation efforts were halted; she was pronounced dead 45 minutes later.

Discussion

Mycophenolate Mofetil (MMF), a prodrug of the immunosuppressant mycophenolic acid, is used in various solid organ and bone marrow transplants and for treating autoimmune conditions such as lupus nephritis, autoimmune hepatitis, myasthenia gravis, and autoimmune cytopenia [9,10]. Lymphocytes are dependent mostly on de novo purine synthesis and thus are affected by mycophenolate the most, as it inhibits IMPDH, the rate limiting enzyme in purine synthesis. However, enterocytes rely around 50% on de novo purine synthesis and the dependency increases in conditions of anorexia, thus they are affected by MMF's inhibition of this pathway [11,12]. As seen in our patient, she had decreased oral intake, which could have contributed to the disease process.

MMF reduces the cell division of enterocytes leading to epithelial injury and adverse symptoms in about 45% of patients ranging from diarrhea (most common), nausea, vomiting, GI bleeding, dysphagia, and abdominal pain [3,13,14]. It is also metabolized into acrylic glucuronide (AcMPAG) which induces pro-inflammatory cytokine release, disrupts cellular functions and contributes to epithelial damage. These mechanisms combined with impaired mucosal defenses and inflammation leads to gastrointestinal toxicity, leading to severe complications like colitis [15]. Adverse symptoms usually appear within 6 months, but some studies have described a long latency period of months to years [16], as evident in our patient who presented them 2 years later. MMF-induced colitis is rare and is diagnosed after all other differentials are excluded as it can present similar to other gastrointestinal (GI) disorders infections. This highlights the need for reporting diverse cases of MMF-associated colitis to improve our understanding of variations in drug tolerance and guide future protocol developments.

A case report on a male heart transplant patient reported MMF-induced colitis after 13 years of use with diarrhea, weight loss, and acute kidney injury, with positive histologic findings and symptoms improving after drug discontinuation [17]. In another case report, a 55-year-old male heart transplant recipient presented with diarrhea after extensive testing for infectious pathogens that returned negative results, a colonoscopy revealed colitis with histopathological findings resembling graft-versus-host disease. After excluding other potential causes and acute cellular rejection, mycophenolate mofetil was discontinued, leading to significant clinical improvement [8].

As described in other case reports and our findings, diagnosing this condition can be challenging due to its close resemblance to other differential diagnoses. A focused review of literature discussing 13 case reports showed that patients mostly reported profuse watery diarrhea and weight loss. Endoscopic findings ranged from normal to ulcerations and erythema in various parts of the colon and sometimes pancolitis [18]. A study exploring the endoscopic features of MMF-induced colitis reported macroscopic findings ranging from erythema to erosions and ulcers, with about half of the patients showing no visible abnormalities.

Histological features of mycophenolate-associated colitis described in the pathology literature include apoptosis, architectural distortion, cryptitis, and increased lamina propria eosinophils [19,20]. The histologic pattern of injury can resemble graft versus host disease but is distinguished by clinical history and by the presence of increased lamina propria eosinophils and absence of neuroendocrine cell aggregates and apoptotic microabscesses [19]. The pattern of injury can also overlap with that of infectious colitis and inflammatory bowel disease, although the latter typically has denser lamina propria chronic inflammation. The findings described in mycophenolate-associated injury align with our patient's biopsy, which showed apoptotic bodies, architectural distortion, and increased lamina propria eosinophils. Given that apoptosis can also be seen with infections such as cytomegalovirus and adenovirus, immunostains for these viruses were performed and were negative.

As most literature on mycophenolate-associated colitis is limited to case reports, a detailed comparison of clinical and radiologic findings with other differentials is needed. There are no clear guidelines for the treatment of MMF-induced colitis and most studies either stopped MMF or patients were supplemented with steroids. MMF-induced colitis can have a serious trajectory in vulnerable populations like heart transplant recipients, highlighting the severity and prognostic implications of the drug. Emphasizing the need for future cohort studies to set guidelines for the diagnosis and treatment of MMF-associated colitis due to its widespread use for both transplant patients and autoimmune diseases.

Conclusion

With advances in medicines and an increase in organ transplants, Mycophenolate mofetil is widely being used in post-transplant immunosuppression. Despite the pros, the gastrointestinal (GI) side effects are a major con to its use. As radiologists become more cognizant of the GI complications associated with MMF, they are increasingly identifying cases of MMF-related colitis—an infrequent but complex condition that is often difficult to diagnose. The limited existing literature on MMF colitis underscores the importance of reporting these cases. By documenting and studying such instances, we can enhance our understanding of this condition, improving our ability to diagnose and manage affected patients effectively in the future.

Author contribution

All authors contributed equally to the writing of this manuscript.

Patient consent

The patient reported in the manuscript signed the informed consent/authorization for participation in research, which includes the permission to use data collected in future research projects such as the presented case details and images used in this manuscript.

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