CASE REPORT

Mycophenolate mofetil-induced colitis in a patient with systemic sclerosis

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SUMMARY

We present the case of a 44-year-old woman affected by systemic sclerosis (SSc) who was admitted to our department for abdominal pain, nausea, vomiting and fever. Imaging studies showed the presence of a thickened colon wall involving the descending colon and the sigma, while a subsequent endoscopy revealed multiple serpiginous ulcers covered with fibrin and exudates. Under the hypothesis of drug-induced colitis, mycophenolate mofetil (MMF), which she was taking for SSc-related interstitial lung disease (ILD), was readily suspended, with a rapid recovery without further treatment. A follow-up colonoscopy showed the complete resolution of the ulcers. This is the first case of MMF-induced colitis in a patient being treated for SSc-ILD.

BACKGROUND

Systemic sclerosis (SSc) is a multisystem autoimmune disorder characterised by immune system activation, vasculopathy and abnormal collagen deposition in the skin and several internal organs, including the gastrointestinal (GI) tract, which is affected in approximately 90% of patients.¹

CASE PRESENTATION

We report herein the case of a 44-year-old woman affected by SSc who was admitted to our department for abdominal pain, nausea, vomiting and fever. Her recent history had started 2 days before admission, when left-sided abdominal pain developed with an abrupt onset and an intensity rated 10/10 on a numerical scale. Pain was followed after a few hours by nausea, vomiting and fever up to 38°C. Because of constipation, the following day her primary care physician prescribed an enema without any significant benefit. Therefore, she was referred to the emergency department of our hospital and was admitted for further evaluation. On physical examination, the patient was alert but uncomfortable. She complained constipation and diffuse abdominal pain more prominent in the left quadrants. The abdomen was tender, but there were no signs of peritonitis. The remaining physical examination was unremarkable, except for the presence of diffuse cutaneous sclerosis and telangiectasias. She was afebrile and blood pressure, heart rate, respiratory rate and oxygen saturation were within normal range. The patient had Scl-70 positive SSc with mild oesophageal and pulmonary involvement from 25 years. She had no comorbidities except for

systemic hypertension. Her medication list included esomeprazole, ramipril, bosentan, acetylsalicylic acid and mycophenolate mofetil (MMF), which had been prescribed 2 months earlier by another SSc clinic.

On admission, MMF was readily withdrawn under the hypothesis of an infectious complication. The immediate management consisted of the administration of intravenous fluids, low residue diet and analgesic drugs such as acetaminophen intravenous plus antispasmodic agents such as rocuronium.

INVESTIGATIONS

Routine blood tests drawn on admission showed leucocytosis with neutrophilia ($16.000 \times 10^6/L$) and markedly elevated inflammatory markers (C-reactive protein 23 mg/dL, erythrocyte sedimentation rate 35 mm/hour).

A bedside abdominal ultrasound examination showed the presence of diverticula and a thickened and oedematous colic wall involving the descending colon and the sigma.

The latter finding was later confirmed by contrast-enhanced CT that did not reveal any other abnormality.

A subsequent colonoscopy revealed mucosal hyperaemia and multiple serpiginous ulcers covered with fibrin and exudates involving the transverse and descending colonic mucosa, with rectal sparing (figure 1A).

DIFFERENTIAL DIAGNOSIS

Our differential diagnosis included infectious colitis, drug-induced colitis, new-onset inflammatory bowel disease (IBD), SSc-associated GI involvement and mesenteric ischaemia.

Among infectious causes of colitis, cytomegalovirus (CMV) infection is the primary concern in immunocompromised patients. Endoscopic features of CMV colitis may include diffuse erythema, ischaemia, erosions and ulcers.²

Endoscopic appearance of drug-induced colitis can resemble ulcerative colitis, infectious colitis and ischaemic colitis. Though non-steroidal anti-inflammatory drugs are the most frequent cause of drug-induced colitis, in our patient, MMF was most likely implicated. Colitis is frequently diagnosed in transplant recipients treated with MMF (up to 10%), but the prevalence of colitis in patient taking MMF for other indications is unknown. In MMF-induced colitis, rectal sparing is almost universal.³

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Figure 1 The colonoscopy revealed mucosal hyperaemia and multiple serpiginous ulcers involving the transverse and descending colonic mucosa (A) and the complete resolution of the ulcers after mycophenolate mofetil discontinuation (B). The histopathological examination showed ulceration, granulation tissue and hyalinised appearance of the mucosa and submucosa (C and D).

New-onset IBD was considered as a possible diagnosis in our patient, although the endoscopic evidence of rectal sparing virtually excluded ulcerative colitis.

In patients with SSc, any segment of the GI tract from the mouth to the anus may be affected, but GI tract involvement usually manifests as a dysmotility syndrome or with the presence of mucosal vascular malformations. Though collagenous colitis has been reported to be associated with SSc, with a rather rare occurrence,⁴ overt inflammatory colitis is not a hallmark of SSc.

Mesenteric ischaemia is a rare complication in patients with cardiovascular risk factors, especially in those with established atherosclerotic vascular disease. However, our patient did not present any of these features.

TREATMENT

Since MMF discontinuation, the GI symptoms and the systemic inflammation biomarkers progressively decreased, reaching normal values after 5 days, without any additional treatment, which corroborated the hypothesis of drug-induced colitis. Thus, the patient was discharged 7 days after the admission without any prescription but the cessation of MMF.

OUTCOME AND FOLLOW-UP

The histopathological examination documented ulceration, granulation tissue and hyalinised appearance of the mucosa and submucosa, all findings suggestive of ischaemic colitis (figure 1C,D). CMV-DNA was negative in the specimen.

Therefore, the most likely diagnosis was MMF-induced colitis.

A repeated colonoscopy 1 month after MMF suspension showed complete resolution of the ulcers with the presence of scar tissue above the mucosal layer (figure 1B).

DISCUSSION

To our knowledge, this is the first reported case of colitis induced by MMF in a patient with SSc. Other authors previously reported the onset of colitis 22 months after beginning of MMF treatment in a patient with polymyositis.⁵ Conversely, MMF is a well-known cause of drug-induced colitis in transplant recipients.³

MMF is an immunosuppressive drug initially used in organ transplantation to reduce rejection risk, but nowadays it has expanded its indications for the treatment of patients with autoimmune systemic diseases, such as systemic lupus erythematosus (SLE). MMF is also increasingly being used for the treatment of SSc-ILD.^{6–8}

MMF exerts its immunomodulatory effects by inhibiting de novo purine synthesis, which leads to decreased proliferation of activated lymphocytes, thus resulting in reduction of antibody production, changes in inflammatory cells recruitment and induction of apoptosis. The exact mechanism leading to the development of colitis is unknown, yet.⁹ Histopathological findings of MMF colitis include a normal/near normal appearance as well as IBD-like, graft-versus-host disease-like, ischaemia-like and self-limited colitis-like changes.¹⁰

In conclusion, those who take care of patients with autoimmune systemic diseases should be able to recognise colitis as a rare complication of MMF treatment and be aware that drug discontinuation is usually effective without any additional therapy.

Learning points

- Gastrointestinal tract is involved in a number of patients with systemic sclerosis, but overt inflammatory colitis is not a hallmark of the disease.
- Mycophenolate mofetil is known to induce an inflammatory colitis with different patterns and clinical presentations.
- Colitis should be accounted as a rare but worrisome treatment complication in patients with autoimmune systemic diseases taking mycophenolate mofetil.

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