CASE REPORT

Not your usual diarrhoea: severe colonic toxicity of mycophenolate due to intestinal CMV and EBV infection

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SUMMARY

We report a case of a 52-year-old woman, on immunosuppressive treatment with mycophenolate due to a history of giant cell myocarditis (GCM), who presented with new-onset severe blood-tinged diarrhoea after a cytomegalovirus (CMV) primoinfection. An extensively prolonged mycophenolate-related colitis was seen after withdrawal of mycophenolate due to an intestinal Epstein-Barr virus (EBV) infection—a rarely seen event itself. We postulate that colonic toxicity was triggered by CMV infection and perpetuated by intestinal EBV replication/infection.

BACKGROUND

Mycophenolate is a frequent immunosuppressive therapy for prevention of allograft rejection and under evaluation for the treatment of various autoimmune disorders. However, long-term observations show relevant gastrointestinal side effects related to mycophenolate treatment including persistent diarrhoea. Case reports suggest rapid clinical improvement of diarrhoea upon dosage adjustment or withdrawal of mycophenolate.

This case report shows the exceptional course of an extensively prolonged mycophenolate-related diarrhoea and highlights an intestinal cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection as the possible pathomechanism of ongoing mycophenolate-associated colitis.

CASE PRESENTATION

A 52-year-old woman on immunosuppressive medication (mycophenolate mofetil 180 mg twice daily and sirolimus 1 mg once daily due to a history of a giant cell myocarditis (GCM) 6 years prior to presentation (endomyocardial biopsies; figure 1)) presented with new-onset severe blood-tinged diarrhoea with up to 10 episodes a day, without abdominal pain. She reported intermittent mild fever, weight loss and weakness. History of travel, toxic agents or new medication was unremarkable.

Two months prior to this episode, the patient was successfully treated for a CMV primoinfection with ganciclovir 900 mg twice daily for 14 days with close monitoring of mycophenolate blood levels according to potential drug interactions.

On clinical examination the patient was underweight (body mass index (BMI) 17 kg/m²), but orientated, afebrile and normotensive. She had no signs of abdominal tenderness, hepatosplenomegaly or lymphadenopathy. Laboratory results revealed C

reactive protein (CRP) 82 mg/L. Hypoalbuminaemia (25 g/L (ref. >35)), hypophosphataemia (0.71 mmol/L (ref. >0.80)) and hypokalaemia (3.3 mmol/L (ref. >3.5)) were newly present.

INVESTIGATIONS

CMV—as well as EBV replication—was detectable in the peripheral blood. CMV colitis was suspected and the patient was started intravenous treatment with ganciclovir. Stool cultures were negative. The colonoscopy revealed an erosive colitis with superficial ulcerations of the left hemicolon extending from the descending colon to the rectum (figure 2A). Histopathological examination showed nonspecific lymphoplasmacellular infiltration and therefore failed to determine a distinct diagnosis. While CMV was not detected (under treatment with ganciclovir), EBV genome was detectable by in situ hybridisation (figure 2B) proving intestinal EBV infection.

DIFFERENTIAL DIAGNOSIS

In an immune-compromised patient presenting with new-onset diarrhoea the spectrum of differential diagnoses includes a wide spectrum of acute infectious diarrhoea. Ischaemic colitis seems unlikely in this middle-aged person without abdominal pain or relevant vascular risk factors. Also, new-onset chronic inflammatory bowel disease would be a highly unusual cause of acute and severe diarrhoea in this immunosuppressed individual.

TREATMENT

While the CMV viral load became undetectable under continuous antiviral treatment, EBV remained

Figure 1 Endomyocardial biopsy. Histology showing severe chronic inflammation with eosinophils and multinucleated giant cells (arrows).

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Figure 2 (A) Colon biopsy (descending colon) showing erosive colitis. (B) Histology showing severe lymphocytic and granulocytic inflammation with cryptitis and cryptic abscesses. Inset panel: in situ hybridisation EBV-encoded RNA in situ hybridisation showing several Epstein-Barr virus-infected mononucleated cells (arrow). (C) Colon biopsy (sigmoid) showing severe colitis with ulcerations. (D) Histology showing severe architectural disarray and numerous apoptotic cells in the glandular epithelium (arrow).

detectable and the diarrhoea deteriorated (figure 3). Repetitive colonoscopies revealed distended severe colitis with ulcerations mainly in the distal colon (figure 2C). Histology showed severe architectural disarray, active inflammation and apoptosis at the glandular bases (figure 2D), favouring the differential diagnosis of a drug-toxicity consistent with mycophenolate-induced colitis. CMV was only detected on sporadic cells, but intestinal EBV infection was proven additionally.

Given the life-threatening deterioration, we decided to taper and eventually withdraw the immunosuppressive therapy. After

withdrawal EBV loads transiently stabilised (figure 3), but diarrhoea persisted. We suggested a toxic effect of mycophenolate combined with—and possibly perpetuated by—intestinal infection/persistence of EBV/CMV to cause the diarrhoea in this patient. A trial with high-dose steroids was started intending to control the assumed mycophenolate-induced colitis. While CRP levels diminished, EBV replication increased in an uncontrolled manner (figure 3). Tiptoeing for months around fears of recurring GCM, immunosuppression and EBV replication, it was only after controlled reduction of immunosuppression and B-cell ablation with two doses of the CD20-antibody rituximab (375 mg/m² BSA) (thus removing EBV's primary target, figure 4) that diarrhoea resolved.

OUTCOME AND FOLLOW-UP

The patient remains in a very good condition with a normal BMI and EBV loads remain detectable at low levels 1.5 years after weaning-off steroids and B-cell ablating treatment with rituximab. Her cardiac function remains stable with no evidence of GCM recurrence without any immunosuppressant therapy.

DISCUSSION

We postulate that mycophenolate-related colitis was triggered by CMV infection and perpetuated by intestinal EBV replication/infection. Mycophenolate commonly causes diarrhoea, often in a dose-dependent manner.¹ Pathophysiology remains incompletely understood. Mycophenolic acid (MPA) inhibits de novo purine synthesis among lymphocytes responding to stimulation, hence evolving its immunosuppressive effect.² Similarly, the enterocyte proliferation also depends on de novo purine synthesis, offering a plausible explanation for MPA-induced gastrointestinal toxicity. In vitro, MPA can promote the release of inflammatory cytokines such as IL-6 and TNF- α .³ A combination of MPA-induced, cytokine-mediated inflammation and suppressed intestinal regeneration has been proposed to be a dominant pathomechanism of mycophenolate-induced colitis.⁴

Figure 3 Cytomegalovirus/Epstein-Barr virus load (GEq/mL) and C reactive protein (mg/L) throughout the disease course (September 2010–March 2013). Relevant medication is indicated with graded black illustrating dose reductions.

Figure 4 Postulated mechanisms of action of rituximab for B-cell depletion in Epstein-Barr virus-infected B cells.

Importantly however, after withdrawal of mycophenolate severe prolonged colitis is rarely seen, suggesting that additional factors were involved in this patient.^{5–6} While mycophenolate-related gastrointestinal side effects most commonly appear during the first months of treatment,¹ severe diarrhoea developed more than 5 years into mycophenolate exposure and upon CMV primoinfection in the patient. While histopathology was most compatible with mycophenolate-induced colitis, intestinal EBV and—initially—CMV involvement were documented as well. We, therefore, suggest that CMV primoinfection triggered mycophenolate toxicity, which subsequently was perpetuated despite withdrawal of mycophenolate through ongoing intestinal EBV replication/infection. Of note, in a report by Woywodt *et al*,⁷ clinically apparent CMV reactivation was found to occur more frequently in patients treated with mycophenolate, as compared with other immunosuppressive agents. Clinically apparent EBV infection of the gastrointestinal tract is rare. Aside from patients with post-transplant lymphoproliferation, case studies have identified gastrointestinal EBV involvement in patients with inflammatory bowel disease. In line with the hypothesis that EBV may have perpetuated colitis in the here-reported patient, in these case studies a relation of gastrointestinal EBV replication and exacerbation/protracted clinical disease is suggested.^{8–10}

Learning points

- Mycophenolate is a frequent immunosuppressive therapy with diarrhoea as a commonly seen side effect. Dose reduction or withdrawal should result in rapid clinical improvement.
- Prolonged diarrhoea after withdrawal of mycophenolate needs further investigation for other or additional causes of diarrhoea.
- A change of colonic microenvironment due to intestinal cytomegalovirus and Epstein-Barr virus infection is a possible pathomechanism of severe and prolonged mycophenolate-related colonic toxicity.

Contributors HS summarised and interpreted the clinical data and wrote the report. JE and CH supervised the study, discussed and interpreted data and helped in writing the report. LT contributed in clinical data and helped in writing the report.

Competing interests None.

Patient consent Obtained.

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