Pediatr Pol 2022; 97 (3): 260-263
DOI: https://doi.org/10.5114/polp.2022.120122
Submitted: 07.03.2022, Accepted: 30.05.2022, Published: 30.09.2022

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

CASE REPORT

Mycophenolate mofetil-related colitis in a paediatric patient after kidney transplant

Natalia Oleksik[1,2], Monika Głowinkowska[1,2], Maria Szczepańska[2], Katarzyna Bąk-Drabik[2], Wioletta Jarmużek[3]

[1]Students' Association, Medical University of Silesia, Katowice, Poland
[2]Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Students' Association, Medical University of Silesia, Katowice, Poland
[3]Department of Nephrology, Kidney Transplantation and Hypertension, the Children's Memorial Health Institute, Warsaw, Poland

ABSTRACT

Mycophenolate mofetil (MMF) is an immunosuppressive agent, the gastrointestinal side effects of which include abdominal pain, diarrhoea, and vomiting. MMF may also cause symptomatic colitis, although it is a rare condition. We present herein the case of a boy with chronic kidney disease, lasting since the neonatal period, and caused by *WT1* gene mutation. The patient developed colitis during an immunosuppressive therapy applied after a kidney transplant. Histopathology of intestinal biopsy specimens revealed features of MMF-related colitis. A modification of the immunosuppressive treatment and the implementation of a nutritional programme to the patient resulted in the disappearance of clinical signs and helped in a gradual body weight gain.

KEY WORDS:

children, mycophenolate mofetil, kidney transplant, colitis.

INTRODUCTION

Mycophenolate mofetil (MMF) is one of the immunosuppressive drugs commonly used after solid organ or bone marrow transplantation [1].

MMF is one of the medicinal products that can induce colitis (other causes of colitis include inflammatory bowel disease, infection, ischemia, radiation-caused injuries). MMF-induced symptomatic colitis is a rather rare condition [2, 3].

In the majority of cases of colitis, manifested among others by diarrhoea and abdominal pains, a combined assessment is necessary, taking into account laboratory data, clinical signs, and colon biopsy specimens, in order to obtain a correct diagnosis and design an appropriate therapeutic management [4].

CASE REPORT

A male patient, 6 years and 10 months old, after bilateral nephrectomy and kidney transplantation, was urgently admitted to the Department of Nephrology for recurrent vomiting. The patient was born in the 37th week of pregnancy via caesarean section. The one-minute Apgar score was 7. From the third day of life peritoneal dialysis was applied due to impaired kidney function (serum creatinine 268 μmol/l) and anuria not responding for conservative therapy. The cause of chronic kidney disease was initially unrevealed and unspecified. Only when a Wilms tumour was identified in the patient, when he was 2 years old, were targeted genetic diagnostics carried out, confirming the presence of *WT1* gene mutation. The patient was treated according to the International

ADDRESS FOR CORRESPONDENCE:

Natalia Oleksik, Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Students' Association, Medical University of Silesia, Katowice, 3 Maja 13-15, 41-800 Zabrze, Poland, e-mail: nat.oleksik@gmail.com

Society of Paediatric Oncology 2001 treatment programme in its 2006 modification (preoperative chemotherapy, removal of the right kidney with the tumour, postoperative chemotherapy for intermediate-grade cancer in stage II, according to the AV2 regimen – actinomycin-D + vincristine).

When the boy was 5 years and 6 months old, a kidney was transplanted from a deceased donor with a simultaneous Bricker loop procedure for permanent urine drainage. An antiviral prophylaxis with valacyclovir was applied for the donor/recipient cytomegalovirus serological status. An immunosuppressive treatment was implemented in the patient, based on MMF, tacrolimus, and prednisone. The administered MMF was used in a daily dose from 800 mg to 1200 mg under the control of the transplant centre. The treatment was well tolerated by the patient.

On admission to the Department of Nephrology, the boy's general condition was assessed as fairly good; however, the child was apathetic and weakened. A physical examination of the patient revealed the following abnormalities: pale skin, partial dryness of oral mucosa, exteriorised Bricker fistula with a stoma bag, cryptorchidism, and psychomotor retardation. His body mass was 21 kg (25th percentile) and body height was 113 cm (third percentile).

Laboratory tests revealed the following deviations from normal values: C-reactive protein 50 mg/l (normal < 0.5 mg/l), an increased percentage of monocytes in peripheral blood smear, and anaemia (haemoglobin – 10.4 g/l). An intravenous antibiotic therapy (cefuroxime) was introduced into the treatment protocol, together with parenteral hydration (ped300) and the permanent immunosuppressive treatment was continued (tacrolimus, prednisone, MMF 2 × 400 mg – 38 mg/kg/day). During hospitalization, the boy presented with multiple vomiting incidents and diarrhoea with the presence of mucus and, periodically, of blood. The abdominal ultrasound imaging showed a 4-mm thickening of the colon wall from the splenic flexure to 4 mm, with an increased vascular flow. Stool examinations revealed the *Clostridium difficile* antigen and toxins. Oral metronidazole was added to the treatment regimen. Following 14-day therapy with metronidazole, clinical improvement was achieved in terms of resolution of bloody diarrhoea. However, in light of the observed decrease in body weight, persistently elevated C-reactive protein (28 mg/l), and abdominal pain, the decision was taken to perform diagnostics with upper and lower gastrointestinal endoscopy 2 weeks after the end of the antibiotic therapy of *Clostridium difficile* infection (CDI).

No macroscopic findings were observed in the gastroscopy, and the picture of histopathological specimens was normal. During colonoscopy, due to difficult anatomical conditions, the instrument was inserted only into the descending colon, revealing inflammatory lesions, such as several ulcerations, their diameter being 0.5–2 cm, surrounded by a ridged pattern, where ulceration areas were scattered on the macroscopically unchanged sigmoid mucosa (Figure 1). The biopsy specimens showed abnormal crypt architecture (dilation with a reduced number of cup cells, single apoptotic bodies, an increased mitotic activity and crypt microabscesses plus a local presence of degenerated crypts). Inflammatory exudate, composed of plasmocytes, lymphocytes, neutrophils, eosinophils, and numerous dilated capillaries, was focally present in the interstitium. The cover epithelium remained uninfiltrated by inflammatory cells and was partially desquamated (Figure 2). The microscopic picture, combined with the clinical data, provided solid evidence of drug-related lesions, described as MMF-related colitis.

The obtained results were consulted with the Department of Nephrology, Kidney Transplantation, and Hypertension of the Child Health Centre in Warsaw and with the collaborating Department of Gastroenterology, where the patient was hospitalised. The previous treatment was modified by replacing MMF by azathioprine (25 mg/day).

After less than 4 weeks, the patient was urgently admitted to our hospital again for vomiting and the pres-

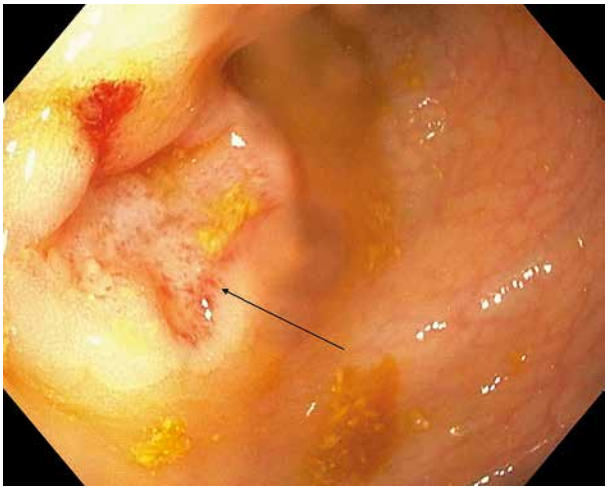

FIGURE 1. Colonoscopic image of sigmoid mucosa with inflammatory changes in the form of ulcerations, surrounded by ridged structures

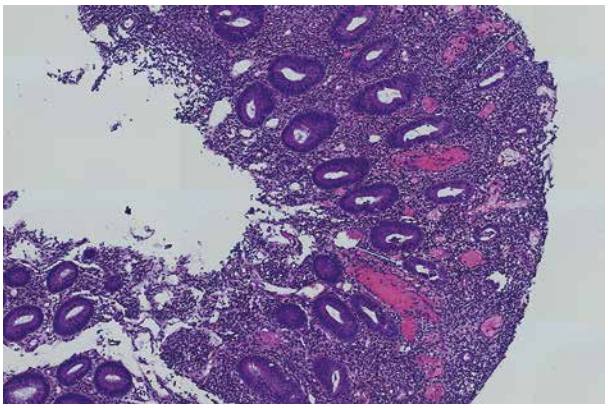

FIGURE 2. Abnormal crypt architecture and inflammatory exudate in the histopathological picture of biopsy specimens, obtained from the sigmoid colon mucosa

ence of blood in the stool. On the previous day, the boy started empirical therapy with cefuroxime. On admission, the patient's general condition was moderate, with physical signs of dehydration. A stool examination again revealed CDI. The empirical antibiotic therapy was continued, and metronidazole was added, achieving improvement in the boy's clinical state.

The prolonged antibiotic therapy and the modified immunosuppressive therapy, based on tacrolimus, azathioprine, and prednisone, and the introduction of exclusive enteral nutrition with an oral polymeric diet (enteral feeding with a whole-protein-based liquid formula with the exclusion of solid foods and most usual drinks), resulted in resolution of the clinical symptoms with normalization of the inflammatory parameters and some improvement of the biochemical parameters plus a gradual body weight gain.

DISCUSSION

According to recommendations of the Polish Transplantation Society, the standard immunosuppressive regimen after renal transplantation assumes a combination therapy, involving calcineurin inhibitor, MMF, and glucocorticosteroids [5].

Even several years after the completion of renal replacement therapy, encapsulating peritoneal sclerosis (EPS) should also be considered in the differential diagnosis, regarding vomiting and abdominal pain in patients on long-term dialysis, as well as in those after kidney transplant. Encapsulating peritoneal sclerosis is associated with persistent, intermittent, or recurrent adhesive bowel obstructions, caused by a wide range of adhesions of a diffusely hypertrophied peritoneum. Ultrasonography (USG) may help identify distended and clustered bowel loops, covered with a thick layer of fibrous membrane [6]. Regarding our patient, automated peritoneal dialysis was maintained for 5 years, and USG revealed imaging features not characteristic for EPS.

In a group of 33 paediatric kidney transplant recipients, the most common MMF-related adverse effects were infections whereas haematological toxicity (most often anaemia and leukopenia) occurred in over half of the children [7]. *Clostridium difficile* infection was diagnosed twice in our patient. Regarding solid organ recipients, CDI develops more often in the early period after transplantation, which is associated with certain risk factors, including immunosuppression, frequent hospitalisations, and previous antibiotic therapy. *Clostridium difficile* infection may irreversibly deteriorate the transplanted kidney function [8, 9]; therefore, an early diagnosis is crucial. During CDI colonoscopy may reveal elevated creamy white plaques that coalesce into pseudomembranes on the colonic mucosa whereas the microscopic abnormalities frequently associated with CDI involve typical mushroom-shaped pseudomembranes comprised of fibrin, mucus, neutrophils, and necrotic cells [10, 11]. No characteristic features of CDI were observed in the endoscopic and histologic examinations in our patient.

According to a retrospective review, diarrhoea was the main indication for colonoscopy referral in patients with MMF-related colitis. Other reasons for colonoscopy included screening for colorectal cancer, gastrointestinal bleeding, weight loss, abdominal pain, and abnormal imaging studies [12]. More importantly, colonoscopy revealed no macroscopic abnormalities in up to 47% of the patients with MMF-related colitis, and the diagnosis was obtained by histopathological examination, thus indicating the need for routine mucosal biopsies to confirm the diagnosis. Among the patients with abnormal colonoscopy results the most common findings included erythema, erosions, or ulcers [12]. In an endoscopic examination of our patient, several scattered ulcers of 0.5–2 cm in diameter were found on the macroscopically unchanged sigmoid mucosa.

Sixty-nine per cent of the MMF users who had a colonic biopsy due to gastrointestinal symptoms revealed histological changes, disturbances in the crypt architecture and apoptosis being the most common irregularities [13]. This type of abnormality was also found in our patient. Histological changes, associated with the use of MMF, may resemble self-limiting colitis, graft vs. host disease, or inflammatory bowel disease, which may cause additional diagnostic difficulties [3, 13]. Moreover, the image of histopathological changes may be atypical; therefore, it may be difficult for a pathologist to obtain a correct diagnosis without the information that the patient is on MMF therapy [14].

CONCLUSIONS

In MMF-related colitis, the resolution of symptoms or a significant improvement can be achieved either by reducing the MMF dosage or by discontinuation of MMF treatment [14]. Similarly in our patient, the modification of the immunosuppressive regimen, in which MMF was replaced by azathioprine, and the applied nutritional therapy, based on oral diets, resulted in the improvement of the patient's clinical condition and in alleviation of the gastrointestinal complaints.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Querfeld U, Weber LT. Mycophenolate mofetil for sustained remission in nephrotic syndrome. Pediatr Nephrol 2018; 33: 2253-2265.
2. Geboes K, Van Eyken P. Inflammatory bowel disease unclassified and indeterminate colitis: the role of the pathologist. J Clin Pathol 2009; 62: 201-205.

3. Phatak UP, Seo-Mayer P, Jain D, et al. Mycophenolate mofetil-induced colitis in children. J Clin Gastroenterol 2009; 43: 967-969.
4. Patil DT, Odze RD. Biopsy diagnosis of colitis: an algorithmic approach. Virchows Arch 2018; 472: 67-80.
5. Durlik M, Przybyłowski P. Zalecenia dotyczące leczenia immunosupresyjnego po przeszczepieniu narządów unaczynionych. Fundacja Zjednoczeni dla Transplantacji, Warszawa 2018.
6. Zagożdżon I, Żurowska A. Otarbiające stwardnienie otrzewnej u dzieci dializowanych otrzewnowo. Forum Nefrol 2020; 13: 22-29.
7. Berger I, Haubrich K, Ensom MHH, et al. Relationship of limited sampling strategy and adverse effects of mycophenolate mofetil in pediatric renal transplant patients. Pediatr Transplant 2019; 23: e13355.
8. Farooq PD, Urrunaga NH, Tang DM, et al. Pseudomembranous colitis. Dis Mon 2015; 61: 181-206.
9. Villanacci V, Reggiani-Bonetti L, Leoncini G, et al. Histopathology of non-IBD colitis. A practical approach from the Italian Group for the study of the gastrointestinal tract (GIPAD). Pathologica 2021; 113: 54-65.
10. Riddle DJ, Dubberke ER. Clostridium difficile infection in solid organ transplant recipients. Curr Opin Organ Transplant 2008; 13: 592-600.
11. Kujawa-Szewieczek A, Adamczak M, Kwiecień K, et al. Analysis of Clostridium difficile infections in patients hospitalized at the neurological ward in Poland. Postepy Hig Med Dosw 2016; 70: 505-513.
12. Calmet FH, Yarur AJ, Pugazhendhi G, et al. Endoscopic and histological features of mycophenolate mofetil colitis in patients after solid organ transplantation. Ann of Gastroenterol 2015; 28: 366-373.
13. Selbst MK, Ahrens WA, Robert ME, et al. Spectrum of histologic changes in colonic biopsies in patients treated with mycophenolate mofetil. Mod Pathol 2009; 22: 737-743.
14. Kim K, Gardner JM, Schwartz M, et al. Mycophenolate mofetil-related colitis. A case report. Korean J Pathol 2010; 44: 333-337.