Gastric ulcer despite no acid in a renal allograft recipient: what is the link?

Keywords: CMV disease; gastric ulcer; kidney transplantation

A 33-year-old female patient with end-stage renal disease underwent successful cadaveric renal transplantation in February 2005. The patient’s immunosuppressive regimen comprised thymoglobulin (ATG Fresenius AG, Germany) 100 mg/day for induction, corticosteroid (methylprednisolone 500 mg/day for 3 days and followed by oral prednisolone 1 mg/kg/day), mycophenolic acid (MPA) (Myfortic, Novartis Pharma Stein A.G., Switzerland) 1440 mg/day. The cytomegalovirus (CMV) status of the patient was seronegative (R–), whilst it was seropositive for donor (D+). The allograft immediately functioned, and serum creatinine levels decreased to 0.9 mg/dl. Tacrolimus was initiated at a dose of 0.1 mg/kg/day 3 days after the operation, and thymoglobulin was used for 5 days. The tacrolimus dose was titrated based on trough levels. Trimetoprim-sulphamethoxazole, flucanozole and acyclovir were given for prophylactic therapy. Omeprazole was also given for gastroduodenal protection. There were no postoperative complications, and the patient was discharged 9 days after the operation.

The patient was readmitted to the hospital 6 weeks after the transplantation, because of nausea, vomiting, severe malaise and abdominal pain. On physical examination, the patient was afebrile and haemodynamically stable. The abdomen was flat and soft with minimal epigastric tenderness. The remainder of the examination was unremarkable. Initial laboratory data showed a haemoglobin level of 11.2 g/dl, total white blood cell count of 6300/mm³ and platelet count of 165,000/mm³. A chest X-ray showed clear lung fields. Serum electrolytes, blood urea nitrogen and creatinine were normal. The serum ALT level was 33 IU/l, AST level was 32 IU/l, ALP level was 234 IU/l, GGT level was 39 IU/l and CRP level was 9.36 mg/l. Urinalysis was within normal limits. CMV-IgM and CMV-IgG titres were not elevated. Upper gastrointestinal endoscopy revealed two mucosal ulcerations in the antrum while the patient was on proton pump inhibitor therapy.

Questions

What could be the aetiological factor for gastric ulcer in this patient?
What should be done for definite diagnosis?
What therapy would you initiate?
Answer to the quiz on the preceding page

Gastrointestinal CMV disease was diagnosed on the basis of CMV-DNA and histopathological examination of the gastric biopsy (Figures 1 and 2).

Comment

The aetiological factors for gastric ulcer in the post-transplantation period include excessive acid secretion due to operation stress, pre-transplant peptic ulcer disease, Helicobacter pylori (HP), gastrointestinal CMV disease and drugs [MPA/mycophenolate mofetil (MMF), corticosteroids and/or nonsteroidal anti-inflammatory drugs (NSAID)].

In the present case, the patient was on a proton pump inhibitor, omeprazole, with a dose of 20 mg/day. Chen et al. [1] suggested that the use of methylprednisolone pulse for acute rejection and a history of pre-transplant peptic ulcer were independent risk factors for post-transplant peptic ulcer disease. The history of pre-transplant peptic ulcer disease was not detected in our patient and previous gastroduodenoscopy was normal. There was no acute rejection episode and NSAID was not used in the post-transplant period. Teenan et al. [2] investigated the role of HP in renal transplant recipients and HP was identified in the gastric antrum of 48% of the patients and its positivity was strongly associated with symptomatic dyspepsia, with gastritis and with peptic ulceration. However, no evidence of HP was detected in our patient.

In our case, routine weekly whole blood polymerase chain reaction (PCR)-based CMV monitoring was performed and it was negative a week before admission to the hospital. On admission, CMV-DNA was checked again and it was found to be positive by PCR (Amplicor, CMM Roche, 3640 copy/ml). In addition, histological examination of gastric biopsy specimens revealed intranuclear CMV inclusion bodies (Figure 1). On the basis of these findings, gastrointestinal CMV disease was diagnosed. Intravenous ganciclovir 5 mg/kg/bid (Cymevene, F. Hoffman-La Roche, Switzerland) was started, and MPA dose was reduced to 720 mg/day. Intravenous immunoglobulin (0.5 g/kg total dose) was also given. The patient’s symptoms completely disappeared after 5 days of treatment. After 21 days of ganciclovir treatment, a second endoscopy was performed and the gastric ulcers were found to be healed completely. Also, CMV-DNA became negative and the patient was discharged with valganciclovir treatment (900 mg/day) for an additional month. Omeprazole was kept unchanged during this period.

In kidney allograft recipients, major risk factors for CMV disease are thymoglobulin or OKT3 induction and status of donor and recipient serology (D+,R−) [3]. Exposure to the virus, as indicated by the presence of detectable CMV IgG antibodies in the plasma, increases with age in the general population and is present in more than two-thirds of donors and recipients prior to transplantation [4]. CMV disease occurs most commonly when the donor is seropositive and the recipient is seronegative as was noted in our case. The incidence of infection is as high as 60–70% in D+,R− patients [5].

CMV is the most common viral gastrointestinal pathogen affecting organ transplant recipients [4]. The gastrointestinal tract is involved with CMV infection in 10–30% of patients [6]. It can cause oesophagitis, gastroenteritis, small bowel obstruction, colitis, proctitis, pancreatitis and haemorrhage. The severity of gastrointestinal CMV infection in transplant patients varies considerably from asymptomatic to lethal disease [5].

In gastrointestinal CMV disease, the main complaints are epigastric pain, nausea and vomiting. Ulcerations, erosions and mucosal haemorrhage are the primary macroscopic findings. In the diagnosis of gastrointestinal CMV infection, the detection of the virus in the mucosa is essential. Peter et al. [7] recommended qualitative PCR of biopsy material. They evaluated 200 solid organ transplant recipients with upper gastrointestinal symptoms. In that study, CMV infection was diagnosed in ~40% of the patients using PCR, whereas only approximately one-fifth
demonstrated typical histologic features of invasive CMV disease such as inclusion bodies. We showed CMV infection by immunohistochemical investigation. MMF therapy seems to increase the risk of tissue-invasive CMV infection. Kaplan et al. [8] showed that 90% of patients who presented with persistent epigastric pain during the first 6 months post-transplantation had evidence of CMV infection in either the gastric mucosa or small intestine. In their study, an MMF dose of >2 g/day almost reached statistical significance as a risk factor. They suggested that gastrointestinal CMV infection may be caused by a local effect of MMF on the gastrointestinal tract. It is possible that MMF may predispose activation of CMV infection in the upper gastrointestinal tract, by producing local inflammation along with its immunosuppressant activity. In another study, Meulen et al. [9] suggested that the use of MMF did not affect the severity of symptoms, frequency of tissue invasive disease, or frequency or duration of treatment with ganciclovir in the patients with CMV disease.

Although MPA and MMF have similar pharmacological activity, MPA has been suggested to have lower gastrointestinal side effects. However, there are conflicting results on that. In our case, the patient was on MPA 1440 mg/day and after the diagnosis of gastrointestinal CMV, the dose of MPA decreased to 720 mg/day. The tacrolimus (6 mg/day) and prednisolone (12 mg/day) doses were kept constant.

Treatment options for CMV infection are antiviral therapy and reduction of immunosuppression. Commonly used antiviral agents for CMV are ganciclovir and valganciclovir [10]. Hyperimmune CMV globulin cannot prevent CMV infection, but has been shown to decrease CMV disease significantly. Foscarnet, a competitive inhibitor of viral DNA polymerase, can be used in ganciclovir-resistant patients.

In conclusion, CMV disease may be presented in several clinical forms including gastrointestinal involvement. An unusual presentation can delay the diagnosis and beginning of therapy, requiring a high level of suspicion by physicians treating patients with renal transplants. Reduction of immunosuppression in combination with antiviral therapy is a preferable choice of treatment. In addition, hyperimmune CMV globulin can be given in selected patients.

Conflict of interest statement. None declared.

References


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