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Case Report

Small bowel transplantation complicated by cytomegalovirus tissue invasive disease without viremia

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ABSTRACT

We report on a small bowel transplant patient, donor/recipient seropositive (D+/R+) for cytomegalovirus (CMV), with a clinical course complicated by CMV disease. Anti-CMV prophylaxis was given for 100 days. Immunosuppression consisted of alemtuzumab, tacrolimus, mycophenolate mofetil and prednisolone. Five months posttransplant, CMV tissue invasive disease of the upper gastrointestinal tract was evident without the presence of viremia, tested by quantitative polymerase chain reaction (PCR). Complete viral load suppression was achieved with intravenous ganciclovir, followed by valganciclovir for secondary prophylaxis. Mycophenolate mofetil and prednisolone were discontinued. Shortly thereafter the patient presented with recurrent CMV and candida esophagitis. While on ganciclovir and caspofungin, the patient developed CMV tissue invasive disease of the ileal graft, with persistent absence of viremia. Foscarnet and CMV immunoglobulin were added. Viral load declined to undetectable levels; however, clinical improvement did not occur due to occurrence of graft rejection. Despite infliximab and high dose prednisolone, graft rejection was progressive, requiring surgical explantation of the graft. This case highlights the importance of additional diagnostic tools such as endoscopy including PCR analysis of tissue samples. Extension of primary antiviral prophylaxis interval up to 6 months and prolonged retreatment for recurrent CMV disease may be useful to avoid severe CMV-related complications.

1. Case importance

Cytomegalovirus (CMV) remains one of the most common pathogens affecting recipients of solid organ transplants [1–3]. Despite improved measures regarding monitoring, prophylaxis and treatment, CMV continues to adversely impact graft function and survival [1,4,5], particularly in those patients with a seropositive donor/seronegative recipient (D+/R−) constellation [6]. Although anti-CMV prophylaxis has been proven to be effective in reducing the incidence for CMV while on antiviral coverage, concerns have been raised about late onset disease, which occurs after discontinuation of prophylaxis [1,4]. Emphasis has therefore been put on prolonging posttransplant antiviral prophylaxis for high-risk patients [7].

Apart from the D/R serostatus, the type of allograft is an important factor when assessing the risk for CMV. For instance, recipients of intestinal transplants are at particular risk for developing CMV disease [8]. Consequently, postprophylaxis preemptive strategies have been recommended to identify patients with high risk for late onset CMV disease [7]. Preemptive therapy is used on patients with viremia, on the assumed basis that viremia is a reliable predictor for subsequent organ involvement. However, tissue invasive disease might as well occur in the absence of viremia, requiring tissue analysis for diagnosis. Monitoring with blood based CMV assays, as used for preemptive measures, may therefore easily miss the diagnosis.

2. Case description

We present a case of a 52-year-old female small bowel transplant recipient. Transplantation was performed in November 2011 due to short bowel syndrome. The recipient had an intermediate

Abbreviations: CMV, cytomegalovirus; CMVIG, anti-CMV immunoglobulin; d, day(s); DNA, deoxyribonucleic acid; D+/R+, seropositive donor/seropositive recipient; D+/R−, seropositive donor/seronegative recipient; i.v., intravenous; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; WHO, World Health Organization.

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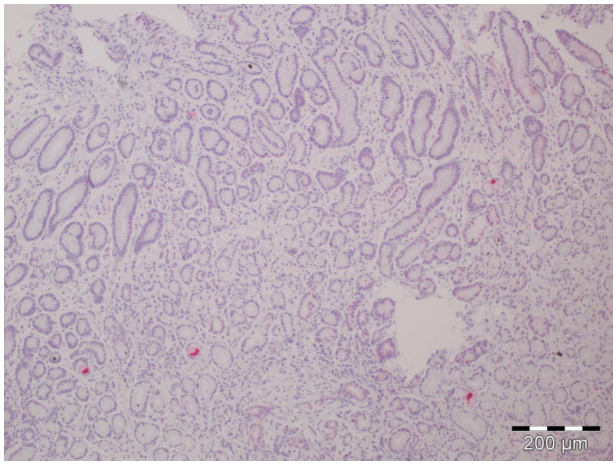

Fig. 1. Histopathological analysis of a gastric biopsy specimen. Hematoxylin-eosin staining (original magnification, 10×) reveals inclusion bodies consistent with tissue invasive cytomegalovirus disease of the stomach.

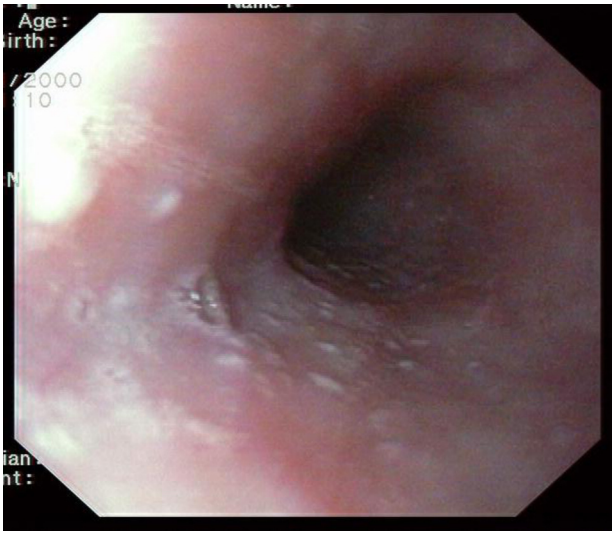

Fig. 2. Candida and cytomegalovirus (CMV) esophagitis. Inflamed esophageal mucosa with whitish plaques typical for candida. Suspected concurrent CMV infection was confirmed by polymerase chain reaction of biopsy specimens.

risk profile as both, donor and recipient were seropositive (D+/R+) for CMV, and posttransplant antiviral prophylaxis was performed with intravenous (i.v.) ganciclovir (5 mg/kg/day [d]), followed by valganciclovir (900 mg/d) for a total of 100 d. Immunosuppression consisted of alemtuzumab (30 mg, d 0 and 1), tacrolimus (initial target trough level 8–10 and 6–7 ng/μL thereafter), mycophenolate mofetil (MMF, 2000 mg/d) and prednisolone (started at 1000 mg intraoperatively, tapered down to a maintenance dose of 5 mg/d). Frequently performed serum-based CMV polymerase chain reaction (PCR) assays during and after antiviral prophylaxis remained negative. Overall, the initial clinical course was uneventful. However, in May 2012 the patient presented with odynophagia and emesis. Endoscopy revealed ulcerative esophagitis and gastritis. Immunohistochemistry of biopsy specimens showed inclusion bodies typical for CMV (Fig. 1). Tissue samples were positive for CMV-deoxyribonucleic acid (DNA), analyzed by quantitative real time PCR using COBAS® AmpliPrep/COBAS® TaqMan® System (Roche Molecular Systems, Pleasanton, CA, USA) and COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (Roche Diagnostics, Branchburg, NJ, USA; lower limit for quantification: 682.5 IU/mL, reference: 1st WHO standard). Serum samples were negative for CMV-DNA (Versant® kPCR Molecular System and RealStar® CMV PCR Kit 1.2, both Altona Diagnostics GmbH, Hamburg, Germany, reference: 1st WHO standard, lower limit for quantification: 200 IU/mL).

Antiviral therapy was initiated with i.v. ganciclovir without any changes in immunosuppressive therapy. However, upon further increase of tissue viral load, immunosuppression was reduced by discontinuing MMF and prednisolone. Furthermore, anti-CMV immunoglobulin (CMVIG, Cytotect®, Biotest) 2 × 50 IU/kg was given 1 week apart.

Several weeks of treatment resulted in endoscopically evident improvement. Tissue viral load declined to undetectable levels and valganciclovir (900 mg daily) was continued for secondary prophylaxis. However, 3 weeks later, candida and recurrent CMV esophagitis (Fig. 2) was evident still without viremia, and ganciclovir and caspofungin were started. Again, improvement was seen within a few weeks by follow-up endoscopies and declining CMV-DNA levels in tissue biopsies taken from esophagus. During the following course, while still on ganciclovir, the patient developed fever and diarrhea. Repeatedly taken blood, urine and stool cultures were negative for bacterial and fungal pathogens. Symptoms were consistent with CMV tissue invasive disease of the ileal graft, established by endoscopy (Fig. 3A–C) and detection of CMV-DNA in tissue samples with persistent absence of viremia. Immunosuppression was switched to combine low dose tacrolimus (target trough level 3–4 ng/μL) and everolimus (target trough level 2–3 ng/μL). Antiviral coverage was extended with high dose CMVIG (100 IU/kg/d for 1 week), and foscarnet (180 mg/kg/d) was added for suspected UL97 kinase mutation. Under this regimen tissue viral load declined to undetectable levels, confirmed by two negative PCR assays on samples taken 2 weeks apart. A mutation-mediated drug resistance was ruled out by genetic analysis. The patient continued to experience abdominal pain and diarrhea with endoscopy revealing scarring inflammation of the graft. Symptoms were consistent with histologically confirmed graft rejection (Fig. 4) which persisted despite treatment with high dose steroids (prednisolone 250 mg/d for 3 d). Although therapy was escalated with intravenous infliximab (5 mg/kg once) [9], graft rejection was progressive, requiring surgical graft explantation in November 2012. In December, the patient was discharged from hospital in a stable condition requiring parenteral nutrition. Valganciclovir was given as secondary CMV-prophylaxis for a total of 6 months. The patient continues to be regularly followed at our clinic and is listed for retransplantation. At the last follow-up visit in November 2013, she remained free of CMV-infection. Given the unfortunate clinical course with a CMV-positive donor, a seronegative allograft is considered for retransplantation.

3. Other similar and contrasting cases in the literature

To date, the scientific literature addressing clinically significant CMV disease in intestinal transplant recipients is scarce. In a recent report by Bachmann et al. [10] a small intestine transplant recipient with high-risk profile (CMV D+/R−) developed a primary CMV infection despite receiving valganciclovir prophylaxis. Viral genome sequencing revealed a strain variant with the UL97 mutation N510S which however confers no significant ganciclovir resistance [11]. Switching of antiviral treatment to i.v. administration of ganciclovir successfully eliminated CMV viremia in this case. One can only speculate that altered absorption of orally ingested drugs in the presence of intestinal allograft might have played a role (Fig. 5).