Abstract

We observed a patient with de novo acute Crohn’s disease in the setting of very late cytomegalovirus activation in the blood and in the colon, 40 years after kidney transplantation, which has not been reported to date. Antiviral therapy associated with everolimus was effective without major adverse events. It remains unclear if cytomegalovirus infection was the trigger or the consequence of acute inflammatory bowel disease post-transplantation.

ABBREVIATIONS

CMV: Cytomegalovirus; IBD: Inflammatory Bowel Disease; MMF: Mycophenolate Mofetil; mTOR: Mammalian Target of Rapamycin; PCR: Polymerase Chain Reaction

INTRODUCTION

Cytomegalovirus (CMV) infection usually occurs during the first year post solid organ transplantation [1]. In transplanted patients, CMV effects include direct effects as tissue-invasive disease (colitis, gastritis, pneumonitis, retinitis, etc) and/or indirect effects with long term and potentially severe consequences. Indeed, CMV has been associated with decreased graft survival, increased recipient morbidity and mortality, cardiovascular events, new-onset diabetes mellitus and post-transplantation lymphoproliferative disorders [2,3].

Inflammatory bowel diseases (IBD) are chronic diseases of the digestive tract characterized by inflammation of the intestinal mucosa. The pathogenesis of IBD includes genetic, immunologic and microbiologic factors. They lead to an unbalanced inflammatory response against commensal gut flora [4]. Common treatments are 5-aminosalicylate and corticosteroids, and in severe or refractory forms immunosuppressive drugs (cyclosporine, azathioprine) or immunomodulatory drugs (infliximab) are used. IBD may occur after solid organ transplantation and be classified as de novo disease or as exacerbation of a pre-existing disease. CMV infection of the intestine has been associated with severe steroid resistant forms of IBD.

We observed a patient with de novo acute Crohn’s disease in the setting of very late CMV activation (40 years after kidney transplantation). It remains unclear if CMV infection was the trigger or the consequence of acute inflammatory bowel disease post-transplantation.

CASE PRESENTATION

A 64-year-old woman developed renal insufficiency in 1969 due to membranoproliferative glomerulonephritis. She required dialysis and was finally transplanted in 1971. The initial immunosuppression regimen consisted in lymphocyte-depleting polyclonal antibodies, azathioprine and high doses of corticosteroids. Azathioprine was replaced by 1 g per day
mycophenolate mofetil (MMF) in 1997 because of chronic gout treated with allopurinol. Corticosteroids were lowered and stopped in 2005 because of severe osteoporosis.

The patient developed chronic diarrhea in May 2012 (5 stools/24 hours) with weight loss of 4 kg (8lbs) and an anal fistula. She was admitted in the renal transplantation department. Video capsule endoscopy did not show any abnormalities of the small intestine. Microbiological tests were all negative, including PCR tests for adenovirus, rotavirus, norovirus, Clostridium difficile culture, standard stool culture and intestinal parasites. Whole blood CMV DNAemia analysis became positive (6400 copies IU/mL) at the same time, whereas it had been negative (She received three months of valganciclovir post-transplantation because of the risk of CMV reactivation: CMV IgG were positive prior to transplantation but negative in the donor). Coloscopy showed pancolitis and proctitis with ulcerations. Magnetic resonance imaging and CT scan indicated Crohn’s disease. Histology showed ulcerations and cellular infiltration dominated by neutrophils. Moreover, owl eye intranuclear inclusions suggested CMV infection (Figure 1a) subsequently confirmed by immunohistochemistry (figure 1B). Serum creatinine was 120 µmol/L, CRP: 12 mg/L, leucocytes: 4.8 G/L (4-10).

The patent was initially treated with antiviral therapy (intravenous ganciclovir 200mg/day 10 days followed by oral valganciclovir 2x450mg/day for 3 weeks), providing transitory improvement of symptoms and negative CMV DNAemia.

CMV DNAemia became positive again in May 2013 (1600 copies/mL) and colonoscopy showed persisting lesions of CMV-related ulcerative colitis and a severe persisting anal fistula associated with chronic diarrhea. At that time, she was still treated only by MMF (1g/day). We changed the immunosuppressive treatment by replacing MMF with everolimus (mammalian target of rapamycin inhibitor) at a dose of 0.5mg x 2 per day combined with antiviral therapy (intravenous ganciclovir 230mg/day three days followed by oral valganciclovir 2x450mg/day for 3 weeks). After one week she has improved clinically and magnetic resonance imaging two months later showed radiologic improvement. CMV DNAemia became negative after two weeks. In July 2014, she was well without antiviral treatment (serum creatinine: 150 µmol/L).

DISCUSSION

We report a case of acute IBD associated with a first CMV reactivation, 40 years after renal transplantation. Most cases of CMV infection/disease occur during the first year following SOT. Late CMV disease (beyond one year) is rare (4%) [1] and very few cases of late-onset CMV infection have been reported more than 10 years after transplantation. A decrease in CMV-specific CD8+ T-cells was described in these cases [5]. The patient had a risk of CMV reactivation because she was infected prior to transplantation. She received CMV prophylaxis by valganciclovir during 3 months post-transplantation. CMV reactivation occurred even tough corticosteroids were stopped during the follow-up.

CMV has been reported to be associated with IBD. It is therefore unclear if CMV is a trigger for acute intestinal inflammation or only a nonpathogenic bystander. In one study, the prevalence of CMV on colon biopsy in active IBD was 10% in 129 immunocompetent patients [6]. Moreover CMV infection has been reported to be associated with more frequent and severe exacerbation of ulcerative colitis [7]. In liver graft recipients, CMV infection was shown to be associated with the development of IBD [8]. CMV infected mice had increased risk of colitis after exposure to Dextran Sulfate Sodium [9]. The authors suggested that CMV increases gut permeability, making mice more susceptible to colitis. In addition CMV may sustain inflammation and digestive lesions through different mechanisms such as up-regulation of TNF-α, prostaglandin E2 and leukotriene B4 [10].

The treatment of IBD associated with CMV infection in organ graft recipients includes two options: antiviral therapy and/or modification of the immunosuppressive therapy. Remission of acute IBD was reported to increase to 80% if antiviral treatment (i.v. ganciclovir or oral valganciclovir) was given in steroid-refractory ulcerative colitis with colonic CMV infection [7].

Initially antiviral therapy was started, but because of persisting infection, we replaced MMF by an mTOR inhibitor. mTOR inhibitors have been associated with a lower incidence of CMV infection in kidney transplantation regardless of the CMV serostatus of the donor and/or the recipient [11]. mTOR inhibitors may inhibit viral protein synthesis and viral DNA without lowering the degree of immunosuppression compared to MMF. Level of CMV-specific CD8+ T-cells has been reported higher after 6 and 24 months post transplantation in patients treated with everolimus compared to MMF [12]. Thus, if everolimus is not recommended to treat Crohn’s disease, it may be an interesting alternative in case of CMV associated with acute IBD.

In summary, CMV infections in recipients are very uncommon after the first year post transplant. To our knowledge, we report the first case of acute IBD associated with very late CMV infection forty years after kidney transplantation. This case highlights the importance of the detection of CMV in mucosal biopsy specimens from the colon by immunohistochemistry and/or PCR in case of IBD, whatever the time post-transplant. Antiviral therapy may be needed, combined with modification of immunosuppressive regimen to obtain clinical remission. mTOR inhibitors may be particularly useful to break the vicious circle between CMV and IBD.
ACKNOWLEDGMENT

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

REFERENCES


