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Case Report

Colectomy for Refractory Cytomegalovirus Colitis Post-allogeneic Transplantation

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Abstract

Cytomegalovirus (CMV) reactivations are frequent complications after allogeneic haematopoietic cell transplantation. In the current era of pre-emptive antiviral therapy and prophylaxis, late-onset CMV disease, in particular CMV colitis, is emerging and many transplant recipients have multiple risk factors for resistant or refractory CMV disease. Despite the current availability of potent (but toxic) antiviral agents, such as (val)ganciclovir, foscarnet and cidofovir, and the expected arrival of antivirals with different mechanisms of action (letermovir and maribavir) and non-overlapping toxicities, a subset of high-risk patients will remain refractory to all these treatments options, especially in the absence of CMV-specific immunotherapy. Herein we present a case of complicated multi-drug refractory CMV colitis in a haplo-identical allo-HCT recipient with concomitant intestinal GvHD that was successfully treated with total colectomy.

Keywords: Cytomegalovirus; Allogeneic; Hematopoietic cell transplantation colitis; Refractory; Colectomy

Abbreviations: Allo-HCT: Allogeneic haematopoietic cell transplantation; ANC: Absolute neutrophil count; Bid: Twice daily; CMV: Cytomegalovirus; GI: Gastrointestinal; GvHD: Graft-versus-host-disease; IU/mL: International units per millilitre; OD: Once daily; G-CSF: Granulocyte colony stimulating factor; PCR: Polymerase chain reaction; Tid: Thrice daily; TNF: Tumor necrosis factor; µL: Microliter.

Introduction

Cytomegalovirus (CMV) is highly prevalent in the general population where it establishes latency after primo infection. In immunocompromised hosts, such as allogeneic haematopoietic cell transplant (allo-HCT) recipients, reactivation of the latent virus is estimated to occur in 60-70% of CMV-seropositive recipients, especially when receiving a graft from a CMV-seronegative donor [1]. If not adequately treated, such reactivation (or infection) may lead to CMV end-organ disease which conveys a high burden of morbidity and mortality. Historically about 10-40% of allo-HCT recipients developed CMV disease (usually interstitial pneumonia) which carried a high mortality rate [2]. More recently, in the era of pre-emptive antiviral treatment, the gastrointestinal (GI) tract has become the most commonly involved end-organ [3].

The incidence of early-onset CMV disease has gradually decreased over the last decades as a result of pre-emptive strategies i.e. based on regular real-time quantitative polymerase chain reaction (PCR) screening on whole blood, serum or plasma and starting antiviral treatment when the viral load exceeds an institutional-determined threshold. However late-onset CMV disease (i.e. after the first 100 days after allo-HCT) is on the rise [1,3]. Persistent profound lymphocytopenia and specifically low CD4 T-lymphocyte counts (<50/µL) at 3 months after allo-HCT have been identified as major risk factors for these late-onset CMV manifestations [1,2].

Since the introduction of ganciclovir in the 1980's, foscarnet and cidofovir in the 1990's and the oral prodrug valganciclovir in the 2000's, clinicians have access to potent CMV-specific antivirals. However, each agent comes with its specific toxicity profile, including myelotoxicity and renal injury. Ganciclovir (or

valganciclovir) and foscarnet are drugs of choice for the primary treatment. Current guidelines for second-line therapy suggest switching to the alternative of the drug that was used in first-line [2]. Granulocyte colony-stimulating-factor (G-CSF) can be added in order to prolong therapy in case of ganciclovir-induced neutropenia. Cidofovir is only recommended as third line option because of its considerable nephrotoxic potential. In addition, it is advised to reduce the dose of immunosuppressants whenever possible [1,2].

A subset of CMV infections and/or diseases responds sub optimally to antiviral treatment and is considered treatment-refractory. This clinical definition comprises cases of both drug-resistant CMV (based on the genotypic detection of mutations known to confer resistance to antiviral agents) and other mechanisms of refractoriness based on inadequate host response and/or drug delivery [1,2,4]. While genotypic resistance occurs only in a minority of refractory cases in allo-HCT recipients, clinical refractoriness is much more prevalent and host as well as viral risk factors have been well-identified [4-6]. Refractory and/or resistant CMV disease is clearly associated with a worse overall survival and treatment options are limited due to the limited number of available antiviral drugs, drug-associated serious toxicities and possible cross-resistance [3-6]. Herein we present a case of biopsy-proven early-onset CMV colitis that was refractory to the available antiviral therapies. Total colectomy was seen as the only available alternative which proved to be successful.

Case report

In September 2018, a 59-year old CMV-seropositive Caucasian man with acute undifferentiated leukaemia in first complete remission underwent an allo-HCT from a CMV-seronegative haplo-identical donor. The conditioning regimen consisted of fludarabine (150 mg/m²), cyclophosphamide (29 mg/kg) and oral busulfan (8 mg/kg), followed by post-transplant cyclophosphamide (100 mg/kg). Graft-versus-host disease (GvHD) prophylaxis included mycophenolate mofetil (till day +35) and tacrolimus. Intravenous acyclovir (5mg/kg tid) was given to prevent herpes simplex virus reactivation until the time of engraftment. On day +28, because of asymptomatic confirmed blood CMV PCR positivity, therapy with oral valganciclovir (900 mg bid) was started pre-emptively at a CMV viral load of 6 123 IU/mL (Figure 1). On day +44 the patient was diagnosed with stage 2 acute GvHD of the skin (MAGIC grade I) for which oral methylprednisolone (0.25 mg/kg od) was started. Valganciclovir was stopped on day +55 after obtaining two consecutive negative blood PCR results. On day +70 the patient presented with high-volume diarrhoea, abdominal pain and anorexia. A computed tomography (CT) scan of the abdomen showed pronounced thickening of the entire colonic wall, most notably of the ascending and transverse colon; endoscopic examination revealed numerous rectal ulcers with patchy areas of seemingly normal mucosa. Histopathology of sigmoid tissue showed extensive crypt destruction and ulceration of the mucosa with a remarkable number of apoptotic cell bodies in the remaining viable crypts, compatible with grade 2 acute intestinal GvHD. A diagnosis of biopsy-proven MAGIC grade IV acute GvHD (stage 4 lower gastrointestinal involvement) was made for which treatment with high-dose intravenous methylprednisolone (2 mg/kg daily) was started. One week later, on day +77, CMV PCR screening on blood became strongly positive (19496 IU/mL); pre-emptive therapy with intravenous ganciclovir (5 mg/kg bid) was initiated. On day +83, the results of immunohistochemistry (IHC) on the colonic tissue specimens showed multifocal positivity for CMV (Figure 2) suggesting concurrent intestinal CMV disease and acute GvHD. Five days later after tapering of daily methylprednisolone dose (1 mg/kg), the patient developed more abdominal complaints with signs of peritoneal tenderness on clinical examination. A repeat abdominal CT scan showed manifest worsening when compared to the baseline CT scan and because of a suspicion of flare-up of the acute GvHD, the daily methylprednisolone dose was again increased (2mg/kg). A repeat endoscopy on day +91 revealed an increased number of ulcers with no remaining areas of normal mucosa. Histopathological examination again showed extensive crypt destruction and ulceration of the colonic mucosa. Moreover there were no clear signs of apoptosis in the remaining viable crypts yet numerous atypical monocytoid cells were noted in the stroma, suspect for CMV virocytes. Four days later IHC confirmed the abundant presence of CMV inclusions in the aforementioned monocytoid cells. Because the colitis was presumed to be predominantly caused by CMV, methylprednisolone was tapered and ganciclovir was continued at the standard dose, although the blood PCR had become negative by day +95. Ganciclovir was stopped on day +119 because viral inclusions were no longer detected on repeat biopsy specimens of the colon.

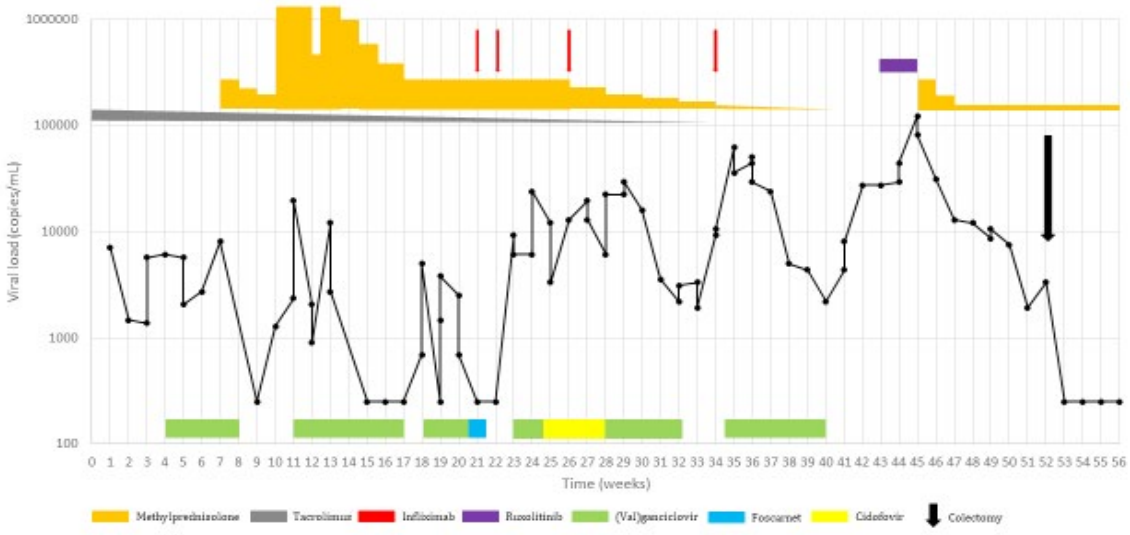

Figure 1: Schematic representation of our case in time. Horizontal axis: time after HCT in weeks. Vertical axis: CMV viral load (copies/mL). The black dots represent measurements of the viral load by quantitative real-time PCR. The black line is constructed by linear interpolation between sequential measurements.

The arrows and boxes represent treatments. Each type of treatment is represented by another color: orange: methylprednisolone; grey: tacrolimus; red (arrows): infliximab; purple: ruxolitinib; green: (val) ganciclovir; blue: foscarnet; yellow: cidofovir; black (arrow): colectomy. The dimensions of the boxes are approximations for illustrative purposes only. The relative width is an approximation of the time of exposure to each treatment. The relative height of the boxes is not proportional to the dose except for methylprednisolone and tacrolimus. The arrows represent the time of single administrations of a particular treatments.

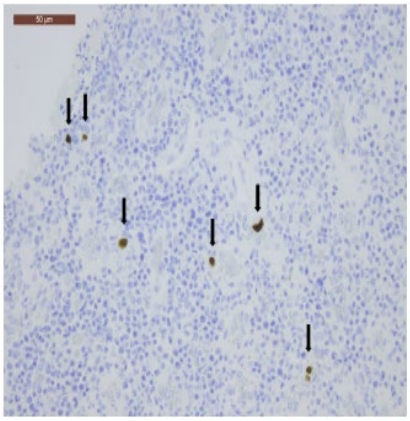

Figure 2: Histological findings. Specimen from the sigmoid colon after colectomy: immunohistochemistry reveals numerous CMV positive stromal cells (arrows) in the granulation tissue (IHC CMV, OM x200).

However, diarrhoea continued and because blood CMV PCR turned positive again on day +123 (692 IU/mL), endoscopy was repeated. Despite obvious endoscopic improvement with only a few remaining colonic ulcers to see, IHC on colonic tissue specimens again showed the presence of CMV inclusions. Intravenous ganciclovir was reinstalled on day +126 in combination with anti-CMV-polyclonal immunoglobulins. An additional whole body ^{18}FDG-PET-CT scan showed persistent colonic wall thickening on CT with scintigraphically intense uptake of ^{18}FDG in the transverse and descending colon in the ascending colon as well as moderate uptake

in the recto sigmoid colon. On day +141, endoscopy showed an normal ileum but signs of severe inflammation throughout the whole length of the colon. While on day +144 blood CMV PCR was negative, histopathology of biopsies sampled at different colonic levels showed extensive crypt destruction and ulceration of the colon mucosa with presence of viral inclusions yet without clear signs of apoptosis in the remaining viable crypts. Genotyping on tissue specimen identified the CMV as wild type; no resistance mutations against reference anti-CMV drugs were detected. Hence, we concluded that the patient was suffering from clinically resistant or refractory CMV colitis. On day +144, second-line therapy with intravenous foscarnet (60mg/kg tid) was started. However, since the patient's abdominal condition deteriorated rapidly with biochemical evidence of severe inflammation it was decided to start anti-TNF-therapy (infliximab) following multidisciplinary consultation. Both the diarrhoea and abdominal tenderness improved significantly so the colitis was considered responsive to infliximab. Foscarnet was discontinued after one week due to acute kidney injury; CMV PCR however had become negative. One week later, intravenous ganciclovir was restarted following a new CMV reactivation on blood (9215 IU/mL). A few days later, adenovirus was also detected on stool samples and treatment was switched to cidofovir (5 mg/kg weekly). On day +195, after having received three weekly administrations of cidofovir, the patient presented with fever, abdominal tenderness, and severe colitis on abdominal CT scan. Treatment with meropenem was started empirically and later switched to vancomycin when *Enterococcus faecium* bacteraemia was documented. Intravenous ganciclovir was added for a suspected flare of CMV colitis given the blood CMV PCR of 6123 IU/mL. The patient developed a second episode of bacteraemia with *Bacteroides thetaiotamicron*, necessitating another switch of the antibiotic therapy to amoxicillin/clavulanic acid. On day +227 ganciclovir was stopped because of severe neutropenia (ANC <500/µL) with a blood CMV PCR level of 3317 IU/mL; G-CSF treatment was started. On day +242 intravenous ganciclovir was restarted (with G-CSF support) when the volume of diarrhoea increased and blood CMV PCR level rose by more than 1 $\log_{10}$ to 62073 IU/mL. Following two more episodes of bacterial blood stream infections *(Parabacteroides distasonis* and *Escherichia coli*, respectively*)* and in light of persistent symptoms of diarrhoea*,* a repeat intestinal endoscopy of was done on day +302, showing extensive ulceration and inflammation of the colon wall with no remaining patches of normal mucosa yet with the remarkable presence of pseudomembranes. The latter finding could be explained the following day when the diagnosis of *Clostridium difficile* associated diarrhoea was confirmed. Fresh intestinal tissue biopsies showed a limited number of apoptotic bodies in several tubular glands, compatible with histopathological GvHD grade 1 which prompted the initiation of the JAK2 inhibitor ruxolitinib (5mg bid) on day +303. On day +306 the abundant presence of numerous CMV viral inclusions was yet again confirmed by IHC. After two weeks ruxolitinib was switched to methylprednisolone since the patient failed to improve. Blood CMV PCR rose to its highest level on day +312 (peak level of 122675/mL) after which methylprednisolone was quickly tapered. Another multidisciplinary consultation was held with both the gastroenterology and abdominal surgery department. In view of the clinical evolution and the evidence provided by repeated scans, endoscopies and histopathological examinations we concluded that the patient was suffering from a severe ulcerative colitis that was most likely attributable to persistent CMV disease and proven to be refractory to all medical treatment available at that time. On day +367 the patient underwent a total colectomy with retention of the anal sphincter muscles and rectum and placement of an end ileostomy. Histopathological examination of the resected colon confirmed the diagnosis of active CMV colitis. Already two days later blood CMV PCR was negative and remained so for the following 6 months. Opioid analgesics were quickly tapered off to stop and the patient was discharged 19 days after surgery. More than 2 years after transplantation he is followed up in the outpatient clinic. His general condition remains well without the need for immunosuppressive therapy.

Discussion

To the best of our knowledge, we present the first case of radical colectomy to control a case of refractory biopsy-proven CMV colitis post allo-HCT. Our CMV-seropositive patient presented with multiple host-related risk factors for refractory CMV disease, including haplo-identical transplantation with a CMV-seronegative donor, delayed immune reconstitution, prolonged and repeated exposure to anti-CMV drugs, recurrent CMV reactivations and active GvHD.[4-6] The link between acute intestinal GvHD and CMV GI disease has been clearly established: retrospective data indicate that CMV GI disease is found in some 10-25% of histologically proven acute intestinal GvHD cases either as a simultaneous event or a sequential diagnosis separated only by a narrow time window. Indeed, CMV disease typically presents after exposure to high-dose corticosteroids as first-line treatment for the earlier presenting GvHD. Given the considerable overlap of both clinical and endoscopic features between CMV colitis and acute intestinal GvHD, distinguishing between them is especially challenging without histopathological examination. Swift and repeated endoscopy with tissue sampling is absolutely mandatory for confirmation of a clinical diagnosis [7,8].

Treatment options for patients not responding to first (ganciclovir), second (foscarnet), and even third-line (cidofovir) therapies are extremely limited. Combining antivirals usually results in unacceptable toxicity and the concomitant use of regular or even CMV-specific immunoglobulins has never proven to be of any benefit outside the setting of CMV pneumonia. Leflunomide and artesunate have *in-vitro* activity against CMV

but should never be used as monotherapy; evidence for their efficacy is insufficient and limited to some reported cases [1,2]. Although the viral terminase inhibitor letermovir has recently been approved for prevention of CMV infection and disease in CMV-seropositive recipients, its activity in settings of high viral load (such as CMV disease) appears to be limited by the rapid development of resistance [9]. Maribavir, which is an orally available benzimidazole that blocks nuclear egress of viral capsids through the inhibition of protein kinase UL97, seems to be very promising in a phase II and III study in resistant/refractory cases. The drug is active in vitro against CMV strains that are resistant to ganciclovir, foscarnet, or cidofovir and has a favourable safety profile, without associated myelosuppression or nephrotoxicity [10,11]. However, maribavir was not available at the time for our patient. Admittedly, there is a growing body of evidence for the use of immunotherapy specifically targeting CMV virus, most importantly by transferring CMV-specific T cells that are derived from the (CMV-seropositive) stem cell donor, or from a third party donor [11]. Unfortunately these techniques are not widely available and should still be considered investigational.

Hence, given the lack of alternative treatment options, the frequent exacerbations of diarrhoea (whether or not by GvHD) as well as the persistence of CMV viral inclusions on repeated colonic biopsies, we decided to present the patient for total colectomy. Moreover the frequent occurrence of bloodstream infections with intestinal flora convinced us that the persistent and active colitis would remain an uncontrollable source of bacterial translocation leading to potentially life-threatening bloodstream infections as well as frequent and prolonged hospital admissions. Although not previously reported in allo-HCT recipients, colectomy is an established treatment option for refractory CMV disease in the setting of ulcerative colitis [12,13].

In conclusion, we report on a case of complicated multi-drug refractory CMV colitis in an allo-HCT recipient with concomitant intestinal GvHD that was successfully treated with total colectomy.

Conflict of Interest

Arnout van Besien: Nothing to declare.

Johan Maertens has received lecture fees from MSD and Shire/Takeda and has participated in advisory boards of MSD and Shire/Takeda.

Mariëlle Beckers has received lecture fees from Novartis and BMS/Celgene and has participated in advisory boards of BMS/Celgene.

Hélène Schoemans has received financial compensation for advisory boards (Incyte, Janssen, and Novartis), speaker's fees (Novartis, Incyte, Jazz Pharmaceuticals, and Takeda), travel grants (AbbVie, Celgene, Gilead, and Incyte) and research funding (Novartis).

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