IDCases 29 (2022) e01608

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Intrathecal cytomegalovirus immunoglobulin for CMV encephalitis post allogeneic stem cell transplantation

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ARTICLE INFO

Keywords:
Cytomegalovirus
Allogeneic hematopoietic stem cell transplantation
Encephalitis

ABSTRACT

We report the outcome of a 43 year old man who developed fatal ventriculoencephalitis due to cytomegalovirus (CMV) infection 7 months post allogeneic stem cell transplant. He failed multiple lines of treatment, including intravenous ganciclovir, foscarnet, and CMV-specific immunoglobulins, without improvement in CSF CMV copies. Novel intrathecal administration of CMV immunoglobulins was given but did not lead to clearance of CMV from CSF. No adverse effects related to intrathecal CMV immunoglobulins were observed. Notably, throughout this period, CMV in blood remained undetectable. This case highlights the difficulty in treating CMV encephalitis, and that novel therapeutic approaches are needed.

Introduction

Cytomegalovirus (CMV) is a potential infectious complication in allogeneic hematopoietic stem cell recipients (alloHSCT). Prevention of CMV disease in high-risk alloHSCT recipients includes the use of a prophylaxis agent such as letermovir [1] or a pre-emptive treatment strategy. However, late-onset CMV disease can occur in these patients after the completion of prophylaxis. Cytomegalovirus encephalitis is a rare presentation of CMV disease that has a high mortality [2,3], and as such novel antiviral strategies may be required. One therapeutic strategy proposed has been the intrathecal administration of high-titer CMV immunoglobulin [4]. We report a patient with cytomegalovirus encephalitis with high CSF CMV titer and low peripheral blood CMV titer; treated with intrathecal (IT) CMV specific immunoglobulin (Cytogam).

Case presentation

A 43-year-old-man with acute myeloid leukemia (AML) received a 9/10 mismatched (DQB1) unrelated peripheral stem cell transplant (4.31 $\times 10^6$ CD34 cells/kg) in May 2020 with myeloablative conditioning consisting of renal-function adjusted fludarabine (30 mg/m^2 x 3 Ds) and total body irradiation (200 cGy BID x 6 days). Graft versus host disease (GVHD) prophylaxis comprised thymoglobulin (total dose of 2 mg/kg), post-transplant cyclophosphamide (50 mg/kg x 2 days), and cyclosporine. The recipient was CMV seropositive, while the donor was CMV seronegative. He received Letermovir as CMV prophylaxis from day (D) + 20 until D+ 102.

On D+ 83 post-transplant, he was diagnosed with grade 2 graft versus host disease (GVHD) involving the duodenum and treated successfully with budesonide continuous release formulation and cyclosporine. On D+ 115 he received a single dose of rituximab for EBV viremia (1.22 $\times 10^6$ IU/mL) as per institutional policy. He experienced CMV reactivation on D+ 121 (2120 copies/mL of plasma) and D+ 172 (2210 copies/mL of plasma), measured using CMV quantitative polymerase chain reaction (Roche cobas® CMV quantitative nucleic acid test for use on the cobas® 6800, Roche Molecular Diagnostics, Laval, QC, Canada). Both incidences were treated successfully with valganciclovir.

On D+ 150 the patient experienced transient neurological symptoms with nystagmus, blurred vision and dizziness; brain MRI suggested two small lesions in the right cerebellum, the appearances of which were non-specific in nature. Lumbar puncture (LP) on + 151 no evidence of infection or disease relapse. Subsequent MRI on Day + 189 showed

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https://doi.org/10.1016/j.idcr.2022.e01608
Received 25 July 2022; Received in revised form 17 August 2022; Accepted 17 August 2022
Available online 19 August 2022

interval increase in the size of the central right cerebellar lesion with similar signal changes in the midbrain/ medial thalami and right parietal white matter which were concerning for central nervous system relapse of AML; however, bone marrow examination showed complete remission on D+ 199.

At this time, he experienced intermittent right temporal headache and minimal right ptosis. Further brain imaging was performed with similar results, though concern remained for possible relapse or possible viral infection.

Repeat LP on D+ 230 detected CMV 6.8×10^6 copies/mL (altona Cytomegalovirus PCR Kit v1.0, altona Diagnostics, Hamburg, Germany) in the cerebrospinal fluid (CSF), and the patient was admitted to hospital for treatment of CMV encephalitis with ganciclovir 5 mg/kg twice daily, subsequently increased to 7.5 mg/kg twice daily. Repeat CSF CMV PCR on D+ 242 showed 3.02×10^5 copies/mL, a 1 log reduction. Due to the myelosuppressive effects of ganciclovir, he briefly received foscarnet 180 mg/kg, but this was discontinued due to lung and renal toxicity, and ganciclovir was resumed on D+ 258. By D+ 306, CSF CMV PCR showed 3.24×10^3 copies/mL. Ganciclovir was briefly withheld due to acute kidney injury, and the patient was admitted to the intensive care unit for respiratory distress. Ganciclovir resumed on D+ 323, and unfortunately, CMV in CSF had increased to 1.56×10^4 copies/mL. CSF CMV resistance testing confirmed *UL54* DNA polymerase antiviral sensitivity. Subsequent CSF CMV PCR showed no decrease in copy numbers despite continued ganciclovir treatment (renally dose adjusted). Following infectious diseases specialist recommendation, novel intrathecal (IT) CMV immunoglobulin therapy using Cytogam® 0.25 g on D+ 350 was given, followed by IT Cytogam® 0.5 g on D+ 357 and D+ 364. The patient tolerated the treatment well, and no adverse effects were observed. The patient also received immunoglobulins on D+ 365. However, CMV CSF copy numbers did not improve and by D+ 364, CMV CSF increased to 5.05×10^4. The treatment was deemed ineffective and IT Cytogam® was abandoned. Ganciclovir was discontinued and by D+ 382, CSF CMV increased to 5.05×10^4. Throughout this period, from D+ 230 until D+ 382, CMV PCR in the patient's blood was checked at least once weekly and remained negative (Fig. 1).

Unfortunately, the patient experienced many complications throughout the hospitalization, including respiratory distress, BK-virus associated hemorrhagic cystitis, acute kidney Injury, ongoing pancytopenia and significant anasarca. The patient eventually succumbed to his infection and other complications on D+ 426.

Discussion

Although our patient unfortunately demised from CMV encephalitis, this case raised several important issues of interest to the allogeneic stem cell transplant community. To our knowledge, this is the first reported case of IT Cytogam® given for CMV encephalitis in alloHSCT recipients. The treatment was considered safe, although ultimately was not effective. Potential reasons for this include uncertainty regarding dosing. Fujiwara and colleagues [4] demonstrated clearance of CMV in CSF after 3 doses of IT high-titer CMV immunoglobulin; however, they used a

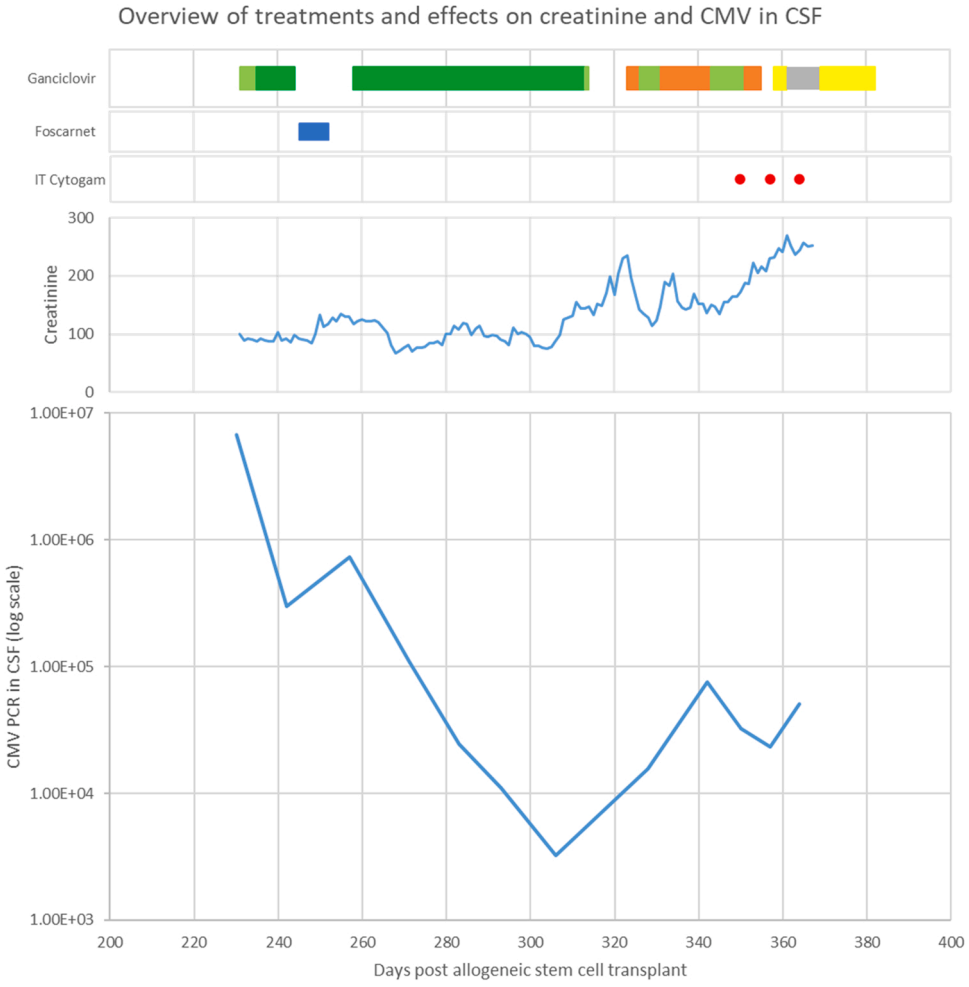

Fig. 1. Patient clinical course while being treated for CMV in CSF. A) Medications used to treat CMV in CSF, which included ganciclovir, foscarnet, and IT Cytogam. The color of ganciclovir corresponds to the dose: light green (10 mg/kg/day), dark green (15 mg/kg/day), orange (5 mg/kg/day), yellow (2.5 mg/kg/day), and gray (1.25 mg/kg/day). B) The patient's serum creatinine (μmol/L), which worsened with continued antiviral treatment. C) CMV PCR of CSF (in copies/mL).

different product and gave concomitant foscarnet and ganciclovir. Our patient experienced recurrent renal injury and concurrent treatment with foscarnet would have led to unacceptable renal toxicity, whereas ganciclovir administration was hampered by pancytopenia.

Importantly, neither AML relapse nor CMV encephalitis have been pathologically proven; however, subtle and fluctuating neurological deficits, abnormal brain MRI findings and high levels of CMV viral load in the CSF and were strongly suggestive of CMV encephalitis. Since CSF cytology revealed no evidence of malignant cells, these data support the diagnosis of CMV encephalitis, not of AML relapse. Proper evaluation of the CSF is therefore strongly warranted in alloHSCT with neurological symptoms in the context of ongoing or recent CMV viremia.

In our patient, a high viral load was detected in the CSF, while the peripheral blood viral load was low or negative. This was similarly reported [5] in CSF of a patient with acquired immunodeficiency syndrome and ventriculoencephalitis, where a very high viral load in CSF ($>10^6$ copies/mL) compared with a modest viral load in peripheral blood. A further patient with CMV ventriculoencephalitis experienced a similar disconnect between very high CSF CMV copies and modest levels in blood [6]. Thus, negative blood PCR for CMV DNA should not be considered to exclude CMV replication elsewhere.

An important issue raised by the treatment of the CMV ventriculoencephalitis is the therapeutic failure of ganciclovir despite UL54 sensitivity due to potentially inadequate CSF drug concentrations [5]. Ganciclovir CSF penetration has been reported to be 24–67% [7], whereas foscarnet is reported to have somewhat better CSF penetration of 54–80%; however, it is associated with high inter-individual variability [8].

A review of the literature has revealed that CMV encephalitis in alloHSCT recipients has a high mortality [2], with 10 of a series of 11 patients ultimately demising. This high mortality is likely related to the same factors contributing to the development of the disease—impaired T-cell immunity, high rate of viral replication, relatively low penetration of antiviral drugs into the CNS and antiviral resistance [2]. Initial testing indicated that the CMV contained in the CNS was sensitive to conventional drug therapy; it has been previously reported that CMV may compartmentalize and 'sub-clones' may acquire drug resistance [6], potentially detectable only by deep sequencing.

There is limited information in the medical literature regarding the use of intrathecal immunoglobulin. It is reported that $< 0.002\%$ of a blood dose of intravenous immunoglobulin reaches the hippocampus in murine models [9], and thus a correspondingly limited amount of CMV immunoglobulin would be expected to penetrate the CNS. The use of CMV immunoglobulin intrathecally has been successfully reported previously. A patient who developed CMV meningitis after HSCT and was treated with the combination therapy of intrathecal high-titer CMV immunoglobulin and antiviral drugs. He was diagnosed with CMV meningitis based on pleocytosis and CMV DNA in the cerebrospinal fluid (CSF). Intravenous ganciclovir, foscarnet, and immunoglobulin were administered; however, CMV DNA in the CSF was continuously detected. The addition of intrathecal high-titer CMV immunoglobulin resulted in CMV DNA in the CSF becoming undetectable [4]. It is suggested that high-titer CMV immunoglobulin administered intrathecally may neutralize cell-free CMV and inhibit cell-to-cell virus spread [4]. In addition, clinical immunoglobulin administration guidelines suggest that intrathecal delivery of immunoglobulin may produce more durable responses in cases of viral meningoencephalitis [10]. In contrast to the published report, our patient did not survive owing to the complications of his treatment, and CMV DNA could be persistently detected in the CSF.

Recent novel therapeutics have investigated the use of focused ultrasound to disrupt the blood-brain barrier (BBB) to improve permeability and delivery of therapeutic agents. MR-guided focused ultrasound combined with intravenously injected microbubbles has previously been shown to safely open up the BBB [11]. More recently, this novel technology has been used successfully in humans [12], as well as the effective delivery of an IVIG dose through the BBB to the CNS in a murine model [9]. Future advances and wider adoption of MR-guided focused ultrasound could potentially add another therapeutic option for the treatment of CMV encephalitis.

What may be a potential game-changer is the use of adoptive therapies. A Chinese group has reported the successful treatment of CNS CMV infection through the intrathecal administration of adoptive CMV specific T lymphocytes, which may be a promising avenue for treatment of patients with refractory CMV encephalitis [13].

In conclusion, CMV encephalitis is a rare and fatal complication of alloHSCT with suboptimal treatment options due to toxicity from ganciclovir and foscarnet. We report that the administration of IT Cytogam® to alloHSCT recipients appears to be safe and a potential option for these patients, but clearly further studies are required to determine optimal dosing strategies.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Ian Pang: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Sanjay Singhabahu**: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Igor Novitzky-Basso**: Visualization, Writing – original draft, Writing – review & editing. **Tony Mazzuli**: Writing – review & editing. **Shahid Husain**: Writing – review & editing. **Jonas Mattsson**: Supervision, Writing – review & editing.

Conflict of interest

The authors declare that they have no conflict of interest. A summary of relevant information will be published with the manuscript.

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