Antiviral Therapy Defiant Polyviral Retinitis Post Hematopoietic Allogeneic Stem Cell Transplant

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Abstract

Cytomegalovirus (CMV) retinitis is an uncommon presentation post allogeneic transplant and can be vision-threatening. This case demonstrates the occurrence of mixed viral retinitis (CMV and varicella zoster virus) post allogeneic stem cell transplant despite multiple prophylactic antiviral therapies, and features CMV retinitis in the absence of CMV DNAemia.

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ABSTRACT

Background: Cytomegalovirus (CMV) retinitis is an uncommon presentation post allogeneic transplant and can be vision-threatening. Our case demonstrates the occurrence of polymerase chain reaction proven mixed viral retinitis (cytomegalovirus and varicella zoster virus) post allogeneic stem cell transplant despite multiple prophylactic antiviral therapies, and features CMV retinitis in the absence of CMV DNAemia. This case highlights the emerging challenge of late CMV disease occurring during secondary prophylaxis with Letermovir.

Case presentation: A 21-year-old female with acute myeloid leukemia presented with mixed viral retinitis (cytomegalovirus and varicella zoster virus) post allogenic transplant. This presentation occurred despite ongoing prophylaxis for both of these viruses, as well as following two courses of treatment for CMV viremia, with a documented negative CMV PCR in the blood prior to the presentation with retinitis. The patient was treated with intravenous Ganciclovir and subsequently transitioned to oral Valganciclovir with resolution of the retinitis.

Conclusions: We report a rare case of polyviral retinitis in a post-allogeneic stem cell transplant patient, with polymerase chain reaction of the aqueous fluid demonstrating two viral populations. With very little existing literature on either mixed viral retinitis or CMV retinitis during Letermovir prophylaxis, this case expands the literature on both topics.

BACKGROUND

Cytomegalovirus virus (CMV) infection predominantly affects immunocompromised individuals.[1] CMV infection can lead to CMV disease and has been associated with non-relapse mortality following allogeneic hematopoietic stem cell transplant.[2] CMV disease post allogeneic transplant commonly affects the lungs or gastrointestinal tract.[1,2] CMV retinitis remains an uncommon presentation post allogeneic transplant and can be vision-threatening.[3-6] Implementation of prophylaxis and preemptive strategies have reduced the incidence of CMV disease to 10% in the first year post allogeneic transplant.[2,7]Our case demonstrates the occurrence of polymerase chain reaction (PCR) proven mixed viral retinitis (CMV and varicella zoster virus VZV) post allogeneic stem cell transplant despite multiple prophylactic antiviral therapies, and features CMV retinitis in the absence of CMV DNAemia. This case also highlights the emerging challenge of late CMV disease occurring during secondary prophylaxis with Letermovir. To our knowledge this represents the first reported case of polyviral retinitis in this clinical context.

CASE REPORT

We report the case of a previously healthy 21-year-old female diagnosed with acute myeloid leukemia (AML) February 2020 after presenting with a two week history of shortness of breath, decreased exercise tolerance, and lightheadedness. Her karyotyping results confirmed complex cytogenetics, with monosomy X and double minute chromosomes indicating MYC locus. With regards to her molecular studies, she had undetectable FLT3 and NPM1 mutation, undetectable RUNX1, undetectable CBF/MYH11, undetectable BCR-ABL, and undetectable PML-RARA. Next generation sequencing (NGS) did not demonstrate any clinically significant variants. Her baseline viral serologies demonstrated that she was nonreactive for Hepatitis B, Hepatitis C, and HIV.

The patient was started on induction therapy with 3 + 7 Daunorubicin and Cytarabine on February 22, 2020, with a view to proceed with a stem cell transplant consolidation after achieving remission. Her post-induction course was complicated by culture-negative febrile neutropenia and a right middle lobe pneumonia for which she was treated with Piperacillin-Tazobactam, and subsequently stepped down to Ciprofloxacin and Amoxicillin-Clavulin once she clinically improved. She remained on prophylaxis with Acyclovir and Fluconazole during this time period. Following induction chemotherapy, she was treated with high dose Cytarabine for consolidation therapy starting March 31, 2020, as a bridge to stem cell transplant.

Pre-transplant screening revealed CMV IgG positive, CMV IgM negative, Varicella Zoster Virus (VZV) IgG positive, and Herpes Simplex Virus (HSV) indeterminate.

She subsequently underwent an allogeneic unrelated donor mismatched 8/10 myeloablative stem cell transplant, day zero was July 10, 2020. There was minor ABO incompatibility, with the donor O positive and recipient B positive. The donor was CMV seronegative. A hybrid conditioning regimen was used due to the 8/10 mismatch from an unrelated donor, with Fludarabine/Busulfan 4 (Flu/Bu 4) plus antithymocyte globulin (ATG), with post-transplant cyclophosphamide, and omission of methotrexate. Post-transplant, on July 28, she was found to have early CMV reactivation, with a serum CMV level of 10,980 units per mL plasma (4.04 log units per mL plasma). She was leukopenic at that time, with a recovered neutrophil count of 0.7. She was started on intravenous (IV) Ganciclovir 5mg/kg twice daily. Unfortunately, following three weeks of treatment with Ganciclovir, the patient's CMV level remained elevated, with a level of 91,025 units per mL plasma (4.96 log units per mL plasma) on week 2 of treatment, and a level of 14,520 units per mL of plasma on week 3 (4.16 log units per mL plasma). At that time, Ganciclovir was discontinued, and she was initiated on Foscarnet 90 mg/kg twice daily on August 28. Resistance testing was performed and did not demonstrate any evidence of resistance to Ganciclovir or Foscarnet. Following treatment with Foscarnet, her CMV PCR became negative on September 14. She was subsequently started on Letermovir 240 mg daily as secondary prophylaxis. Throughout this period of time she also remained on oral prophylaxis with Acyclovir 800 mg bid, Fluconazole 400 mg daily, and Septra double strength 1 tablet on Monday, Wednesday, and Friday.

Unfortunately, on September 21, follow up CMV PCR was positive, with 3.75 log units per mL plasma, and at that time, a decision was made to resume Foscarnet, with an induction dose for three weeks, and then subsequently a maintenance dose initiated, which she completed on November 3.

At the time of her third CMV reactivation episode on September 21, she also had evidence of reactivation of EBV for the first time and was treated for this with a dose of rituximab on September 24, with subsequent negative EBV levels.

While on treatment with Foscarnet, she developed mild graft versus host disease of the gut, with apoptotic bodies demonstrated on endoscopy biopsy. This was treated conservatively with Budesonide 1 mg oral three times per day and Beclomethasone 3 mg oral four times per day which were gradually weaned with resolution of her symptoms. On November 3, following her completion of Foscarnet, repeat CMV testing was negative. EBV testing was also negative at that time. The patient was restarted on Letermovir and continued on her other prophylactic agents (Acyclovir, Septra and Fluconazole).

In late November 2020, the patient experienced new onset blurry vision in the right eye. She was assessed by Ophthalmology with clinical findings demonstrating stellate keratic precipitates, peripheral retinal vascular sheathing and active unilateral hemorrhagic retinitis in two separate foci in a vascular distribution. One area of retinitis was encroaching on the macula and threatening vision. In the clinical context a working diagnosis of viral retinitis was suspected, further supported by subsequent ocular coherence (OCT) and fundus fluorescein angiography (Image 1). An urgent anterior chamber paracentesis was performed and sent for HSV, VZV and CMV PCR testing followed by an intravitreal injection of Ganciclovir 2 mg. PCR of the aqueous humour confirmed the presence of both CMV and VZV. Serum CMV PCR performed at that time was negative. She completed two weeks of intravenous Ganciclovir induction therapy (5mg/kg), then extended one additional week at maintenance dosing but unfortunately still had some mild retinitis activity. She was then transitioned to oral Valganciclovir therapy (900 mg twice daily). The retinitis resolved fully showing excellent clinical response after the 3rd week of Valganciclovir dosing and no further evidence of active viral retinitis as of her last examination of Mar 10, 2021. Repeat serum CMV PCR performed March 2021 remained negative.

DISCUSSION:

We report a rare case of polyviral retinitis in a post-allogeneic stem cell transplant patient, with PCR of the aqueous fluid demonstrating two viral populations, CMV and VZV, which occurred despite ongoing prophylaxis for these two viruses, and despite completing two courses of treatment for CMV viremia, with a documented negative CMV PCR in the blood prior to the presentation with retinitis. CMV sensitivity testing

performed indicated sensitivity to both agents used for previous treatment (Ganciclovir and Foscarnet)[8]. As the CMV serum PCR was undetectable at the time of the presentation with CMV retinitis, it is unlikely that this presentation was driven by resistance to treatment. Presentation of CMV retinitis was likely multifactorial driven by early CMV reactivation, low CD4 counts and delayed CD4 lymphocyte recovery in the first 100 days post-transplant which are all associated with late CMV disease. Other potential contributing factors are poor CNS and poor retinal penetration of Letermovir. With very little existing literature on either mixed viral retinitis or CMV retinitis during Letermovir prophylaxis[9], this case serves to expand the literature on both topics. The case also highlights the need to expand efficacy data on secondary prophylaxis with Letermovir to address an unmet therapeutic need. To our knowledge this represents the first documented case of mixed viral retinitis in this therapeutic context.

Figure 1:

Fundus image right eye showing hemorrhagic retinitis and retinal vasculitis, more prominent inferotemporally in the distribution of the inferotemporal vascular arcade vessels with an additional more subtle area of involvement superonasally. Areas of retinal whitening (white arrows), hemorrhage (red arrows) and retinal vascular sheathing (yellow arrows) indicative of vasculitis could be discerned by clinical examination

Declarations:

Ethics Approval: Not applicable

Consent: Consent for the publication of this case report has been provided by the patient.

Conflict of Interest Statement: All authors declare no conflicts of interest.

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