Bispecific antibody therapy-associated opportunistic infections: cytomegalovirus retinitis and chronic salmonellosis in a non-HIV patient

Cytomegalovirus (CMV) retinitis is a vision-threatening disease associated with HIV infection and is rarely encountered in patients without HIV infection. Here, we present the first reported case of bilateral CMV retinitis and chronic salmonellosis in association with the use of elranatamab (Pfizer, Incorporated, New York), a bispecific T-cell engager antibody. This manuscript was written in accordance with the ethical norms in place at our institution and jurisdiction and the patient has signed an informed consent agreeing to the publication of the manuscript and image.

An 80-year-old female was diagnosed with monoclonal immunoglobulin (Ig) λ multiple myeloma, revised International Staging System (R-ISS) stage II 18 years previously. Her previous medical history was notable for stage I lobular carcinoma of the breast in 2009 treated with a modified radical mastectomy, sentinel lymph node biopsy, and no adjuvant chemotherapy. She has remained in remission on tamoxifen until present. The patient was also maintained on entecavir due to chronic, suppressed hepatitis B infection and underwent surgical resections of a thyroglossal duct cyst and a thyroid nodule 40 years previously. Multiple myeloma presented with back pain. Magnetic resonance imaging showed multi-level spine involvement and a para-vertebral mass at T7. The bone marrow assessment showed 80% involvement with λ-restricted plasmocytes. The patient had a IgG λ monoclonal para-proteinemia of 27 g/L and no high-risk cytogenetics findings with a *CCND1*-IGH rearrangement and trisomy 11. Albumin and β-2 microgobulin were 18 g/L and 20 g/L respectively. By current standard, the patient had an R-ISS stage II disease at presentation. From April 2007 to December 2015, she was treated with BiRD (clarithromycin/biaxin, revlimid and dexamethasone) after two debulking cycles of high-dose dexamethasone. She was subsequently treated with carfilzomib, pomalidomid, and dexamethasone until March 2016, when she developed congestive heart failure. The patient was then switched to daratumumab, pomalidomide, and dexamethasone. Ixazomib was added to this regimen in November 2017. In August 2018, the regimen was changed again to toIxazomib, venetoclax and dexamethasone to achieve control of the para-proteinemia. When she was diagnosed with hypogammaglobulinemia in 2019, the patient started monthly subcutaneous injections of intravenous IgG (IVIG) dosed according to her monthly IgG levels. Venetoclax was stopped due to severe diarrhea and ixazomib was discontinued when the patient developed progressive disease.

In 2023, the patient started elranatamab, a bispecific T-cell engager (BiTE) antibody that targets CD3 on T cells, binding them to the B-cell maturation antigen (BCMA) to induce T-cell mediated myeloma cell killing. Within 1 month, the patient's appetite deteriorated, she developed grade 2 fatigue and palmar desquamation. Two months after starting treatment, the patient developed CMV viremia of 6,195 IU/mL (3.79 $\log^{10}$ IU/mL), which was suppressed within a month of starting valgancyclovir and continued to be monitored regularly. Three months after starting elranatamab, the patient developed severe, watery diarrhea and was diagnosed with salmonellosis by positive *Salmonella nontyphi* polymerase chain reaction (PCR) stool testing. She received 7 days of ciprofloxacin but her diarrhea persisted for 6 months. Her elranatanab was stopped after 3 months of therapy due to her significant weakness and weight loss. At month 5, the patient fell and sustained a subdural hemorrhage.

At month 9, the patient developed bilateral visual loss that progressed rapidly over 3 weeks to the point where she could no longer read or see faces clearly. A dilated fundus examination showed vitritis and confluent areas of retinal necrosis and hemorrhage along the major retinal vascular arcades, right eye more diffusely involved than the left (Figure 1A, B). Serum CMV PCR was positive with a quantitative CMV DNA load of 71.90 IU/mL (1.86 $\log^{10}$ IU/mL) and CMV was detected by PCR from aqueous humor sampling. HIV and *Toxoplasma gondii* IgM and IgG antibodies were negative, no monoclonal proteins were identified on immunofixation and serum electrophoresis and serum protein levels were normal. The absolute neutrophil count was 0.66 cells/L, and IgG level was 6.2 g/L, just under the cutoff of 700 putting her in the category of mild hypogammaglobulinemia despite on-going IVIG therapy. There was no CD4 count available at diagnosis but 1 month later, her CD4 was 155 cells/μL, CD8 was 437 cells/μL, and CD4:CD8 ratio was 0.36. The patient was treated with intravenous ganciclovir followed by oral valganciclovir dosed for renal failure and intravitreal foscarnet injections, which continued until vision stabilized and then improved. Subsequently, the patient was hospitalized twice, once for bacterial pneumonia and then for Coronavirus 2299E pneumonitis. One year after cessation of elranatamab, the patient's eyesight remained stable, she did not develop any new infections, her weight returned to baseline, and she reconstituted her CD4 counts to 694 cells/μL.

CMV retinitis is most commonly observed in patients with HIV and severely impaired cellular immune responses. Despite underlying dysregulation in cellular immune re-

sponse in multiple myeloma, CMV retinitis is not known to complicate myeloma. Most reported cases of CMV retinitis in non-HIV affected patients were observed in the context of systemic immunosuppression or even local, intravitreal steroid injections.[1] CMV retinitis is prominently associated with leukemia, lymphoma, solid organ or hematopoietic stem cell transplantation, and, occasionally, systemic lupus erythematosus.[1-3] A review of 15 patients with non-HIV associated CMV retinitis included patients with immunocompromising conditions on immunosuppressant chemotherapies, including one patient who received a BiTE antibody, teclistamab, for relapsed multiple myeloma.[3] CMV retinitis is commonly seen in patients with HIV when the CD4 count falls below 50 cells/μL. However, the CD4 count in patients without HIV with CMV retinitis are not particularly low suggesting that there is more than simply CD4 cells preventing CMV-associated disease in the eye.[2,3] There has been one report of CMV retinitis following anti-B cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell therapy.[4] No cases of CMV end-organ injury like retinitis or opportunistic *Salmonella nontyphi* infection have been reported so far to our knowledge.[5]

Multiple myeloma is primarily a disorder of humoral immune response. Myeloma patients are at an increased risk of infections due to disease-related reduction in polyclonal immunoglobulins and disruption of cellular immune response mediated by T cells.[6] T-cell-mediated immune responses mounted through $CD4^+$ T cells, $CD8^+$ T cells, and NK cells[7] are essential for the immune response to CMV in immunocompetent hosts. In multiple myeloma, the plasma cell expresses BCMA. The BiTE antibodies, like elranatamab, cause T-cell activation by simultaneous binding to CD3 on T cells and BCMA on myeloma cells which, in turn, activates cell death signaling pathways in the plasma cells.[8] They can have on-target/off tumor effect on the normal plasma cells causing their destruction which can contribute to the inherent humoral immunosuppression.

There is a growing concern about T-cell exhaustion associated with BiTE agents which, in the case of BCMA-targeting agents, seems to carry increased infectious risk relative to CAR T cells[9,10] although the exact mechanisms need further exploration. In our case, the $CD4^+$ T-cell count was low during BiTE treatment and normalized after cessation of therapy suggesting that elranatamab, and possibly prior myeloma therapy, did not irreversibly compromise the T-cell compartment. Severe immune deficiency manifesting as multiple opportunistic infections including CMV retinitis and chronic salmonellosis, as in our case, underscores these concerns. Further, the targeting of BCMA specifically may lead to high infectious risk, through, as of yet, poorly understood effects of the immune system since BCMA is expressed on multiple types of B-lineage lymphocytes[11-13] Infections have been noted to be the most common side effects associated with elranatamab (any grade 69.9% and grade 3-4 39.8%).[8] Seven instances of CMV reactivation

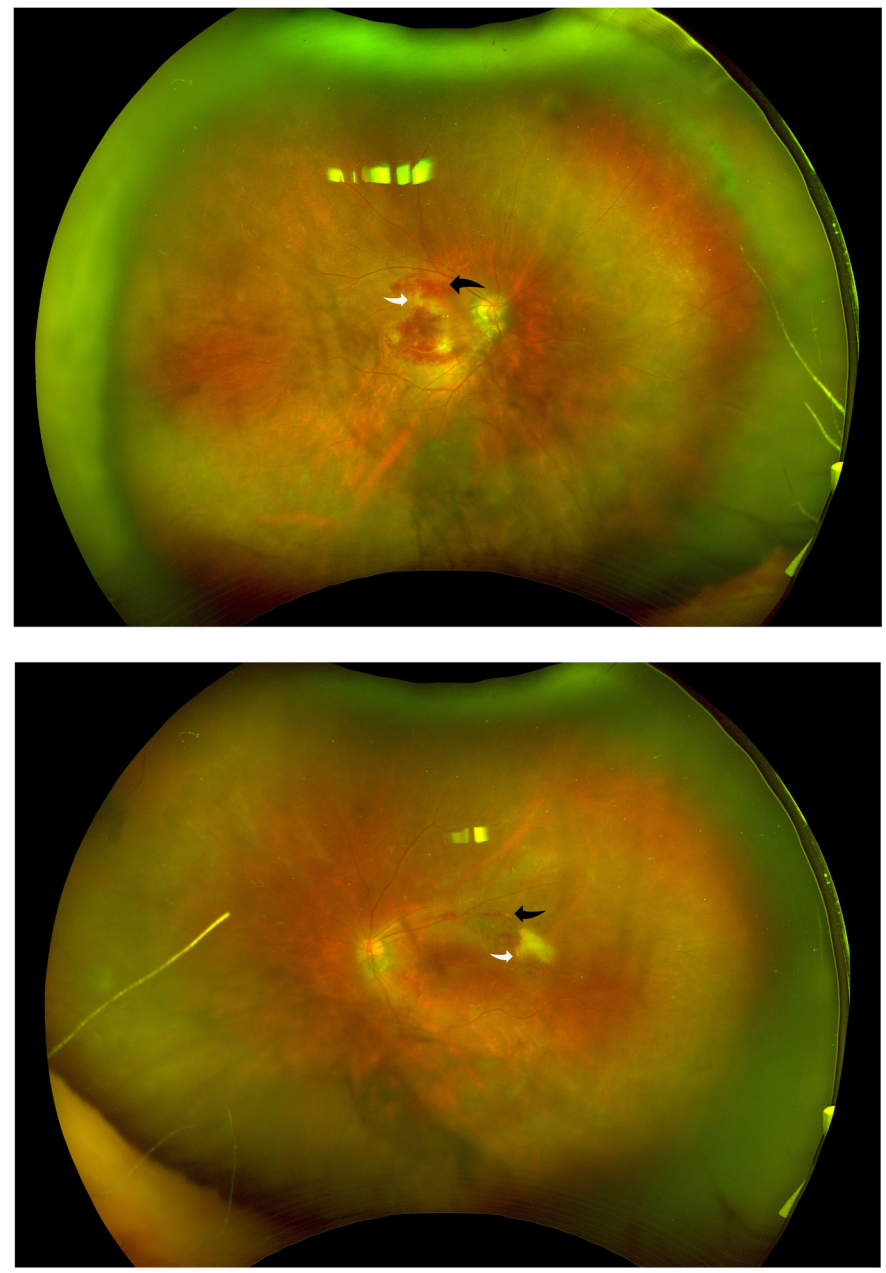

Figure 1. Fundus photos of both eyes that demonstrate vitritis, retinal necrosis, and retinal hemorrhages along the major retinal vascular arcades. White arrows point to retinal necrosis and black arrows point to retinal hemorrhage. (A) Right eye and (B) left eye.

(5.7%) and one instance of primary CMV infection (0.81%) were noted.[8] Accelerated approvals and single-arm studies can limit a comprehensive evaluation of the adverse effect profile of these novel therapies. The landmark trial, MagnetisMM,[8] reported adverse effects within 90 days of treatment cessation, whereas our patient experienced multiple infections during the 6 months after the cessation of therapy. This underscores the role of post-marketing vigilance.

Recently published expert guidance recommends monthly IVIG treatment for patients with IgG levels below 4 g/L, a history of two or more severe, encapsulated bacterial infections, a life-threatening infection or bacterial infection with poor response to antibiotic therapy.[14,15] Lancman *et al.* noted universal hypogammaglobulinemia after BCMA therapy in a series of 37 patients with high rates of infection despite IVIG therapy.[16] The infection risk continued even after achieving myeloma disease control with the median time to first grade 3-5 infection of 18.7 months post BCMA

therapy. IVIG should be continued throughout the duration of immunoparesis which is better monitored by rates of infection rather than relying solely on Ig levels since an individual's ability to mount antibodies can vary according to the pathogen.[15]

Despite the ongoing concerns about infections associated with T-cell depletion, formal guidance on the prevention, monitoring, and management of these infections is lacking on the drug label,[8] as well as, the implementation toolkit designed by the manufacturer,[9] which contributes to the oversight of serious infectious complications. As many as 15.4% of patients in one cohort had no detectable CMV in the blood prior to onset of visual symptoms,[3] making screening for CMV viremia insufficient to monitor for CMV retinitis. As demonstrated by our case, administration of IVIG and monitoring IG levels may also be insufficient for preventing CMV reactivation. Further study is necessary to better understand the immune defects generated by the new T-cell activating therapies, particularly BCMA-targeted agents in multi-treated myeloma patients to develop better screening protocols to prevent end-organ CMV reactivation and other opportunistic infections.

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Contributions

Study design, data collection, manuscript writing and editing by MRC-P. Manuscript writing by PS. Manuscript writing and editing by JSD. Data collection and manuscript editing by MS. Data collection by HR. Manuscript editing by JT. Study design, data collection, manuscript writing and editing by MK.

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