Probable Donor-Derived Cytomegalovirus Disease After Keratolimbal Allograft Transplantation

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Purpose: To report a case of probable donor-derived cytomegalovirus (CMV) infection after keratolimbal allograft (KLAL) transplantation.

Methods: Observational case report.

Results: A 41-year-old man with a history of aniridic keratopathy and limbal stem cell deficiency underwent KLAL in his right eye. Preoperatively, he was negative for CMV IgG and IgM. Postoperatively, he was maintained on tacrolimus and mycophenolate mofetil for systemic immunosuppression; he was also on prophylactic valganciclovir (for CMV) and trimethoprim/sulfamethoxazole (for pneumocystis pneumonia) for 1 month. Approximately 5 weeks postoperatively, he developed a nonproductive cough, rhinorrhea, and dyspnea. His condition did not improve with oral azithromycin or levofloxacin. He developed worsening symptoms over the next 2 weeks despite therapy. The serum CMV polymerase chain reaction was positive, and he was readministered valganciclovir with subsequent resolution of symptoms.

Conclusions: We present the first case of CMV disease in a seronegative patient who received a presumed CMV-seropositive donor KLAL. Similar to solid organ transplantation, prophylactic and therapeutic management of CMV infection is necessary in the setting of systemic immunosuppression.

Key Words: cytomegalovirus, keratolimbal allograft, limbal stem cell deficiency, systemic immunosuppression

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Cytomegalovirus (CMV) is a common herpesvirus infection that typically causes mild symptoms (if any) in the general population; however, the virus can potentially produce severe symptoms in immunocompromised patients.[1] Although it can be transmitted through saliva, urine, and most other bodily fluids of infected individuals, CMV can also be spread through infected organs and blood products. Lifetime CMV latent infection and IgG seropositivity are developed after a primary infection, followed by potential intermittent reactivation.[2] CMV seroprevalence for individuals aged above 60 years has been noted to be greater than 80%.[3]

CMV infection is one of the most common infections after solid organ transplantation, and it can lead to graft rejection and loss as well as cause patient morbidity and mortality.[4] CMV disease typically presents during the period of maximal immunosuppression between 6 weeks and 6 months posttransplantation and can vary from a mild viral syndrome to life-threatening multiorgan involvement (including pneumonitis, hepatitis, retinitis, and gastrointestinal disease).[5] The risk of transmission is highest in a seronegative patient who receives a transplant from a CMV-seropositive donor.[6]

The keratolimbal allograft (KLAL) is a type of ocular surface stem cell transplantation to treat eyes with limbal stem cell deficiency. Systemic immunosuppression (SI) is crucial to the success of KLAL in stabilizing the ocular surface.[7] We report the first case of CMV disease in a seronegative patient who likely received a CMV-seropositive donor KLAL.

CASE REPORT

A 41-year-old man with a history of congenital aniridia, bilateral aniridic keratopathy (stage IV), and resultant total limbal stem cell deficiency underwent unremarkable KLAL for his right eye. Preoperatively, his visual acuity was count fingers, and intraocular pressure was 19 mm Hg in the right eye. Two months before surgery, he was administered 2 mg tacrolimus twice daily (BID, lowered to 1 mg bid to achieve trough blood levels of 8–10 ng/mL) and 1000 mg mycophenolate mofetil bid to ensure that the SI was tolerated. Our ocular surface transplantation patients are comanaged with an organ transplant specialist with experience with these immunosuppression medications. Preoperative laboratory tests including complete blood count, basic metabolic panel, hepatic function panel, lipid panel (except for elevated triglycerides), urinalysis, hepatitis A, hepatitis B, hepatitis C, HIV-1/2, Epstein–Barr virus, and CMV (negative for IgG and IgM) were all unremarkable. His medical history was significant for pacemaker placement for atrioventricular block and well-controlled asthma. The patient also underwent preoperative evaluations by his internist and cardiologist. Details of the KLAL procedure have been described previously in detail.[8]

Postoperatively, he was maintained on 225 mg prophylactic valganciclovir daily (for CMV) and trimethoprim/sulfamethoxazole single-strength every Monday, Wednesday, and Friday (for pneumocystis pneumonia) for 1 month. His ocular surface fully reepithelialized within 3 weeks. Approximately 5 weeks postoperatively, he developed a nonproductive cough, rhinorrhea, dyspnea, and fever/

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chills. His condition did not improve with oral azithromycin and subsequent levofloxacin, each given for empirical treatment of community-acquired pneumonia (positive chest x-ray at an urgent care clinic), and he was admitted for worsening symptoms over the next 2 weeks despite therapy. On examination, he was afebrile, and his vital signs were stable; there was mild expiratory wheeze with an otherwise unremarkable physical examination. Workup including complete blood count, basic metabolic panel, arterial blood gas, lactate, coagulation studies, chest x-ray, chest computer tomography, respiratory viral panel, Streptococcus pneumoniae antigen (urine), legionella antigen (urine), urinalysis, serum galactomannan assay (aspergillus), serum beta-D glucan (Fungitell), fungal complement fixation serologies (aspergillus, blastomyces, coccidioides, and Histoplasma antibodies), and nondiagnostic cultures did not reveal any evidence of acute lung disease. Given the negative workup and positive response to symptomatic treatment, the patient was discharged. Approximately 1 week later, the serum CMV polymerase chain reaction was returned with a positive result (400 IU/mL), and he was readministered valganciclovir 900 mg bid. His mycophenolate mofetil was also decreased to 500 mg bid. The patient was evaluated by and followed by an infectious disease specialist. There was resolution of symptoms over the next couple of weeks, and his quantitative CMV polymerase chain reaction titer was 0 IU/mL after 3 weeks of treatment. Last examination 3 months after KLAL revealed 20/200 visual acuity with a stable ocular surface. The patient will remain on valganciclovir 900 mg bid for 6 months.

DISCUSSION

The majority of the literature about CMV infection in the setting of SI is derived from kidney and other solid organ transplant patients. CMV infection is one of the most common infections after solid organ transplantation.[4] The frequency of CMV infection after kidney transplant varies from 50% to 80% of recipients, whereas CMV disease (symptomatic, acute infection) is observed in 20% to 60%.[9] CMV-seronegative recipients receiving solid organ transplants from CMV-infected–seropositive donors are at the highest risk for CMV replication and disease.[10]

Our CMV-seronegative patient demonstrated an acute infection 5 weeks after KLAL. The eye bank was contacted to inquire about the CMV status of the donor. CMV is currently not tested for eye-only donors; there also was no stored donor blood or serum available (for our donor cornea or the mate cornea) for serology testing, as samples are discarded after 30 days. The donor was a 66-year-old woman with a history of coronary artery disease who died secondary to cardiogenic shock. Given that greater than 80% of individuals aged 60 and older are seropositive for CMV, it is highly probable that the KLAL donor was the source of CMV in the case of our patient.[3] Even if viral levels were low, it is possible that in an immunosuppressed patient this was a high enough threshold to lead to disease.

To our knowledge, this was our first patient who has acquired a symptomatic CMV infection of the 274 patients we have followed while on SI. This incidence is much lower than that seen in other solid organ transplantation patients. Similarly, a study by Holland et al[11] examining CMV infection transmission after corneal transplantation found the risk to be much lower than in solid organ transplantation procedures. In seronegative individuals receiving a corneal graft from a seropositive donor, over 90% remained seronegative, and none of these individuals who seroconverted (albeit none were immunosuppressed) were symptomatic.[11] Nafar et al[10] found that a higher immunosuppressive regimen was associated with a higher risk of CMV infection. The discrepancy in the frequency of CMV disease is possibly related to the fact that our patients are typically healthier than solid organ transplantation patients, and our SI regimen is less aggressive (eg, higher target trough levels of tacrolimus for kidney transplant patients). We are also able to taper off SI for some patients.

Patients at high risk for CMV infection benefit from prophylactic regimens, particularly ganciclovir. Nafar et al[12] demonstrated that oral ganciclovir for 12 weeks had the same outcome as intravenous ganciclovir with no serious side effects. Approximately 6 months before this case, our prophylaxis regimen (225 mg valganciclovir daily) for CMV was reduced from 12 to 4 weeks to balance both the protective effects and side-effect profile of valganciclovir. After this case, we have revised our CMV prophylaxis regimen. Valganciclovir treatment (450 mg daily) for CMV IgG-negative recipients is maintained for 6 months, as the donor is presumed to be CMV positive, given the high incidence of CMV seropositivity in the general population. For CMV IgG-positive recipients, valganciclovir treatment (450 mg Monday, Wednesday, and Friday) is maintained for 3 months.

When a surgeon identifies an adverse reaction, this is reported to the eye bank, allowing them to coordinate an investigation. Based on their findings, a level of imputability (ie, likelihood that a serious adverse reaction in a recipient can be attributed to the tissue applied) is assigned. The levels of imputability are designated (adapted from Vigilance and Surveillance of Substances of Human Origin): Not Assessable (insufficient data for imputability assessment); Excluded (conclusive evidence beyond reasonable doubt for attributing adverse reactions to alternative causes); Unlikely (evidence clearly in favor of attribution to alternative causes); Possible (evidence is indeterminate); Likely/Probable (evidence in favor of attribution to the tissue); and Definite/Certain (conclusive evidence beyond reasonable doubt for attribution to the tissues/cells) (Eye Bank Association of America [EBAA]. Guidance Document for Investigating and Reporting Adverse Reactions to the EBAA. June 2014. http://restoresight.org/wp-content/uploads/2014/06/MAB-Agenda-Book-as-June-10-2014.pdf, Accessed March 29, 2017.) This case would fall under the category of "Likely/Probable."

We present the first case of CMV disease in a seronegative patient who received a presumed CMV-seropositive donor KLAL. Similar to solid organ transplantation, prophylactic and therapeutic management of CMV infection is necessary in the setting of SI. Coordination of care with an organ transplant specialist to manage SI can provide ocular surface stability in patients with limbal stem cell deficiency with an acceptable complication profile, including opportunistic infections.

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