Epstein-Barr Virus-Related Bilateral Acute Retinal Necrosis in a Patient With X-linked Lymphoproliferative Disorder

X-linked lymphoproliferative disorder (XLPD) is a hereditary disease that stems from a deletion Xq 23-25 that negates the functions of an immune response to the Epstein-Barr virus (EBV). Males who inherit the mutation develop a spectrum of conditions that include fatal infectious mononucleosis, hypogammaglobulinemia, B-cell lymphomas in extranodal sites, and aplastic anemia after EBV infection. Although the virus has previously been implicated in chorioretinitis and retinal vasculitis in patients with infectious mononucleosis, to our knowledge there is only 1 report in the literature of retinal necrosis associated with XLPD. Herein we present the case of a 10-month-old boy with XLPD and pathologically confirmed retinal necrosis.

Report of a Case. A 10-month-old boy was referred for a dilated fundus examination prior to bone marrow transplantation for aplastic anemia secondary to XLPD. The patient’s serologic test results were positive for EBV, cytomegalovirus (CMV), and herpes simplex virus (HSV). He was able to fix and follow with the left eye, but the right eye did not appear to see. Examination of the anterior segment in the right eye revealed an afferent pupil defect, posterior synechiae, and ruberosis. The vitreous in the right eye was hazy owing to cellular infiltration. Funduscopy revealed widespread yellow-white retinal opacification and multiple retinal hemorrhages. A retinal detachment was present in the superior nasal quadrant. Left eye examination revealed 3 small vitreous fluff balls, pronounced white swelling and hemorrhaging of the optic nerve head, whitish infiltration of the retina (Figure 1) with retinal hemorrhages, and inflammatory sheathing of some retinal blood vessels. Numerous round and oval-shaped atrophic-appearing retinal pigment epithelial lesions measuring approximately 300 µm in diameter were scattered throughout the entire peripheral fundus (Figure 2). Some of these lesions coalesced into large geographic areas of atrophy.

The patient underwent a diagnostic 3-port pars plana vitrectomy and retinal biopsy in the blind right eye. Two 1 × 1-mm sections of retina with active-appearing infiltrates were excised from the nasal and superior quadrants. Vitreous samples were submitted for cultures, and the retinal specimens were submitted for cytology and in situ hybridization for CMV, EBV, HSV, and herpes zoster virus (HZV).

The retinal biopsy specimen showed linear sections of hemorrhagic and necrotic retinal tissue (Figure 3), with diffuse replacement of the photoreceptor layer by irregular layers of large multinucleated cells with enlarged nuclei. These hyperchromatic nuclei exhibited vesicular chromatin with prominent chromocenters, shallow indentations, and focal lobulation. The surrounding cytoplasm was sparse and synctial. A mixed population of T cells and B cells was demonstrated by immunohistochemical staining.

Figure 1. Fundus photograph of the left eye demonstrating whitish infiltration of the retina with retinal hemorrhages, and inflammatory sheathing of retinal blood vessels in a patient with Epstein-Barr virus-related acute retinal necrosis.
In situ hybridization studies of the retinal biopsy specimen were positive for EBV (Figure 4) but negative for CMV, HSV, and HZV. Cultures for bacteria, Toxoplasma, and fungi were negative in the vitreous specimens.

The patient underwent successful bone marrow transplantation. The inflammation eventually resolved in the right eye leaving behind extensive chorioretinal scarring that spared the macula. The right eye proceeded to phthisis bulbi.

Comment. Epstein-Barr virus is a lymphotrophic DNA virus of the herpesvirus family that replicates in epithelial cells and infects and transforms B lymphocytes, resulting in polyclonal B-cell activation.

Epstein-Barr virus can cause 2 types of cellular infections: (1) a productive replicative infection in which mature infectious virus particles are assembled and released, resulting in cell death or (2) a nonproductive infection in which the virus is incorporated into and replicates within the host DNA but remains in the latent state in transformed B cells. The virus stimulates polyclonal B-cell activation, and the action of the B lymphocytes is subdued by various host-defense mechanisms that include interferon, natural killer cells, cytotoxic T cells, neutralizing antibodies, and antibody-dependent cellular cytotoxicity.

Manifestations of XLPD result from a defective lymphoproliferative control locus that cannot regulate cellular and humoral responses to EBV. The 3 main manifestations of the disease may develop as a result of the following mechanisms: excessive suppression of B cells, which leads to hypogammaglobulinemia; uncontrolled cytotoxic lymphoid cells that produce necrotic lesions in tissue that leads to fulminant hepatitis or the virus-associated hemophagocytic syndrome; and sustained polyclonal B-cell proliferation, which can eventually lead to a monoclonal B-cell malignancy.

Liver and bone marrow lesions in patients with XLPD show overwhelming infiltration by polyclonal EBV-positive cells and extensive tissue necrosis although the hepatocytes and bone marrow cells are uninfected per se. Immunologic study findings from these patients demonstrate uncontrolled cytotoxic responses against uninfected hepatocytes and bone marrow cells as well as EBV-infected lymphocytes. Both T cells and natural killer cells participate in the indiscriminate cytotoxic activity against uninfected hepatocytes and bone marrow cells.

The patient in the current case initially had evidence of EBV-infected lymphoid cells in his bone marrow as determined by in situ hybridization. He also had necrotizing vasculitic skin lesions, which showed an intense perivascular infiltrate of EBV-positive lymphocytes in the deep dermis although no virus was detected within the dermal cells. Finally, as described in the current report, the patient developed a hemorrhagic necrotizing retinitis. The retina had extensive infiltrates of atypical lymphoid cells consisting of both B and T cells in addition to numerous macrophages although no virus was de-
ected in the retinal cells. Results of in situ hybridization for CMV, HSV, and HZV were negative as were tests for bacteria, fungi, and Toxoplasma; meanwhile, in situ hybridization revealed numerous atypical lymphocytes that were positive for EBV.

Chorioretinitis associated with EBV infection is a rare complication that has only recently been described. The pathogenesis of this complication, however, remains to be resolved. One mechanism that may explain this finding is bystander-killing activity that results from cytotoxic T cells. Fulminant hepatitis and necrotizing skin lesions, for example, occur in patients with XLPD although the parenchymal cells are not directly infected by the virus. Another possible mechanism that can explain the extensive retinal necrosis in the absence of EBV positivity in the retinal cells is lymphocytic vasculitis. The lymphocytic infiltrates, presence of thrombosed blood vessels, and extensive hemorrhagic necrosis of the retina seen in the retinal biopsy specimens in the current case suggest the possibility of an occlusive retinal vasculitis secondary to EBV.

Although the EBV DNA detected in the current case resided in B cells and not in retinal cells, we believe that the retinal necrosis was linked to EBV and may be explained by a secondary process such as ischemic injury from the vasculitis or a cytotoxic bystander-killing mechanism.

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This study was supported in part by a Departmental Challenge Grant from Research to Prevent Blindness, Inc, New York, NY, to the Department of Ophthalmology, University of Cincinnati College of Medicine.

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Primary Orbital Extraskeletal Ewing Sarcoma

Extraskeletal Ewing sarcoma is a rare soft tissue sarcoma histologically indistinguishable from osseous Ewing sarcoma. Tefft et al first described the tumor in children with paravertebral soft tissue masses. Subsequent larger case series have shown that the tumor has a predilection for the paravertebral area and lower extremities. The tumor most often occurs in the extremities and paraspinal areas and has been reported to occur in the head and neck region in 5% to 11% of patients.

While osseous Ewing sarcoma, both primary and metastatic, has been reported in the orbit, to our knowledge, ours is the first case of extraskeletal Ewing sarcoma to occur in the orbit. Furthermore, extraskeletal Ewing sarcoma manifesting as late as the sixth decade of life has not been reported, to our knowledge. We report a case of primary orbital extraskeletal Ewing sarcoma in a 56-year-old man, which was diagnosed using monoclonal antibody 013 to the p30/32 MIC2 gene product, CD99.

Report of a Case. A previously healthy 56-year-old white man had an 8-month history of progressive right upper eyelid swelling, diplopia, dizziness, and a right-sided headache. His medical history was significant for mild chronic obstructive pulmonary disease treated with albuterol inhalers as needed. On ophthalmic examination, the left eye was normal. His visual acuity was 20/100 OD and 20/30 OS, with a + right afferent papillary defect. He had right upper eyelid swelling. Her tel measurements showed 8 mm of right exophthalmos. The right orbit exhibited resistance to retroper- sion. Examination of ocular motility revealed limited movement of the right eye in all gaze positions. Funduscopic examination of the right eye revealed choroidal folds and mild optic nerve edema.