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**OCULAR POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) WITH LOW-GRADE, EXTRANODAL MARGINAL ZONE LYMPHOMA (MALT)-LIKE MORPHOLOGY**

**Clinical History**

An 8-year-old developmentally delayed boy underwent orthotopic heart transplantation at the age of 3 years for decompensated heart failure following presumed viral myocarditis. His initial post-operative period was complicated by primary graft dysfunction, from which he recovered, and also by cerebrovascular accidents resulting in bilateral hemiparesis and right visual field loss. Given he was an EBV mismatch, his EBV blood levels were monitored regularly. Over the following year, he developed chronic low-grade EBV viremia that peaked at 19,800 copies/mL of whole blood with concurrent elevation of liver enzymes, attributed to EBV hepatitis, which resolved with reduction of his immunosuppression. Following this episode, he maintained EBV blood levels at <2,000 copies/ml.

Five years following transplant surgery, he presented to the pediatric eye clinic for persistent bilateral eye redness and rubbing. Eye examination revealed a visual acuity of 20/40 using crowded HOTV optotypes in both eyes. Anterior segment examination showed bilateral minimal conjunctival injection, small keratic precipitates in the right eye and larger mutton-fat keratic precipitates in the left eye. There were also bilateral 3+ anterior chambers (AC) cellular reaction with flare and multiple iris nodules in the left eye only. Posterior segment examination was normal in both eyes. Routine blood work-up two weeks prior to presentation showed normal cell count, liver enzymes and electrolytes, and positive serum EBV PCR with a count <2000 copies/mL. Initial work-up was negative for rheumatoid factor, ANA and infectious causes of uveitis. A biopsy of one of the left eye iris nodules was performed and revealed features of post-transplant lymphoproliferative disorder. Brain MRI, a whole-body PET scan, and a CSF analysis showed no systemic lymphoproliferative process.

Lacking improvement following topical steroids and stopping mycophenolate mofetil, treatment with the anti-CD20 antibody, rituximab, was initiated. Four systemic and five intraocular injections were administered weekly for 4 weeks. Over the course of treatment, he showed gradual reduction in the size of iris lesions, keratic precipitates and AC cellular reaction. One week following his last injections, both eyes were quiet with no AC cellular reaction and disappearance of the iris masses. However, after 3 months, he developed bilateral recurrence of anterior chamber (AC) reaction and keratic precipitates but not the iris nodules. AC tap was negative for malignancy documenting only few CD3 and CD20 lymphocytes. He was treated with a further single intravitreal injection of rituximab and a single injection of methotrexate in each eye. Within two weeks, the keratic precipitates resolved completely and he was left with only trace cellular reaction in the AC which was successfully controlled with topic corticosteroids. Approximately 8 months later, he has maintained this improvement with no keratic precipitates or AC reaction in either eye. His bilateral visual acuity is 20/30.

**Pathology Findings**

The biopsy of one of the left iris nodules revealed an infiltrate of small CD20-positive B-cells with numerous intermixed plasma cells, that had restricted, monoclonal, expression of kappa immunoglobulin light chain. The lesion was diffusely positive for EBV on immunohistochemical studies. The proliferating cells were small with morphology resembling extra-nodal marginal zone lymphoma. Hence, a diagnosis of post-transplant lymphoproliferative disorder (PTLD) with marginal zone lymphoma-like features was made.

**Discussion**

Post-transplant lymphoproliferative disorder (PTLD) is a well-known complication of prolonged immunosuppression in patients receiving solid organ and bone marrow transplantation. Its incidence varies from 2 to 10%, and it may affect a number of different organs including GI tract, liver, lung, CNS, lymphoid tissues, and only rarely the eye. Younger age, active Epstein-Barr virus infection and intense immunosuppression are considered risk-factors.

Morphologically, PTLDs are lymphoid or plasmacytic, generally EBV-driven proliferations, which comprise a spectrum ranging from EBV-positive polyclonal proliferations to monoclonal proliferations indistinguishable from a subset of the B-cell, less often T-cell lymphomas recognized in immunocompetent patients. Extra-nodal marginal zone (MALT) lymphoma and other indolent B-cell lymphomas occurring in the post-transplant setting were not considered a type of PTLD at the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues. In 2011 however, Gibson *et al* described 4 patients with PTLD-like proliferations that were EBV-positive and had typical morphology of MALT lymphoma, suggesting that extranodal marginal zone lymphoma in post-transplant setting should be included in the PTLD classification. All 4 patients responded to immune restitution.

Despite PTLD being common among transplant recipients, there have been only about 20 cases of ocular PTLD reported in literature. As shown by Iu and collaborators, in their review of the literature, the time interval from transplantation to the presentation of ocular PTLD varied from months to several years. Most patients were young, ages 2 to 14 years old; only 4 were adults, ages 58 to 68. Presenting symptoms included red eye, blurred vision, floaters, eye pain, photosensitivity, diplopia and iris lesions, while a third of the patients were asymptomatic. The most common ocular signs were iris nodules and mutton-fat keratic precipitates (13 of 20 patients). Signs of posterior segment involvement included vitritis, subretinal mass and optic disc swelling. In approximately half of the patients, the eye was the only site of involvement by the PTLD. Morphologically, these cases varied from polyclonal polymorphous proliferations to lymphomas. To our knowledge, this is the first case reported in the literature of PTLD involving the eye with MALT-like histologic features (Bata *et al.)*.

Our patient was treated with combined systemic rituximab and intraocular injections. Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen found on the surface of B-cells, has been increasingly used in the treatment of CD20 positive PTLD in the pediatric age group, with only a few reports of intraocular usage. Pulido *et al* presented initial evidence that rituximab could potentially be used to treat primary intraocular lymphoma infiltrates by demonstrating that this agent can penetrate full thickness retina. Kitzmann *et al* reported its use in five eyes of three patients, none of whom developed signs of toxicity. Our patient showed a complete response initially to this combination but had a recurrence of the keratic precipitates and AC cellular reaction a few months later, for which he was treated with further intraocular injections but no systemic injections. On his last follow-up, 8 months after the initial injection, the patient has not developed signs of ocular toxicity.

In summary, this case is unique in several accounts. It provides further evidence that MALT-like lymphoproliferative lesions should be included in the classification of PTLD. It also adds further evidence to the well-established concept that a high EBV titre at the time of the diagnosis is not a prerequisite to diagnose PTLD, and it demonstrates that combined systemic and intraocular rituximab can be effective in treating ocular PTLD. However, as recurrences often occur, long-term monitoring is needed.

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