Taiwan Journal of Ophthalmology 5 (2015) 140–142

Contents lists available at ScienceDirect

Taiwan Journal of Ophthalmology

journal homepage: www.e-tjo.com

Case report

# Ocular post-transplant lymphoproliferative disorder

Yun-Wen Chen, Hun-Ju Yu, Yi-Chieh Poon, Hsi-Kung Kuo*

*Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan*

ARTICLE INFO

*Article history:*
Received 6 April 2014
Received in revised form
26 May 2014
Accepted 9 June 2014
Available online 1 August 2014

*Keywords:*
post-transplant lymphoproliferative disorder

ABSTRACT

We report a case of an iris tumor with mutton-fat keratic precipitates in a young patient after liver transplantation surgery. A 6-year-old girl underwent liver transplantation for congenital biliary atresia and was subsequently immunosuppressed with oral cyclosporine. We examined her 5 years after transplantation because of a "white nodule in her left eye," which had been detected by her father one day before visiting our clinic. Ophthalmological examinations revealed symmetric visual acuity and normal afferent papillary reflex. Slit-lamp examination revealed a depigmented iris nodule approximately3 × 2 mm with mutton-fat keratic precipitates in the anterior chamber. Fundus examination was unremarkable, and computed tomography (CT) of the head, neck, and abdomen showed normal findings. Based on the suspicion of post-transplant lymphoproliferative disorder (PTLD), therapy was initiated, which included tapering cyclosporine and topical mydriatics. After 2.5 months, the lesion resolved and no more mutton-fat keratic precipitates were identified in the anterior chamber. In this PTLD case, the patient presented with an iris nodule and mutton-fat keratic precipitates, and the ocular PTLD presentation resolved spontaneously after tapering cyclosporine.



## 1. Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are a spectrum of diseases caused by lymphoplasmacytic proliferations that occur as a result of immunosuppression following solid organ or allogeneic hematopoietic cell transplantation.[1] The spectrum of PTLDs ranges from polymorphic, polyclonal proliferations with features of viral infection, to monomorphic, monoclonal proliferations, usually of the B-cell type.[2] Primary ocular PTLDs represent a distinct, late-onset, polyclonal lymphoproliferation primarily affecting pediatric transplant patients.[3] The uveal tract becomes infiltrated by a mixture of lymphocytes and plasma cells, and is often associated with the presence of Epstein-Barr virus (EBV).[4] In this case report, we present a patient who underwent liver transplantation and subsequently developed presumed ocular PTLD complications, which resolved after adjusting immunosuppression therapy.

## 2. Case Report

A 6-year-old girl underwent liver transplantation for congenital biliary atresia and was placed on immunosuppression therapy with oral cyclosporine (30 mg/day), with a mean cyclosporine level of 524 ng/mL in her blood during the 5$^{th}$ post-transplant year. Five years after liver transplantation, she presented with a "white nodule in her left eye", which had been detected by her father the day before attending our clinic. There was no previous history of traumatic injury to the eye, and she denied any systemic discomfort. Visual acuity was 20/50 in both eyes, eye movements were full and free and intraocular pressures were within normal limits. The patient had normal light reflex in both eyes, but the examination of the anterior segment revealed a highly vascularized, hypopigmented iris nodule situated on the peripheral iris in her left eye (Fig. 1). Multiple mutton-fat keratic precipitates were noted, but there were no cells in the anterior chamber (standardization of uveitis nomenclature, SUN grade 0). The vitreous cavity was clear with no other mass lesions detected on B-scan ultrasonography or dilated fundus examination. Examination of the right eye was unremarkable. Physical examination and systemic surveys including computed tomography (CT) of the head, neck, chest, and abdomen were performed and were within normal limits. Laboratory investigation of the patient's blood was positive for EBV DNA, Epstein-Barr nuclear antigen-antibody (EBNA-Ab) (>1.640), and EB-Viral

Conflict of interest: In relation to this case report, the authors declare that there are no conflicts of interest.

* Corresponding author. Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, 123 Dapi Road, Niaosong District, Kaohsiung 833, Taiwan.
*E-mail address:* fangpc@adm.cgmh.org.tw (H.-K. Kuo).

http://dx.doi.org/10.1016/j.tjo.2014.06.001

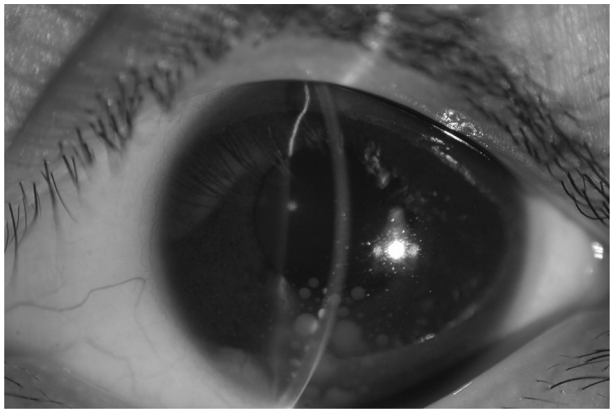

**Fig. 1.** Hypopigmented neoplasm located between 7:00 and 8:00. Multiple mutton-fat keratic precipitates noted.

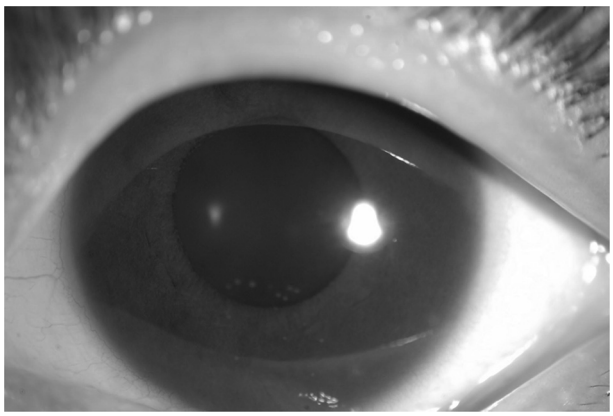

**Fig. 2.** Resolved iris neoplasm and clear anterior chamber. Mutton-fat keratic precipitates have almost disappeared.

Capsid Antigen IgG antibody (EB-VCAG) (>750 U/mL), and was negative for EB-Viral Capsid Antigen IgM antibody (EB-VCAM).

On suspicion of ocular PTLD without systemic involvement, topical steroid and cycloplegic eye drops were given, along with the adjustment of systemic cyclosporine dosage to 15 mg/day. Cyclosporine levels in the blood and liver function tests were monitored regularly. Six weeks after adjustment of the systemic cyclosporine dosage, her blood cyclosporine levels dropped to 211 ng/mL, and the iris nodule resolved spontaneously (Fig. 2). The patient is currently maintained on oral cyclosporine 15 mg/day, without additional immunosuppressive agents needed, and shows no signs of graft rejection so far.

## 3. Discussion

Making a correct diagnosis is the essential first step in managing a pediatric patient with uveitis, which requires detailed history taking thorough ophthalmic examination and selected laboratory tests. Examination under general anesthesia may be needed in young patients should they be incapable of cooperating during the examination. For patients with suspected PTLD, differential diagnosis that needed to be ruled out include, iris melanoma, retinoblastoma, juvenile xanthogranuloma, and intraocular foreign bodies.[1,5]

PTLDs are characterized by an uncontrolled proliferation of B-cells as a result of immunosuppression following solid organ or allogeneic hematopoietic cell transplantation. Immunosuppressive therapy inhibits T-cell function, which leads to a reduction in B-cell growth suppression. Diagnosis of PTLD is based on both clinical and histological criteria. Children were considered to have clinical evidence suggestive of PTLD when there was evidence of lymphadenopathy, tonsillar hypertrophy, or extranodal masses on physical examination.[6] In ocular PTLD, a mixture of lymphocytes and plasma cells diffusely infiltrates the uveal tissue. Cho et al[7] reported that anterior uveitis and iris nodules are the most common ocular manifestations of PTLDs, but the posterior segment can also be involved.

In young patients who have received organ or bone marrow transplantation, it is reported that the 1-year post-transplantation ocular complication rate is 16% (including cataract, keratoconjunctivitis sicca secondary to Graft-versus-host-disease (GVHD), cytomegalovirus retinitis, PTLD, strabismus, transient visual loss, preseptal cellulitis, allergic periorbital edema, and conjunctivitis) in USA,[4] whereas PTLDs occurs in 3% of all liver transplantation recipients.[4] The prevalence of PTLD in adult patients following liver transplantation was reported to be 1.1% in a separate study.[8] The incidence of PTLD is significantly higher in children (9.7%) than in adults (2.9%), with an overall average incidence of 4.3%.[9] Persistent monoclonal immunoglobulins in liver transplantation recipients was also associated with a 23% incidence of PTLD.[10] The average time interval between transplantation to PTLDs diagnosis is 50 months with a range of 5–140 months.[8] In our patient, a 6-year-old girl, the interval between transplantation and PTLD diagnosis was 60 months.

The majority of PTLD cases are associated with EBV infection.[11,12] EBV induces uncontrolled proliferation of B-cells, which are normally regulated by cytotoxic T-cells and natural killer cells.[11] Treatments for PTLD include prophylactic high-titer anti-EBV intravenous immunoglobulin[13] in high-risk (donor was EBV positive, recipient was EBV negative) pediatric recipients, intravenous ganciclovir in high-risk EBV-positive donors to EBV-negative recipients,[14] and immunosuppressive therapy reduction.[7] In previous studies, EBV monitoring has been shown to be useful in high-risk transplant recipients.[6] In the study by Ho cyclosporine was reduced to one-half of the original dosages after PTLD was diagnosed.[15] In our patient, tapering the dosage of cyclosporine (from 30 mg/day to 15 mg/day) led to the resolution of the iris nodule presumed to be due to PTLD.

Our patient's laboratory test for EB-VCAG was positive, but the EB-VCAM was negative, indicating that she had a history of EBV infection, but the infection was not in the acute phase. Parker et al[16] suggested that patients must be monitored for EBV seroconversion at the initial presentation of PTLD and then monthly (IgM to IgG against VCAs) until the stable appearance of IgG EBNA-1. If the lymph node or tonsillar enlargement does not improve, or worsens, a biopsy should be performed. In our patient, EBV seroconversion to IgG was present in the beginning of her clinical course. For the evaluation of PTLD, Dhillon et al[8] reported an investigation protocol which included biopsy of the tumor/lymph node mass for histology, CT scans for staging (head, neck, chest, and abdomen), and analysis of peripheral blood (full blood count, flow cytometry for monoclonal B cells, EBV serology, and EBV load).

In the present case, the patient showed no signs of systemic involvement and neurological symptoms. Because of the young age of this patient and the family's concerns regarding the risk of general anesthesia and complications of biopsy, including infection, bleeding, and loss of vision, biopsy of the iris nodule was not performed. However, our patient was followed up closely, with progressive regression of the iris tumor noted after reduction of cyclosporine levels, and complete resolution of the tumor by 6 weeks. Nevertheless, in a patient with mass lesions or lymphadenopathy due to suspected PTLD, where no documented improvements have been noted after the reduction of immunosuppressive therapy, a low threshold for biopsy is warranted to confirm diagnosis.

In conclusion, the incidence of PTLD is higher in children than in adults, and the majority of cases appear to be related to the presence of EBV. In our case, the diagnosis of PTLD was made based on her history after having had a liver transplantation, the presence of past EBV infection, and the regression of the iris tumor after adjusting the immunosuppressant dose. When a patient is suspected of having PTLDs, adjunctive evaluations may include staging with CT of major organs, bone marrow aspiration, and peripheral blood measurements and analysis including titers for EBV antibodies. The patients should undergo frequent and careful monitoring, and biopsy of the tumor lesion whenever possible to provide a definite pathological diagnosis.

## References


1. Wistinghausen B, Gross TG, Bollard C. Post-transplant lymphoproliferative disease in pediatric solid organ transplant recipients. *Pedilatr Hematol Oncol*. 2013:520–531.
2. Swerdlow SH. Post-transplant lymphoproliferative disorders: a morphologic, phenotypic and genotypic spectrum of disease. *Histopathology*. 1992;5: 373–385.
3. O'hara M, Loyd 3rd WC, Scribbick FW, Gulley ML. Latent intracellular Epstein-Barr Virus DNA demonstrated in ocular posttransplant lymphoproliferative disorder mimicking granulomatous uveitis with iris nodules in a child. *J AAPOS*. 2001;1:62–63.
4. Bradfielf YS, Kushner B, Gangnon RE. Ocular complications after organ and bone marrow transplantation in children. *J AAPOS*. 2005;9:426–432.
5. Majumder PD, Biswas J. Pediatric uveitis: an update. *Oman J Ophthalmol*. 2013;6:140–150.
6. Rowe DT, Qu L, Reyes J, Jabbour N, Yunis E, Putnam P, et al. Use of quantitative competitive PCR to measure Epstein-Barr virus genome load in the peripheral blood of pediatric transplant patients with lymphoproliferative disorders. *J Clin Microbiol*. 1997;35:1612–1615.
7. Cho AS, Holland GN, Glasgow BJ, Isenberg SJ, George BL, McDiarmid SV. Ocular involvement in patients with posttransplant lymphoproliferative disorder. *Arch Ophthalmol*. 2001;119:183–189.
8. Dhillon MS, Rai JK, Gunson BK, Olliff S, Oliff J. Post-transplant lymphoproliferative disease in liver transplantation. *Br J Radiol*. 2007;80:337–346.
9. Jain A, Nalesnik M, Reyes J, Pokharna R, Mazariegos G, Green M, et al. Post-transplant lymphoproliferative disorders in liver transplantation: a 20-year experience. *Ann Surg*. 2002;236:429–436.
10. Paqeaux GP, Bonnardet A, Picot MC, Perrigault PF, Coste V, Navarro F, et al. Prevalence of monoclonal immunoglobulins after liver transplantation: relationship with posttransplant lymphoproliferative disorders. *Transplantation*. 1998;65:397–400.
11. Ho M, Miller G, Atchison RW, Breinig MK, Dummer JS, Andiman W, et al. Epstein-Barr virus infections and DNA hybridization studies in post-transplantation lymphoma and lymphoproliferative lesions: the role of primary infection. *J Infect Dis*. 1985;152:876–886.
12. Wu L, Rappaport DC, Hanbidge A, Merchant N, Shepherd FA, Greig PD. Lymphoproliferative disorders after liver transplantation: imaging features. *Abdom Imaging*. 2001;26:200–206.
13. Green M, Reyes J, Webber S, Rowe D. The role of antiviral and immunoglobulin therapy in the prevention of Epstein-Barr virus infection and post-transplant lymphoproliferative disease following solid organ transplantation. *Transpl Infect Dis*. 2001;3:97–103.
14. McDiarmid SV, Jordan S, Kim GS, Toyoda M, Goss JA, Vargas JH, et al. Prevention and preemptive therapy of postransplant lymphoproliferative disease in pediatric liver recipients. *Transplantation*. 1998;66:1604–1611.
15. Ho M, Jaffe R, Miller G, Breinig MK, Dummer JS, Makowka L, et al. The frequency of Epstein-Barr virus infection and associated lymphoproliferative syndrome after transplantation and its manifestations in children. *Transplantation*. 1988;45:719–727.
16. Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients – BCSH and BTS Guidelines. *Br J Haematol*. 2010;149: 675–692.