Ocular Involvement in Patients With Posttransplant Lymphoproliferative Disorder

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Objectives: To describe ocular disease in 3 patients with posttransplant lymphoproliferative disorder (PTLD) and to identify the frequency of such ocular involvement.

Methods: Medical record reviews. Using Kaplan-Meier analysis, we calculated the frequency of ocular involvement among pediatric patients with systemic PTLD after liver transplantation.

Results: Each patient had bilateral anterior chamber cells. Biopsy of an iris nodule from a patient who had undergone cardiac transplantation confirmed the diagnosis of PTLD, but no signs of systemic PTLD were found. The other 2 patients had systemic PTLD after liver transplantation; 1 presented with iris nodules in both eyes and a subretinal mass in the left eye, while the other had bilateral anterior chamber cells only. Ocular signs improved slowly after reduction of immunosuppressive drug therapy. Ophthalmological examinations were performed on 22 of 25 pediatric patients with PTLD after liver transplantation; 2 had ocular disease. Kaplan-Meier analysis indicated a 20% risk of ocular involvement at 3 years after development of PTLD (95% confidence intervals, 0%-50%).

Conclusions: Posttransplant lymphoproliferative disorder should be considered in the differential diagnosis of uveitis after organ transplantation. Anterior chamber cells and iris nodules are the most common ocular signs, but the posterior segment can be involved. Ocular involvement can occur without evidence of systemic disease and can be asymptomatic. Reduction of immunosuppressive drug therapy is an appropriate treatment.


POSTTRANSPLANT lymphoproliferative disorder (PTLD) results from an abnormal proliferation of lymphocytes that occurs in the setting of immunosuppression after surgery. It is characterized by a spectrum of disease findings that ranges from benign polyclonal polymorphic B lymphocyte hyperplasia to monoclonal B lymphocyte lymphoma.1,2 Experimental and clinical evidence supports the notion that Epstein-Barr virus, which can be oncogenic in immunodeficient hosts, is responsible for PTLD.1,2

Posttransplant lymphoproliferative disorder can appear months to years after transplantation.3-5 The overall prevalence of PTLD seems to be less than 5%, but rates vary with the type of organ transplanted and the nature of the immunosuppression.5 The manifestations of PTLD are protean, and they include constitutional symptoms, lymphadenopathy, upper airway obstructive symptoms, alterations in mental status, neck stiffness, local neurologic findings, gastrointestinal perforation or obstruction, graft dysfunction, or localized solid tumor masses. Widely disseminated disease can occur.

Ocular involvement with PTLD has been described infrequently as isolated case reports.6-9 We report 3 additional patients with ocular manifestations of PTLD who had signs and symptoms of uveitis. We also calculated the frequency of ocular disease among all pediatric patients who were being observed at our institution for systemic PTLD after liver transplantation.

RESULTS

Characteristics of the 3 patients with PTLD and ocular involvement are summarized in the Table. Common features included anterior chamber cells (all cases) and iris nodules (cases 1 and 2). The disease was bilateral, albeit asymmetrical, in all cases. One patient (case 2) had posterior segment involvement consisting of a subretinal mass with optic disc swelling.
PATIENTS AND METHODS

PATIENTS

The following information was obtained from the records of 3 patients with PTLD and ocular involvement who had been referred to the Jules Stein Eye Institute: age, sex, type of organ transplanted, reason for organ transplantation, immunosuppressive drugs used, nature of systemic PTLD, treatment for PTLD, ocular and visual symptoms, initial visual acuity, slitlamp biomicroscopic examination findings, intraocular pressure, dilated fundus examination findings, and the course of disease, including response to treatment.

An iris nodule was excised surgically from 1 patient for diagnostic purposes and was examined by light microscopy after staining with hematoxylin and eosin. Immunohistochemical studies were performed to determine the clonality of the lesion, and in situ RNA hybridization studies were performed to detect the presence of Epstein-Barr virus.

We routinely perform complete ophthalmological examinations on all patients at the University of California, Los Angeles (UCLA), Medical Center who have undergone liver transplantation and have a history of systemic PTLD. All patients are followed up in the practice of 1 author (S.V.M.). We reviewed the ophthalmic examinations of these patients to determine the rate of ocular involvement in this population.

We identified previously reported cases of ocular involvement in patients with PTLD through computerized literature searches for the years 1966 through 2000 using MEDLINE. This study conformed to regulations of the UCLA Office for the Protection of Human Subjects.

REPORT OF CASES

Case 1

A 14-year-old boy underwent cardiac transplantation for a congenital cardiac anomaly and was subsequently immunosuppressed with oral cyclosporine (5.7 mg/kg per day) and oral azathioprine (0.46 mg/kg per day), with a mean cyclosporine level of 161 ng/mL during the fourth posttransplant year. We examined him 5 years after transplantation because of a "lump on the iris," which had been detected on routine eye examination. He had no visual disturbance or ocular symptoms. Uncorrected visual acuity was 20/20 OU. Pupils were round and reactive to light without an afferent pupillary defect. Slitlamp biomicroscopic examination revealed normal eyelids, noninflamed ocular surfaces without focal lesions, and clear corneas. There were rare to occasional cells in the right anterior chamber and 3+ cells in the left anterior chamber. There was minimal flare in both eyes. The right iris appeared normal. The left iris had numerous nonpigmented nodular elevations consistent with mass lesions arising from the iris stroma (Figure 1). On dilated examination, both vitreous bodies were clear, and there were no fundus lesions in either eye. Laboratory studies included a normal complete blood cell count with differential, nonreactive purified protein derivative skin test, normal chest x-ray films, and nonreactive fluorescent treponemal antibody absorption test. There was no serologic evidence of toxoplasmic, cryptococcal, or coccidioidal infections. Results of a bone marrow biopsy were negative for abnormality. Computed tomographic scan of the chest and abdomen did not show any mass lesions. Serologic tests for Epstein-Barr virus infection were performed yearly on a routine basis and had been positive for the previous 4 years; the most recent test results had been consistent with active infection (viral capsid antigen immunoglobulin G, >1:2560; viral capsid antigen immunoglobulin M, >1:120; early antigen, >1:2560; Epstein-Barr nuclear antigen, >1:20), but the patient has no history of PTLD.

Therapy was initiated using topical prednisolone acetate 1% every hour with no change in size of the iris nodules or in severity of the anterior chamber cellular reactions. An incisional biopsy of an iris nodule in the left eye was performed through a superonasal limbal incision 3 months after initial visit. Light microscopic examination showed a dense collection of plasma cells and slightly atypical lymphocytes (Figure 2). Immunoperoxidase staining showed an equal mixture of \( \lambda \) and \( \kappa \) light chains. In situ hybridization studies for Epstein-Barr virus were positive (Figure 3). A diagnosis of PTLD was made on the basis of these results. Azathioprine administration was discontinued, and the dose of cyclosporine was decreased to 2.3 mg/kg per day. Prednisone (0.11 mg/kg per day) and acyclovir sodium (53.3 mg/kg per day) were added 4 months after the presentation. The iris nodules were noted to decrease in size after 3 months, and the anterior chamber cellular reaction continued to decrease during the subsequent 6 months.

Case 2

A 5-year-old girl underwent liver transplantation for end-stage liver disease resulting from biliary atresia and was subsequently maintained on cyclosporine (14.0 mg/kg per day), until ophthalmologic examination was 26 months (range, 10-116 months). The mean age at the time of ophthalmologic examination for this population was 8 years, with a median age of 7 years.

Only the 2 girls in our case series had ocular disease. On the basis of our experience, Kaplan-Meier analysis (Figure 5) indicates that the risk for development of ocular involvement is 20% at 3 years after diagnosis of systemic PTLD (95% confidence intervals, 0%-30%). Confidence intervals have been included to show that a large degree of uncertainty exists because of the small sample sizes. The intervals may be inaccurate, however, because the calculation of these intervals in a Kaplan-Meier analysis is based on the assumption of large sample results.

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azathioprine (1.6 mg/kg per day), and prednisone (0.25 mg/kg per day), with a mean cyclosporine level during the third posttransplant year of 130 ng/mL. She developed fever of unknown origin, tonsillar enlargement, and cervical and axillary lymphadenopathy approximately 3 years after transplantation and was diagnosed with PTLD by tonsillar biopsy. At that time, her anti–Epstein-Barr virus IgG titer was noted to be highly elevated (1:2560). Azathioprine was stopped, cyclosporine was decreased to 13.0 mg/kg per day, and acyclovir (35 mg/kg per day) was added to her treatment regimen.

We examined her 4 years after transplantation when she complained of mild photosensitivity in both eyes. Visual acuity was 20/30 OD and 4/200 OS. The right pupil was briskly reactive to light, while the left pupil was sluggishly reactive to light. There was a trace afferent pupillary defect in the left eye. On slitlamp biomicroscopic examination, there were numerous nonpigmented nodules in the iris stroma of both eyes. Examination of the anterior chamber revealed 2+ cells in the right eye and 3+ cells in the left eye. Flare was prominent in both eyes. There were mutton fat keratic precipitates in both eyes. The left eye had nearly 360° of posterior synechiae. In the left eye, there was optic disc edema with elevation of much of the posterior pole because of a subretinal mass (Figure 4). A presumed diagnosis of PTLD was made, given the history of systemic PTLD and similarity of the iris nodules to those previously noted in case 1. Initial therapy consisted of topical prednisone acetate 1% every 2 hours and cyclopentolate 1% at bedtime. The cyclosporine dosage was reduced to 10.4 mg/kg per day 2 months after our initial examination. During the next 1 month, the iris nodules of both eyes disappeared, and the subretinal mass in the left eye flattened with the return of visual acuity to 20/50 OS. The cyclosporine dosage was further decreased to 5.2 mg/kg per day 6 months later, followed by an episode of decreased vision, with increased anterior chamber cells and increased peripapillary infiltration in the left eye. Intravenous ganciclovir was added to the treatment regimen and cyclosporine was stopped. During the next 2 months, inflammation and the peripapillary infiltrate decreased, and visual acuity returned to 20/40 OS. Blood tests for Epstein-Barr virus remain markedly positive at 847 viral DNA copies or μg DNA by polymerase chain reaction (PCR) technique.

Case 3

A 10-year-old girl underwent liver transplantation because of biliary atresia. Because of hepatic artery thrombosis in the first allograft, a second liver transplant was performed 1 month later. She was immunosuppressed with tacrolimus for chronic rejection, but the drug was discontinued 3 years later after she developed generalized lymphadenopathy and was diagnosed with PTLD, based on results of mediastinal lymph node and liver biopsies. Immunosuppression therapy was temporarily stopped, and a regimen of acyclovir (34.8 mg/kg per day) was started. Administration of cyclosporine (7.0 mg/kg per day) and prednisone (0.1 mg/kg per day) was eventually resumed. She subsequently had 1 episode of acute allograft rejection approximately 3 years after the initial transplantation. The mean cyclosporine level during the fifth year after transplantation was 210 ng/mL.

We examined her 6 years after initial transplantation, following identification of asymptomatic bilateral anterior uveitis on routine examination, and initiation of therapy using topical 1% prednisolone acetate every 4 hours in the left eye and homatropine 3% twice daily in the left eye. Visual acuity was 20/20 OD and 20/25 OS. Both pupils were reactive to light without afferent pupillary defects. She had palpable cervical adenopathy. Corneas were clear. Examination of the anterior chambers revealed occasional cells in the right eye and 2+ cells in the left eye. Flare was minimal in both eyes. There were remnants of old keratic precipitates in the left eye. No iris nodules were seen and there were no posterior synechiae. Lenses were clear. Intraocular pressure was 14 mm Hg OD and 16 mm Hg OS. There were cells in the anterior vitreous humor of the left eye. Optic discs appeared normal. No posterior segment inflammatory lesions were seen in either eye. A presumed diagnosis of PTLD with ocular involvement was made on the basis of history and lack of other identified causes. Cyclosporine doses were reduced only moderately (3.5 mg/kg per day) because of ongoing liver rejection. The frequency of topical prednisolone acetate 1% was raised to 7 times daily in both eyes. Administration of homatropine 3% was stopped. There was a transient episode of elevated intraocular pressure (38 mm Hg) of uncertain cause in the right eye. Topical prednisolone was discontinued temporarily in the left eye, but there was no appreciable change in the level of cells, and it was reinstituted without an increase in intraocular pressure. During the following several months, vision remained stable with little change in the level of anterior chamber cells, despite changes in the frequency of topical medications. Blood tests for Epstein-Barr virus remain elevated at 492 viral DNA copies or μg DNA by PCR technique.

Of the 22 patients, 19 were immunosuppressed with tacrolimus and 3 patients were immunosuppressed with cyclosporine. None of the patients receiving tacrolimus had ocular involvement, whereas 2 of the 3 patients receiving cyclosporine had ocular involvement (P = .013 [Fisher exact 2-tailed test]). The boy who had undergone cardiac transplantation and developed PTLD with ocular involvement, and was not included in the series of 22 patients, was also receiving cyclosporine.

**COMMENT**

Posttransplant lymphoproliferative disorder is defined as an abnormal proliferation of lymphoid cells in a patient receiving immunosuppressive therapy following organ transplantation. The disorder is thought to occur as the result of failure of the host immune system to defend against Epstein-Barr virus infection by limiting the T-lymphocyte responses that normally control the proliferation of the B lymphocytes infected with the virus. In general, the use of immunosuppressive therapies in the setting of solid organ transplantation is associated with a 20-fold to 50-fold increased risk of lymphoproliferative disease.²

In the early 1980s, Hanto et al³ defined the clinical features of PTLD and suggested a role for Epstein-Barr virus in its pathogenesis. In a report of 6 transplantation patients with lymphoproliferative lesions, all had evidence of oropharyngeal Epstein-Barr virus shedding, and 5 had multiple copies of the Epstein-Barr virus ge-
nome in the tumor tissue. Epstein-Barr virus infection also results in lymphoproliferative diseases in several animal models. Mice with severe combined immunodeficiency develop lymphoproliferative disease after intraperitoneal injection of Epstein-Barr virus–seropositive blood. The cotton-top tamarin, an Old-World primate, develops fatal lymphoproliferative disease after inoculation with Epstein-Barr virus. Posttransplant lymphoproliferative disorder may appear clinically in several ways. Some patients develop an infectious mononucleosis-like illness with pharyngitis, fever, tonsillitis, lymphadenopathy, and hepatosplenomegaly. Others have a localized disease that is more likely to be extranodal than nodal. One of the most common initial sites of PTLD is the central nervous system, which is involved in 28% of cases in the transplantation population. Among patients treated with cyclosporine and tacrolimus, the gastrointestinal tract is the most common site of presentation. Patients may present with abdominal pain, gastrointestinal bleeding, symptoms of obstruction, or bowel perforation. Lymph node, bone marrow, kidney, liver, and lung involvement is also common. The disorder can also appear in the allograft with organ dysfunction and failure.

Factors associated with the development of PTLD include young age, primary Epstein-Barr virus infection, type of organ transplanted, and type and intensity of immunosuppression. Epstein-Barr virus–associated PTLD is more common in pediatric than in adult transplant recipients because many pediatric patients, particularly liver recipients, fulfill the other high-risk criteria. In addition, there is increasing use of partial liver grafts from adults, who are frequently Epstein Barr virus–positive, in noninfected pediatric recipients. It has been estimated in several studies that the rate of primary, asymptomatic Epstein-Barr virus infection in seronegative pediatric recipients is between 60% and 80%, and that approximately 50% of children are seronegative before transplantation. Symptomatic Epstein-Barr virus disease develops in a subset of infected children, and PTLD more commonly occurs with primary infection. Data from many small North American series suggest a lifetime risk for the development of PTLD for renal allograft recipients of less than 1%, while it is 2% to 4% for adult liver allograft recipients, slightly higher for heart recipients, and as high as 10% for heart-lung recipients.

Ocular involvement in patients with PTLD is thought to be unusual. We identified only 4 cases of intraocular involvement in the medical literature. Brodsky et al reported the case of a 7-year-old girl who was immunosuppressed with cyclosporine after liver transplantation. She developed bilateral iris tumors associated with...
anterior chamber cells and flare, and mutton-fat keratic precipitates, but no posterior segment abnormalities. Robinson et al\textsuperscript{7} reported the case of a young girl who was receiving cyclosporine after liver transplantation and developed multiple large pigmented iris nodules associated with 1+ to 2+ anterior chamber cellular reactions in both eyes and fine-sized and medium-sized keratic precipitates, but no posterior segment involvement. In these 2 cases, the patients did not have a known diagnosis of systemic PTLD, although 1 patient had splenomegaly.\textsuperscript{6,7} In the case reported by Brodsky et al,\textsuperscript{6} the large iris tumors responded to irradiation, while nodules in the case reported by Robinson et al\textsuperscript{7} resolved with the reduction of cyclosporine dosage. Clark et al\textsuperscript{8} reported a case of intraocular PTLD in a 2-year-old boy who developed unilateral anterior chamber inflammation (1+ cells) and an iris tumor. This patient was immunosuppressed with cyclosporine and prednisone after undergoing liver transplantation at age 4 months, but had no evidence of systemic PTLD. Wedge resection of the iris lesion was performed with no recurrence at 6 months' follow-up. Ocular involvement has also been reported in an adult with PTLD. Demols et al\textsuperscript{9} reported the case of a 59-year-old man with PTLD after lung transplantation, who developed an anterior chamber cellular reaction and a subretinal, plaque-like lesion with overlying retinal vascular occlusion in one eye. The posterior lesion resolved with acyclovir and a reduction of cyclosporine dosage. Post-transplant lymphoproliferative disorder has also been reported to involve the orbit.\textsuperscript{23}

Our study suggests that the risk of ocular involvement in pediatric liver transplantation patients with PTLD to be 20% at 3 years, although the risk cannot be stated with certainty because of the small sample sizes. The prevalence of ocular involvement associated with transplantation of other organs is not known.

There is evidence that the rate of PTLD after first orthotopic liver transplantation in children who are immunosuppressed with tacrolimus can be decreased if high-risk recipients (Epstein-Barr virus–positive donor, Epstein Barr virus–negative recipient) are treated preemptively with a course of intravenous ganciclovir. Levels of Epstein-Barr virus in peripheral blood are also monitored by PCR technique in these patients; if Epstein-

### Patients With Posttransplant Lymphoproliferative Disorder and Ocular Involvement

<table>
<thead>
<tr>
<th>Factor</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age at presentation, y</td>
<td>14</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Organ transplanted</td>
<td>Heart</td>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>Systemic PTLD*</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Interval from transplantation to diagnosis of PTLD, mo</td>
<td>61</td>
<td>53</td>
<td>68</td>
</tr>
<tr>
<td>Interval from diagnosis of systemic PTLD to ocular involvement, mo</td>
<td>NA</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>Visual acuity at initial visit</td>
<td>Cyclosporine, azathioprine</td>
<td>Cyclosporine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Anterior chamber cells at initial visit</td>
<td>C2</td>
<td>C2</td>
<td>C2</td>
</tr>
<tr>
<td>OD</td>
<td>20/20</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>OS</td>
<td>20/20</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>Posterior synechiae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>Occasional</td>
<td>2+</td>
<td>Occasional</td>
</tr>
<tr>
<td>OS</td>
<td>3+</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>Iris nodules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>OS</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fundus</td>
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<td></td>
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</tr>
<tr>
<td>OD</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>OS</td>
<td>Normal</td>
<td>Subretinal mass, optic disc swelling</td>
<td>Normal</td>
</tr>
<tr>
<td>Treatment</td>
<td>Topical corticosteroid, decreased immunosuppressive drugs, oral acyclovir</td>
<td>Topical corticosteroid, decreased immunosuppressive drugs, intravenous ganciclovir</td>
<td>Topical corticosteroid</td>
</tr>
<tr>
<td>Course</td>
<td>Slow decrease in cells, resolution of nodules</td>
<td>Slow improvement in vision, decrease in cells, reduction in size of subretinal mass and optic disc swelling; recurrent cellular reaction 7 mo after initial visit followed by improvement in vision and decreased cells in response to intravenous ganciclovir and discontinuation of cyclosporine</td>
<td>Stable</td>
</tr>
<tr>
<td>Duration of follow-up, mo</td>
<td>24</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Final visual acuity</td>
<td>20/20</td>
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<tr>
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<td>20/20</td>
<td>20/30</td>
<td>20/20</td>
</tr>
<tr>
<td>OS</td>
<td>20/20</td>
<td>20/40</td>
<td>20/20</td>
</tr>
</tbody>
</table>

* PTLD indicates posttransplant lymphoproliferative disorder.
Barr virus levels rise, tacrolimus levels are dropped. Using this protocol, the rate of PTLD in one study fell from 10% to 5%. No information is available regarding the potential effect of such protocols on ocular involvement in those patients who do develop PTLD.

Our 3 cases and the 4 cases reported previously in the medical literature have many common features, although the signs and severity of ocular involvement varied between cases. All cases had anterior chamber cells. Iris nodules were a common, although not universal, finding. Each of our cases and 2 of the 4 previously reported cases were bilateral, although findings were asymmetrical. Bilaterality is consistent with the fact that PTLD is a multifocal condition. Our case 2, with severe panuveitis and a subretinal mass, shows that children with PTLD may develop posterior segment lesions as described by Demols et al30 in an adult. There was no distinct difference in the ocular manifestations between the cardiac transplantation patient and liver transplantation patients in our series.

The clinical course of the ocular disease seems to be chronic and fluctuating. In case 2, inflammation was unchanged for 4 months, followed by dramatic improvement for 4 months, followed again by recurrent inflammation. Ocular lesions showed minimal response to topical corticosteroids, but there was a slow response to lowering of immunosuppressive drugs. Response of ocular lesions to decreased immunosuppressive drugs was not observed for 2 to 4 months.

The role of antiviral medication for treatment of PTLD is undetermined. Davis et al31 reported a lower rate of PTLD in patients receiving intravenous ganciclovir followed by high-dose oral acyclovir. Two of our 3 patients (cases 2 and 3), both of whom had a history of PTLD, were already receiving acyclovir when they were diagnosed with ocular involvement. In contrast, oral acyclovir may have contributed to improvement seen in the other patient (case 1). This observation might suggest viral resistance to acyclovir with chronic therapy or that virus replication might not play as important a role in pathogenesis during the later stages of PTLD as it does at disease onset.

There is increasing evidence that the use of a more potent, multiagent approach to immunosuppression, which has resulted in improved graft survival in many types of organ transplantation, has accelerated the development of PTLD. The OKT-3 cell, a monoclonal antibody that specifically targets cells bearing the CD3 determinant, results in a decrease in the number and function of circulating T lymphocytes and is associated with an increased risk of PTLD.17,19,20–28 Newell et al20 reported that use of OKT-3 for corticosteroid-resistant rejection increased the risk of developing PTLD. Morgan and Superrina20 reported 7 cases of PTLD in 66 pediatric liver transplantation patients. All 7 of the 43 patients who received OKT-3 had PTLD, compared with none of the 23 patients who did not receive OKT-3. Swinnen et al20 also reported the rate of PTLD to increase from 1.3% to 11.4% in a group of cardiac allograft recipients receiving OKT-3.

Cyclosporine may also increase the rate of PTLD.31 Tanner et al32 demonstrated that Epstein-Barr virus–infected human peripheral blood mononuclear cells cultured in the presence of cyclosporine showed increased proliferation of Epstein-Barr virus–infected B lymphocytes and increased expression of interleukin 6 in T lymphocytes, when compared with those cultured without cyclosporine, thereby promoting B lymphocyte proliferation and immortalization. Although tacrolimus immunosuppression has also been associated with an increased risk of PTLD in children,33 there was a significant association between the use of cyclosporine as an immunosuppressive agent and ocular involvement in our series. A causal relationship cannot be determined; other unrecognized factors such as disease severity may have influenced both the choice of drug and the development of ocular lesions.

Our series provides additional evidence that PTLD can involve the eye, and, to our knowledge, gives a more detailed description of its ocular manifestations than has been provided in previously reported cases. It provides an estimate of the risk for ocular involvement not previously available from isolated case reports. It also provides additional evidence that the spectrum of ocular manifestations includes posterior segment lesions, and that a localized form of PTLD can occur in the eye without systemic disease.

Posttransplant lymphoproliferative disorder can present as a masquerade syndrome and should be considered in the differential diagnosis of uveitis in immunosuppressed patients. Although we are unable to establish the rate of disease precisely, screening of all children with PTLD seems to be appropriate; 2 of our 3 cases were identified on routine examinations. The prognosis for systemic PTLD is variable depending on the severity, extent, location, and malignancy of the infiltrating cells and their response to treatment. The same is probably true for ocular lesions.

Subsequent to submission of this manuscript, another case of ocular involvement in a child with PTLD was published.34 A 4-year-old girl who had undergone cardiac transplantation developed iris lesions and an anterior chamber cellular reaction as seen in our case 1. Studies revealed the iris lesion to be a monoclonal neoplasm of B cell origin. It regressed with local radiation therapy.
This additional case emphasizes that the spectrum of possible ophthalmic manifestations of PTLD can include lymphoma.

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REFERENCES


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