Infectious Ocular Complications in Orthotopic Liver Transplant Patients

Genovefa A. Papanicolaou, Burt R. Meyers, Wayne S. Fuchs, Samuel L. Guillory, Meryl H. Mendelson, Patricia Sheiner, Sukru Emre, and Charles Miller

We report the frequency and type of infectious ocular complications following orthotopic liver transplantation (OLT) and review diagnostic and therapeutic strategies. During the period September 1988 through November 1994, 684 patients underwent OLT at Mount Sinai Hospital (New York). Nine orthotopic liver transplant patients (1.3%) developed ocular infections: *Candida albicans* endophthalmitis (2), *Aspergillus fumigatus* endophthalmitis (1), cytomegalovirus retinitis (4), herpes simplex virus keratitis (1), and varicella-zoster virus panophthalmitis (1). The mean time from OLT to ocular symptoms was 42 days for patients with fungal infections and 128 days for patients with viral infections. Blurred vision was the commonest symptom (five of nine cases). The mean duration of follow-up was 2 years (range, 33 days to 5 years). Permanent loss of vision occurred in three patients, five had improvement in visual acuity, and one died of disseminated aspergillosis 33 days after OLT. Infectious ocular complications following OLT may occur as isolated events or with disseminated disease. Fungal infections occur earlier (mean, 42 days after OLT) than viral infections (mean, 4 months after OLT). The clinical presentation may be atypical; aggressive vitreoretinal procedures and serial examinations may be required to establish the diagnosis. Cytomegalovirus retinitis in orthotopic liver transplant patients may not require life-long maintenance therapy with antiviral agents.

Infectious ocular complications have been reported following solid organ and bone marrow transplantation [1–4]. The optic fundus may be affected by an opportunistic infection that is an independent focus or part of a systemic infection. In addition, noninfectious ocular complications, which are usually attributed to the direct toxic effects of immunosuppressants, may occur [2–6]. Clinical manifestations of ocular infections in transplant patients are often atypical; mixed infections or noninfectious complications may coexist [7, 8]. Timely diagnosis and administration of specific treatment are essential for preservation of vision. We report the types and frequency of ocular infections that occurred in liver transplant patients at Mount Sinai Hospital (New York) during a 6-year period. The clinical presentations and diagnostic and therapeutic strategies are reviewed.

Patients and Methods

All patients underwent orthotopic liver transplantation (OLT) at The Mount Sinai Medical Center. Patients with ocular symptoms were referred for ophthalmology consultation. Subsequently, these patients were followed up longitudinally for response to treatment and outcome. Records of patients with ocular infections were reviewed for demographics, indication for OLT, immunosuppressive treatment, episodes of rejection, postoperative complications, time from OLT to ocular infection, findings of ocular examination, presence of systemic disease, therapy, surgical procedures, and outcome of ocular infections.

Immunosuppressive therapy with cyclosporine, azathioprine, and steroids was given until May 1994 as follows: cyclosporine—5 mg/kg orally twice a day (dose adjusted until whole blood trough level was 350–400 ng/mL); azathioprine—1–2 mg/kg orally once a day (dose adjusted based on WBC count); and steroids—intravenous hydrocortisone (1,000 mg intraoperatively), intravenous methylprednisolone (200 mg, 160 mg, 120 mg, 80 mg, and 40 mg [in four divided doses] on postoperative days 1, 2, 3, 4, and 5, respectively), and prednisone (20 mg orally per day). Over 1 year, the prednisone dosage was reduced to 5–10 mg orally per day.

From 1991 to May 1994, 138 patients received tacrolimus (0.05 mg/kg orally twice a day; dose adjusted until whole blood trough level was 10–20 ng/mL) in randomized trials and as rescue therapy. Since June 1994, tacrolimus has been used as standard immunosuppressive therapy except for patients with hepatitis C virus cirrhosis who receive OKT-3 monoclonal antibodies (5 mg intravenously daily for 10 days) and immunosuppressive therapy with cyclosporine, azathioprine, and steroids. Rejection episodes were treated with a recycle of steroids. Rejection not responding to steroid recycle was treated with OKT-3 monoclonal antibodies.

All recipients received acyclovir (800 mg orally four times a day for 3 months followed by 200 mg orally twice a day for...
From 3 September 1988 through 11 November 1994, 684 patients underwent OLT. Ocular infections occurred in nine (1.3%) of these patients. The demographics and baseline clinical characteristics of the patients with ocular infections were similar to those of the whole group of patients who underwent OLT. There were four females and five males; the mean age of the nine patients was 47.2 years (range, 5–57 years), compared with 45 years for all transplant recipients. The demographics and clinical characteristics of the nine patients are shown in table 1. Six patients were treated for rejection.

Three patients developed endophthalmitis due to fungi (Candida albicans, two; Aspergillus fumigatus, one). CMV retinitis occurred in four patients; varicella-zoster virus panophthalmitis and herpes simplex virus (HSV) keratitis were found in one patient each. The mean time from OLT to ocular symptoms was 42 days (range, 13–60 days) for patients with fungal infections and 128 days (range, 47–240 days) for patients with viral infections. The clinical presentations of the nine patients are listed in table 2. Five patients presented with blurred vision; 2, with ocular pain; 1, with opacification of the cornea; and 1, with loss of vision. Bilateral disease occurred in one patient with C. albicans endophthalmitis and in one with CMV retinitis.

The diagnosis of fungal infection was made by gram staining of vitreous fluid in two cases; C. albicans was detected in one case, and A. fumigatus was detected in the other. Patient 1 was treated initially for toxoplasma chorioretinitis with sulfamethoxazole, pyrimethamine, and folinic acid. Follow-up examination 2 weeks later showed dense vitreitis with vitreous strands (figure 1). The patient underwent pars plana vitrectomy. Culture of the vitreous yielded C. albicans. Patient 2 was initially asymptomatic when funduscopy examination was done. However, she later developed blurred vision while receiving treatment with amphotericin B, and results of follow-up funduscopic examination were consistent with candidal endophthalmitis. Patient 3 was intubated and unresponsive when opacification of the cornea developed. The diagnosis of A. fumigatus endophthalmitis was made by staining of vitreous fluid obtained by vitreal aspiration; disseminated aspergillosis was noted at autopsy.

The diagnosis of viral infection was made on the basis of the funduscopic appearance. Three patients with CMV retinitis had serological evidence of acute CMV infection (i.e., the presence of IgM antibodies). Patient 7 had CMV retinitis and concomitant CMV pneumonia.

The treatment and outcome of ocular infections are shown in table 3. Systemic amphotericin B therapy (dose range, 1–2 g) was used to treat fungal endophthalmitis. Patient 1 required treatment with vitrectomy and intravitreal amphotericin B in addition to intravenous amphotericin B therapy. Patients with CMV retinitis received ganciclovir therapy (mean dosage, 5 mg/kg every 12 hours for 23 days). One patient also received intravenous immune globulin treatment (500 mg/kg). HSV keratitis was treated with oral acyclovir (1,000 mg/d) and 1% trifluridine ophthalmic drops. The mean duration of follow-up was 2 years (range, 33 days to 5 years).
Table 2. Presentation and diagnosis of ocular infections in nine orthotopic liver transplant recipients.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Diagnosis</th>
<th>Days after OLT</th>
<th>Ocular symptom(s)</th>
<th>Results of eye examination</th>
<th>Concomitant conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Candida albicans</em> endophthalmitis, OS</td>
<td>60</td>
<td>Blurred vision</td>
<td>4+ vitreitis, white strands; VA: hand motion, OS</td>
<td>Repeated OLT, surgical wound infection, candidemia, HSV hepatitis</td>
</tr>
<tr>
<td>2</td>
<td><em>C. albicans</em> endophthalmitis, OU</td>
<td>13</td>
<td>Asymptomatic, then blurred vision</td>
<td>White lesions, retinal hemorrhages; VA: 20/20, OU</td>
<td>Poor graft function, stage IV enccephalopathy, multiple episodes of sepsis</td>
</tr>
<tr>
<td>3</td>
<td><em>Aspergillus fumigatus</em> endophthalmitis, OS</td>
<td>25</td>
<td>Opacification of cornea</td>
<td>Opacification of cornea, OS</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>4</td>
<td>Varicella-zoster virus panophthalmitis, OS</td>
<td>47</td>
<td>Tearing pain</td>
<td>Retinal necrosis, uveitis, secondary glaucoma; VA: 20/400, OS</td>
<td>Rejection, CMV colitis, candidal esophagitis, gastrointestinal Kaposi’s sarcoma</td>
</tr>
<tr>
<td>5</td>
<td>HSV keratitis, OS</td>
<td>90</td>
<td>Tearing pain</td>
<td>Branching dendrite, epithelial ulceration; VA: 20/100, OS</td>
<td>CMV pneumonitis with intranuclear inclusions, seroconverted to CMV (IgM antibodies)</td>
</tr>
<tr>
<td>6</td>
<td>CMV retinitis, OD</td>
<td>240</td>
<td>Blurred vision</td>
<td>Hemorrhages, cotton-wool spots, retinal edema, hemicentral retinal vein occlusion</td>
<td>CMV IgM antibodies, lacunar infarct at left putamen</td>
</tr>
<tr>
<td>7</td>
<td>CMV retinitis, OU</td>
<td>150</td>
<td>Blurred vision</td>
<td>Exudative retinopathy, diabetic retinopathy; VA: 20/30, OD; 20/50, OS</td>
<td>Seroconverted to CMV (IgM antibodies)</td>
</tr>
<tr>
<td>8</td>
<td>CMV retinitis, OD</td>
<td>180</td>
<td>Loss of vision</td>
<td>Papillitis, peripapillary hemorrhage; VA: hand motion, OD</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CMV retinitis, OS</td>
<td>60</td>
<td>Blurred vision, vomiting, vertigo</td>
<td>Dilated vessels, retinal vein occlusion; VA: 20/200, OS</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. CMV = cytomegalovirus; HSV = herpes simplex virus; OD = right eye; OLT = orthotopic liver transplantation; OS = left eye; OU = both eyes; VA = visual acuity.

Permanent total loss of vision occurred in three patients. A patient with CMV retinitis (case 8) presented with serological evidence of CMV infection (presence of IgM antibodies) and papilledema (figure 2); this patient did not respond to ganciclovir treatment, and her condition progressed to loss of vision. Another patient with CMV retinitis (case 9) had serological evidence of acute CMV infection; this patient responded to intravenous ganciclovir therapy but had subsequent retinal vein occlusion. One patient with varicella-zoster virus panophthalmitis (case 4) developed a blind, painful eye that required enucleation. Five patients had improvement in visual acuity following treatment; one patient died of disseminated aspergillosis 33 days after OLT.

Discussion

The incidence of ocular infections following kidney, heart, and bone marrow transplantations has been previously reported to vary between 2% and 5% [2–4]. In our study, the incidence of ocular infections in orthotopic liver transplant patients was 1.3%. Fungal infections appeared earlier (mean, 42 days) than viral infections (mean, 128 days). This finding is in agreement with prior reports of the timing of ocular infections in the posttransplantation period [2, 3]. Life-threatening bacterial and fungal infections tend to occur in the early postoperative period. During that time, patients are still suffering from the direct or
Table 3. Treatment and outcome of ocular infections in nine orthotopic liver transplant recipients.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Procedure</th>
<th>Treatment (dose)</th>
<th>Outcome</th>
<th>Duration of follow-up (d) after OLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vitrectomy</td>
<td>iv AmB (1 g total)/IC AmB (5 μg)</td>
<td>Improvement; VA: 20/100, OS</td>
<td>399</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>iv AmB (2 g total)</td>
<td>Healing, normal vision</td>
<td>1,789</td>
</tr>
<tr>
<td>3</td>
<td>Vitreal aspiration</td>
<td>iv AmB (300 mg total)</td>
<td>Death due to disseminated aspergillosis (brain, meninges, heart, lungs,</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>kidneys)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Enucleation</td>
<td>iv acyclovir (10 mg/kg q8h for 21 d)</td>
<td>Loss of vision in OS; died of recurrent hepatitis C</td>
<td>591</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>po acyclovir (200 mg five times a day</td>
<td>Healing</td>
<td>1,981</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 14 d; 1% trifluridine ophthalmic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>drops (1 g q2h for 5 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>iv ganciclovir (5 mg/[kg · d] for 21 d)</td>
<td>Improvement</td>
<td>1,217</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>iv ganciclovir (5 mg/[kg · d] for 30 d);</td>
<td>Improvement; died of hemorrhage and sepsis</td>
<td>286</td>
</tr>
<tr>
<td></td>
<td></td>
<td>iv foscarnet (90 mg/[kg · d] for 30 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>iv ganciclovir (5 mg/[kg · d] for 14 d);</td>
<td>Loss of vision in OD</td>
<td>271</td>
</tr>
<tr>
<td></td>
<td></td>
<td>iv immunoglobulin (500 mg/kg once)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>Retinal vein thrombosis, loss of vision in OS</td>
<td>356</td>
</tr>
</tbody>
</table>

NOTE. AmB = amphotericin B; IC = intravitreal; OD = right eye; OLT = orthotopic liver transplantation; OS = left eye; VA = visual acuity.

indirect effects of underlying disease, major surgery, risk of wound and nosocomial infections, and large doses of immunosuppressants. The early postoperative period also covers the incubation period of herpesviruses, like CMV, HSV, and Epstein-Barr virus, that may be transmitted during transplantation or reactivated because of immunosuppression.

In our study, CMV retinitis was the most common ocular infection. CMV retinitis was first described in immunocompromised hosts in 1959 [9]. CMV retinitis is the most common opportunistic infection in patients with AIDS, occurring in up to 40% of patients [10, 11]. In transplant patients, the appearance of CMV retinitis is typical, with characteristic vessel sheathing, edematous and hemorrhagic lesions with actively extending borders, and a pallid necrotic center [12]. Larger lesions can be confused with retinitis associated with toxoplasmosis or candidal infection or with retinal vein occlusion when there are extensive hemorrhages [13]. In one report [14], the use of tacrolimus as immunosuppressive therapy was associated with an increased incidence of CMV retinitis.

The natural history of CMV retinitis may be different in immunocompromised patients with AIDS than in those without AIDS. In patients with AIDS, if left untreated, CMV retinitis causes partial or complete visual loss [10]. Intravenous infusions of ganciclovir or foscarnet are required for maintenance therapy [15]. Immunocompromised patients without AIDS may be asymptomatic at the time of diagnosis in up to 50% of the cases [12]. Before the availability of specific antiviral treatment, a number of patients’ conditions improved as requirements for maintenance immunosuppressive therapy diminished in the late posttransplantation period [12]. Since the availability of specific treatment, resolution has been reported following induction therapy alone [16–18].

In our study, the conditions of two of four patients with CMV retinitis improved with induction therapy, and disease did not recur during follow-up; none of these patients received maintenance therapy. However, one patient died of a nonrelated cause at 7 months of follow-up. Currently, the exact incidence of CMV retinitis in liver transplant patients is unknown. Since relapse or retinal detachment may occur [19], we recommend careful follow-up of patients whose disease has resolved.

In our study, two of four cases of CMV retinitis developed in CMV-seronegative recipients of a CMV-seropositive liver. Patient 7 had concomitant CMV pneumonia; because of persistent shortness of breath, he was treated with a prolonged course of ganciclovir therapy and subsequent foscarnet therapy. Preexisting diabetic retinopathy in this patient obscured the diagnosis of CMV retinitis. The use of immunosuppressive therapy with OKT-3 monoclonal antibodies for hepatitis C may have contributed to the development of CMV disease and the late mani-
Candidal endophthalmitis usually presents with distinctive signs demonstrated by funduscopic examination [21]. In case 1, the funduscopic appearance was atypical, and there was no clinical or laboratory evidence of disseminated candidal infection. This patient probably had transient candidemia during hospitalization for OLT, with subsequent seeding of the eye. The appearance of “stranding,” which has been reported by other investigators [22], led to initial therapy for toxoplasmosis.

This case underlines the need for an early aggressive workup with vitreal aspiration when the diagnosis is unclear. In case 2, candidal endophthalmitis was diagnosed in the context of hospital-acquired candidemia. Retinal involvement with candidemia may occur in 37% of patients [23, 24]. Ophthalmologic examination is recommended for asymptomatic patients with candidemia and risk factors [25].

Disseminated fatal aspergillosis developed in a gravely ill patient (case 3) while empirical treatment with fluconazole was being administered. Panophthalmitis is usually a manifestation of generalized aspergillosis [26]. A recent report [27] described seven cases of aspergillus endophthalmitis associated with OLT; the cases were diagnosed at autopsy (all with disseminated infection). The use of low doses of amphotericin B has been shown to reduce the incidence and mortality rate associated with invasive aspergillosis in bone marrow transplant patients [28]. In addition, itraconazole has been used successfully as therapy for patients with chronic granulomatous disease [29]. However, invasive aspergillosis has occurred in liver transplant recipients receiving low doses of amphotericin B [30] and bone marrow transplant patients receiving fluconazole therapy [31].

Patient 5 developed HSV keratitis and CMV colitis shortly after a rejection episode. In addition, this patient had esophageal candidiasis and gastrointestinal Kaposi’s sarcoma. The additional immunosuppressants used for treatment of rejection may have contributed to the reactivation of HSV and CMV diseases. Herpetic lesions in the immunocompromised host tend to persist or recur with topical therapy in up to 33% of cases within 24 months unless the dose of immunosuppressive medications is reduced [32]. Our patient responded to oral acyclovir therapy without recurrence.

A variety of pathogens, including Nocardia species, Listeria monocytogenes, Toxoplasma gondii, Fusarium species, Pseudallescheria boydii, Scedosporium species, Cryptococcus neoformans, Aspergillus species, and Coccioides immitis, have been reported to cause ocular infections in transplant patients [27, 33–41]. Aggressive vitreoretinal diagnostic procedures are recommended for selected patients, since the vitreous humor is the intraocular site with the highest yield of bacterial and fungal pathogens. Smears should be treated with gram, Giemsa, and periodic acid–Schiff stains and examined. Fluorochrome stains are sensitive for detecting mycobacteria or fungi. Concentrating the fluid obtained by vitrectomy by means of centrifuging or passing through a Millipore filter (Millipore, Marlborough, MA) may increase the yield. Cytological examination of the vitreous specimen is important since ocular malignancy is a potential complication of the immunosuppressed state [2, 42].

Standard prophylactic regimens for liver transplant patients offer some protection against pathogens that may cause ocular infections. Trimethoprim-sulfamethoxazole prophylaxis for P. carinii infection is also effective against infection due to T. gondii, L. monocytogenes, and Nocardia species. Acyclovir therapy has been shown to reduce the incidence of CMV disease in orthotopic liver transplant patients [43]. However, its efficacy in preventing CMV retinitis in these patients has not been studied.

Current approaches to the management of ocular infections include intravitreal antibiotic therapy and novel antiviral and antifungal therapy in combination with mechanical vitrectomy. Amphotericin B has been the standard treatment of candidal endophthalmitis; a cure rate of 92% has been associated with this therapy [44]. Fluconazole has minimal toxic effects, is well absorbed orally, and achieves high concentrations in the chambers of the eye [45, 46]. A limited number of studies have reported cure rates of up to 94% among patients with candidal endophthalmitis who were treated with fluconazole [47]. Liposomal amphotericin B therapy may be of value, but studies are needed to prove its efficacy. Oral ganciclovir, intravitreal ganciclovir, foscarin, and cidovir are currently used in the management of patients with AIDS and CMV retinitis [15]. Some of these treatment modalities may prove useful for the transplant population.

In conclusion, infection should always be considered in liver transplant patients with ocular symptoms. The funduscopic appearance in orthotopic liver transplant patients may be atypical, and findings may be superimposed on noninfectious preexisting pathology. A high index of suspicion and aggressive intravitreal procedures may be needed to establish a diagnosis. Treatment should be directed against the specific pathogen, with reduced doses of immunosuppressants whenever possible. Selected patients may benefit from screening and planned eye examinations following transplantation.

References
