Incidence and clinical characteristics of ocular infections after heart transplantation: a retrospective cohort study


Abstract: Background: Ocular infections associated with organ transplantation are well documented following renal and liver transplantation; however, few studies have reported ocular infections following heart transplant.

Methods: We retrospectively studied patients who underwent heart transplantation in the Mayo Clinic Cardiac Transplant Program from January 1st 1988 through June 30th 2006.

Results: We report the frequency and type of ocular infections among 313 heart transplant recipients. There were eight patients (2.5%) diagnosed with ocular infections including three cases of ophthalmic zoster, one case of cytomegalovirus retinitis, one case of *Aspergillus fumigatus* endophthalmitis, one case of *Haemophilus influenzae* conjunctivitis, one case of blepharitis, and one case of preseptal orbital cellulitis.

Conclusions: Ocular infections are rare after heart transplantation and usually present within the first year post-transplantation. The majority can be regarded as opportunistic infections which may be indicative of infections at other body sites. Ocular infections after heart transplantation may be associated with significant morbidity and visual loss if not promptly diagnosed.

Background

Ocular infections associated with organ transplantation have been well documented following renal transplantation (1) and liver transplantation (2), but few studies have reported ocular infections following heart transplantation (3–6). Some have suggested that solid-organ transplant recipients require regular ophthalmic screening because the visual prognosis is poor in the face of ocular infections, and early detection may improve prognosis (7). However, results of a recent study (3) did not favor screening of asymptomatic individuals following heart, lung, or heart–lung transplantation, due to the low prevalence of ocular infections reported in this population (0.87%). We report the frequency and type of ocular infections following heart transplantation at Mayo Clinic (Rochester, MN, USA).

Patients and methods

We performed a retrospective cohort study of all patients who underwent heart transplantation in the Mayo Clinic Cardiac Transplant Program from January 1st 1988 through June 30th 2006. Two patients who did not provide consent for review of their medical record (Minnesota Statute 144.335) were not included in the analysis.

We collected data regarding patient demographics, health behaviors, work history, medical conditions, indications, and preparation for transplant,
post-transplant medications, history of ocular infection and follow-up. The observation period for each patient began on the date of transplantation and continued until October 1st 2006. The primary outcome was the diagnosis of ocular infection as reported by the treating physician. The Mayo Clinic Transplant Database, Diagnostic Index Database, Mayo Clinic Clinical Laboratories Database and paper and/or electronic medical records were used as sources of information.

Patients in the Cardiac Transplant Program at Mayo receive lifelong prophylaxis with trimethoprim-sulfamethoxazole (unless they have a relevant allergy to trimethoprim-sulfamethoxazole). If allergic, *Toxoplasma gondii* donor seropositive/recipient seronegative patients receive daily pyrimethamine for three months. The varicella-zoster virus (VZV) virus vaccine was introduced during the study period. Therefore, patients who were seronegative likely received this vaccine soon after it became available. All transplant candidates received the conjugate 23-valent pneumococcal vaccine pre-transplant. Antiviral prophylactic strategies changed over time; current post-transplant antiviral prophylaxis include valganciclovir for all cytomegalovirus (CMV) donor-seropositive/recipient-seronegative heart transplant recipients for 3 months after transplantation. Acyclovir (if the patient is not receiving ganciclovir or valganciclovir) is administered for six wk.

**Results**

A total of 313 patients who underwent heart transplantation from 1988 to 2006 were studied (median 52 yr of age, range: 0.1–73). The most common causes of heart failure were idiopathic dilated cardiomyopathy and ischemic heart failure, collectively causing heart failure in 198 of 313 patients (63%).

Eight of 313 patients (2.5%) were diagnosed with ocular infections (Table 1) including three cases of ophthalmic zoster infection, one case of CMV retinitis, one case of *Aspergillus fumigatus* endophthalmitis, one case of preseptal orbital cellulitis, one case of blepharitis, and one case of *Haemophilus influenzae* conjunctivitis. In addition, one patient had three episodes of self-limiting iritis, but was not included as no clear infectious etiology was demonstrated. The median age of the patients with ocular infections was 62.5 yr (range: 0.1–64). Immunosuppressive regimens at time of infection consisted of combinations of cyclosporine A (eight patients), prednisone (four patients), azathioprine (four patients), and mycophenolate mofetil (two patients).

Six patients developed ocular infections within 16 months post-transplantation, with five of them occurring within one yr after transplantation. More than four yr after transplantation, patient 7 developed preseptal orbital cellulitis probably related to an insect bite. No cultures were obtained. She received intravenous vancomycin followed by oral amoxicillin-clavulanate for 10 d with complete resolution of signs and symptoms. Patient 8 was diagnosed with bacterial blepharitis eight yr after transplantation; symptoms and signs responded to topical erythromycin. The most common presenting symptom was eye pain and/or a red eye (six patients, 75%). One patient (patient 5) had blurry vision as the presenting symptom. Patient 4 was asymptomatic and was diagnosed with CMV retinitis during ophthalmological screening. Clinical findings led to immediate diagnosis in six patients. Culture of vitreous fluid and conjunctival secretions yielded a diagnosis in the other two patients (patients 5 and 6).

Three patients (patients 1, 2, and 3) had ophthalmic zoster (37.5% of all ocular infections) and all had positive pre-transplant VZV serologies. Patient 1 presented with decreased consciousness and lesions on the scalp and cornea. Cerebrospinal fluid polymerase chain reaction for VZV was positive. Although he received intravenous acyclovir without delay, he has been dependent in daily activities since this episode. Patient 2 presented with left periorbital headache followed by a blistering skin eruption of the left temporal region. She had no fever, neck stiffness, or visual disturbances. An abnormality in the left vasofrontal parenchymal region just above the cavernous sinus and near the region of the optic canal was seen on magnetic resonance imaging, possibly reflecting vascular involvement with VZV. Polymerase chain reaction of the skin lesion was positive for VZV. She was treated with a two-wk course intravenous acyclovir followed by oral valacyclovir. Patient 3 presented with an itchy red eye and skin lesions involving the left forehead and left upper eyelid. Oral acyclovir was started and the patient recovered quickly.

Patient 4 had CMV retinitis of the left eye which was discovered on routine eye examination 16 months following cardiac transplantation. Funduscopy showed peripheral retinitis. Polymerase chain reaction for CMV of blood was repeatedly negative. She received intravenous ganciclovir for two months followed by a six-month course of oral ganciclovir, with resolution of the retinitis. Seven yr later, she developed multiple episodes of CMV duodenitis and gastritis. She died eight yr after transplantation due to cardiac failure accompanied by pulmonary infection with *A. fumigatus*. 

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**Ocular infections in heart transplant recipients**

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485
Table 1. Characteristics of patients with ocular infections after heart transplantation

<table>
<thead>
<tr>
<th>Patient/age/gender</th>
<th>Biology of heart failure</th>
<th>Year of transplantation</th>
<th>Donor (D)/Recipient (R) serology mismatch*</th>
<th>Hypertension/Diabetes</th>
<th>Time from transplant to infection (months)</th>
<th>Immunosuppressive regimen at the time of ocular infection</th>
<th>Presenting symptoms</th>
<th>Diagnostic tests</th>
<th>Diagnosis</th>
<th>Systemic involvement</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/63/M</td>
<td>Amyloidosis</td>
<td>2005</td>
<td>No</td>
<td>Yes/No</td>
<td>12</td>
<td>Cyclosporine, prednisone</td>
<td>Conjunctival erythema and confusion</td>
<td>Polymerase chain reaction in cerebrospinal fluid positive for VZV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ophthalmic zoster right eye</td>
<td>Right V1 dermatomal zoster with central nervous system involvement</td>
<td>Intravenous acyclovir (2 wk)</td>
<td>Recovery with eye sequelae; dependent status</td>
</tr>
<tr>
<td>2/54/F</td>
<td>Amyloidosis</td>
<td>2000</td>
<td>Donor serologies unavailable</td>
<td>No/No</td>
<td>12</td>
<td>Cyclosporine, azathioprine</td>
<td>Left peri-orbital pain with left head rash, corneal lesion and conjunctival injection</td>
<td>Polymerase chain reaction from skin lesion positive for VZV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ophthalmic zoster</td>
<td>Left cavernous sinus involvement</td>
<td>Intravenous acyclovir followed by oral valacyclovir (4 wk); valacyclovir suppression</td>
<td>Recovery with no eye sequelae; post-herpetic neuralgia</td>
</tr>
<tr>
<td>3/60/M</td>
<td>Dilated cardiomyopathy</td>
<td>1993</td>
<td>Toxoplasma gondii (D&lt;sup&gt;+&lt;/sup&gt;, R&lt;sup&gt;-&lt;/sup&gt;)</td>
<td>No/Yes</td>
<td>9</td>
<td>Cyclosporine, azathioprine, prednisone</td>
<td>Eye itching</td>
<td>Clinical diagnosis</td>
<td>Ophthalmic zoster</td>
<td>No</td>
<td>Oral acyclovir (2 wk)</td>
<td>Recovery with no sequelae; no visual symptoms at anytime</td>
</tr>
<tr>
<td>4/56/F</td>
<td>Ischemic cardiomyopathy</td>
<td>1999</td>
<td>Epstein-Barr virus (D&lt;sup&gt;+&lt;/sup&gt;, R&lt;sup&gt;-&lt;/sup&gt;)</td>
<td>No/Yes</td>
<td>16</td>
<td>Cyclosporine, mycophenolate mofetil, prednisone</td>
<td>Asymptomatic</td>
<td>Peripheral retinitis lesion in fundus</td>
<td>CMV&lt;sup&gt;c&lt;/sup&gt; retinitis</td>
<td>No</td>
<td>Intravenous ganciclovir (2 months) followed by a 6-month oral ganciclovir</td>
<td>Recovery with no sequelae; no visual symptoms at anytime</td>
</tr>
<tr>
<td>5/56/M</td>
<td>Ischemic cardiomyopathy</td>
<td>1993</td>
<td>No</td>
<td>No/No</td>
<td>5</td>
<td>Cyclosporine, azathioprine</td>
<td>Blurry vision right eye</td>
<td>Vireous fluid culture</td>
<td>Aspergillus fumigatus endophthalmitis</td>
<td>Disseminated A. fumigatus endocarditis</td>
<td>Ophthalmologic injections, Intravenous deoxycholate followed by lipid complex amphotericin B (3 wk), aortic valve replacement, long-term itraconazole</td>
<td>Recovery with no sequelae</td>
</tr>
<tr>
<td>6/20/M</td>
<td>Congenital</td>
<td>2004</td>
<td>Donor serologies unavailable</td>
<td>No/No</td>
<td>12</td>
<td>Cyclosporine, mycophenolate mofetil, prednisone</td>
<td>Purulent drainage and conjunctival injection</td>
<td>Conjunctival swab</td>
<td>Haemophilus influenzae bilateral conjunctivitis</td>
<td>No</td>
<td>Recovery with no sequelae</td>
<td></td>
</tr>
<tr>
<td>7/0.1/F</td>
<td>Congenital</td>
<td>2001</td>
<td>CMV&lt;sup&gt;d&lt;/sup&gt; (D&lt;sup&gt;+&lt;/sup&gt;, R&lt;sup&gt;-&lt;/sup&gt;)</td>
<td>No/No</td>
<td>54</td>
<td>Cyclosporine, azathioprine</td>
<td>Swelling and redness of the right upper and lower eyelid</td>
<td>Clinical diagnosis</td>
<td>Preseptal orbital cellulitis</td>
<td>No</td>
<td>Intravenous vancomycin followed by oral amoxicillin-clavulanate (10 days)</td>
<td>Recovery with no sequelae</td>
</tr>
<tr>
<td>8/58/M</td>
<td>Dilated cardiomyopathy</td>
<td>1994</td>
<td>No</td>
<td>No/Yes</td>
<td>108</td>
<td>Cyclosporine</td>
<td>Eye itching, eyelid sore</td>
<td>Clinical diagnosis</td>
<td>Blepharitis</td>
<td>No</td>
<td>Topical erythromycin (2 wk)</td>
<td>Recovery with no sequelae</td>
</tr>
</tbody>
</table>

*Epstein-Barr virus, cytomegalovirus, or Toxoplasma gondii.

<sup>b</sup>Varicella zoster virus.

<sup>c</sup>Cytomegalovirus.
Ocular infections in heart transplant recipients

Patient 5 developed double and blurry vision in his right eye five months after cardiac transplantation. Ophthalmological exam revealed retinitis, vitreitis, and iridocyclitis. Fungal endocarditis involving his tricuspid aortic valve, and acquired from his donor, was diagnosed. The details of this case have been previously reported (8). Smear and culture of vitreous fluid were positive for A. fumigatus confirming the diagnosis of Aspergillus endophthalmitis. A. fumigatus was isolated from an aortic valve vegetation and from a skin lesion on the right hand. He underwent valve replacement with a homograft. Intravenous combined with intravitreous doxycholate followed by lipid complex amphotericin B was administered. After 12 d, intravenous therapy was switched to oral therapy with itraconazole 300 mg three times a day. His vision gradually improved to normal. At follow-up five yr after completion of amphotericin B therapy, he had no evidence of recurrent fungal infection, but continued to take itraconazole 200 mg orally twice daily.

Three patients developed bacterial ocular infections. Patient 6 presented with redness of both eyes along with bilateral eye pain and purulent drainage. He denied blurry or decreased vision. A conjunctival swab grew H. influenzae, and he was successfully treated with trimethoprim-sulfamethoxazole and polymyxin B sulfate ophthalmic solution. Patient 7 developed sudden swelling of the right upper and lower eyelid following an insect bite on the right temple. Over four h, the swelling progressed to the point that the patient was not able to open her eye. Intravenous vancomycin and oxacillin were initiated, followed by a 10-d course of amoxicillin-clavulanate, with excellent outcome. Patient 8 presented with eye itching nine yr after transplant, was diagnosed with blepharitis, and was successfully treated with topical erythromycin.

Discussion

Advances in effective antimicrobial prophylactic strategies have led to a decline in the incidence of opportunistic infections in heart transplant recipients. Ocular infections have been described as the most common cause of ocular disease in one study, affecting up to 2% of patients undergoing heart, lung, or combined heart-lung transplantation (4). The ocular infections incidence in our cohort of 313 patients (2.5%) is slightly higher than previously reported rates (0.87–2%) (3, 4). However, one patient developed a post-insect bite infection four yr from transplant (patient 7) and another developed blepharitis nine yr from transplant (patient 8); no culture was available yet both patients were classified as bacterial infections. Thus, the actual incidence in our cohort might be closer to 6/313 or 1.9% which is just outside the upper range of previous publications cited. An unknown proportion of ocular infections may have nothing to do with the cardiac transplant. A control population would be of limited use in this regard since the development of infectious diseases in the cardiac transplant population must be regarded as a complex interaction between pre-transplant risk factors, a complicated surgical procedure, and several post-surgical factors (i.e., immunosuppressive regimens).

Ocular infections typically occur months to years following transplantation, with fungal generally occurring earlier than viral infections (4). The majority of ocular infections in our cohort were opportunistic infections, which occurred within the first 18 months after transplant. Therefore, ophthalmologic screening might be justified every 3–6 months during the first 18 months after heart transplant.

The majority (62%) of patients with opportunistic ocular infections had infection with VZV or CMV. Herpes viruses are the most common pathogens involved as ocular infections, most commonly causing keratitis, acute retinal necrosis, or retinitis (4). It has been proposed that viral retinitis may be more frequent in heart than in the liver or renal transplant recipients (4). A previous study reported acute retinal necrosis as the most common manifestation of opportunistic herpes virus infection of the eye (4); surprisingly, none of our patients developed acute retinal necrosis. We observed three ophthalmic zoster infections without retinal involvement. The median time between transplant and VZV reactivation in these patients was 11 months. All patients presented with skin lesions. Ophthalmic zoster is a serious disease with substantial periocular edema in the early phase of the disease and contraction scars in the late phase; it can lead to incomplete eyelid closure and corneal exposure (9). One patient had concomitant central nervous system involvement with VZV and has been described previously (10).

Clinical suspicion of ophthalmologic zoster infection in heart transplant recipients should prompt immediate treatment with acyclovir.

One patient had CMV retinitis diagnosed late in the post-transplantation period during a routine examination. Previous reports have emphasized CMV as the most common retinal pathogen in transplant recipients (5, 6). Some authors have reported a low incidence (0.2%) of CMV retinitis in heart transplant recipients, similar to ours (0.3%), and have postulated that CMV retinitis is
unlikely to occur unless there is concomitant microvasculopathy (4). Despite being diabetic and hypertensive, our patient did not have evidence of retinopathy. Solid organ transplant patients with CMV retinitis do not often have extra-ocular manifestations of CMV disease (11). CMV retinitis is a clinical diagnosis; however, the possibility of ocular infections caused by Toxoplasma gondii, VZV or herpes simplex virus should be considered if there is not good clinical response to empirical treatment. Ganciclovir remains the treatment of choice with foscarne or cidofovir as rescue alternatives (12).

Transplant recipients are at risk for metastatic fungal intraocular infection because of their immunosuppressed status and because of the large number of invasive vascular procedures performed (13). One patient had fungal endophthalmitis due to a donor-acquired infection manifesting relatively early post-transplant. Aspergillus endophthalmitis has been previously reported in solid organ transplant recipients (4, 14, 15), as has Candida albicans endophthalmitis (13). Endogenous endophthalmitis is a rare cause of Aspergillus infection mostly seen in immunocompromised patients (15). Fungal ocular infections generally have had a poor prognosis, despite aggressive treatment, as the fungus has often disseminated to other sites, and recovery of vision may not occur due to the extensive retinal necrosis and choroidal damage (16). Our patient was diagnosed and treated early and lesions resolved with prolonged antifungal treatment and without significant visual loss. A definitive diagnosis of fungal ocular infection is based on histology and culture of appropriate specimens; however, vitreous biopsies are not always obtainable. Amphotericin B is a standard treatment, but has poor intraocular penetration (17), and should therefore be combined with intravitreal injections. Voriconazole has shown to have good penetration into the eye and may be a useful alternative, especially in conjunction with intravitreal voriconazole (18).

Ocular bacterial infections have not been previously emphasized in this population. We report conjunctivitis caused by H. influenzae and preseptal cellulitis, probably caused by Staphylococcus or Streptococcus species. H. influenzae is a cause of pneumonia in solid organ transplant recipients, usually occurring after the first year following transplantation. Little is known about the immunogenicity of the H. influenzae conjugate vaccine in these patients. In one study (19), a single dose of the conjugate vaccine was administered at various times after transplantation to 43 adult renal transplant recipients who did not have protective titers against H. influenzae type B at the time of immunization. Although 35% developed protective antibodies (compared with 71% of healthy control subjects), the optimal timing of vaccine administration and durability of response are not known. It is not possible to make a recommendation about the routine use of the H. influenzae vaccine in adult transplant candidates or recipients based on the published data. Cultures are not usually recommended for the initial diagnosis and therapy of conjunctivitis; however, because of the immunosuppressed state of these patients, cultures may be useful. Bacterial conjunctivitis may be treated with inexpensive non-toxic topical antibiotics.

Our study has several limitations. First, this is a retrospective study and so cases may have been missed, though our database is a prospective database. Second, we might have underestimated the occurrence of ocular infections in our cohort. As reported by other authors (3), ocular symptoms may be ignored and remain unreported as they have relatively minor consequences to the patient in the post-transplant period, particularly if transitory. Moreover, as Mayo is a referral hospital, some patients may be diagnosed with and treated for ocular infections elsewhere.

Advances in infection prevention and treatment strategies over the last two decades have led to an improvement in the outcome of heart transplant recipients. As survival improves, it becomes increasingly important to identify and aggressively treat all infectious complications. Ocular infections are rare after heart transplantation, but may affect quality of life after recovery and cause devastating visual lost. Herpesviruses and fungi (e.g., Aspergillus species) account for the majority of ocular infections in this population. Visual symptoms in heart transplant recipients warrant rapid ophthalmic assessment. Vitreous aspiration for Gram stain, fungal stain, and culture may be helpful to reveal the microbiology, enabling appropriate treatment.

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Disclosures

The authors report no conflicts of interest.
References


Ocular infections in heart transplant recipients