Endogenous *Aspergillus* Endophthalmitis Occurring After Liver Transplantation: A Case Report


**ABSTRACT**

Endogenous *Aspergillus* endophthalmitis (AE) is a rare complication of invasive aspergillosis in transplant patients. In this report, we have described a patient who underwent liver transplantation because of drug-induced cholestatic cirrhosis and developed AE at 2 weeks after the surgery. The patient was a 22-year-old man who received a right liver lobe from his father. The operation was uneventful but the patient developed signs and symptoms of small-for-size syndrome after the second day of surgery. The patient received intense immunosuppression with methylprednisolone for 3 days, tacrolimus and mycophenolate mofetil from the first day after the operation, with ceftriaxone and metronidazole as prophylactic antibiotics. Because of signs of respiratory distress with pneumonia, vancomycin and amphotericin B were added empirically to his regimen. Polymerase chain reaction for aspergillus DNA in the blood was positive. The patient received one course of methylprednisolone pulse therapy for signs of acute rejection at day 10, and tacrolimus was changed to sirolimus because of a rising serum creatinine and convulsions. After 2 weeks, the patient’s symptoms improved and liver function tests were normal, but the complained of sudden intense pain in the left eye with unilateral blurred vision, redness, and other signs of endophthalmitis upon examination by an ophthalmologist. After 24 hours, visual acuity decreased to light perception. AE was confirmed by microscopy and culture of the vitreous fluid and retinal biopsy. Despite changing amphotericin to intravitreal injection of voriconazole followed by intravenous voriconazole and transient resolution of the symptoms, no improvement was seen in visual acuity. Pain and signs of inflammation in the eye recurred after 2 weeks. At last the patient underwent enucleation for resistant infection and fear of involvement of the other eye by aspergillosis or sympathetic ophthalmia.
ENDOPTHALMITIS is an intraocular infection caused by bacteria or fungi. Endogenous fungal endophthalmitis (EFE) is a known complication of disseminated fungal infections. The frequency of EFE among patients with systemic fungal infections has been reported to vary between 9% and 45%. Even though it is a rare condition and affects vision seriously, therapeutic options are limited. Candida albicans and Aspergillus spp are the most frequently isolated organisms in fungal cases. Most fungal infections are observed among patients with underlying immune deficiency states, such as transplant recipients generally during the first 3 to 6 months following the procedure. For example, in renal transplant patients, Aspergillus is the commonest cause of systemic fungal disease with an incidence ranging from 0.4% to 2.4% and a high mortality of 56% to 100%. The lungs or sinuses are usually the primary site of infection with possible dissemination to other organs, particularly the central nervous system. In this report, we have described an unusual dissemination of systemic aspergillosis after liver transplantation.

CASE REPORT

The patient was a 65-kg, 22-year-old man who received the right liver lobe from his father. The patient received intense immunosuppression with methylprednisolone (1 g/d) for 3 days (replaced with oral prednisolone 20 mg/d from day 4); oral tacrolimus (4 mg/d) and mycophenolate mofetil (MMF; 2 g/d) from the first day after the operation as well as ceftriaxone and metronidazole as prophylactic antibiotics. The graft size was 670 g. The frozen section histological appearance did not show micro- or macrovesicular steatosis. The operation was uneventful but the patient developed signs and symptoms of small-for-size syndrome after the second day, which was manifested as tachycardia, tachypnea, accelerated jaundice, and severe ascites. His ascites drainage was over 3 L/d and total bilirubin (BR) level increased to 28 mg/dL. Because of pulmonary secretions and fever, vancomycin and intravenous amphotericin B (Fungizone, Squibb; 50 mg/d) were added over 3 L/d and total bilirubin (BR) level increased to 28 mg/dL. Signs and symptoms of pulmonary aspergillosis improved; Liver function tests became normal; total BR level decreased to 4 mg/dL. Signs and symptoms of pulmonary aspergillosis improved; tachycardia, tachypnea, and ascites completely subsided. Chest X-ray appearance became near normal.

Despite improved clinical signs after 4 more days, he complained of sudden intense pain in the left eye with unilateral blurred vision, floaters, foreign body sensation, and redness. His oral temperature was 37°C, and general condition was good. The initial ophthalmologic exam showed only mild conjunctivitis associated with mild uveitis, but the second exam 24 hours later revealed intense scleral injection and subconjunctival edema with signs of uveitis. Visual acuity was 20/20 at first but decreased to light perception after 24 hours. Extraocular motions and pupillary reflexes were intact. Fundoscopic examination revealed a cloudy vitreous with multifocal areas of chorioretinitis scattered throughout the posterior pole of left eye. The right eye was normal. Vitreous aspirate revealed branching hyphae and polymorphonucleocytes were seen on Giemsa stain, consistent with aspergillus endophthalmitis (AE). Intravitreal injection of voriconazole (100 µg/0.1 mL) was performed on 3 consecutive days. Amphotericin was changed to intravenous voriconazole (Vfend, Pfizer; 400 mg/d). Prednisolone dose was decreased to 10 mg/d and MMF to 1 g/d. There was no improvement in visual acuity, but the patient’s symptoms subsided to near normal. After 2 weeks, the ophthalmologic symptoms recurred without systemic or pulmonary signs or symptoms of aspergillosis. Blood PCR for aspergillosis was negative but again the vitreal aspirate revealed the previous pathological appearance. At last, after 1 more week the patient underwent enucleation for resistant infection and fear of involvement of the other eye by aspergillosis or sympathetic ophthalmia. Pathological examination of the removed globe by silver stain revealed branching septate hyphae consistent with Aspergillus species. Intravenous voriconazole was changed to the oral form and discontinued after a total period of 12 weeks with no recurrence of systemic or focal aspergillosis after 12-month follow-up.

DISCUSSION

Endogenous fungal endophthalmitis EFE usually occurs secondary to dissemination to the eye of organisms from a distant focus via the blood stream. While 2% to 15% of all endophthalmitis cases are estimated to occur in this fashion, involvement of the eye after improving systemic signs and symptoms of aspergillosis as seen in our patient is an unusual event. In the study of Feman et al, EFE occurred in only 282 patients (2.4%) who had evidence of disseminated disease. Our patient was under systemic treatment with amphotericin B and his eye was acutely involved by aspergillosis without any trauma or evidence of previous eye problem. It is our belief that if a fungal infection of the eye had been identified earlier as a consequence of greater understanding of the disease, and if we had changed the antifungal treatment to voriconazole sooner, it may have prevented the retinal destruction. Takebayashi et al showed that because the stage of EFE advances with time between initial symptoms and beginning therapy, and because of the high correlation between the stage of EFE and the final visual acuity, it is important that treatment be begun as soon as possible. Thus, in patients with visual symptoms who are susceptible to opportunistic infections, early consultation with an ophthalmologist is highly recommended. Unfortunately, because of the rarity of this disease in our center, the ophthalmologist did not suspect AE as a cause of patient's complaint at the first eye examination.

Disorders of neutrophil function play a major role in the development of infections in invasive aspergillosis models. This effect is observed after steroid therapy for steroids facilitate the development of infection by impairing defense mechanisms. Use of methylprednisolone pulse therapy in our patient before onset of endophthalmitis may have been a predisposing factor. A recent review showed that 43% of
all AE cases (36/84) had received corticosteroids. Eye involvement without relapsing systemic symptoms of aspergillosis may have been due to the poor penetration of amphotericin into the internal milie of the eye. The lack of antifungal drugs with high blood-ocular permeability produces an extremely poor visual prognosis. Amphotericin B has poor intraocular penetration. At least in two other reports, AE occurred in patients on systemic amphotericin B treatment. Currently, there is no study ascertaining whether prophylaxis with the new antifungals, such as voriconazole, can prevent serious complications, such as AE, in high-risk groups.

In conclusion, our case illustrated that all liver transplant recipients presenting with nonspecific ocular symptoms should be investigated for AE, especially when they have received any modality of antirejection therapy. The small number of case reports and the diversity of treatment regimens and outcomes make identification of optimal therapy difficult, but it seems that the best treatment for AE would include early vitrectomy and systemic plus intravitreal voriconazole injections.

REFERENCES