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Necrotizing Encephalitis Caused by Disseminated *Aspergillus* Infection after Orthotopic Liver Transplantation

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Key Words

Orthotopic liver transplant · Aspergillosis · Necrotizing encephalitis

Abstract

Liver transplantation is the only available treatment for some patients with end-stage liver disease. Despite reduction in mortality rates due to advances related to surgical techniques, intensive medical management and immunosuppressive therapy, invasive fungal infections remain a serious complication in orthotopic liver transplantation. We report the case of an 18-year-old male diagnosed with autoimmune cirrhosis in 2009 who was assessed and listed for liver transplantation for massive variceal hemorrhage. One year after listing a successful orthotopic liver transplantation was performed. Uneventful early recovery was achieved; however, he developed pulmonary and neurological *Aspergillus* infection 23 and 40 days after surgery, respectively. Antibiotic therapy with voriconazole and amphotericin was started early, with no major response. Neuroimaging revealed multiple right frontal and right parietal lesions with perilesional edema; surgical management of the brain abscesses was performed. A biopsy with periodic acid-Schiff and Gomori stains revealed areas with mycotic microorganisms morphologically consistent with *Aspergillus*, later confirmed by culture. The patient developed necrotizing encephalitis secondary to aspergillosis and died. Necrotizing encephalitis as a clinical presentation of *Aspergillus* infection in an orthotopic liver transplant is not common, and even with adequate management, early diagnosis and prompt antifungal treatment, mortality rates remain high.

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Introduction

Orthotopic liver transplantation is the only definitive therapeutic option for patients with end-stage liver disease. However, invasive fungal infections are an important cause of post-transplantation mortality in solid organ recipients, and their incidence, particularly for candidiasis and aspergillosis, varies from 1.4 to 42% of cases [1]. In solid organ transplant recipients, disseminated fungal infections by *Candida* spp. account for 59.0%, by *Aspergillus* spp. for 24.8%, by *Cryptococcus* spp. for 7.0% and by other molds for 5.8% [2]. Despite prompt diagnosis and early management, mortality due to fungal infections depends on the type of transplant and can range between 3 and 100% [1, 3]. Fungal infections frequently occur in the first month post transplantation [4], and their incidence differs in frequency and specific etiology according to the type of transplanted organ, procedure and transplantation center [5]. The clinical presentation of fungal infections can range from asymptomatic to disseminated and the clinical presentation of central nervous system infection may be subtle and difficult to diagnose, with life-threatening infections [6].

Case Report

We report the case of an 18-year-old male diagnosed with autoimmune cirrhosis in 2009 who was assessed and listed for liver transplantation for massive variceal hemorrhage. His past medical history revealed an ostium secundum managed uneventfully with percutaneous Amplatzer 2 years before liver transplantation. Pre-transplantation pharmacological management included propranolol (20 mg t.i.d.), azathioprine (50 mg q.d.), vitamin E (400 IU q.d.) and multivitamin supply. Assessment for transplantation was successfully overcome with no contraindication. Laboratory tests demonstrated leukopenia $4.58 \times 10^3/\mu\text{l}$ (normal $5\text{--}10 \times 10^3/\mu\text{l}$), with lymphocytes 27.14% (normal 30–40%), anemia (hemoglobin 12.4 g/l [normal 12–16 g/dl], hematocrit 38.5% [normal 45–54%]), thrombocytopenia (platelets $45 \times 10^3/\mu\text{l}$ [normal $150\text{--}450 \times 10^3/\mu\text{l}$]), alkaline phosphatase 225 U/l (normal 32–91 U/l), total serum bilirubin 1.64 mg/dl (normal 0.3–1.9 mg/dl), direct bilirubin 0.9 mg/dl, indirect bilirubin 0.74 mg/dl, severity score of CHILD A and MELD 11. Variceal banding was successfully performed.

Previous chest X-rays were normal. However, during surgery the patient experienced desaturation and we immediately performed an X-ray, which detected right superior and inferior lobar atelectasis; the symptoms improved with positive pressure therapy. On-site bronchoscopy found purulent tracheal secretions. On the fifth postoperative day he developed clinical sepsis, needing management at the intensive care unit. Because of increased cholestasis, endoscopic retrograde cholangiopancreatography and biliary stenting were performed; additionally, we performed a cardiothoracic focus search because his clinical past, apart from transesophageal echocardiography, was normal.

A month after liver transplantation, because of persistent tracheal secretions, sputum cultures were taken, finding *Aspergillus* spp. A thoracic CT scan showed multiple nodes in both lungs, with imaging patterns of tree-in-bud opacities, suggesting pulmonary *Aspergillus*. Despite fungal treatment including posaconazole, caspofungin, amphotericin B and aciclovir, the patient developed neurological symptoms including left hemiplegia, severe headache and mental status changes. Magnetic resonance imaging of the brain showed multiple right frontal and right parietal lesions with perilesional edema (fig. 1). The patient underwent biopsy of brain lesions under stereotactic guidance. Despite treatment, he developed multiple organ failure and he died 48 days after liver transplantation.

The explanted cirrhotic liver revealed abundant copper deposits (fig. 2a, b). Complementary studies including aldehyde fuchsin and periodic acid-Schiff without diastases revealed areas of hepatic parenchyma with significant deposits of copper and its binding protein, mostly at periseptal location, in some foci a very small amount and in others complete absence, minimum focal intracanalicular cholestasis and no Mallory bodies or major ballooning. These findings together with the clinical suspicion of a metabolic disease were consistent with Wilson's disease; what is striking, however, is the absence of other histologic findings characteristic of this condition in the active state, including Mallory bodies, ballooning and prominent nuclear pseudoinclusions, among others.

Trucut liver biopsy obtained 4 days after transplantation showed a hepatic parenchyma with hepatocanalicular cholestasis from zone 3 to zone 2 and focally in zone 1. Apoptotic hepatocytes, Kupffer cells with abundant pigment and sinusoidal congestion were also observed. Trichrome staining showed no fibrosis, Kupffer cells with rich resistant periodic acid-Schiff-diastase (PAS-D)-positive material and some intracytoplasmic iron deposits (+/++++). Histochemical study for cytomegalovirus was negative. The described findings corresponded to a mild acute cellular rejection, Banff score 4/9 (portal swelling 2, ductulitis 1, endotheliitis 1) associated with hepatocanalicular cholestasis.

From the cerebral collection (frontal right abscesses), H&E and histochemical staining with PAS-D, Ziehl-Neelsen, Gram and Gomori were performed. Fragments of brain parenchyma showed edema, extensive necrosis, neutrophil infiltration in abundant quantity, apoptotic cells and presence of abundant septate hyphae angled at 45°, morphologically compatible with *Aspergillus* spp. (fig. 2c, d), corroborated by the PAS-D and Gomori stains. The Ziehl-Neelsen and Gram stains were negative for acid-alcohol-resistant bacilli and bacteria, respectively. A diagnosis of necrotizing encephalitis with organisms morphologically compatible with *Aspergillus* structures was made.

Discussion

Fungal infections are among the most common complications in transplantation. *Candida* and *Aspergillus* account for 70–90% of all cases [5]. In liver transplantation both organisms explain the vast majority of invasive fungal infections and are considered as a significant cause of morbidity and mortality. When the central nervous system is compromised by an abscess, *Aspergillus* is the most common etiology and has a tendency to spread to any other organ through hematogenous dissemination [7]; however, these infections usually grow very slowly, making the clinical information decisive for the presumptive diagnosis.

For both bacterial and fungal agents, fever, headache, vomiting and altered sensorium are the presenting symptoms of intracranial abscess, with mortality rates varying between 10 and 15% [8]. Our patient presented altered state of consciousness, measles, tachycardia and fever 15 days after transplantation. Unfortunately the outcome was consistent with some descriptions that established the patient's neurological status at presentation as a significant predictor of outcome, with an increased mortality rate in those who present with altered mental status and rapid neurological deterioration [9, 10].

Despite correct surgical techniques, immunosuppressive therapy and advanced medical treatment, fungal infections remain a significant cause of post-transplantation morbidity and mortality [11]. In case of clinical suspicion of fungal infection, cultures will confirm the infectious agent; however, the sensitivity of fungal cultures is relatively low, thus some authors suggested that measuring *Aspergillus* antigens such as galactomannan in clinical samples such as plasma, serum, bronchoalveolar lavage fluid or cerebrospinal fluid would be

useful for diagnosis [12]. In our case, suspicion of infection justified the bronchoalveolar lavage that indeed revealed the primary *Aspergillus* infection.

The current recommendation in cerebral *Aspergillus* infection includes surgical excision and debridement of the abscess, antifungal therapy and reduction in the immunosuppressive regime after liver transplantation [12]. This last issue was difficult to achieve in our case due to the progressive cholestasis, altered liver function tests and the mild acute cellular rejection proven with the transplant biopsy. Similarly, our patient was not at high risk for fungal infection; antifungal prophylaxis does not reduce overall mortality, and its beneficial effect has been predominantly associated with the reduction of *C. albicans* infection and mortality [13]. It is therefore essential to have in place an effective approach focus in prevention and based on predicted infection risk, including local antimicrobial resistance patterns and surveillance of specific risk factors [14].

Conclusion

Regardless of adequate surgical techniques and immunosuppressive therapies, this case presents the challenges in diagnosing and treating fungal infections in solid organ transplantation. Even though brain abscesses caused by *Aspergillus* are not common in orthotopic liver transplantation, we emphasize that in immunocompromised patients who develop mental status changes, seizures or focal neurological findings, despite prompt medical intervention there are predominantly worse outcomes among liver and heart transplant recipients [2, 10]. Certainly, prospective studies are needed to accurately assess the risk of fungal infections and antifungal prophylaxis prior to transplantation to help informed decision-making focus on effective prevention and treatment.

Disclosure Statement

The authors declare that there is no conflict of interests regarding the publication of this article.

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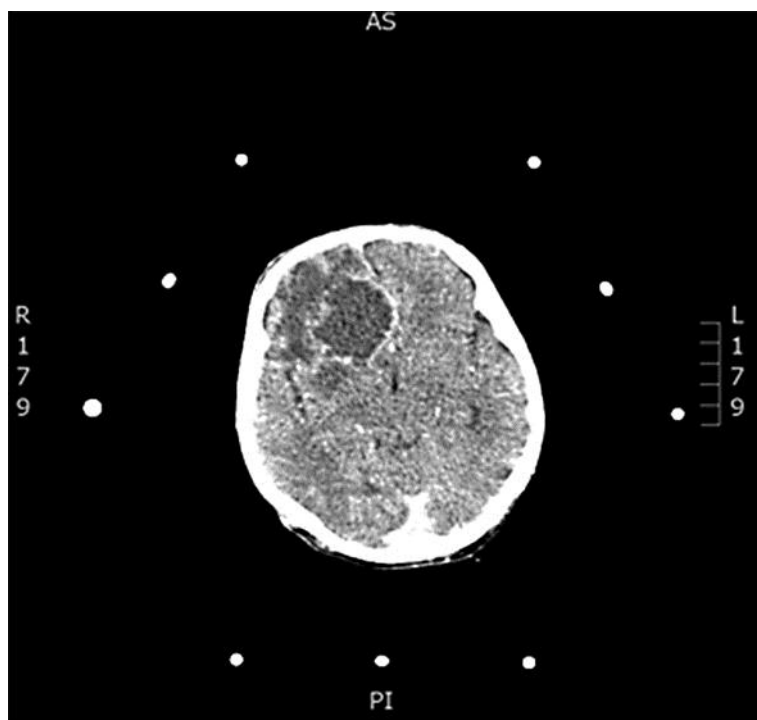


Fig. 1. CT scan showing multiple right frontal lesions.

Barrera-Herrera et al.: Necrotizing Encephalitis Caused by Disseminated *Aspergillus* Infection after Orthotopic Liver Transplantation

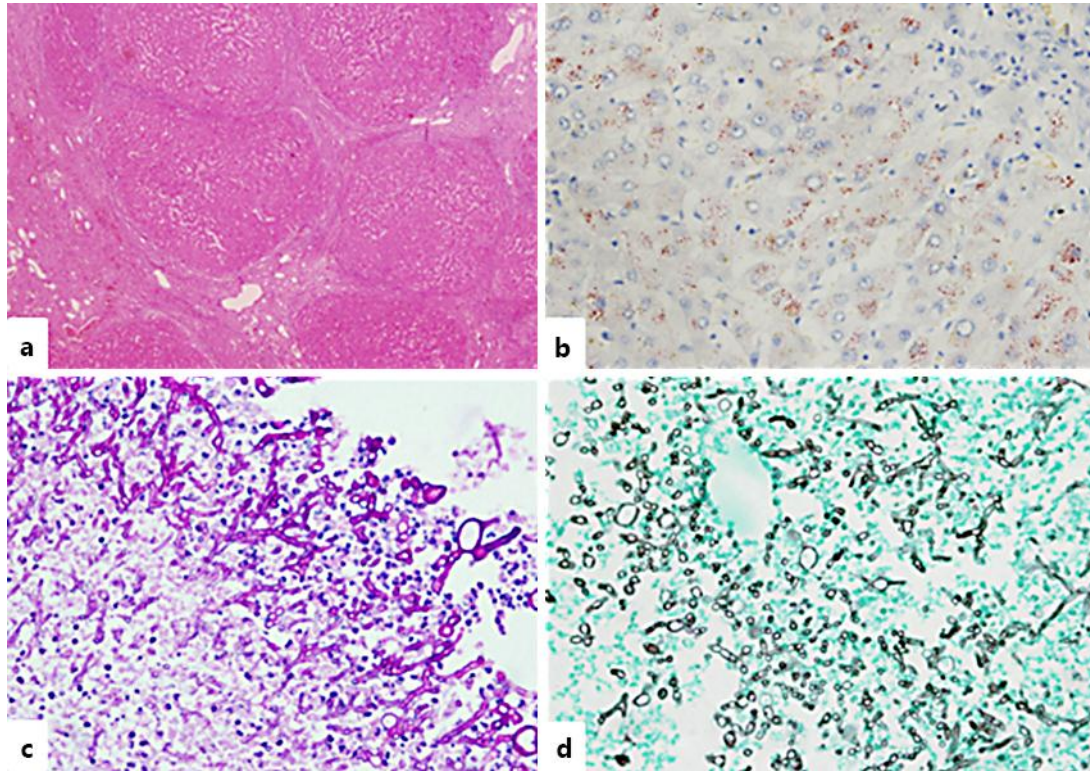


Fig. 2. **a** Explanted cirrhotic liver. H&E, $\times 40$. **b** Explanted liver with multiple copper deposits. Copper, $\times 40$. **c, d** Brain abscess, PAS-D, $\times 40$ (**c**) and Gomori, $\times 40$ (**d**), presenting formations morphologically consistent with *Aspergillus* spp.