CASE REPORT

Primary cutaneous aspergillosis with lung involvement in a transplant patient

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Summary Invasive pulmonary aspergillosis (IPA) is a rare, life-threatening infection in liver transplant recipients. Here, we report a case of primary cutaneous aspergillosis with following lung involvement in a liver transplant recipient. The survival rate of patients with IPA can be increased by early diagnosis using high-resolution computed tomography, a combination of two effective antifungal agents, temporal reduction or cessation of immunosuppressive drugs, and surgical intervention with video-assisted thoracoscopic surgery.

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1. Introduction

Invasive pulmonary aspergillosis (IPA) is a rare, life-threatening infection in liver transplant recipients. The incidence of IPA in liver transplant recipients has been reported to be 1–8%, with a mortality rate ranging from 83% to 88%.1 Major risk factors associated with IPA include renal insufficiency, requirement for dialysis, cytomegalovirus (CMV) infection, excessive immunosuppression, re-exploration, extensive use of broad-spectrum antibiotics, and organ dysfunction.2 Early diagnosis, fungicidal therapy, surgical debridement, and reduction in immunosuppression have been reported to contribute to successful treatment.3

The gold standard for diagnosis involves the use of invasive procedures, such as bronchoscopy and lung biopsy,4 to obtain tissue specimens for culture and histological examination. Laboratory examinations, such as polymerase chain reaction and detection of galactomannan, have been shown to be beneficial in the assessment of liver transplant recipients.5,6 Computed tomography, particularly high-resolution computed tomography (HRCT), has been reported to aid in the early detection of IPA.7 Hereby we present the case of a liver transplant recipient with primary cutaneous aspergillosis followed by lung involvement, who was managed successfully through detection with the aid of HRCT followed by the administration of a combination antifungal therapy.
Surgical intervention was employed for removing the remaining pulmonary lesion.

2. Case report

A 44-year-old man, 50 kg in weight and 152 cm in height, with a history of alcohol-related liver cirrhosis, underwent orthotopic liver transplantation. The piggyback technique was used for vascular anastomosis and duct-to-duct anastomosis without a T-tube was used for biliary reconstruction. Blood loss was about 3500 mL. He recovered uneventfully and was discharged 15 days after the operation. Immunosuppressive medication consisted of a triple therapy with tacrolimus, myfortic, and prednisolone in the first 3 months. All the medications were tapered progressively.

The patient was readmitted with a distended abdomen, jaundice, and fever on postoperative Day 24. Liver biopsy revealed focal necrosis and ballooning of hepatocyte with a positive CMV stain. Treatment began with intravenous ganciclovir infusion, 5 mg/kg twice daily for 10 days. His conditions improved and he was discharged. After discharge, an oral dose of valganciclovir 900 mg once daily was prescribed as usual for the following months.

Three months after the transplantation, the patient noticed a nodule on his back. Excisional biopsy showed cutaneous aspergillosis with necrotizing inflammation (Fig. 1). There was no fever, jaundice, or any other systemic symptom associated with this incidental finding. A chest radiograph revealed no abnormal finding (Fig. 2A). No antifungal medication was prescribed in the clinic.

One month after the excisional biopsy of the back nodule, the patient developed high fever with cough. At that time, a physical examination showed yellowish skin discoloration, coarse breathing sounds over both lung fields, and negative findings for the abdomen. The routine workup included sputum culture/stain, urine routine/culture, blood culture, and serum tests for virus including CMV, Epstein–Barr virus, varicella-zoster virus, hepatitis B virus, and hepatitis C virus. A chest X-ray revealed multiple nodules scattered throughout both lungs, with the largest nodule (measuring 3 cm) being in the upper lobe of the right lung (RUL; Fig. 2B). HRCT demonstrated multiple patches infiltrating both lungs, and the largest nodule showed adjacent ground-glass opacity, which was considered to be IPA (Fig. 3A). Laboratory tests revealed a normal white cell count (4500/µL), with a left shift, and elevated values in the liver function test GOT/GPT (100/88 U/dL) and bilirubin total/direct (5.8/4.8 mg/dL). C-reactive protein was 17.7 mg/L.

Empiric treatment was initiated with ceftriaxone 1 g every 12 hours, intravenous caspofungin 50 mg per day, and oral voriconazole 200 mg every 12 hours. The patient was on his usual medication, which consisted of an oral dosage of trimethoprim/sulfamethoxazole, but all the immunosuppressive drugs were tapered or discontinued. Three days later, his spiking fever came down slowly. Another week later, the fever subsided completely, and the liver functions returned to normal. We then stopped ceftriaxone and started low-dosage immunosuppressive drugs. After 1 month of medication, HRCT showed that the lung lesions became mostly invisible, except for the largest nodule in the RUL, which nevertheless was decreased in size and better defined (Fig. 3B). Thoracoscopic wedge resection of the nodular lesion was performed, and the pathologic report revealed chronic granulomatous inflammation. He was discharged 12 days after the operation. An oral dose of voriconazole 200 mg every 12 hours was prescribed to be continued for another 2 weeks at home. He remained in a stable condition during follow-up for more than 1 year.

3. Discussion

IPA is a rare, life-threatening infection in patients who undergo solid organ transplantation. Many studies suggest that the choice of antibiotics should be based on the reports of positive serum/tissue tests or cultures. However, cultures or biopsies are often time consuming and sometimes lack sensitivity. Polymerase chain reaction is neither standardized nor commercially available. False-positive results in galactomannan detection have been described in up to 13% of liver transplant patients. Herein, we present a case of primary cutaneous aspergillosis with secondary lung involvement in a liver transplant recipient. An early diagnosis was made based on HRCT findings, and the patient received a combination of antifungal drugs and video-assisted thoracoscopic surgery (VATS) for the residual pulmonary nodule.
HRCT has been used successfully as a diagnostic tool in the IPA for bone marrow transplant recipients.\textsuperscript{7,8} Based on the typical signs of IPA on HRCT, a 68% reduction in antifungal usage was achieved.\textsuperscript{7,8} Moreover, patients without these typical signs on HRCT did not have a diagnosis of IPA.\textsuperscript{8} HRCT served as an early diagnostic tool in this patient.

Several studies have suggested that a combination therapy with antifungal agents may improve efficacy over monotherapy.\textsuperscript{9,10} Successful outcomes were observed in 55% of neutropenia patients or transplant recipients at the end of the combination therapy.\textsuperscript{9,10} There are no specific guidelines or recommendations for the use of combination therapy in IPA. For our patient, we prescribed a combination of antifungal agents and terminated all the immunosuppressive drugs to “wake up” the immune defenses against the fungus temporally. That might have helped improve his response to the infection.

The pulmonary nodule that remained even after prolonged antifungal treatment is the so-called fungal ball or mycetoma.\textsuperscript{11} It may cause massive hemoptysis or recurrence, and can even prove fatal. These events occur in 50–80\% of cases.\textsuperscript{11} Surgery is the only definitive modality of treatment.\textsuperscript{11} It has to be noted that, in recent years, the development of VATS has reduced postoperative pain and

**Figure 2** Chest radiography: (A) there are no abnormal nodules or lesions within the lung field; (B) multiple nodular masses scattered within the lung field.

**Figure 3** High-resolution computed tomography findings: (A) multiple nodular masses of different sizes scattered at both pulmonary parenchymas (the largest nodule, about 3 cm in size, is located in the right upper lobe with adjacent ground-glass opacity); and (B) after 1 month of medication, the lung nodules have decreased in size and number.
hospital stay, with a marked decline in mortality and morbidity. In our opinion, VATS helped in the successful completion of treatment for IPA in our patient.

CMV infection can also be a causative factor of IPA. This patient received a graft from a CMV-seropositive donor, and so his graft was positive for CMV infection about 3 weeks after transplantation. On his discharge after the CMV infection, we prescribed a usual dose for the prevention of possible CMV. Two months later, he developed a cutaneous lesion. There is no evidence or report to support that the CMV infection was related to the cutaneous fungal infection.

The cutaneous aspergillosis in this patient was classified as the primary type. Surgical excision of the infected tissue combined with the use of antifungal agents is the treatment of choice for solid organ transplant recipients with cutaneous aspergillosis. Excision of the infected cutaneous nodule without administering antifungal agents can be a risk factor for the following lung involvement.

IPA is uncommon but harbors a high mortality in liver transplant recipients. The survival rate can be elevated by early diagnosis with HRCT, effective administration of antifungal agents, temporary reduction or cessation of the immunosuppressive drugs, and performance of safe VATS later, if necessary.

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References


