Invasive aspergillosis after liver transplantation: A rare case of multisystem involvement and successful treatment

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Summary

Background: Aspergillosis is a rare but severe opportunistic fungal infection in liver transplant patients. Early and definitive diagnosis is crucial for selecting antifungal therapy and adjusting immunosuppressive regimens to improve patient outcomes. *Case report:* A 46-year-old male, three months post-liver transplant, was hospitalized with fever, neutropenia, left hemiparesis, leg pain, and skin lesions. CT angiography revealed partial femoral and calf artery occlusion, while brain MRI suggested invasive fungal infection. Skin biopsy confirmed *Aspergillus* infection. The patient was treated with voriconazole and tacrolimus, leading to significant improvement. After one month of antifungal therapy, he achieved stable liver function and was discharged. This case highlighted the importance of early diagnosis and appropriate treatment in managing *Aspergillus* infections.

Keywords: *Liver transplantation, Invasive Aspergillosis, Voriconazole.*

I. BACKGROUND

Opportunistic fungal infections are not only severe complications but also among the leading causes of mortality in organ transplant recipients, particularly those undergoing liver transplantation. Immunosuppressive therapy, essential for preventing graft rejection, significantly increases the risk of invasive fungal infections, which, if misdiagnosed or untreated, can lead to poor outcomes or death.

Candida species are the most common opportunistic pathogens, followed by *Aspergillus* species[1]. The mortality associated with opportunistic aspergillosis ranges from 25% to 69%; however, *Aspergillus*-associated mortality has been found to be higher in liver transplant as compared with other organ transplants[2].

Aspergillus infections present variably, from asymptomatic cases to severe systemic complications such as meningitis and cerebral abscess, often requiring invasive diagnostic methods[3]. Early detection is crucial for timely antifungal treatment, optimizing immunosuppressive therapy, and preserving graft function.

This report details a case of disseminated aspergillosis affecting the central nervous system, vascular system, and subcutaneous tissues in a liver transplant recipient with neutropenia. The patient was successfully treated with antifungal therapy, antiplatelets, and granulocyte colony-stimulating factor, alongside adjusted immunosuppressive therapy.

II. CASE PRESENTATION

A 46-year-old male, three months post-liver transplant from a living donor, was hospitalized with fever, left-sided weakness, and bilateral leg pain. Symptoms began two weeks prior, with a mild-to-moderate fever (38 - 38.5°C) followed by progressive weakness in the left arm and leg. The patient also experienced exertional leg pain, relieved by rest, and developed dark, well-demarcated, painless subcutaneous macules (Figure 1).

His medical history included alcoholic decompensated cirrhosis (MELD score 30). The liver

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transplant (right lobe) was uneventful, with induction immunosuppression using basiliximab (20 mg) and maintenance triple therapy. This included a preoperative 500 mg methylprednisolone bolus, tapered to 40 mg before discharge, then stopped after one month. Mycophenolate mofetil (1g/day) was initiated on post-op day 3, while tacrolimus (0.1mg/kg/day) was adjusted to maintain a trough level of 10 - 12ng/ml.

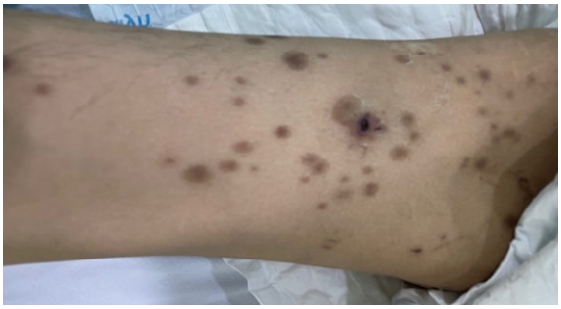

Figure 1. Skin lesions at admission

On post-operative day 11, the patient developed hospital-acquired pneumonia with bacteremia, presenting with persistent high fever (39°C). Blood and sputum cultures confirmed *Acinetobacter baumannii* infection. He was treated with oxygen therapy and a combination of meropenem (3 g/day) and polymyxin E (9 MUI/day) based on antibiotic sensitivity. Fever resolved after five days, and he completed 14 days of antibiotic therapy in the ICU. During treatment, the patient developed acute kidney injury but recovered fully without dialysis. He was discharged on post-operative day 38 with continued immunosuppressive therapy and infection prevention.

Post-discharge, the patient maintained dual-drug immunosuppression with tacrolimus (trough level 10 - 12ng/ml) and mycophenolate mofetil (MMF) (1g/day). Antifungal prophylaxis with fluconazole (6mg/kg/day) and Pneumocystis pneumonia prophylaxis with trimethoprim/ sulfamethoxazole (480/80mg) were administered, while no Cytomegalovirus prophylaxis was given. Aspirin (100 mg/day) was prescribed to prevent hepatic embolism.

Three months post-transplant, the patient presented with left-sided weakness (muscle strength 3/5 in arm and leg), bilateral lower limb pain aggravated by walking, and dark, well-demarcated, painless subcutaneous macules on the thighs and calves. He also had a mild-to-moderate fever (38 - 38.5°C). Upon hospitalization, symptoms worsened, with muscle strength declining to 2/5, rendering him bedridden.

Laboratory tests revealed neutropenia (WBC 479 cells/µl) and elevated inflammatory markers (CRP: 134mg/L, procalcitonin: 13.6ng/ml). CT angiography showed partial occlusion of multiple iliac and tibial arteries with collateral circulation (Figure 2), while lung and maxillofacial CT scans showed no fungal lesions. Abdominal CT confirmed normal portal vein flow and hepatic artery status. T2-weighted MRI detected characteristic fungal lesions-ring-shaped with peripheral hyperintensity and central necrosis in the cerebellum, thalamus, parietal-occipital region, and right brainstem (Figure 3), without cerebral vessel occlusion.

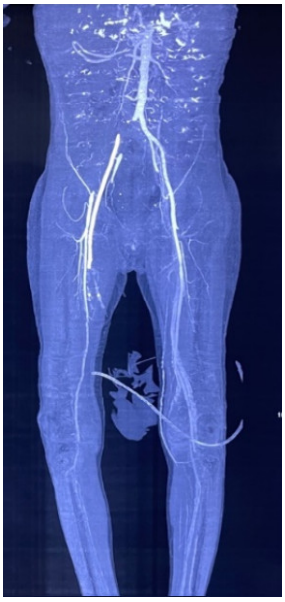

Figure 2. CT scan imaging showing occlusion of the right common iliac artery, right external iliac artery, anterior tibial artery, posterior tibial artery, and bilateral peroneal arteries.

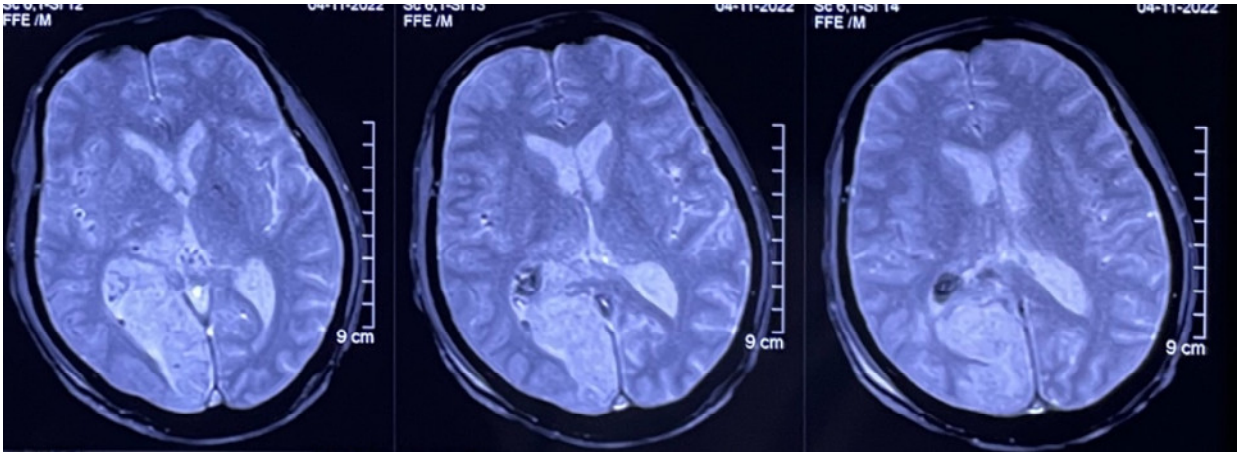

Figure 3. Cranial T2-weighted MRI showing ring-shaped lesions with increased peripheral signal and necrotic foci in the centers of the thalamus, parietal-occipital region, and right brainstem.

Cerebrospinal fluid analysis revealed inflammation (9 leukocytes/mm^3, protein: 1.19 g/L), and PCR tested positive for *Aspergillus spp*. Suspecting fungal infection, a skin biopsy and microbiological cultures (sputum, blood, and skin) were performed. Histopathology confirmed *Aspergillus* infection, showing chronic inflammation with eosinophils, macrophages, fungal spores, and 45-degree branching hyphae (Figure 4), though all cultures were negative.

This patient met the 2020 EORTC/MSG criteria for invasive aspergillosis[4], with brain (parietal-occipital region, right brainstem), vascular (multiple arterial occlusions), and skin involvement three months post-liver transplantation in the setting of neutropenia. Following a definitive diagnosis, antifungal therapy with voriconazole was initiated per IDSA (2016) guidelines[5]. The patient received an initial intravenous dose of 4 mg/kg every 12 hours, later transitioned to oral administration until discharge.

Immunosuppressive therapy was adjusted: MMF was discontinued, and tacrolimus was tapered to maintain a trough level of 4–6 ng/ml. G-CSF was administered for three consecutive days, normalizing WBC count with no further neutropenia. Dual antiplatelet therapy (aspirin 100 mg + Plavix 75 mg) was added. Liver function remained stable without signs of rejection. With significant clinical improvement, the patient was discharged.

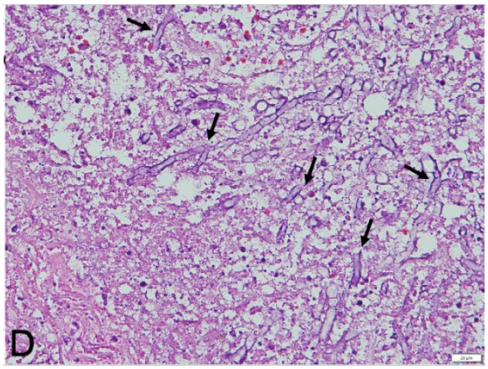

Figure 4. Histopathological image of a skin biopsy showing *Aspergillus* hyphae branching at sharp angles under high magnification (black arrow).

The patient continued daily voriconazole treatment. The immunosuppressive regimen was changed to tacrolimus monotherapy (trough concentration 8-10 ng/ml) and combined with dual antiplatelet therapy after discharge. After 5 months of follow-up, liver function normalized, the patient fully recovered, with no remaining skin lesions (Figures 1A, 1B), and no signs of rejection.

III. DISCUSSION

In this report, we presented a patient with aspergillosis after liver transplantation from a living donor. Invasive aspergillosis (IA) is a serious and life-threatening complication in organ transplant recipients, particularly in patients with neutropenia or those receiving high-dose immunosuppressive therapy. Multiple factors influencing the risk of

developing an IA infection in liver transplant recipients have been reported[1]. Pre-transplant risk factors included alcoholic cirrhosis [6] and high MELD score [7]. Post-transplant risk factors included a long-term stay in the intensive care unit and renal failure. In liver transplant patients, IA occurs more frequently in the early period of 1-3 months after transplantation. Although the overall incidence of IA in liver transplantation ranges from 1-9%, the mortality rate remains high, up to 90%, and in cases with CNS involvement, nearly 100% [8].

However, early diagnosis of IA remains a significant challenge, and most patients are diagnosed through a combination of clinical presentation, CT/MRI imaging, and pathological examinations of suspected fungal infection before a positive culture is available. In this case, three months after liver transplantation, the patient developed invasive fungal infection with disseminated disease and central nervous system involvement. Additionally, the patient developed arterial invasion along the right lower limb and skin lesions. A proven diagnosis of IA was suggested by the CT scan image, cerebrospinal fluid PCR, and pathological findings of the skin biopsy [4]. We initiated antifungal treatment with voriconazole according to the current guidelines [5]. Along with antifungal therapy, the immunosuppressive regimen was adjusted by withdrawing MMF and reducing the tacrolimus dose to maintain a target trough concentration of 4-6 ng/ml. Dual antiplatelet therapy was also added. After one month of intensive antifungal therapy, the patient's condition stabilized, and the patient was discharged from the hospital.

Voriconazole is the preferred treatment for IA, particularly for cerebral fungal abscesses, and is associated with fewer side effects than Amphotericin B, improving survival rates. However, its interaction with immunosuppressive drugs, due to voriconazole's inhibition of CY3A4 activity, requires careful monitoring to avoid drug toxicity.

Due to the grave prognosis of IA, antifungal prophylaxis regimens still seem to vary widely. A recent study proposed the prophylactic use of voriconazole in liver transplant patients [9], but it poses a cost burden for patients in resource-limited countries where the national health insurance system does not reimburse for this cost. Thus, a definitive diagnosis of IA based on a comprehensive and rigorous workup, including a combination of histopathology, microbiology, serology, and imaging data in the relevant clinical setting, is critical for proper antifungal therapy to save patients. In previously reported cases, one patient was treated with a combination of surgery and antifungal therapy with voriconazole, while another survived with treatment using liposomal amphotericin B and surgery [10]. To our knowledge, this is the first reported case of IA after liver transplantation successfully treated in Vietnam.

Several risk factors for IA in liver transplant recipients are well-established, with neutropenia below 500 cells/µl being a predictor of mortality [11]. Neutrophil dysfunction, often exacerbated by steroid therapy, plays a significant role in infection development. In this case, granulocyte-colony stimulating factor (G-CSF) was administered to support the patient's immune response. After three consecutive doses, the patient's leukocyte count increased to 7 G/L. While G-CSF is commonly used in post-transplant neutropenia, there are currently no studies demonstrating its effectiveness in treating invasive fungal infections in neutropenic transplant patients.

IV. CONCLUSIONS

This report describes a rare case of disseminated *Aspergillus* infection in a liver transplant recipient with neutropenia. The patient was successfully treated with voriconazole, granulocyte-colony stimulating factor, dual antiplatelet therapy, and tacrolimus monotherapy. Voriconazole effectively treated the fungal infection, while tacrolimus monotherapy prevented rejection and complemented antifungal therapy. Adjunctive treatments also supported the management of infections and vascular occlusions.

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