Delayed Graft Dysfunction due to Invasive Hepatic Mucormycosis After Living Donor Liver Transplantation

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Mucormycosis is a rare but emerging fungal infection complicating solid organ transplantation. It is associated with a high mortality rate. We describe an unusual case of hepatic mucormycosis in a living donor liver transplant recipient presenting as delayed graft dysfunction, which was successfully treated with combination of liposomal amphotericin B and oral posaconazole therapy, without surgical resection. The patient had clinical improvement with normalization of liver function tests. (J CLIN EXP HEPATOL 2020;10:629–632)

A 57-year-old gentleman, with long-standing uncontrolled type 2 diabetes mellitus, underwent right lobe living donor liver transplantation due to chronic Budd–Chiari syndrome. The donor was a 48-year-old woman with body mass index of 25 and no comorbidities. The graft–recipient weight ratio was 0.77. The cold and warm ischemia times were 160 and 55 min, respectively. There were 2 donor hepatic ducts, spectacted which were anastomosed to the recipient's common hepatic duct. The postoperative course was uneventful, and the patient was discharged on postoperative day 22. The patient was on a triple immunosuppressive regimen including tacrolimus, mycophenolate mofetil, and steroids. He was also under fluconazole prophylaxis for 2 weeks. As the patient could not tolerate tacrolimus because of its neurotoxicity, he was switched to oral microemulsified cyclosporine in the 2nd week. Later, he was switched to everolimus at 10th week because of nephrotoxicity of cyclosporine. Subsequently, he remained on everolimus maintenance immunosuppression. The mean Tac level in the first 2 weeks was 6 ng/ml and later mean C0/C2 for cyclosporine was 150/803 ng/ml. There was no episode of acute cellular rejection. Post-living donor liver transplant, he had cytomegalovirus infection (treated with antivirals), hyperglycemia (controlled with insulin), and a brief period of neutropenia within 30 days of transplant.

The patient developed deranged liver function tests (LFTs) at 5 months after transplantation. Computed tomography (CT) showed multiple hypodense lesions in all segments of the liver allograft, largest being 1.6 cm in segment 6 (Figure 1a, b). Blood cultures were sent (which were later found to be negative), and the patient was put on high-end empirical antibiotics (ceftriaxone + sulbactam, colistin, tigecycline) in view of suspected multiple abscesses but there was no improvement. Magnetic resonance cholangiopancreatography ruled out anastomotic biliary stricture. Liver biopsy from the liver lesions was performed 2 weeks later due to the persistence of the abscesses, which revealed angio-invasive fungal infection suggestive of mucormycosis (Figure 2). Microbiologists and infectious diseases specialists opinion was taken, and the patient was started on liposomal amphotericin B (dose – 5 mg/kg/day) and oral posaconazole (dose – 5 ml, 200 mg per oral, TID). As there were multiple lesions, surgical resection or drainage was not possible. After 2 months of antifungal combination treatment, there was clinical improvement but a repeat CT did not show any interval change in the size of the liver lesions. The patient was on minimal immunosuppression at this time (everolimus to keep a level of 1–2 ng/L and mycophenolate mofetil 250 mg BD).

After 3 months of combined antifungal treatment, amphotericin B was stopped. The patient showed clinical improvement but no radiological resolution. These were “ghost” lesions (Figure 1c, d). Posaconazole was continued for another 3 months. The patient was well for 18 months after cessation of all treatment with normal LFTs. Later, the patient developed coronary artery disease and died because of sudden cardiac arrest.

DISCUSSION

Mucormycosis is a rare but emerging fungal infection complicating solid organ transplantation (SOT), with a

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Abbreviations: CT: computed tomography; LDLT: living donor liver transplantation; LFT: liver function test; SOT: solid organ transplantation

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Figure 1 CT triphasic abdomen images – (a, b) Hypertrophied liver allograft showing multiple hypodense lesions or abscess/metastasis (c, d) Post-treatment after 6 months and 'ghost' lesions. CT, computed tomography.

cumulative incidence of 2% during the first year.¹ Liver transplantation has been implicated as a risk factor for disseminated disease and earlier occurrence of this infection in comparison with other types of SOT.² The associ-

ated mortality rate is high,³ and surgical debridement is frequently required as part of the treatment.⁴ Antifungal treatment is usually based on amphotericin B lipidic formulations, while posaconazole is the only commercially

Figure 2 Liver biopsy showing hepatic mucormycosis. (a) (Hematoxylin and Eosin (H&E) stain, 40X) – coagulative necrosis typical of mucormycosis. (b) (Grocott methenamine silver (GMS) stain) – showing large broad-based aseptate fungi. (c) (H&E) and (d) (GMS) – showing angioinvasion by the fungi.

available triazole with extended spectrum activity against zygomycetes.⁴

Common clinical settings for mucormycosis include diabetes (type I and type II), hematological malignancy, hematopoietic stem cell transplantation, and SOT.^{5,6} Among SOT recipients, those who receive intense immunosuppression for graft rejection have heightened risk for development of mucormycosis. In this case, the risk factors can be SOT, diabetes requiring high doses of insulin in the first 3 months, and the episode of neutropenia in the first month of transplant.

Singh *et al*² in a prospective, matched case-control study further advanced our understanding of the risks for development of mucormycosis in SOT recipients. The presence of renal failure, diabetes mellitus, and history treatment with voriconazole and/or caspofungin was significantly associated with a higher risk of mucormycosis, whereas tacrolimus was associated with a reduced risk of mucormycosis. Liver transplant recipients had a greater probability of developing a disseminated infection; they also developed mucormycosis significantly earlier (median of 0.8 months) after transplantation than did others (median of 5.7 months).² Our case was diagnosed 5 months after transplant.

There are only a few cases of mucormycosis following liver transplantation described in the medical literature. Hepatic involvement of mucormycosis is rare and is usually thought to arise from gastrointestinal disease, although dissemination uncommonly occurs from other sources.⁷ Hepatic mucormycosis has been associated with direct ingestion of naturopathic medicine containing *Mucor* species and is well documented among neonatal patients.^{8,9} Hepatic mucormycosis is readily seen on abdominal imaging. Typical CT findings include the presence of hypodense hepatic lesions surrounding vessels without a mass effect, representing areas of liver necrosis due to fungal thrombosis. These findings are not specific but suggest the presence of an angioinvasive organism.¹⁰ In some cases, radiological disappearance of liver lesions may take several months after antifungal treatment, which is similar to our case.

Previous reports of mucormycosis in liver transplant recipients have shown mortality rates of 50%–100%.¹¹ Although surgical treatment is often desirable and one of the mainstreams of treatment for *Mucorales* along with prompt effective antifungal therapy, our case shows that clinical success can be achieved with adequate combination of antifungal therapy, as in another recently published case.¹² Surgery was not possible in this case as he had multiple lesions. We had considered radiofrequency ablation for the ghost lesions but deferred it as there was significant clinical improvement and stable LFTs after combined antifungal therapy.

Lipid formulations of amphotericin B are preferred over other formulations to preserve renal function for

primary treatment of mucormycosis in SOT recipients.¹³ As there are no comparative studies for treatment of mucormycosis, selection of a particular lipid formulation of amphotericin B is usually dictated by the agent that is available in a given institution's formulary. Protection of renal function in a solid organ transplant recipient carries higher priority and warrants the use of a lipid formulation of amphotericin B. Although there are no systematic data on the use of posaconazole in combination therapy, it is reasonable to consider it as an option for long-term treatment due to the safety profile and oral route of administration of the therapy. Another issue involving posaconazole therapy is the potential for drug-drug interactions. Posaconazole is a potent inhibitor of cytochrome enzymes including cytochrome 3A4; this inhibition results in drug interactions with most immunosuppressive agents, such as cyclosporine, tacrolimus, and sirolimus.¹⁴ Thus, their serum levels and toxicity monitoring are desirable during posaconazole therapy, and a 50% dose reduction may be warranted. Our case developed GI side effects and skin acne and rashes due to prolonged use of posaconazole which was managed symptomatically and by dose reduction.

To conclude, we present a rare presentation of postliver transplant mucormycosis which manifested as liver graft dysfunction and space-occupying lesions and was successfully treated with combination of antifungal therapy without surgical intervention.

AUTHOR CONTRIBUTIONS

Dr Rohan Jagat Chaudhary – data acquisition, drafting of the article; Dr Narendra Singh Choudhary – conception, critical review; Dr Neeraj Saraf – conception, critical review; Dr Dheeraj Gautam – input for Pathology; Dr Tarun Piplani – input for radiology; Dr Thiagarajan Srinivasan – critical review; Dr Prashant Bhangui – critical review; Dr Sanjiv Saigal – conception, critical review; Dr Amit Rastogi – critical review; Dr Arvinder Singh Soin – conception, writing and approval of final version.

CONFLICTS OF INTEREST

The authors have none to declare.

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