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Diagnostic and Therapeutic Challenges in a Liver Transplant Recipient with Central Nervous System Invasive Aspergillosis

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Abstract

This is a case report of central nervous system (CNS) invasive aspergillosis (IA) in a liver transplant recipient, which illustrates the utility of enzyme-based diagnostic tools for the timely and accurate diagnosis of IA, the treatment challenges and poor outcomes associated with CNS IA in liver transplant recipients.

We report on a 17-year-old male liver transplant recipient (LTR) with central nervous system (CNS) invasive aspergillosis (IA). He was originally from Armenia and immigrated to the United States 10 years prior to presentation, with a history of cirrhosis due to autoimmune hepatitis. He received an orthotopic liver transplant (cytomegalovirus donor/recipient positive) from a 53-year-old male Caucasian donor. His induction and maintenance immunosuppression consisted of methylprednisolone and prednisone, mycophenolate mofetil and tacrolimus, respectively. Tacrolimus was discontinued on post-transplant day (PTD) 4 due to acute renal insufficiency. His prophylactic regimen included ganciclovir intravenously (IV), trimethoprim-sulfomethoxazole, and fluconazole. His post-transplant course was complicated by acute respiratory distress with diffuse bilateral ground-glass opacities on computed tomography (CT) of his chest requiring intubation on PTD 6. A bronchoscopy (PTD6) demonstrated bloody secretions in the distal airways. Bronchoalveolar lavage (BAL) was negative by smear and culture for bacterial, mycobacterial, and fungal organisms, by polymerase chain reaction (PCR) for respiratory viruses, and by direct fluorescent antibody for *Pneumocystis*. Plasma quantitative PCR for CMV and adenovirus and serum and BAL galactomannan enzyme immunoassay (GM EIA) were negative. Methylprednisolone (1000mg IV daily x3 doses) tapered to prednisone (1mg/kg daily orally) was initiated for a presumptive diagnosis of diffuse alveolar hemorrhage. On

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Conflicts of Interest

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PTD 15, he developed generalized tonic-clonic seizures. A magnetic resonance imaging (MRI) of the brain on PTD 15 showed multiple rounded lesions with peripheral enhancement in the left thalamus, right occipital and temporal, and left frontal and parietal subcortical white matter. The white blood cell count (WBC) was 20,820 cells/mm^3, with an absolute lymphocyte count of 390 cells/mm^3. Cerebrospinal fluid (CSF; PTD 18) revealed a WBC of 471 cells/mm^3 (377 neutrophils), glucose of 53 mg/dL, and protein of 107 mg/dL. A left frontal brain biopsy (PTD 18) revealed a necrotic lesion containing many septated branching hyphae and the culture was positive for *Aspergillus fumigatus*. Serum, CSF and BAL GM EIA were positive with an optical density index (ODI) of 20.20, 7.87, and 0.83, respectively. The CSF and BAL fungal cultures remained negative. Despite aggressive medical therapy with high dose IV voriconazole and co-administration of micafungin, the patient expired on PTD 33 due to intracerebral hemorrhage.

IA is a rare complication in LTR that most often occurs early post-transplant and has been associated with poor outcomes [Bonham CA et al, 1998; Neofytos D et al, 2010; Pappas P et al, 2010]. Although survival in patients with IA has significantly improved since the 1990's, LTR with IA tend to have worse outcomes compared to other solid organ transplant recipients [Neofytos D et al, 2010; Upton et al, 2007; Garcia-Vidal C et al, 2008; Nivoix Y et al, 2008; Neofytos D et al, 2009]. In addition, mortality in patients with CNS IA is higher compared to other forms of IA (e.g. pulmonary), with case fatality rates ranging from 88-99% [*Denning DW, 2001; Lin SJ et al, 2001*]. This case illustrates the utility of enzyme-based diagnostic tools for the timely and accurate diagnosis of IA and the treatment challenges associated with CNS IA.

Serum or BAL GM EIA may be used to establish a probable diagnosis of IA in the appropriate setting based on consensus guidelines [*De Pauw B et al, 2008*]. As GM is a water-soluble carbohydrate, it can be detected in fluids other than blood, including the CSF [*Klont RR et al, 2004*]. The diagnosis of CNS IA based on a positive CSF GM EIA has been reported in case-reports or series [Klont RR et al, 2004; Verweij P et al, 1999; Machetti M et al, 2002; Viscoli C et al, 2002]. Although the test has not been validated for use in non-blood, non-BAL specimens, it can be a useful diagnostic tool in the appropriate setting and when used with caution by experienced clinicians. The differential diagnosis of brain lesions in LTR and other immunocompromised hosts is broad. Prompt initiation of appropriate therapy is essential to achieve successful clinical outcomes. In cases that a brain biopsy is not feasible or cannot be obtained in a timely fashion, a positive CSF GM EIA may help establish a diagnosis of probable CNS IA and lead to initiation of appropriate treatment.

Voriconazole is the preferred agent for the treatment of CNS IA, as the concentration of voriconazole in the CSF can be up to 50% of that in plasma [*Walsch TJ et al, 2008; Lutsar I et al, 2003*]. Higher than standard doses of voriconazole may be required for the treatment of CNS IA, with close monitoring of drug levels, in order to ensure therapeutic concentrations of the drug in the CNS. In addition, LTR may exhibit variable drug metabolism early post-transplant due to post-surgical ischemia and reperfusion of the transplanted organ. Currently, there are no definitive guidelines with regards to appropriate dosing of voriconazole in patients with CNS IA and LTR. Estimating the dose of voriconazole for the treatment of this early post-transplant infection in a pediatric patient who received an organ from an adult donor was challenging. In fact, standard dose of voriconazole (loading dose of 6mg/kg IV every 12 hours x 2 doses, followed by 4mg/kg IV every 12 hours) was initiated and seven days later a trough voriconazole level was 0.3 mg/dl. Dose was increased to 8mg/kg every 12 hours and the drug trough level increased to 3.9 mg/dL 4 days later. We believe that drug metabolism in this case was altered due to the young age of the recipient and/or as a result of the recent liver transplantation. Notably, due to faster drug metabolism, higher doses may be required in pediatric patients [*Walsh TJ et al, 2008; Walsh TJ et al, 2004*]. In addition, a

recent study demonstrated that donor characteristics may have no significant correlation with voriconazole pharmacokinetics [*Johnson HJ et al, 2010*]. Clearly, more data are required to better understand the metabolism and appropriate dose adjustments of voriconazole early in LTR. The utility of combination therapy of voriconazole with an echinocandin for the treatment of IA, in general and CNS IA in particular, remains to be defined. However, based on retrospective data, the poor prognosis associated with this infection and the relatively benign adverse event profile of echinocandins, combination therapy in patients with severe CNS IA should be considered [*Marr KA et al, 2004; Singh N et al, 2006*].

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