Intracerebral Hemorrhage Related With *Penicillium* Species Following Deceased-Donor Liver Transplant

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**Abstract**

Early or late posttransplant opportunistic infections are among the leading complications after liver transplant. The source of early posttransplant opportunistic infections is usually the patient, the implantation of an infected graft, contamination during a surgical procedure, or invasive interventions performed at the intensive care unit. A 10-year-old male patient with Wilson disease (Pediatric End-Stage Liver Disease Score of 42, Child-Pugh score of 12, total bilirubin 40 mg/dL, platelet count 55,000/mL, hemoglobin level 6.3 g/dL, albumin level 1.7 g/dL, urinary copper level 4305 µg/24 h) was closely monitored in the pediatric intensive care unit of our liver transplantation center for care of a worsened general status. A deceased-donor liver transplant was performed using a right lobe liver graft (ex vivo split) obtained through the national organ sharing network. The patient developed rightward deviation of eyes and altered consciousness after the procedure and underwent cranial magnetic resonance imaging and computerized tomography examinations. The cranial magnetic resonance image, taken on the third postoperative day, revealed lesions consistent with embolic infarction, and the computed tomography scan, taken on the eighth day, showed intracerebral hemorrhage. Decompressive craniotomy, which included hematoma drainage and catheter placement, was performed. Culture and histopathologic examinations of the hematoma material revealed *Penicillium* species of fungi. However, the patient died before a definitive diagnosis was made. The aim of this report is to raise awareness on early posttransplant opportunistic infections of the central nervous system presenting with intracranial hemorrhage following liver transplant.

**Key words:** Liver transplantation, Neurologic complications, Opportunistic fungal infections

**Introduction**

Since the first successful liver transplant (LT) performed by Starzl and group in 1967, LT has become the criterion standard treatment option for many liver disorders, especially end-stage chronic liver disease and acute liver failure.1 Despite the introduction of modern immunosuppressive drugs, establishment of highly equipped intensive care units, and advances in surgical techniques, posttransplant surgical and medical complications continue to be significant problems.2 Opportunistic infections constitute a major portion of posttransplant complications.2,3 Posttransplant opportunistic infections (PTOI) mostly arise at a late period of LT.3,4 However, patient exposure to some risk factors before transplant can facilitate the emergence of PTOIs at an early period of LT.4 Posttransplant opportunistic infections may arise in every organ and tissue, including the central nervous system. The prevalence of posttransplant opportunistic central nervous system infections (CNSIs) is about 5%, which has been reducing in parallel to advances in patient care.3,4 The most common causes of posttransplant opportunistic CNSIs are viruses and fungi.3 The most common causative agents include *Candida* and *Aspergillus* species and *Cryptococcus neoformans*.3 Here, we report the first case of *Penicillium* species-related CNSI in the literature, which caused signs and symptoms consistent with post-LT intracranial hemorrhage.
A 10-year-old male patient (Child-Pugh score of 12, class C, Pediatric End-Stage Liver Disease score of 42, body mass index of 15.6 kg/m²) was admitted to the Department of Pediatric Gastroenterology, Liver Transplant Institute, Inonu University, Faculty of Medicine (Malatya, Turkey) for jaundice. His mother stated that he developed symptoms of fatigue and weakness several months before his presentation and started to “turn yellow” 4 days earlier. Neither the child nor any of his family members had any history of liver disease. On physical examination, there was hepatosplenomegaly, jaundiced skin and sclerae, grade 1 encephalopathy, and concave abdominal dullness on percussion (ascites). He was hospitalized in a pediatric intensive care unit for both further work-up and close monitoring. His blood test results were as follows: total bilirubin of 40 mg/dL (range, 0.2-1.2 mg/dL), direct bilirubin of 27.9 mg/dL (range, 0-0.5 mg/dL), aspartate aminotransferase of 126 U/L (range, 5-34 U/L), ammonia level of 123 μg/dL (range, 31-123 μg/dL), international normalized ratio of 4.5 (range, 0.8-1.2), activated partial thromboplastin time of 89 seconds (range, 28-35 s), prothrombin time of 52.7 seconds (range, 9.5-13.5 s), albumin level of 1.7 g/dL (range, 3.8-5.4 g/dL), creatinine level of 0.46 mg/dL (range, 0.7-1.2 mg/dL), platelet count of 55,000/mL (range, 150,000-400,000/mL), and hemoglobin level of 6.3 g/dL (range, 13.6-17.2 g/dL). Serum parvovirus immunoglobulin M (IgM), hepatitis B surface antigen, measles IgM, mumps IgM, herpes simplex virus IgM, Epstein-Barr virus viral capsid antigen IgM, anti-hepatitis A virus IgM, and cytomegalovirus IgM levels were all negative. His blood copper level was 168 μg/dL (range, 70-155 μg/dL); the 24-hour urinary copper excretion amount was 4305 μg/24 hours (range, 3-35 μg/24 h). Based on clinical and laboratory results, the patient was considered to have decompensated Wilson disease.

A cranial magnetic resonance image (MRI) was taken to demonstrate any neurologic components of the disease. A fluid-attenuated inversion recovery (FLAIR) MRI revealed nonspecific focal intensities in parieto-occipital subcortical white matter (Figure 1). A deceased-donor LT was performed using a right lobe liver graft (ex vivo split) obtained through the national organ sharing network. On the first and second postoperative days, the patient exhibited marked improvements of hemato-logic parameters, except for thrombocyte count (27,000/mL). However, a rightward deviation of eyes was detected on postoperative day 3, and a contrast-enhanced cranial MRI was taken at the suggestion of the pediatric neurologist. Compared with the preoperative MRI examination, the latter MRI examination showed an increase in both the number and size of cortical and subcortical lesions (Figure 1, panel 2), which were considered to be foci of embolic infarction or abscesses (Figure 1, panel 3). The patient later regained consciousness and started to be fed orally. However, he developed fever (38°C) and altered consciousness (Glasgow coma score on 9) on postoperative day 7. A cranial computerized tomographic examination taken on postoperative day 8 revealed dilatation of lateral ventricles, hypodense areas consistent with edema, and a hemorrhagic focus causing leftward shift in the frontoparietal region (Figure 2). A decompressive surgical craniotomy, including hematoma drainage and placement of a drainage catheter, was performed.
No abscess focus or purulent materials during craniotomy process were found.

Figure 2. Contrast-Enhanced Cranial Computed Tomography Image

Results show dilated lateral ventricles, hypodense areas consistent with edema, and a hemorrhagic focus, causing leftward shift in the frontoparietal region (white arrow). Contrast-enhanced cranial computed tomography also shows 2 different abscessed foci in the left hemisphere (yellow arrows).

Despite fluid resuscitation and inotropic support after the craniotomy procedure, the patient remained hemodynamically unstable and his liver parameters and electrolytes also began to worsen. Although the patient was given supportive therapies, the patient died on postoperative day 15. Both culture and pathology examinations of the hematoma material taken from the craniotomy procedure yielded *Penicillium* species (Figure 3). The histopathologic examination of the native liver specimen revealed no signs of fungal infection.

Figure 3. Histochemical Examination Demonstrating Septated Hyphae With Grocott-Gomori’s Methenamine Silver Stain (×20)

Discussion

More than 50% of patients developing opportunistic CNSI after LT die despite appropriate therapy.3-5 Opportunistic infections that develop in the central nervous system within the first month after LT are termed as early CNSI, for which the most important risk factors include pretransplant colonization, pretransplant latent infection, prolonged pretransplant intensive care unit admission, infections of graft origin, prolonged surgery, early graft dysfunction, invasive catheterization, blood transfusions, fulminant liver failure, prolonged posttransplant intensive care unit admission, and prolonged ventilation.3-6 In contrast, opportunistic infections developing after the first month are termed as late CNSIs. High-dose steroid/immunosuppressive agents or antilymphocyte medications such as OKT3 used for acute rejection episodes are the most important risk factors for late CNSIs.3-5 Although a significant proportion of opportunistic CNSIs occur at a late period, early CNSIs may occur in the presence of the above-mentioned predisposing factors.4 As for the present case, the pretransplant prolonged stay at an intensive care unit was an important risk factor. A low albumin and high bilirubin level coupled with pancytopenia also contributed to an increased susceptibility to opportunistic infections. When our patient’s preoperative cranial MRI was reevaluated, it was speculated that brain lesions detected by that examination may have actually been septic foci. Based on a review of all available data, we may hypothesize that our patient contracted a fungal infection. This hypothesis was corroborated by the absence of any signs of fungal infection in another transplant recipient, to whom the left lobe of the deceased-donor liver graft was transplanted, effectively eliminating the possibility of an infection of graft transmission.

Viruses and fungi are the most common etiologic agents of PTOIs; bacteria and parasites are responsible for a lower number of PTOIs.3,5 The incidence of post-LT fungal infection ranges between 10% and 40%.5 Fungal colonization may be detected in many body regions of patients with risk factors. Fungi cause disseminated infection after invading mucosal barriers and gaining access to systemic circulation. Fungal CNSIs mostly develop as a result of the dissemination of systemic fungal infections and rarely fungal sinusitis.3,5 The most common microbiologic agents responsible for opportunistic...
fungal CNSIs are *Aspergillus* species, *Cryptococcus neoformans*, and *Candida* species.\(^3\)\(^5\)-8\) Opportunistic fungal CNSI infections also develop with other fungus species, albeit extremely rarely.

To our knowledge, no previous studies of a post-LT CNSI caused by a *Penicillium* species have been reported in the English medical literature. Hence, this is the first report of a *Penicillium*-associated post-LT CNSI. Furthermore, although there are some reports of intracerebral hematoma secondary to *Candida* and *Aspergillus* species, no case of a *Penicillium*-associated post-LT intracerebral hematoma has ever been reported.\(^7\) Our report is also the first report from this standpoint. *Penicillium* species are a species of fungi found as a part of normal flora of indoor and outdoor air, and approximately 225 subspecies have been defined to date.\(^9\) The most potent pathogen of this group is *Penicillium marneffei*, which has a similar invasion capacity as *Aspergillus* species.\(^9\) Systemic dissemination almost always occurs in patients with immunosuppression due to various reasons.\(^9\)

Clinical signs and symptoms suggestive of a posttransplant opportunistic CNSI should be taken seriously and investigated at once. Initial symptoms are masked in a significant proportion of these patients since they are immunocompromised and hemodynamically unstable during follow-up.\(^3\) Fungal CNSIs usually cause signs and symptoms suggestive of meningitis, meningoencephalitis, cerebral hemorrhage, and abscess formation.\(^3\) Fungal brain abscesses or intracerebral hematomas may sometimes become manifest with seizure activity or focal neurologic deficits.\(^3,5\) The most common reason of intracerebral hematomas are mycotic aneurysms that develop as a result of the erosion of vascular wall by fungi. Our patient also probably had intracranial hemorrhage secondary to a similar mechanism. However, a low post-LT platelet count led to a greater bleeding severity. More importantly, the post-LT cranial MRI was interpreted by a radiologist as embolic infarction rather than septic infarction or abscess. Hence, we started enoxaparin on the basis of cranial MRI report. Enoxaparin may have possibly contributed to increased severity of bleeding that occurred secondary to mycotic aneurysm(s).

A high index of suspicion is the key for definitive and differential diagnoses of posttransplant fungal CNSIs. Fungal CNSIs should be considered in the differential diagnosis of low-density solitary or multiple lesions (perhaps abscess) with minimal contrast enhancement and of lesions with annular contrast enhancement and edematous periphery on cranial computed tomography or MRI taken for any indication.\(^5\) Definitive diagnosis can be made by demonstrating fungi by histopathologic examination or by molecular tests such as immunofluorescence assay and polymerase chain reaction. Treatment options include multiple antifungal agents, including fluconazole, itraconazole, voriconazole, amphotericin B, caspofungin, and echinocandins. Despite this, fungal infections involving the central nervous system have an excessively high mortality rate.\(^5\) Mortality risk is significantly increased by fungal infections causing intracerebral hemorrhage and signs of lateralization, as in our case.

This report has 2 main limitations. First, although we showed a fungal infection with *Penicillium* species by both microbiologic and histopathologic examinations of the fluid sample obtained at craniotomy, we lacked necessary equipment and thus failed to show the *Penicillium* subspecies responsible for the clinical signs and symptoms. Second, the cranial lesions were falsely interpreted by both the preoperative and postoperative radiologic examinations, which we believe resulted from the inexperience of radiologists in such cases. Here, we primarily aimed to raise awareness on this issue.

In summary, fungal CNSIs continue to cause high mortality and morbidity despite many advances in diagnostic and therapeutic modalities. Therefore, evaluating all LT candidates for opportunistic infections, determining patients with risk factors for these infections and tailoring their medical therapy accordingly, using prophylactic agents with care, and instituting therapy early in the course of a suspected fungal infection would lead to dramatic improvements in the mortality and morbidity rates of opportunistic fungal CNSIs.

**References**