Successful, combined long-term treatment of cerebral aspergillosis in a liver transplant patient

Parmenion P. Tsitsopoulos, Georgios Tsoulfas, Christos Tsonidis, George Imvrios, Vasilios Papanikolaou, Dimitrios Giakoustidis, Dimitrios Marinopoulos, Dimitrios Takoudas & Phillipos D. Tsitsopoulos

To cite this article: Parmenion P. Tsitsopoulos, Georgios Tsoulfas, Christos Tsonidis, George Imvrios, Vasilios Papanikolaou, Dimitrios Giakoustidis, Dimitrios Marinopoulos, Dimitrios Takoudas & Phillipos D. Tsitsopoulos (2010) Successful, combined long-term treatment of cerebral aspergillosis in a liver transplant patient, Virulence, 1:5, 465-467, DOI: 10.4161/viru.1.5.13110

To link to this article: https://doi.org/10.4161/viru.1.5.13110
Successful, combined long-term treatment of cerebral aspergillosis in a liver transplant patient

Parmenion P. Tsitsopoulos,1 Georgios Tsoulfas,2 Christos Tsonidis,1 George Imvrios,2 Vasilios Papanikolaou,2 Dimitrios Giakoustidis,2 Dimitrios Marinopoulos,1 Dimitrios Takoudas3 and Phillipos D. Tsitsopoulos1

1Department of Neurosurgery; 2Division of Transplantation; Hippokration General Hospital; Aristotle University; Thessaloniki, Greece

Invasive aspergillosis has long been recognized as one of the most significant and often fatal opportunistic fungal infections in liver transplant recipients. We report a case of a liver transplant recipient who developed an Aspergillus fumigatus brain abscess that produced significant neurologic symptoms. The patient was managed successfully with a combination of surgery and medical treatment with Voriconazole. To our knowledge, this is the second such case reported in the literature.

Introduction

Invasive aspergillosis has long been recognized as one of the most significant and often fatal opportunistic fungal infections in liver transplant recipients.1,3 After Candida, Aspergillus species are responsible for most of the systemic fungal infections in the immunocompromised host. Noticeably, when the insult involves the Central Nervous System (CNS), Aspergillus is the second most common pathogen after Cryptococcus Neoformans.4 Although the frequency of invasive aspergillosis ranges only from 1 to 6%, the mortality in these patients exceeds 90%, especially when the CNS is affected.5

We report a case of a liver transplant recipient who developed an Aspergillus fumigatus brain abscess that produced significant neurologic symptoms. The patient was managed successfully with a combination of surgery and medical treatment with Voriconazole. To our knowledge, this is the second such case reported in the literature.

Case Report

A 59-year-old Caucasian female underwent orthotopic liver transplantation for HCV-related end-stage liver disease. She had a past medical history of HCV infection. There was no evidence of any infection in the donor. Immunosuppression consisted of Prednisone, Mycophenolate Mofetil and Cyclosporine (target level around 150 ng/mL). The graft started functioning immediately. The immediate post-operative course was significant only for an ascitic fluid culture positive for multiresistant Klebsiella pneumoniae, which was treated successfully with intravenous administration of Polymyxin E (dose of 2 million IU every 12 hours for 14 days). The patient was discharged on the 25th post-operative day, with Valganciclovir (900 mg a day) and sulfamethoxazole/trimethoprim as standard antibiotic prophylaxis. At a routine follow-up, she remained symptom-free but was found to be cytomegalovirus (CMV) positive with 2,000 copies/μg, without any clinical symptoms. She was then treated with therapeutic doses of Valganciclovir (900 mg twice a day) for six months, with excellent results.

Three months post-transplantation, she manifested partial seizures. Neurological examination revealed a slight right upper limb paresis and an intact level of consciousness and cognition. The seizures were acutely controlled with intravenous clonazepam (0.5–1 mg IV bolus injection). The patient was then given Levetiracetam orally (500 mg X2/day) on a systematic basis. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of the brain displayed a single solid mass (1.4 by 1.6 by 1.9 cm) in the left frontoparietal lobe, Figure 1. The lesion was surrounded by extensive perifocal edema and demonstrated ring enhancement after contrast administration. Due to the altered immune status of the patient, the diagnosis of a brain abscess versus a metastatic mass was initially considered. The decision to proceed with surgery under neuronavigation was made. During the operation, the tumor was found about 1.5 cm from the cerebral cortex and excised easily en bloc, as a solid mass. Pathological examination revealed an abscess with the septate hyphae of Aspergillus fumigatus, Figure 2.

The postoperative course of the patient was uneventful. She was slowly weaned off the antiseizure medication at the 6-month time point. Sinus and pulmonary CTs did not reveal any additional Aspergillus infection. She was also treated with Voriconazole at a dose of 200 mg twice a day orally for six months. Moreover, during the follow-up period she was tested monthly for serum Galactomannan antigen, in addition to surveillance for CMV once every two weeks.

At the 18 month follow-up she was seizure-free, with normal muscle power, while on an MRI there was no evidence of recurrence of the brain lesions. There was an effort to maintain her immunosuppression at an overall lower level (Cyclosporine level around 60–100 ng/mL), given her history of infections and HCV.

*Correspondence to: Georgios Tsoulfas; Email: tsoulfasg@msn.com
Submitted: 05/28/10; Revised: 07/16/10; Accepted: 07/19/10
Previously published online: www.landesbioscience.com/journals/virulence/article/13110
recipients were fatal, as antifungal medica-
tions alone did not prove to be effective
in treating the infection 4,11-16 (Table 1). In
the one of the two patients who survived,
there were significant treatment-related
side-effects, with the predominant one
being renal failure due to antifungal medi-
cation nephrotoxicity. 4 Interestingly, of
the reported cases, no patient was treated
with Voriconazole.4,11-16 In our patient, the
combination of treatment with surgery
and Voriconazole proved to be effective in
achieving an uncomplicated, long-term,
favorable outcome.

Treatment of cerebral aspergillosis in
an immunocompromised patient has to
be approached on several different lev-
els. Specifically, the immunosuppression
issue should be addressed, with the goal
of reducing the level of overall immune
suppression. This is complicated by the
fact that in a liver transplant recipient,
immunosuppression cannot be completely
abandoned, due to the life-saving nature
of the graft. Moreover, several antibiotics
used for Aspergillus treatment, including
Voriconazole, increase cyclosporine and
tacrolimus concentrations, and therefore
dosing adjustments to maintain appropri-
ate levels are needed.17

This brings us to the second issue,
which is the choice of the antifungal
antibiotic. Traditionally, Amphotericin B
and subsequently liposomal amphotericin

Discussion
Numerous factors have been associated
with fungal infections in liver transplant
recipients. These include prolonged opera-
tive time, increased intraoperative infusion
of blood products, gastrointestinal or vas-
cular complications, use of antibiotics and
steroids, HCV infection, retransplantation,
preexisting CMV infection and human her-
pes virus 6 (HHV6) seronegativity before
transplantation.5-10 Patients are placed in a
state of higher immunosuppression, thus
increasing their vulnerability to Aspergillus.
The majority of these infections occur in the
first 6 months after transplantation, when
immunosuppression is at its highest level.

Our case did present within the
expected timeframe, as symptoms started
3 months after liver transplantation and
some of the risk factors were present.
Specifically, she had a history of antimicro-
bial treatment (2 weeks) for the infected
ascitic fluid, as well as a CMV infection
for which she underwent prolonged (6
months) treatment. Furthermore, around
the time of her hospitalization, there had
been some minor construction work in the
vicinity of the transplant unit. However,
no other cases of Aspergillus were subse-
quently reported in our patients during
that time period.

In the literature, most reported cases
of cerebral aspergillosis in liver transplant

Figure 1. Preoperative axial (A) and coronal (B) T1-weighted MRI of the brain with contrast administration demonstrating a well circumscribed mass in the left frontoparietal lobe with marked perifocal edema.

Figure 2. Cerebral abscess with fungal growth (arrow). (Hematoxylin and eosin X100).
have been the predominant choices for Aspergillus treatment; however, serious side-effects such as nephrotoxicity and decreased cerebrospinal fluid (CSF) concentrations have limited its usefulness.\(^{18}\)

Voriconazole as therapy for invasive aspergillosis in immunocompromised patients has shown excellent results compared to Amphotericin B, as well as the advantage of oral bioavailability.\(^{19-23}\)

In the present case, a multi-pronged strategy was applied. The final key to the successful management was the immediate decision to proceed with neurosurgical intervention, which was critical from both a diagnostic and a therapeutic standpoint. With the aid of neuronavigation, a minimal surgical approach was carried out and the mass was removed en bloc, without damaging any areas of the brain. Neuronavigation provides intraoperative orientation of the surgeon and delineates the surrounding neurovascular structures. When needed, fusion of neuronavigation images with the functional data provided by MRI and EEG helps to avoid injuring vital areas of the brain during surgery.\(^{24}\)

In the present case the use of neuronavigation provided excellent accuracy, facilitated the precise planning of the craniotomy and guided the surgeons to the exact location of the tumor. Moreover, surgery was central in allowing a quick resolution of the problem, so that it was not necessary to wait for the antibiotic course to take effect. This way it was possible to decrease the risk of rejection by maintaining the reduced immunosuppression for no longer than absolutely necessary.

In conclusion, cerebral aspergillosis represents a very difficult problem for the liver transplant recipient, with a highly lethal course. Although, in high-risk patients, attempts for antifungal prophylaxis can be made, their efficacy regarding aspergillosis remains questionable. The key elements toward a successful outcome in such cases are a prompt diagnosis, through careful investigation of the presenting neurologic symptoms, identification of the offending microorganism, and, most importantly, an aggressive approach combining surgical and medical treatment.

### References


