ORIGINAL ARTICLE

Immune Reconstitution Syndrome After Voriconazole Treatment for Cryptococcal Meningitis in a Liver Transplant Recipient

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A new entity that comprises symptomatic worsening of an infectious or inflammatory process despite appropriate treatment was described a few years ago in human immunodeficiency virus–infected patients receiving highly active antiretroviral therapy. This entity was defined as immune reconstitution syndrome, and it is believed to result from an intense inflammatory reaction in patients with an appropriately treated infection who recover immunological status. Recently, immune reconstitution syndrome has also been described in transplant recipients, although information is scarce because of its low incidence. Here we describe a new case of immune reconstitution syndrome in a liver transplant recipient after successful treatment of cryptococcal meningitis. ***Liver Transpl 14:1671-1674, 2008.*** **© 2008 AASLD.**

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In May 2006, a 63-year-old man underwent liver transplantation because of end-stage liver disease caused by cryptogenic cirrhosis. His postoperative course was uneventful, his liver function improved rapidly, and there was no evidence of rejection or infectious complications. The immunosuppressive scheme included cyclosporine A (CyA) and prednisone. In February 2007, he complained of gait instability. A cranial computer tomography scan showed ventricular dilatation. The diagnosis of normal pressure hydrocephalus was established, and a ventriculoperitoneal shunt was placed, with resolution of all neurological symptoms. In August 2007, he was admitted because of frontal headache and fever. A cranial computer tomography scan showed a normally functioning shunt with no parenchymal lesions and absence of signs of cranial hypertension. A cerebrospinal fluid (CSF) examination showed 160 white blood cells/mL, a low glucose content (2 mg/dL), and a high protein level (305 mg/dL). Magnetic resonance imaging (MRI) of the brain showed marked supratentorial and infratentorial leptomeningeal enhancement (Fig. 1). The CSF stain and culture were positive for *Cryptococcus neoformans*, as the culture was of the ventriculoperitoneal shunt. Therapy with liposomal amphotericin-B and 5-flucytosine was started, and an external ventricular derivation was placed. CyA was replaced by mycophenolate mofetil (MMF) because of the development of renal failure. The patient's general status improved, his fever disappeared, and CSF biochemical markers improved (Table 1). After 4 weeks of treatment, his therapy was changed to fluconazole, and a new ventriculoperitoneal shunt was placed. Treatment was switched to voriconazole according to antifungal susceptibility. Nine days after starting voriconazole, the patient presented dyplopia. A physical examination revealed left cranial nerve VI palsy. MRI showed worsening of the leptomeningeal enhancement, which had progressed and affected the cerebral trunk (Fig. 2). His CSF biochemical markers were impaired again, CSF cryptococcal antigen was 1:2,

Abbreviations: CSF, cerebrospinal fluid; CyA, cyclosporine A; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IRS, immune reconstitution syndrome; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging.

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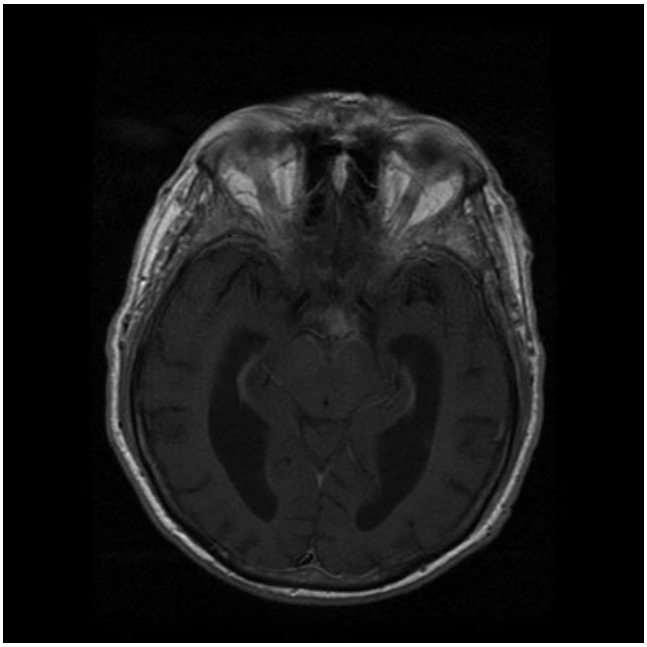

Figure 1. T1-weighted magnetic resonance imaging at diagnosis, showing supratentorial leptomeningeal enhancement.

and the culture was negative. The patient was started on intravenous dexametasone, and voriconazole was maintained. The clinical status, CSF characteristics, and meningeal inflammation on MRI progressively improved, with complete resolution of neurological symptoms in 3 weeks.

DISCUSSION

Meningeal infection by *C. neoformans* has been reported to occur in 0.25% to 6% of liver transplant recipients.[1-3] Its related mortality was as high as 50% of the cases in the original reports,[2] but recent studies have reported a mortality of approximately 20%. This reduction in mortality could be associated with the use of calcineurin inhibitor agents versus other immunosuppressive agents.[3] Treatment usually includes a 4- to 6-week course of combination antifungal therapy with amphotericin-B plus 5-flucytosine followed by oral fluconazole for 6 months. Lumbar drainage to reduce high intracranial pressure may be needed in up to 25% of cases.[4]

Immune reconstitution syndrome (IRS) was initially described in human immunodeficiency virus (HIV)–infected patients affected by opportunistic infections, mainly mycobacteria, *C. neoformans*, cytomegalovirus, hepatitis B virus, and hepatitis C virus, affecting 10% to 25% of patients starting highly active antiretroviral therapy (HAART).[5,6] Proposed criteria include (1) the reappearance or worsening of previous manifestations after an initial response or the development of new manifestations consistent with an infectious or inflammatory process despite appropriate therapy and (2) the appearance of symptoms cannot be explained by a newly acquired infection, by the expected clinical course of a previously recognized infection, or by the adverse effects of therapy.[6] The physiopathology of the phenomenon seems to be related to a restoration of immunity following HAART in HIV patients, and younger age and a low CD4 cell count at baseline have been identified as the main risk factors.[7]

This entity has also been described in transplant recipients, affecting 4 of 83 (4.8%) transplanted patients with *C. neoformans* infection in the only series to date,[8] which included 3 renal recipients and 1 liver transplant patient. IRS in transplant recipients can be a complication of the treatment of other infectious diseases such as CMV[9] and tuberculosis.[10] It has been proposed that a shift in the immunological response to infection, due to the withdrawal of immunosuppressive agents and to the immunomodulatory properties of some antifungal therapy, would lead to a predominance of CD4+ T helper 1 response, with proinflammatory properties mainly mediated by interferon-γ and interleukin-2, which would be responsible for a worsening of symptoms despite a correct and effective antimicrobial treatment.[8] Recently described T regulatory (T reg) and T helper 17 (Th 17) cells may also be involved in the pathogenesis of IRS, mainly because of enhanced Th 17 expression.[11]

When the patient developed cryptococcal meningitis, his immunosuppressive scheme comprised prednisone (10 mg per day) and CyA (75 mg twice daily), with trough levels of CyA around 150 ng/mL (normal range, 50-350). The development of the infection and kidney failure led to stopping CyA and starting MMF (500 mg twice daily), with the same dose of prednisone maintained. Trough levels of MMF in the following days ranged from 0.5 to 1.8 μg/mL (normal range, 2-4). Although blood levels of CyA and MMF didn't completely quantify the real grade of immunosuppression achieved, a lower immunosuppressive environment was probably responsible for the development of the syndrome. In fact, it is widely assumed that calcineurin inhibitors have higher immunosuppressive potency than MMF. Several reports of renal, heart, and liver transplant recipients have shown that the replacement of calcineurin inhibitors with MMF is associated with a higher risk of acute rejection.[12-14]

Management of immunosuppression in the setting of opportunistic infections is not well defined. Reducing the global level of immunosuppression in these cases is widely accepted. However, the development of IRS is a risk in these patients, and it may also be associated with a higher probability of chronic rejection and graft loss, as has been shown in a report of renal transplant recipients.[15] In HIV-infected patients that are diagnosed with opportunistic infections such as *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, and *C. neoformans*, delaying the initiation of HAART until 4 to 8 weeks after therapy is started is usually recommended to minimize the risk of IRS.[16] A similar approach could be used in transplant patients, that is, deferring the reduction of immunosuppression when an opportunistic infection is diagnosed. However, there

TABLE 1. Evolution of Cerebrospinal Fluid Characteristics

Cerebrospinal Fluid	Diagnosis	Week 4	Week 6	Week 8	Week 9	Week 10
Glucose (mg/dL)	2	35	36	15	36	71
Proteins (mg/dL)	305	232	241	320	376	274
White blood cells/mL	160	50	10	140	140	20

NOTE: Worsening of symptoms occurred in week 8.

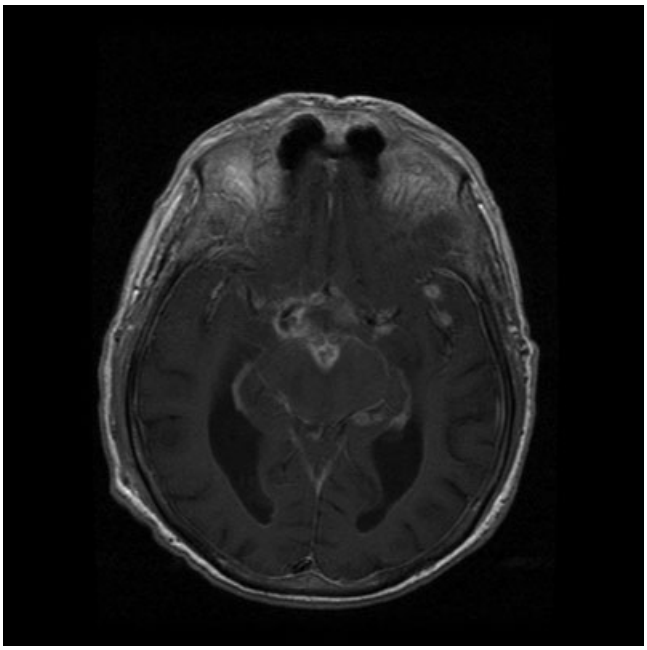

Figure 2. T1-weighted magnetic resonance imaging at symptomatic worsening, showing marked meningeal and cerebral trunk enhancement.

are not enough data to support a particular decision regarding immunosuppression.

Another interesting issue regarding this case is that in our patient, therapy with amphotericin-B and 5-flucytosine was used for 4 weeks, and maintenance therapy with fluconazole was switched to voriconazole a few days before relapse of the symptoms. This change was performed because of the *in vitro* susceptibility of *C. neoformans* isolated in the patient. The median inhibitory concentration was 4 μg/mL for fluconazole and 0.032 μg/mL for voriconazole, suggesting reduced susceptibility to fluconazole.[17] Voriconazole reaches high concentrations in the brain tissue and CSF of immunocompromised patients,[18] and for this reason, it may control CNS infections more easily than other antifungals. In addition, it has been shown that voriconazole increases the release of tumor necrosis factor-α by human monocytes in response to *Aspergillus fumigatus* fragments.[19] Thus, the optimal penetrance of voriconazole in CSF, together with a potential proinflammatory activity, could contribute to the worsening of symptoms in our case. However, further studies are needed to clarify the potential role of specific antifungal therapy in the pathogenesis of IRS.

Management of the syndrome is challenging because of the difficulty of distinguishing it from relapse of an uncontrolled infection. In our patient, in agreement with previous reports, cryptococcal antigen in CSF was positive at very low titers, and the CSF culture was negative. As described in HIV-infected patients,[20] therapy with corticosteroids and maintenance of voriconazole was followed in our case by complete resolution of symptoms in a few weeks.

In summary, cryptococcal meningitis is an infrequent but potentially lethal complication of liver transplantation. IRS may develop after correct treatment in the context of lower immunosuppression in transplant recipients, although antifungal treatments may also play a role in its pathogenesis. Recognition of the syndrome and a differential diagnosis from relapse of an infection are crucial because management is conservative, with corticosteroids being useful in reducing the deleterious inflammatory response.

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