Rhinocerebral Zygomycosis After Liver Transplantation: Therapeutic Challenges in Recipients Treated for Recurrent Hepatitis C

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We report on a 40-year-old male liver recipient who developed a usually highly fatal rhinocerebral zygomycosis while being treated for recurrent hepatitis C. Risk factors included immunosuppressive therapy, episodes of neutropenia and anemia, chronic liver graft dysfunction, posttransplant diabetes, and intermittent renal insufficiency. Aggressive treatment, including maxillary débridement and orbital exenteration, reduction of immunosuppression, as well as prolonged intravenous antifungal therapy, was successful. There was no zygomycosis recurrence during the four-year follow-up. Graft function could be maintained and recurrent hepatitis C histologic findings improved.

The severe life-threatening infection encountered in our liver recipient with recurrent hepatitis C suggests that particular attention must be paid to avoiding overimmunocompromising this large and expanding recipient group. If these patients develop zygomycosis, early diagnosis and aggressive treatment are key to their survival.

INTRODUCTION

The susceptibility of immunosuppressed solid organ hosts to opportunistic infections is well recognized. However, recipients of liver trans-

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plants done for hepatitis C virus (HCV)-related cirrhosis, currently the most common indication for liver transplantation in the United States, face unique additional challenges (1). Their resistance to opportunistic infections may be lowered even further due to (I) posttransplant diabetes, a frequent metabolic complication observed in up to 60% of those recipients (2), (II) varying degrees of chronic renal insufficiency (from HCV-associated membranoproliferative and other forms of glomerulonephritis), which can be worsened by use of calcineurin inhibitors (3), and (III) adverse side effects of the therapy of recurrent HCV infection (e.g., neutropenia, anemia). We illustrate these challenges in a report on one of our recipients who developed a usually highly fatal rhinocerebral zygomycosis while undergoing combination therapy with interferon and ribavirin for recurrent hepatitis C.

CASE REPORT

A 40-year-old male underwent orthotopic liver transplantation for HCV-related liver cirrhosis. Initial posttransplant immunosuppression consisted of cyclosporine, sirolimus, and prednisone. The patient developed post-transplant diabetes mellitus, which was treated with glyburide. Steroids were tapered off by six-months post-transplant. At six-months, the patient was also started on a combination of interferon alpha 2b (1.5–3.0 million units, three times weekly) and ribavirin (range, 200–1200 mg/day) for histologically documented recurrent hepatitis C. Side effects of the antiviral treatment included episodes of neutropenia with absolute neutrophil counts of less than 1000/mm^3, treated with filgrastim, and hemolytic anemia, treated with erythropoietin. The patient never experienced tissue invasive cytomegalovirus (CMV) infection.

At 12 months posttransplant, he developed transient renal insufficiency with creatinine levels not exceeding 2.0 mg/dL.

At 18 months posttransplant, he presented with acute onset of left-sided eye pain associated with loss of vision, diplopia, and headaches. At that time, his immunosuppression consisted of sirolimus (whole blood level 20 ng/mL), and cyclosporine (whole blood level 245 ng/mL; range, 175–230 ng/mL over the preceding three months). Significant findings on physical examination included fever (39°C), left eye proptosis, and left opthalmoplegia. The patient was diagnosed with left-sided orbital apex syndrome (paralysis of all left external ocular muscle nerves, sensory deficit in the distribution of the first segment of the trigeminal nerve, optic nerve lesion). Laboratory data showed total bilirubin 3.5 mg/dL, international normalized ratio (INR) 1.1, aspartate aminotransferase (AST) 1150 units/dL, alanine aminotransferase (ALT) 700 U/dL, albumin 3.2 gm/dL, HCV viral load > 1 × 10^6 IU/mL, white blood cell count 2,700/mm^3, absolute neutrophil count 2,300/mm^3, hematocrit 28% (range, 25% to 27% over the preceding two months), platelets 21,000/mm^3, and multiple random glucose levels > 250 mg/dL over the preceding two months. A computed tomography scan of the head showed opacification of the left sinuses. Cavernous sinus thrombosis could not be ruled out. He was immediately explored surgically and underwent left sphenoidectomy and ethmoidectomy, as well as left maxillary sinus débridement. Overall, the patient required three re-débridements. At the time of the third operation, a left orbital exenteration was necessary due to the extramaxillary involvement. Histopathologic examination of the resected tissue revealed broad, non-septate hyphae consistent with a zygomycete. The subsequent tissue cultures grew *Rhizopus* species. Postoperatively, sirolimus and antiviral treatment with interferon and ribavirin were discontinued and cyclosporine dosage was reduced. A three-month course of I.V. liposomal amphotericin B was given.

Laboratory data immediately after the completion of antifungal therapy showed bilirubin 3.7 mg/dL, INR 1.1, AST 210 U/dL, ALT 260 U/dL, albumin 2.8 gm/dL, absolute neutrophil count 1800/mm^3, HCV viral load >1 × 10^6 IU/mL, hematocrit 31%, and platelet count 81000/mm^3. Repeat liver biopsy at that time revealed mild acute cellular rejection and improvement of hepatic fibrosis from baseline stage 1–2 (at the time of hepatitis C recurrence) to stage 0–1. The rejection was successfully treated with a three-day course of high-dose I.V. steroids.

At one-year follow-up, the patient lacked symptoms or signs of zygomycosis recurrence, while maintaining liver graft function without further episodes of rejection. A protocol liver biopsy one-year after the completion of antifungal therapy showed further improvement in the resolution of liver fibrosis (stage 0), despite HCV persistence as well as abnormal liver tests (bilirubin 2.4 mg/dL, ALT 154 units/dL, AST 136 units/dL). The patient maintained stable liver graft function. At 3.75 years posttransplant, he was diagnosed by open biopsy with an unresectable poorly differentiated pelvic cancer. He expired after undergoing palliative therapy at four-years posttransplant without having experienced zygomycosis recurrence.

DISCUSSION

End-stage liver disease from hepatitis C is currently the most frequent indication (>30%) for liver transplantation in the United States (1). HCV recurrence is nearly universal; 60% to 80% of these recipients develop lesions of chronic hepatitis in the graft (4). The posttransplant management of this rapidly expanding recipient group often involves treatment with interferon and ribavirin, which can cause neu-

tropenia and anemia, respectively (1,4). These recipients therefore face additional unique challenges, especially since they may be more susceptible to infectious complications to begin with. The latter is a result of the potentially concurrent presence of multiple other risk factors, including the pharmacologic immunosuppression, HCV-associated renal dysfunction and posttransplant diabetes (2,3), and cholestasis (4). The reduced immunocompetence of these patients may increase the rate of serious, invasive fungal infections such as the zygomycosis observed in our patient.

Opportunistic zygomycosis fungal infections such as mucor are broadly categorized as pulmonary, rhinomaxillary, rhinocerebral, gastrointestinal or cutaneous (5). Known risk factors include diabetes, CMV infection, renal dysfunction, anemia, iron overload, and corticosteroid therapy or other states of impaired neutrophil and/or mononuclear cell phagocytic function (5).

After solid organ transplantation, these serious infections have a reported incidence of 1%–9% and predominantly affect male patients, usually within six months of transplantation (7–9). The majority of reported zygomycetes infections in solid organ recipients are rhinocerebral or rhinomaxillary (7). The rhinocerebral form is usually highly fatal, while the rhinomaxillary form tends to be less invasive and is associated with more favorable outcomes.

Rhinomaxillary zygomycoses were reported in three patients (9,10,19). One of the 18 reported cases was of the more invasive rhinocerebral form, extending beyond the sinuses (6). In that case, the diagnosis of invasive rhinocerebral mucormycosis was made postmortem at autopsy (6).

In transplant recipients, the treatment of zygomycoses includes aggressive surgical débridement when feasible, reduction of immunosuppression, control and correction of predisposing factors (e.g., diabetes, anemia), and administration of amphotericin B (5,7). The use of the liposomal formulation of amphotericin B may be particularly important and useful in patients with underlying renal dysfunction, such as our recipient (3,10). In spite of aggressive treatment, reported outcomes have remained poor. In the series of Singh et al, the overall mortality rate for zygomycosis in solid organ transplant recipients was 56% (7).

Our case highlights several important points: 1) Particular attention must be paid to avoid overimmunosuppression, particularly in patients on interferon-based therapy for recurrent hepatitis C. In our patient, this was evidenced by elevated immunosuppressive drug levels and multiple episodes of significant neutropenia secondary to interferon; 2) Preexisting or *de novo* posttransplant diabetes, a complication significantly more frequently encountered in HCV-positive than HCV-negative liver recipients, must be approached aggressively to maintain tight control of flucose homeostasis; 3) Posttransplant renal function must be optimized; 4) Neutropenia must be corrected promptly by stopping or reducing the responsible drugs and by giving filgrastim; 5) Anemia, regardless of its etiology, must be prevented (e.g., by individualized ribavirin dosing in the presence of renal dysfunction) and corrected, once it occurs with the use of erythropoietin.

To the best of our knowledge, this is the first reported liver transplant recipient that survived advanced, invasive rhinocerebral zygomycosis. Even with reduction of immunosuppression in the face of a severe, life-threatening zygomycosis it is possible to maintain graft function.

In the absence of effective pharmacoprophylaxis, it is paramount to minimize posttransplant risk factors for these potentially life-threatening infections by maintaining adequate host immune defenses, avoiding recurrent hepatitis C-treatment-related complications, optimizing posttransplant glucose homeostasis, and preventing renal dysfunction. ■

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FROM THE LITERATURE

EUS in Evaluation of Pancreatic Head and Duct Abnormalities With a Normal-Appearing Common Bile Duct

An enlarged head of the pancreas (HOP) or dilated pancreatic duct (PD), with or without a dilated common bile duct (CBD) on CT or MRI in patients without obstructive jaundice, raised suspicion for pancreatic neoplasm, but the clinical significance has not been established.

A retrospective analysis of a prospective database was carried out in a tertiary care university hospital in patients without obstructive jaundice, who underwent EUS and/or EUS-guided FNA for an abnormal CT and/or MRI with an enlarged HOP (N = 67), or a PD, with or without a dilated CBD (N = 43). The final diagnosis was based on definitive cytology, surgical pathology and clinical follow-up.

The EUS examination was performed using a radial echo endoscope, followed by a linear echo endoscope, if a focal pancreatic lesion was identified. Fine-needle aspirates were stained with Dif-Quik and Papanicolaou's methods and were immediately assessed by an attending cytopathologist.

In 110 study patients, the final diagnosis included adenocarcinoma (N = 7), pancreatic intraepithelial neoplasm (N = 1), neuroendocrine tumor (N = 1),

tumor metastasis (N = 1), and benign cyst (N = 3). Thirty-two patients had EUS evidence of chronic pancreatitis and in the remaining 65 patients, the pancreas was normal. The accuracy of EUS and EUS/FNA for diagnosis of pancreatic neoplasm in these patients was 99.1%, with 88.8% sensitivity, 100% specificity, 99% negative predicted value and 100% positive predicted value.

In this retrospective study with surgical confirmation in only a small number of study patients, EUS/FNA appeared highly accurate for diagnosis of pancreatic neoplasm, when there is an "enlarged HOP" or "dilated PD, with or without a dilated CBD," without obstructive jaundice. (Aggarwal B, Krishna N, Labundy J, et al. "EUS and/or EUS-Guided FNA in Patients with CT and/or Magnetic Resonance Imaging Findings of Enlarged Pancreatic Head or Dilated Pancreatic Duct, With or Without a Dilated Common Bile Duct." *Gastro Endosc*, 2008; Vol. 68, 237-242.)

HBV and Intrahepatic Cholangiocarcinoma

To determine whether HBV or HCV infection is a risk factor of intrahepatic cholangiocarcinoma (ITC), baseline demographic and clinical factors in 622 patients diagnosed between 2000 and 2004 with histologically con-

firmed ITC and 24,488 healthy controls were matched 4 to 1 with ITC patients for sex and year of birth.

HBV infection (OR 2.3) but not HCV infection was significantly related to ITC. Other significant risk factors for ITC included liver cirrhosis (OR 13.6), heavy alcohol consumption (OR 6.6), diabetes mellitus (OR 3.2), clonorchis sinesis infection (OR 13.6), and hepatolithiasis (OR 50) and choledochal cysts (OR 10.7).

It was concluded that development of ITC lesions were more closely related to HBV infections than HCV infections in Korea, where both HBV and ITC are endemic. (Lee T, Lee S, Jung S, et al. "Hepatitis B Virus Infection and Intrahepatic Cholangiocarcinoma in Korea: A Case-Controlled Study." *Am J Gastroenterol*, 2008; Vol. 103, 1716-1720.)

Small Bowel Imaging and Crohn's Disease

Because of the uncertainty about the role of new techniques utilizing imaging for diagnosing Crohn's disease and to assess the sensitivity and specificity of capsule endoscopy (CE), CT enterography (CTE), ileocolonoscopy, and small bowel follow-through (SBFT) in the diagnosis of small bowel Crohn's disease, a prospective blinded trial was carried out, evaluating inflammatory bowel disease at an academic medical center.

The patients had known or suspected Crohn's disease. Exclusion criteria included known abdominal abscess and NSAID use. Partial small bowel obstruction at CTE excluded patients from subsequent CE. The patients underwent all four tests over a four-day period.

Sensitivity, specificity and accuracy of each test was evaluated to detect active small bowel Crohn's disease. The criterion standard was a consensus diagnosis, based upon clinical presentation and all four studies.

Forty-one CTE examinations were performed. Seven patients (17%) had an asymptomatic PSBO. Forty patients underwent colonoscopy, 38 had SBFT studies, and 28 had CE examinations.

Small bowel Crohn's disease was active in 51%, absent in 42%, inactive in 5%, and suspicious in 2% of patients. The sensitivity of CE for detecting active small bowel Crohn's disease was 83%, not significantly higher than CTE (83%), ileocolonoscopy (74%), or SBFT (65%). However, the specificity of CE was significantly lower than the other tests.

One patient developed a transient PSBO due to CE, but no patients had retained capsules.

It was concluded that the sensitivity of CE for active small bowel Crohn's disease was not significantly different from CTE, ileocolonoscopy, or SBFT. However, low specificity and the need for preceding small bowel radiography (due to the high frequency of asymptomatic PSBO) may limit the utility of CE as the first line test for Crohn's disease. (Solen C, Loftus E, Fletcher, et al. "Small Bowel Imaging and Crohn's Disease: A Prospective Blinded, Four-Way Comparison Trial." *Gastro Endosc*, 2008; Vol. 68,255-266.)

Treatment of HCV Type I and IV With RVR

The rate of sustained virological response (SVR) in patients infected with HCV genotype I or IV were assigned to 24 weeks of treatment with PEG Interferon Alfa-2A 180 mcg per week plus Ribavirin 1000/1200 mg/day after achieving an rapid virologic response (RVR) at week four in a prospective trial investigating response-guided therapy. These patients were randomized at 48 or 72 weeks of therapy (trial still ongoing).

A total of 150 of 516 patients had an RVR, 143 of whom completed 24 weeks of treatment. Younger patients, leaner patients and those with an HCV RNA level less than 400,000 i.u./ml and HCV genotype IV infections were more likely to achieve an RVR. However, among patients with an RVR, no baseline factor predicted SVR. The SVR rate was 80.4% in patients who completed 24 weeks of treatment, the SVR rate was 86.7 in patients infected with genotype IV and 78.8% in those infected with genotype I. Treatment was well tolerated.

This prospective study confirms that a 24 week regimen of PEG Interferon Alfa-2A plus Ribavirin 1000/1200 mg/day is appropriate in genotype I and IV patients with a low baseline HCV RNA level to achieve an RVR by week 4 of therapy. (Ferenci P, Laferl H, Sherzer T, et al. for the Austrian Hepatitis Study Group. "PEG Interferon Alfa-2A and Ribavirin for 24 Weeks in Hepatitis C Type I and IV Patients With Rapid Virologic Response." *Gastroenterology*, 2008, Vol. 135, 451-458.)