Hepatic candidiasis in a kidney transplant recipient treated successfully with amphotericin B and itraconazole

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Keywords: Candida; hepatic candidiasis; kidney; liver; mycosis; transplantation

The incidence of hepatic candidiasis is difficult to estimate because of diagnostic difficulties. Its frequency was ~7% in a study of 562 adult patients with leukaemia [1]. Hepatic candidiasis (HC), also referred to as chronic disseminated candidiasis, hepatosplenic candidiasis and granulomatous hepatic candidiasis, affects almost exclusively patients undergoing remission induction chemotherapy or bone marrow transplantation for acute leukaemia [2]. It occurs on recovery following prolonged episodes of bone marrow dysfunction and neutropenia [1]. The liver, spleen and sometimes the kidneys are infected with Candida. Occasionally, patients with other types of immunosuppression (aplastic anaemia, lymphoma, sarcoma or liver transplantation) may develop hepatosplenic candidiasis [3]. This is the first reported case of HC in a kidney transplant recipient.

Case

A 37-year-old woman had cadaveric kidney transplantation with five human leukocyte antigen (HLA) compatibilities, after she had been on haemodialysis for 7 years for end-stage renal disease related to diabetic nephropathy with type I insulin-dependent diabetes mellitus. In her past medical history, she had chronic hepatitis B diagnosed during haemodialysis from 7 years for end-stage renal disease related to diabetic nephropathy with type I insulin-dependent diabetes mellitus. In her past medical history, she had chronic hepatitis B diagnosed during haemodialysis follow-up; she was treated with interferon-α for 6 months without evidence of therapeutic response. Prior to kidney transplantation, she had normal liver enzyme tests. Quantitative DNA for hepatitis B virus (AmpliCor HBV Monitor® Test, v2.0, Roche Diagnostics) was 3×10⁶ IU/ml, with a positive HBc antigen. Following kidney transplantation, the immunosuppressive regimen consisted of cyclosporin, mycophenolate mofetil and methylprednisolone. Lamivudine 100 mg/day was started on the first day following transplantation. The post-operative period was marked by increased levels of fasting blood glucose despite high insulin doses, and with two episodes of fever and transient leucopenia lasting for 1 and 3 days, respectively, in relation to infections. The work-up showed Enterococcus fecalis and Escherichia coli in blood and urine cultures, respectively. The first episode occurred 1 week after transplantation and was accompanied by acute tubular necrosis. The antimicrobial treatment consisted of intravenous ciprofloxacin and vancomycin. Sepsis was controlled, and white blood cells returned to normal within 24 h. Renal function gradually improved. The second episode occurred 2 weeks later. Work-up showed a positive cytomegalovirus (CMV) pp65 antigen. The treatment consisted of gancyclovir 150 mg perfusion daily for 14 days, and granulocyte–macrophage colony-stimulating factor for 3 days along with empirical treatment with imipenem [500 mg, intravenously (i.v.) three times a day] and titrated vancomycin. Low grade fever persisted with an increase in alanine aminotransferase (ALT) to 120 IU/ml (normal = 40 IU/ml) and aspartate aminotransferase (AST) to 56 IU/ml (normal = 40 IU/ml). Both decreased progressively with antimicrobial treatment, followed by an increase in γ-glutamyl transferase (γGT) to 300 IU/ml (normal = 78 IU/ml), alkaline phosphatase to 300 IU/ml (normal = 126 IU/ml) and bilirubin to 74 mmol/l. HBV viral load by polymerase chain reaction (PCR) was 1.6 × 10⁷ IU/ml (AmpliCor HBV Monitor® Test, v2.0, Roche Diagnostics). An abdominal ultrasound revealed a heterogeneous liver containing multiple anechoic areas <1 cm in diameter. Magnetic resonance imaging (MRI) showed multiple hepatic lesions, hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences, <1 cm in
diameter, with peripheral enhancement after i.v. gadolinium administration (Figure 1). A signal difference between the right and left lobe of the liver was due to a left lobe portal vein thrombosis (Figure 1). Hepatic haemodynamic studies, including free and wedge suprahepatic venous pressure, and right auricular pressure were normal. Liver biopsy showed a peliotic liver aspect, with a necrotic zone infiltrated with polymorphonuclear cells and evidence of fungal liver infection. The immunosuppressive regimen was decreased to only steroids in decreasing dosage. The patient received liposomal amphotericin B (200 mg/day) for 40 days followed by itraconazole (400 mg/day). Transaminases and bilirubin levels returned to normal whereas GT and alkaline phosphatases decreased to reach a plateau and then re-ascended. Twenty-two days after the end of amphotericin, the patient presented an acute calculous cholecystitis. Endoscopic retrograde cholangiography was normal. A liver biopsy was obtained during cholecystectomy. It showed cysts containing fungal spores and filaments. Liposomal amphotericin B was reintroduced along with itraconazole for 1 month. During treatment, the patient normalized all liver enzyme tests. The tolerance of the treatment was unremarkable. Creatinine levels increased and creatinine clearance decreased during both liposomal amphotericin B treatment periods, but clearance returned to reach a plateau at 40 ml/min after cessation of liposomal amphotericin B treatment. Figure 2 describes the overall course of HC after transplant. The long-term follow-up (2 years) was unremarkable without further complications.

Discussion

HC in solid organ transplantation has been rarely reported in liver transplantation, but never in a renal transplantation setting. Clinical manifestations and liver enzyme test abnormalities are non-specific in HC. In liver transplantation, it occurs as a post-operative complication, whereas in bone marrow aplasia the clinical picture occurs following recovery from neutropenia [3]. In the setting of immunosuppression and solid organ transplantation, differential diagnoses of abnormal liver enzyme tests include infectious (tuberculosis) or non-infectious liver conditions such as veno-occlusive disease and graft-versus-host disease. Known predisposing factors include bone marrow suppression. In the setting of our patient, multiple factors might have contributed, including transient leucopenia, uncontrolled diabetes mellitus, immunosuppression and possibly CMV infection.

An adequate diagnosis is therefore mandatory to initiate the appropriate treatment. However, this is often difficult. Blood cultures are nearly always negative even in the febrile neutropenic phase that precedes the clinical presentation. By ultrasound, the lesions in the liver may have a uniformly decreased attenuation or show a central, high attenuation dot, that has been called a ‘wheel within a wheel’ or ‘bull’s-eye’. By computed tomography (CT), the lesions may be multiple, well-defined 5–15 mm lucencies that show the abscess-like pattern or a central contrast enhancement with a peripheral double ring during the arterial phase [4]. On the portal venous phase, the lesions show a decreased diameter or even become undetectable. By MRI, non-specific lesions with relatively low signal intensity on T1-weighted images and well-defined high signal intensity foci on T2-weighted images have been described [5,6]. MRI is superior to CT and ultrasound in making the diagnosis and differentiating acute, subacute treated and chronic healed lesions [6–8]. The demonstration of fungal elements on liver biopsy is conclusive of the diagnosis. However, it has limits because they are usually found in the centre of the lesion. The presence of a granuloma in the absence of fungal organisms does not rule out the disease, particularly when the patient has already received antifungal treatment. Culturing Candida from liver biopsies is also difficult because of the small size of the specimen and possible previous treatment with antifungal agents [3].

A mortality rate of 40–50% was initially reported in HC, even after prolonged amphotericin B treatment.
Ketoconazole and fluconazole improved the prognosis of affected patients [9]. A success rate of 88% was reported with fluconazole among 16 patients who had either failed or became intolerant to amphotericin B. Formulations of lipid-associated preparations of amphotericin B offer the advantage of high hepatic concentrations [7,10]. Therapy should continue until complete resolution of symptoms and laboratory abnormalities, as well as imaging study abnormalities (either CT or MRI). In some cases, the imaging studies will convert to calcification and this is considered an acceptable end-point. In the setting of solid organ transplantation, there are considerable concerns in using drugs with the potential for renal toxicity. Amphotericin B and to a lesser extent liposomal amphotericin B both are nephrotoxic and may be contraindicated in renal diseases. Moreover, azoles have major interactions with cyclosporin and tacrolimus, predisposing to additive nephrotoxicity that can be preventable by decreasing the dosage of these drugs. Monitoring of serum concentrations of calcineurin inhibitors is therefore recommended when azole treatment is to be introduced or interrupted. In our patient, there was a complete interruption of calcineurin inhibitors during the course of antifungal treatment, thus avoiding such interaction.

In conclusion, HC is rare in solid organ transplant recipients. Diagnosis requires a high index of suspicion, and treatment should be undertaken with a special knowledge of renal toxicity and drug interactions used in the setting of transplantation.

Conflict of interest statement. None declared.

References


*Received for publication: 28.4.05
Accepted in revised form: 1.12.05*