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Case report

COVID-19, rejection, and cutaneous mucormycosis in a long-term liver transplant recipient – the vicious cycle of immunosuppression and opportunistic infections

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ABSTRACT

Opportunistic infections, including fungal infections, are dreaded complications of liver transplantation, particularly early after transplant. We describe the case of a patient that presented 6 years after liver transplant with a *Lichtheimia corymbifera*-infected leg ulcer, following previous COVID-19 infection and moderate rejection requiring steroid pulses. The patient required long-term antifungal therapy, repeated surgical debridement and eventually wound coverage with meshed split-thickness skin graft. Our case illustrates the challenges in the treatment of cutaneous mucormycosis and highlights the difficulties in achieving an accurate balance between the risk of opportunistic infections and rejection in this population.

Introduction

Infections are frequent complications of liver transplantation (LT) and indeed they are amongst the most frequent causes of death both in the early post-LT period and in the long-term. Opportunistic infections, including fungal infections, are paradigmatic of transplant recipients as they require life-long immunosuppression. While opportunistic infections are most frequent in the first months after LT, when the global immunosuppression burden is highest, changes in the net immunosuppression status due to several conditions, particularly increases in immunosuppressive drugs in cases of rejection, may lead to LT recipients presenting with opportunistic infections in the long-term. Additionally, recent data have suggested an association between COVID-19 infection and invasive fungal infections [1]. In this manuscript, we describe the case of a LT recipient that presented cutaneous mucormycosis 6 years after LT, following profound changes in immunosuppressive status in the context of COVID-19 infection and rejection requiring steroid boluses.

Case report

A 64-year-old man with past history of obesity, type 2 diabetes mellitus (DM) and hypertension underwent LT in June 2015 due to non-alcoholic fatty liver disease (NAFLD)-related decompensated cirrhosis. Baseline immunosuppression consisted in everolimus and low-dose tacrolimus due to chronic kidney disease. In June 2020, everolimus was replaced by mophetil mycophenolate (MMF) due to chronic lower limb lymphedema. In November 2020 he was diagnosed with severe COVID-19 infection progressing to organizing pneumonia. MMF was discontinued and tapering steroids were started. After withdrawing prednisone, in June 2021, the patient presented with jaundice and altered liver tests and was eventually diagnosed with biopsy-proven moderate acute cellular rejection, that was treated with methylprednisolone pulses followed by a tapering dose, and increasing dose of tacrolimus. Two months later, the

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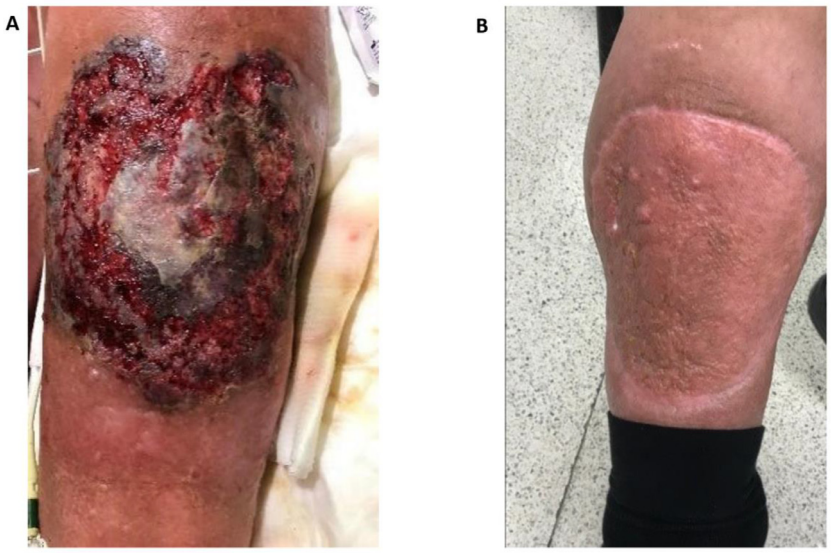

Fig. 1. Images of the necrotic ulcer at diagnosis (A) and after reconstruction with skin graft (B).

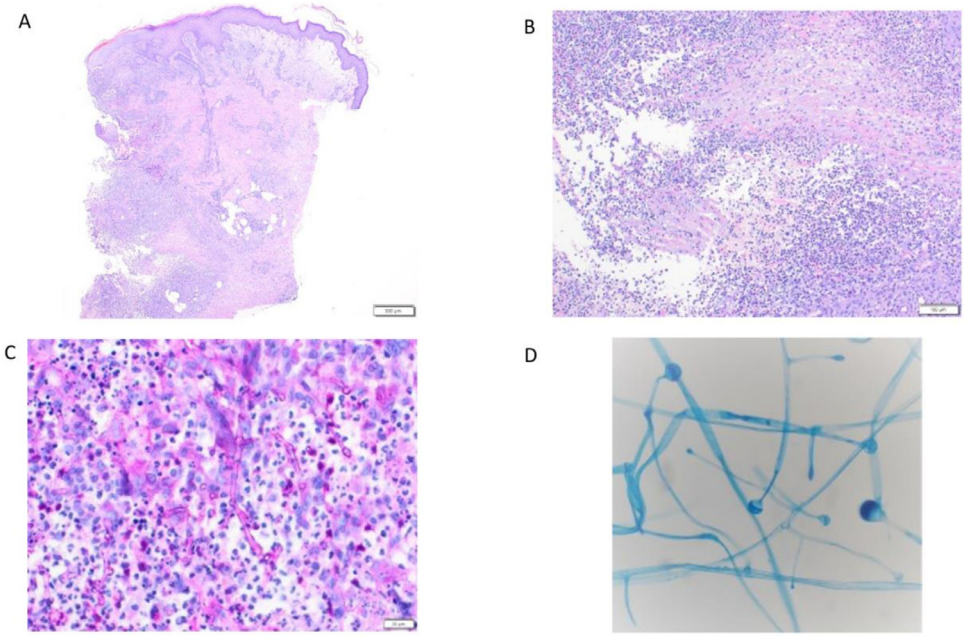

Fig. 2. Punch biopsy that shows skin with epidermal hyperplasia and dense dermal inflammatory infiltrate (2A, H&E 20X), with neutrophil abscess formation (2B, H&E 100X). PAS staining display broad, nonseptal fungal hyphae (2C, PAS 400x). The angle of branching approaches 90° which is a feature of mucormycosis. Microscopic view of fungal culture (2D, x100).

patient presented an ulcer in left leg with edema, erythema and pain; with the suspicion of complicated cellulitis, he was admitted and antimicrobial treatment was started. The color of wound trended to black in the next few days, and necrosis was evident (Fig. 1**A**). The biopsy revealed yeast and hyphae (Fig. 2**A-C**). A microbiological study was positive for Klebsiella pneumoniae BLEA, Enterococcus faecium and aseptate hyphae; fungal culture revealed *Lichtheimia corymbifera*, a fungus in the phylum Zigomycota (Fig. 2**D**). Minimal inhibitory concentrations (MICs) were as follows: amphotericin 1 mg/ml, isavuconazole 1 μg/ml, voriconazole 8 μg/ml, posaconazole 0.125 μg/ml and itraconazole 0.125 μg/ml. Echinocandins MICs were > 8 μg/ml. Amphotericin B and isavuconazole were added to antibiotic treatment and the dose of immunosuppressive agents was reduced. Repeated surgical debridement was done until a normal histopathological examination on the debrided skin and soft tissues was reported. Following surgery, Vacuum Assisted Closure was used for the treatment of the surgical site resulting in a progressive improvement, and successful would coverage with meshed split-thickness skin graft was performed in January 2022 (Fig. 1**B**). Isavuconazole was suspended one month after surgery. Written informed consent was obtained from the patient involved in this case.

Discussion

Mucormycosis is a rare and highly invasive fungal infection caused by Mucorales fungi of the class Zygomycetes. It is associated with a high mortality, particularly in immunocompromised patients and those with DM. Since transplant recipients receive steroids and

other immunosuppressants as part of acute cellular rejection prevention and treatment, this is a population particularly predisposed to developing fungal infections, such as mucormycosis [2]. Other risk factors for mucormycosis include poorly controlled DM, dirty crash injury ulcers, scorch wound, undernourishment, use of broad-spectrum antibiotic, consumption of deferoxamine, and intravenous drug use [3,4]. In addition, since the beginning of the COVID-19 pandemic a significant number of fungal infections in patients with COVID-19 have also been reported in the general population and solid organ transplant recipients, probably associated with the impaired cellular immunity associated with the infection itself and the immunosuppressive regimens used in these patients [1,2]. Cutaneous fungal infections should be considered in the differential diagnosis of any nonhealing or black scar-infected wound that does not respond to broad-spectrum antibiotics in immunocompromised patients.

The risk of fungal infections in LT recipients mostly depends on two main factors: epidemiological exposures and the net state of immunosuppression. For epidemiological exposures, the intensity, the timing and the virulence of the organisms should be considered. The underlying disease and comorbid conditions, foreign bodies, injuries, devitalized tissues, hematomas, effusions, and adhesions help to infection development. Neutropenia and metabolic problems such as protein-calorie malnutrition, uremia, and hyperglycemia also contribute to uncontrolled infection [4]. On the other side, the net state of immunosuppression is a complex function determined by the interactions of several factors such as dose, duration, and temporal sequence of immunosuppressive drugs. In our patient, decreasing doses of immunosuppressive drugs and discontinuation of MMF secondary to COVID19 infection, together with steroids tapering after COVID-19-related organizing pneumonia, resulted in cellular rejection. Then, treatment with methylprednisolone pulses followed by a tapering oral dose was started and the those of tacrolimus was increased. Most probably, the long period of increased immunosuppression caused by the continuum COVID-19 infection-cellular rejection and their corresponding immunosuppressive treatments were capital for the development of the mucor infection, particularly considering that our patient also presented other risk factors such as poorly controlled DM with glycosilated hemoglobing >7% and chronic lymphedema. Interestingly, while other cases of cutaneous mucormycosis have been previously reported in LT recipients [5–8], most of them occurred in the early post-transplant period, when immunosuppression is highest, and the site of infection was predominantly the surgical wound. In contrast, our case was diagnosed in the setting of long-term increased immunosuppression due to COVID-19 requiring steroids, followed by rejection after steroid tapering that required steroid pulses. Indeed, this case illustrates the rollercoaster of immunosuppression and opportunistic infections in LT recipients, and highlights the difficulties in managing these patients particularly considering the scarce tools available to strictly monitor the state of immunosuppression. Actually, the difficulties in precisely balancing the risk of opportunistic infections and rejection depicted in our case highlight the clinical necessity of new biomarkers assessing the net overall state of immunosuppression in LT recipients to avoid the complications derived from over or infra-immunosuppression in this population [9].

Interestingly, our patient presented with COVID-19 infection few months after replacing everolimus with MMF. While this may be merely coincidental and indeed the association is controversial [10], it has been suggested that MMF may be associated with a higher incidence and severity of COVID-19 infection in LT recipients [11]. In addition to MMF withdrawal, steroids were prescribed for COVID-19 associated organizing pneumonia, which eventually resolved without sequalea.

Liposomal amphotericin B, posaconazole, isavuconazole, and itraconazole are at present the main available therapeutic options for cutaneous mucormycosis, although with limited activity in the case of the latter options. More importantly, one of the pillars of treatment is the surgical debridement of the necrotic tissue, which often needs to be performed several times. The musculoskeletal forms are associated with a better prognosis, in part due to the accessibility to obtain histological samples allowing an early diagnosis [12]. We continued amphotericin B and isavuconazole while performing surgical debridement, but due to the large size of ulcer and other factors such as chronic lymphedema and type 2 DM with non-optimal control, surgical intervention with skin grafting was finally necessary.

In summary, we report a difficult case of cutaneous mucormycosis in a long-term LT recipient in the setting of cellular rejection and post-COVID-19 infection. Our case highlights the challenge in terms of management, diagnosis and treatment of these patients. In addition, it illustrates the need for better biomarkers of the status of immunosuppression of LT recipients that help to accurately balance the risk of rejection and opportunistic infections.

Declaration of Competing Interest

The authors of the manuscript “COVID-19, rejection, and cutaneous mucormycosis in a long-term liver transplant recipient – the vicious cycle of immunosuppression and opportunistic infections” declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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