CASE REPORT

Invasive fungal infections: A diagnostic challenge

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ABSTRACT

Introduction: Overall incidence of invasive fungal infections in solid organ transplant recipients is low with the more common infections being invasive candidiasis, aspergillosis and cryptococosis. Zygomycosis comprises of only 0.2%-1.2% of infections in renal transplant recipients with current recommendations advising against routine prophylaxis.

Case: The patient was a 60-year-old male with a history of renal transplant 25 years ago on immunosuppressants, chronic transplant glomerulopathy, squamous cell carcinoma post penectomy and bilateral orchiectomy 2 years ago, controlled diabetes and hypertension who presented with pain in the perineal region for 4 days. On exam he was discovered to be afebrile and had a scrotal skin fold with urethral opening from his previous surgery and 2.5 cm induration and tenderness in the left gluteal fold. He was treated with 5 days of Unasyn. A biopsy was taken to rule out recurrence of squamous cell carcinoma and he was discharged home. The patient returned with worsening perineal pain within 3 days. On exam he had progressive induration with erythema, swelling and tenderness in the perineum. An initial white blood cell count of 15.8 increased to 25.8 and blood cultures remained negative. The computed tomography scan showed diffuse edema in the perineum without any evidence of abscesses. Immunosuppression was held and broad spectrum antibiotics were started. His renal failure progressively worsened eventually requiring continuous renal replacement therapy, intensive care transfer and vasopressor support. The biopsy revealed intermingled fibrous tissue with focal necrosis and no evidence of malignant cells. A repeat incision and debridement (I&D) culture showed growth consistent with mucor. He was started on liposomal amphotericin B and taken to the OR for multiple debridements. Unfortunately he progressed to multisystem organ failure and died after transitioning to comfort care.

Conclusions: Invasive fungal infections remain one of the life threatening differentials for cellulitis like skin lesions, especially for patients not responding to antibiotics and those who are immunocompromised. Early cultures and histopathology of lesions should be done for diagnosis and to avoid delays in treatment.

Key Words: Invasive fungal infections, Solid organ transplant, Mucor, Immunosuppression

1. INTRODUCTION

The overall incidence of invasive fungal infections (IFI) in solid organ transplant (SOT) recipients is low with the more common infections being invasive candidiasis, aspergillosis and cryptococcosis.[1–4] Unlike recipients of liver or lung transplants who are especially vulnerable to invasive candidi- asis and aspergillosis,[1–4] the risk of IFI in kidney transplant re- cipients is low.[1–4] Zygomycosis comprises only 0.2%-1.2% of infections in renal transplant recipients.[1–4] As per another large sized study mucormycosis occurred in 3 of 8,494 renal transplants between 2001 and 2006 and accounted for 28 of 1,208 cases of IFI among all SOT recipients.[5] Currently,

there are no recommendations regarding routine prophylaxis against fungal infections in renal transplant recipients.[1–4] The risk factors include T cell depleting drugs, neutropenia, renal failure, poorly controlled diabetes, prior voriconzole or caspofungin use, hematological malignancies, hematopoetic stem cell transplant (HSCT) and iron overload states.[2] Incidence is also higher in males.[2] Uncontrolled diabetes mellitus is a strong risk factor. One study of SOT and HSCT recipients developing mucormycosis showed the prevalence of diabetes was 43.8%.[6]

Here we present a case of a patient with previous history of renal transplant on immunosuppressive therapy who presented with perineal pain and redness with no response to initial antibiotics. Eventually he was found to have mucor infection of skin and soft tissue which led to graft failure, multisystem organ failure and death within 3 weeks of symptom onset.

2. CASE PRESENTATION

A 60-year-old male with history of renal transplant 25 years ago on daily cellcept and prednisone with no recent dose adjustments, chronic transplant glomerulopathy, squamous cell carcinoma post penectomy and bilateral orchiectomy 2 years ago, controlled diabetes mellitus (last HbA1c 5.5) and hypertension presented to the hospital with pain in the perineal region for 4 days. He was afebrile and on exam he had altered anatomy consisting of scrotal skin folds with urethral opening from his previous surgery and a new 2.5 cm induration and tenderness in the left gluteal fold without any signs of erythema or swelling. He was treated with 5 days of intravenous Unasyn, a biopsy was taken to rule out recurrence of squamous cell carcinoma and he was discharged home with outpatient follow up. The patient returned within 3 days with worsening perineal pain. On exam this time he had progressive induration with erythema, swelling and tenderness in the perineum. Initial white blood cell count of 15.8 increased to 25.8 with blood cultures showing no growth. The pelvic computed tomography (CT) done without contrast due to baseline glomerulopathy, did not show evidence of any gas, necrosis or abscesses. However, stranding fluid running through the perineum and ischiorectal fossa was seen and was more consistent with skin and soft tissue infection. Comparing the CT from a previous admission, the initial localized edema had tremendously increased, becoming more generalized and dependent (see Figures 1 & 2). His immunosuppression was held and broad spectrum antibiotics were started. His renal failure progressively worsened eventually requiring continuous renal replacement therapy (CRRT), intensive care transfer and vasopressor support. The biopsy done on the previous admission revealed intermingled fibrous tissue with focal fat necrosis but no evidence of ma-

lignant cells, angioinvasive necrosis or microbial growth. A repeat incision and debridement (I&D) showed growth consistent with mucor on culture. He was started on liposomal amphotericin B and taken to the OR for multiple debridements. Unfortunately he rapidly progressed to multisystem organ failure and was transitioned to comfort care before subsequently dying. The surgical debridement samples revealed histological evidence of fungal elements (see Figures 3-5).

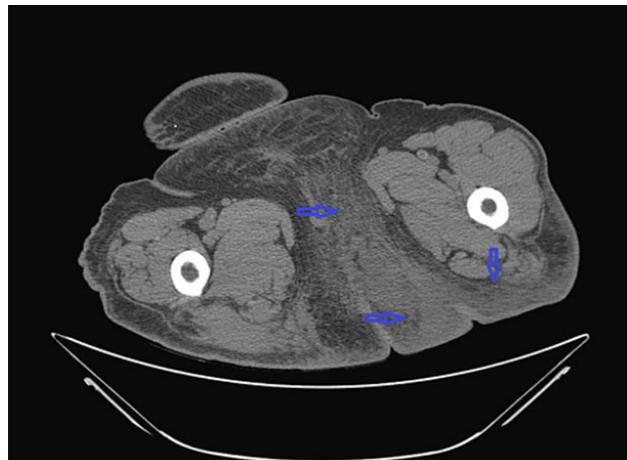**Figure 1.** Initial pelvic CAT scan without contrast showing localized edema, no evidence of gas or abscesses

Figure 2. Repeat pelvic CAT scan without contrast after 10 days with spreading generalized dependent edema, no evidence of gas or abscesses

3. DISCUSSION

IFI are seen in transplant recipients within 3-6 months of transplant but cases after multiple years have also been reported. One review showed 25% of cases occurred after 3 years of transplant.[7] The longest follow up was a case after 9 years of transplant.[8] In our case the patient developed mucormycosis after 25 years of renal transplant and associated immunosuppressive therapy. As per the TRANSNET study

in SOT recipients, mucor involved the lungs in 56%, sinuses or skin in 13%, and was disseminated in 9% of cases.[7] Our patient had multiple risk factors which were contributing to development of an IFI including chronic immunosuppression due to renal transplant, chronic renal failure due to transplant glomerulopathy, diabetes mellitus and male gender.
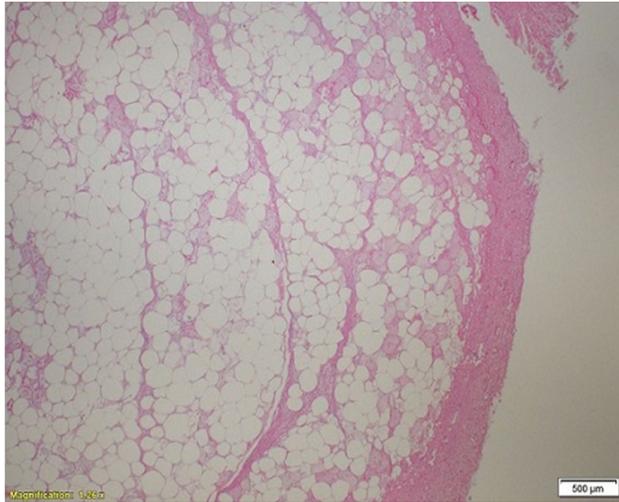

Figure 3. Magnification 40×, showing necrotic adipose tissue from the surgical debridement sample
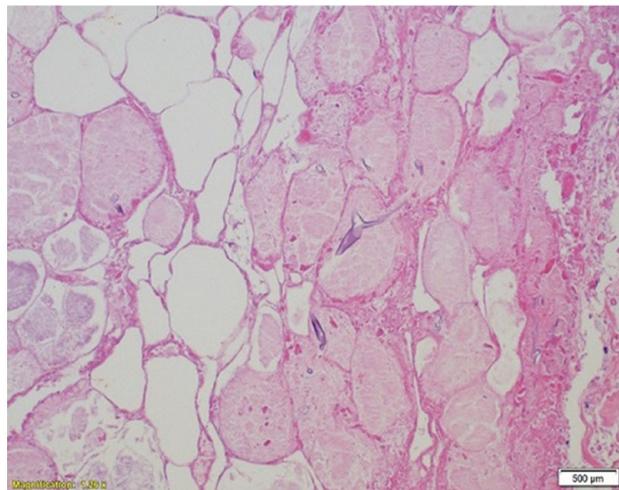

Figure 4. Magnification 200×, showing fat with fungal hyphae from surgical debridement sample

Signs like failure to improve with persistent pain despite broad spectrum antibiotics and histological evidence of fibrosis or necrosis point towards fungal infections especially zygomycosis. Mucorales are angioinvasive leading to hemorrhagic necrosis, vascular thrombosis and tissue infarction.[9, 10] Their hyphae are broad, irregularly branched, thin walled, and sparsely septate and can appear as fibrosis on histopathology.[9, 10] Another review demonstrated direct

exam results were positive in 79% and culture results were positive in 86%.[11] Thus sending samples for both studies is very important to avoid missing the diagnosis. In addition, PCR testing should be considered in cases where the histopathology is suggestive of mucorales but cultures are negative.[10] Our case highlights the concern of missing the diagnosis on initial biopsy, perhaps due to limited sample size on a core biopsy and eventually confirming it on a larger sized surgical debridement sample.
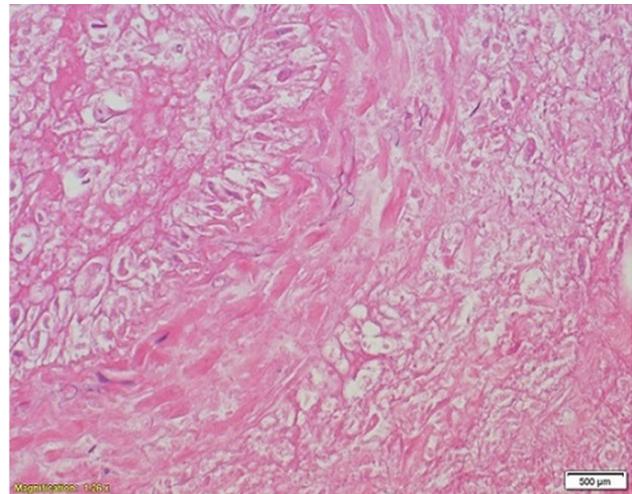

Figure 5. Magnification 400×, showing necrotic vessel with angioinvasive fungal hyphae from surgical debridement sample

The authors recommend maintaining a broad differential diagnosis when a patient is not improving despite appropriate antibiotics for a presumed cellulitis like lesion. This includes skin and soft tissue necrotizing infections, cutaneous metastases or primary cutaneous malignanies, graft versus host disease in hematopoetic stem cell transplant recipients, IFI especially in patients with risk factors, calciphylaxis, sweet syndrome and rare entities like cutaneous anthrax. Limb and life threatening conditions should be ruled out first. Necrotizing skin and soft tissues infections will often have marked pain out of proportion to cutaneous exam and surgical I&D is the "gold standard" for diagnosis and treatment. The surgical specimens should be examined for fungal elements and should also be sent for concurrent tissue cultures in patients with any risk factors for IFI to facilitate early diagnosis before the infection disseminates or clinical condition deteriorates. Due to the angioinvasive nature of non-aspergillus molds, extensive fibrosis might be seen on histopathology. A core biopsy or localized I&D perhaps can be inadequate and may miss areas with visible fungal elements. Lab parameters like 1-3 beta-d glucan (fungitell) assay and galactomannan antigen being helpful in supporting diagnoses of

some fungal infections are usually not positive in zygomycosis. Hence confirmation of early diagnoses relies heavily on large sized debridement sample and concomitant cultures. Recurrence of his squamous cell cancer or cutaneous involvement from other malignancies, carcinoma erysipeloides which is metastatic cutaneous involvement seen in primary lung, breast, colon and oral cavity squamous cell carcinomas were also on the differential but were not supported by the histopathology. Other diagnostic considerations include the following entities like eosinophilic cellulitis which may have a short prodrome of itching and burning preceding the lesions. The histopathology for this shows dermal infiltration with eosinophils and a peripheral eosinophila.[12] Sweet syndrome was also considered and can sometimes appear as cellulitis and usually has well defined erythematous plaques with a mammillated surface with systemic features of arthralgias, myalgias, malaise and fever. Histopathology for this shows dermal infiltration by polymorphonuclear leucocytes.[13] Calciphylaxis is seen mostly in patients with ESRD, lesions are painful and erythematous which can subsequently ulcerate.[14] Familial Mediterranean fever cases have a positive family history and recurrent episodes. It is associated with fever, serositis and erysipelas like lesions, and is usually a clinical diagnosis.[15] Other causes include contact dermatitis which is more pruritic and has suggestive exposure history. This can be often diagnosed on clinical grounds and biopsy shows intraepidermal spongiosis with monocyte and histiocyte dermal infiltration.[16] Insect bites and sting lesions are associated with a history of exposure and pruritus and biopsy shows wedge-shaped dermal mixed inflammatory infiltrate with eosinophils.[16] Fixed drug reactions have a history of reaction with prior exposure to the same drug, are usually associated with itching and burning and can involve lips and/or genitalia. Thus, in all cases the diagnosis can be mainly made on clinical grounds or with evidence from histopathology. However, in a patient with risk factors for IFI, a repeat larger size surgical incision and debridement should be pursued if the initial biopsy is not diagnostic.

Overall mortality rate among SOT recipients with mucor is 38%-48%, much higher than other invasive fungal infections.[1,17–19] In a population of renal transplant patients with IFI the mortalities were 15% for invasive candidiasis, 45% for aspergillosis, 71% for crytpococcosis and 100% for non-aspergillus molds.[1] Delay in the administration of amphotericin based regimens by > 5 days is associated with a 2 fold increase in mortality.[20] Thus early diagnosis and treatment initiation is imperative.

4. CONCLUSION

The diagnosis of mucormycosis is challenging and is often delayed, as the clinical presentation is not very specific and symptoms and signs are often muted by the blunted immune response in these patients. Considering a broad differential including IFI for inflammatory skin and soft tissue lesions in patients with risk factors especially those who are immunocompromised is very crucial. Early tissue sampling for both cultures and histopathology should be done for diagnosis. In patients with risk factors initial negative biopsy should be quickly followed by larger sized debridement to capture the fungal elements for a timely diagnosis so as to prevent extensive tissue necrosis, fungal dissemination and multisystem organ failure.

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