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Case Report

Cutaneous Histoplasmosis in a Renal Allograft Recipient

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Abstract

Solid transplant organ recipients on potent immunosuppressive medications are at an increased risk of infections by atypical organisms including fungi. Often the presentation of such infections is atypical and requires a high degree of clinical suspicion aided by appropriate diagnostic tests to arrive at a diagnosis. We report a renal transplant recipient who presented with an atypical presentation of Histoplasmosis, ten years after transplantation.

Keywords: Solid Transplant Organ; Transplantation; Histoplasmosis

Introduction

Histoplasmosis is a fungal infection, most commonly caused by Histoplasma capsulatum, a dimorphic, soil saprophytic fungus and is endemic to certain parts of the world - Central United States, South America, Caribbean Islands and Asia. Even though it is endemic to these areas, there is increased prevalence of this disease in places where the soil is warm and humid [1]. Humans are infected from the inhalation of conidia which are airborne. In immunocompetent hosts, often the primary infection is subclinical or may cause a mild pneumonitis. The host immune defence is primarily dependant on T cell mediated mechanisms. Renal allograft recipients on immunosuppressive medications which impair the T cell defences subsequently have an impaired cell mediated immunity to counter the organism. This often results in disseminated, extra pulmonary disease [2,3]. Cutaneous presentation has been described in nearly half of all cases of disseminated Histoplasmosis infection [4].

We present a case report of a 34-year-old male, who presented with cutaneous Histoplasmosis, ten years after renal transplantation.

Case Report

A 34-year-old male patient presented with an indurated and erythematous lesion on the right calf of two weeks duration. There was history of low-grade fever of two weeks duration. There was no history of trauma or previous dermatological disease. He was initially evaluated by a local physician and was given one-week course of oral amoxycillin based on the provisional diagnosis of cellulitis. He was a renal allograft recipient, who underwent a live related renal transplantation ten years back, the donor being his haplomatched elder sister.

The induction therapy was two doses of intravenous thymoglobulin (50 mg each dose) with subsequent maintenance dose with triple immunosuppressive - Prednisolone 5 mg daily, Tacro-

limus 1.5 mg twice daily and Mycophenolate mofetil 500 mg twice daily.

His tacrolimus trough levels were in the therapeutic range.

His post-transplant period was uneventful with regards to acute or chronic rejection episodes except for the development of New onset Diabetes after Transplantation six years back which was managed with Insulin and oral hypoglycaemic agents.

His baseline creatinine was 1.6 mg/dl and his glycosylated hemoglobin (Hba1c) was 7.2%.

Since there was no improvement in the skin lesions after the course of oral antibiotics, he presented to our outpatient services. On evaluation he was afebrile, normotensive with no generalised lymphadenopathy. Pulmonary, gastrointestinal, cardiovascular and neurological examinations were normal. There was extensive induration of the skin punctuated by ulcerative lesions and vesicles extending from the lower part of the thigh to the middle of the leg on the posterior aspect (Figure 1).

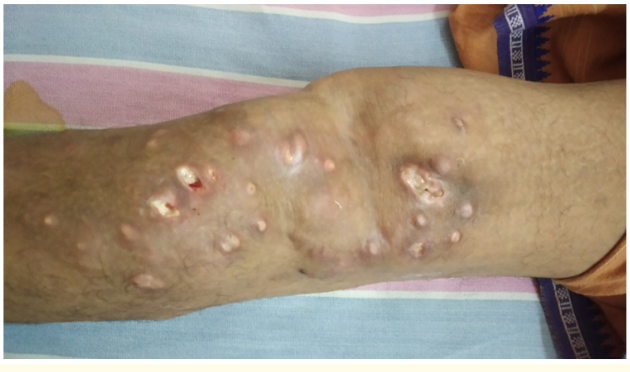

Figure 1: Showing the cutaneous ulcerative and papular indurated lesions.

A differential diagnosis of cellulitis, cutaneous tuberculosis and cutaneous mycosis was suggested after Dermatology consultation and further evaluation was done. Since the lesions were quite extensive and there was suspicion of deep muscular involvement a surgery consultation was done and he was advised to undergo an open biopsy of the lesion. Swabs of the discharge were taken which showed Staphylococcal epidermidis. An ultrasound (usg) and a doppler scan of the right leg was done which was negative for deep vein thrombosis, however usg reported a heterogenous soft tissue lesion with abnormal intrinsic vascularity in right popliteal fossa extending into upper third of the leg, which was suggestive of either a neoplastic or inflammatory lesion. A Magnetic Resonance Imaging (MRI) scan of the leg was done prior to surgical biopsy to evaluate the extend of the lesion. A 1.5 Tesla contrast enhanced MRI scan of the right popliteal region revealed a moderately enhancing heterogenous soft tissue intensity lesion with interspersed cystic areas in the right popliteal region extending from the level of the distal femur into the upper third of the leg posteromedial to the muscles and involving the subcutaneous plane which was suggestive of either a soft tissue sarcoma or an inflammatory mass (Figure 2 and 3). A true cut biopsy of the soft tissue mass was obtained from the right popliteal fossa. Histopathological examination of the lesion showed infiltrates of macrophages, lymphocytes, neutrophils with foci of necrosis and spindle cells. The macrophages contained oval and round intracytoplasmic organisms with single eccentric nucleus, with occasional budding, which stained black with Grocott's methenamine silver (GMS) stain, pink with Per iodic acid Schiff (PAS) and did not stain with Giemsa stain. These fungal organisms were also seen in extracellular space. The culture of the biopsy specimen grew white dense, cottony colonies at 25-30 oC within 4 weeks of incubation. Microscopy showed large thick walled tuberculate macroconidia and small microconidia suggestive of Histoplasma capsulatum (Figure 4)..

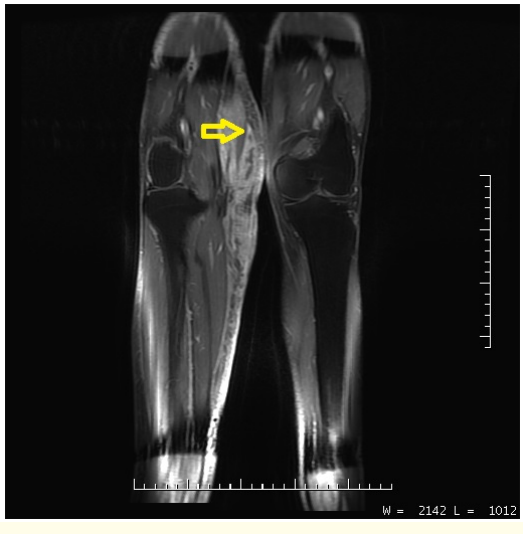

Figure 2: MRI scan: arrow head showing the hyperintense heterogenous soft tissue lesion.

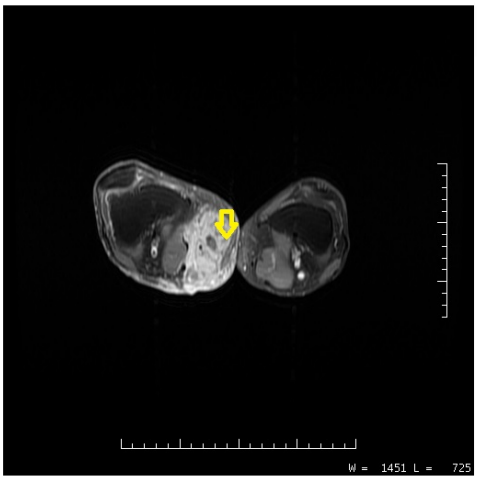

Figure 3: MRI scan cross sectional view showing the hyperintense soft tissue lesion.

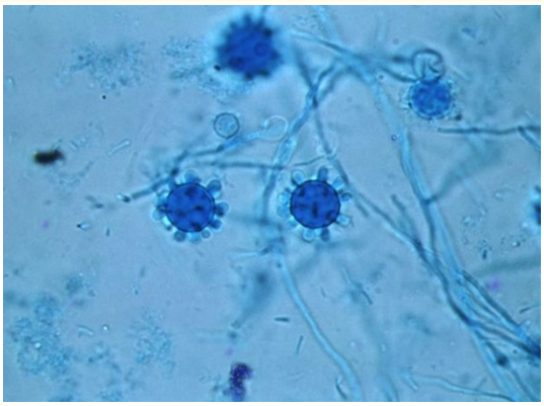

Figure 4: Fungal culture showing tuberculate macroconidia.

He did not have any evidence of pulmonary disease. His chest x ray was normal. There was no evidence of other extra pulmonary manifestations in the form of gastrointestinal, bone marrow or lymph node involvement. He was initially managed with intravenous Liposomal amphotericin B at 5 mg/kg/day daily for two weeks followed by Itraconazole 200 mg twice daily. After three months of treatment his skin lesions have shown improvement with regression of the ulcerative and indurated lesions. The dose of tacrolimus was reduced to 0.5 mg twice daily with periodic monitoring of tacrolimus trough levels. His graft functions are stable and he is on regular follow up in Nephrology outpatient services.

Discussion

Histoplasmosis in general manifests with pulmonary involvement. However, in immunosuppressed patients as in Human Immunodeficiency virus (HIV) positive patients and solid transplant organ recipients on immunosuppression, there is an increased risk of disseminated and pulmonary histoplasmosis [5]. The causes of extrapulmonary infections are reactivation of the previous silent foci of infection, progression of the initial infection along the blood vessels or lymphatics or as a result of direct transmission from an infected graft [6-8]. Progressive Disseminated Histoplasmosis is a multiorgan, severe and often fatal disease [7,8]. It usually involves the liver, spleen, lymph nodes and the bone marrow along with features of systemic inflammatory response with fever, malaise and weight loss [7,8]. It is one of the Acquired Immunity Deficiency Syndrome (AIDS) defining criteria. The usual time period when Histoplasmosis occurs in organ transplant recipients is varied varying from 84 days to 14 years after transplantation [9]. The most common sites of involvement with Histoplasmosis were lung (65%), kidney (29%), bone marrow (29%), cutaneous (25%), liver (18%), gastrointestinal tract (18%), spleen (12%) [5]. However, the majority of the patients with cutaneous involvement there was features of other organ involvement representing a progressive disseminated infection [5]. Patients with isolated cutaneous involvement constituted only 7% of the total number of patients [5]. Histoplasmosis presenting solely as mucocutaneous lesions is uncommon in solid transplant organ recipients and often is accompanied by pulmonary or extra pulmonary involvement [10]. The rarity of this presentation is reflected by the review of the literature, which has reported only a handful of cases [5].

The presentation of the cutaneous lesions in Histoplasmosis is varied and heterogenous, ranging from cutaneous ulcers, subcutaneous nodules with panniculitis, cellulitic plaques, purpuric lesions and papules [5,11]. Our patient presented with subcutaneous nodular as well as ulcerative lesions. An important differential diagnosis is Cutaneous cryptococcal infection which has been reported to present with features of cellulitis mimicking a bacterial cellulitis [12,13]. Culture of the biopsy specimen confirmed the presence of Histoplasmosis.

The definitive diagnosis of Histoplasmosis is made by GMS staining of the organism as an intracytoplasmic and extracellular black yeast like organism in subcutaneous tissue and in macrophages along with the culture of the organism. Narrow septate hyphae with conidia showing typical spikes are seen on lactophenol cotton blue mounts from Sabouraud's dextrose agar after 3 weeks of incubation.

Other diagnostic aids include antigen detection, serology and molecular diagnostics. Antigen detection in the urine or serum carries a 100% sensitivity; however false negative reports occur [14]. The sensitivity of the serology tests is low and varies between 20% to 33% [2,15]. Molecular diagnostics using polymerase chain reaction (PCR) has not been proven superior to other diagnostic methods, false negative results were seen in 31% of patients in which biopsy was positive [16].

If not diagnosed and treated with specific antifungal agents, progressive disseminated Histoplasmosis is fatal in 80% of the patients [17].

Liposomal Amphotericin B, 3 - 5 mg /kg/day is the initial recommended treatment of choice followed by oral Itraconazole in a dose of 200 mg twice daily for at least 12 months to prevent relapse [18]. Amphoteric B led to a favourable outcome in about 94% of the patients [19]. Other alternative antifungals in patients who do not tolerate itraconazole or has contraindications to its use include fluconazole, voriconazole and Posaconazole [20]. Echinocandins are ineffective against histoplasma [21].

Conclusion

In summary, Histoplasmosis can present as an isolated cutaneous involvement in solid organ transplant recipients. The clinical presentation is highly varied and a high index of clinical suspicion along with biopsy and culture helps in arriving at a diagnosis. Early treatment with Liposomal amphotericin followed by a prolonged course of oral Itraconazole is need in these patients to prevent relapse.

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