Primary Cutaneous Histoplasmosis in a Renal Allograft Recipient

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Abstract: The occurrence of histoplasmosis in renal allograft recipients is quite rare. While cutaneous involvement secondary to histoplasmosis has been reported in up to 17 percent of patients with disseminated disease, the occurrence of isolated cutaneous involvement is extremely rare. In this report, we describe the occurrence of primary cutaneous histoplasmosis involving the thigh in a renal allograft recipient. A 27 year old lady, who underwent renal transplantation 9 years ago, presented to us with complaints of painful swelling of her right thigh for 3 months. She noticed small nodular, erythematous lesions on the lateral aspect of her right thigh, which gradually increased in size and coalesced to form a diffuse erythematous swelling. There was no history of fever or trauma. She had diarrhea for 3 months, which subsided after discontinuation of mycophenolate mofetil. There was no history to suggest any other organ involvement. Skin biopsy revealed septal granulomatous panniculitis with focal lobular extension and occasional yeast-like fungi. The tissue was sent for microbiological analysis which revealed Histoplasma capsulatum. After a thorough workup to rule out disseminated histoplasmosis, she was started on oral itraconazole in renal adjusted doses. The lesions started resolving in 1 week. The patient was advised to continue itraconazole for at least one year. However, due to financial constraints, she stopped the medication after 3 months. However, the lesions had completely resolved, with no recurrence till the last follow-up visit.

Keyword: Cellulitis, Cutaneous, Histoplasmosis, Renal, Transplant

Introduction: The occurrence of histoplasmosis in solid-organ transplant recipients is quite rare, with a reported incidence of <0.5% in endemic areas(1),(2),(3). Nevertheless, sporadic occurrence has been reported in several parts of the world, including India(4),(5). Usually a self-limiting illness in immunocompetent individuals, it has the potential to cause disseminated disease in immunocompromised individuals, especially in acquired immunodeficiency disease (AIDS) patients. While cutaneous involvement secondary to
Histoplasmosis has been reported in up to 17% of patients with disseminated disease, the occurrence of isolated cutaneous involvement in renal allograft recipients is extremely rare (4),(6),(7). In this report, we describe the occurrence of primary cutaneous histoplasmosis involving the thigh in a renal allograft recipient. **History** A 17 year old girl with end-stage renal disease due to mesangiproliferative glomerulonephritis underwent living-related kidney transplantation with mother as voluntary kidney donor in February 2003. She was on prednisolone, cyclosporine and azathioprine for maintenance immunosuppression and reached a nadir creatinine of 1.2 mg/dl in the first post-operative week. There were no episodes of rejection. Three years after transplantation, cyclosporine was withdrawn after a protocol graft biopsy and azathioprine was changed to mycophenolate mofetil (MMF), as per the treating unit’s protocol then. She developed chronic allograft nephropathy 7 years after transplantation, with serum creatinine increasing to 1.7 mg/dl. Subsequently, there was progressive deterioration of allograft function, with serum creatinine worsening to 3 mg/dl in 2011. Nine years after transplantation, in October 2012, she presented to us with complaints of painful swelling of her right thigh for 3 months. She noticed small nodular, erythematous lesions on the lateral aspect of her right thigh, which gradually increased in size and coalesced to form a diffuse erythematous swelling, with a few satellite nodules surrounding it. There was no history of fever or trauma. She complained of diarrhea of 3 months duration, with small volume frequent stools, without blood or mucus. There was no history to suggest any other organ involvement. On evaluation, she had pancytopenia, with hemoglobin of 4.8 g/dl, total leucocyte count of 3200 cells/mm³ and platelet count of 140,000/mm³. The white blood cell differential count revealed neutrophils 72%, lymphocytes 19%, monocytes 8%, basophils 1% and eosinophils 0%. Peripheral smear revealed anisopoikilocytosis. Her serum iron, vitamin B12 and folate levels were normal. She had graft dysfunction with serum creatinine of 4.8 mg/dl. A bone marrow was done in view of pancytopenia which revealed mild megaloblastoid erythropoiesis with ringed sideroblasts (>15%) suggestive of myelodysplastic syndrome (MDS). There were no granulomas or any evidence of infection in the bone marrow. The possibility of drug-induced MDS was considered and MMF was discontinued. For evaluation of diarrhea, stool examination was performed which did not reveal any parasites. Colonic biopsy was performed which revealed mild, chronic active colitis, with foci of apoptosis suggestive of MMF-induced changes. There were no granulomas or evidence of infection in the colonic biopsy. Her diarrhea subsided and pancytopenia improved after withdrawal of MMF. The patient was maintained on oral prednisolone 5 mg daily. A skin biopsy was performed from the right thigh which revealed septal granulomatous panniculitis with focal lobular extension and occasional yeast-like fungi (Fig. 1). The tissue was sent for microbiological analysis which revealed fungal hyphae with characteristic tuberculate macroconidia and microconidia of *Histoplasma capsulatum* (Fig. 2).
Figure 1: Skin biopsy revealing multinucleated giant cells (thick arrow) and yeast-like fungi (thin arrow)

Figure 2: Fungal Culture revealing Histoplasma capsulatum

The patient was evaluated for disseminated histoplasmosis with computed tomography of abdomen and chest radiography, which were normal. With no evidence of visceral organ involvement in imaging studies, bone marrow and colonic biopsy, the diagnosis of primary cutaneous histoplasmosis was made and patient was started on oral itraconazole in renal adjusted doses. Symptomatic improvement started in 1 week, with disappearance of satellite nodules. The patient was advised to continue itraconazole for at least one year. However, due to financial constraints, she stopped the medication after 3 months. However, the lesions had completely resolved, with no recurrence till the last follow-up visit. The graft dysfunction remained stable with serum creatinine of 4.9 mg/dl in the last follow-up visit 3 months ago.

Discussion:
The occurrence of histoplasmosis in solid-organ transplant recipients is quite rare, with a reported incidence of <0.5% in endemic areas (1),(2),(3). The most common manifestation in solid-organ transplant recipients is disseminated histoplasmosis, which presents with constitutional symptoms like fever, headache, anorexia, weight loss, and malaise. Hepatosplenomegaly, lymphadenopathy and pancytopenia are common due to reticuloendothelial system involvement. Although our patient had pancytopenia, this was not due to histoplasmosis since bone marrow revealed features of MDS and no evidence of granuloma or infection. Moreover, the pancytopenia recovered after discontinuation of MMF confirming the diagnosis of drug-induced MDS. Cutaneous involvement can occur in up to 17% of patients with disseminated disease and can manifest as papules, pustules, plaques, ulcers, molluscum or wart-like lesions and, rarely, erythema nodosum(8),(9). On the other hand, primary cutaneous histoplasmosis is extremely rare in solid-organ transplant recipients (4),(6),(7). The route of infection in primary cutaneous disease is thought to be direct inoculation of spores through skin and mucous membranes due to minor trauma like thorn pricks. It can manifest as nodules, ulcers, abscesses or molluscum contagiosum-like lesions, without any systemic involvement. Although our patient denied history of trauma, we speculate that direct inoculation of Histoplasma spores could have occurred during occult trauma to the skin of the thigh. Approximately one-third of cases of histoplasmosis occur within the first post-transplant year, when net immunosuppression is maximal(10). Our patient developed histoplasmosis 9 years after transplantation while she was being maintained on a low level of immunosuppression. She did not receive any induction agent prior to transplant, did not
require anti-rejection therapy at any point of time and was only on dual immunosuppression after 3 years of transplantation. This suggests that primary cutaneous histoplasmosis could occur in the post-transplant setting, even when immunosuppression is minimal. This observation is strengthened by the fact that there are multiple case reports of isolated cutaneous histoplasmosis occurring in immunocompetent individuals as well rare reports in transplant recipients occurring several years after transplantation (4),(11).

Conclusion
Primary cutaneous histoplasmosis has to be considered in the differential diagnosis of cutaneous lesions occurring in post-transplant patients, even several years after transplantation, irrespective of the level of immunosuppression.

References


