Case Report

Histoplasmosis presenting as cellulitis 18 years after renal transplantation

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A 49-year-old renal transplant patient, under an 18-year course of immunosuppressive therapy with prednisone and azathioprine and, more recently, prednisone plus mycophenolate sodium, developed a cutaneous-subcutaneous infection caused by *Histoplasma capsulatum*. The clinical presentation consisted of a slowly enlarging, erythematous and infiltrative 25 cm plaque in the major axis on the arm. There was no involvement of the lungs or any other organ. Cure was obtained with itraconazole treatment after 12 months. Histoplasmosis is an uncommon opportunistic infection among solid organ transplanted patients with incidence of 0% to 2.1% observed in a large number of cases. This report describes an atypical cutaneous clinical presentation of a potentially fatal disease in immunosuppressed patients.

**Keywords** histoplasmosis, cellulitis, renal transplantation, itraconazole

Introduction

Increasing susceptibility to life-threatening infections has been associated with prolonged use of immunosuppressive drugs. Systemic mycosis has been reported as one of the most important causes of morbidity and mortality in this group of patients [1,2]. Histoplasmosis is a potentially severe systemic mycosis caused by *Histoplasma capsulatum*, a dimorphic, soil saprophytic fungus, which occurs mainly in specific endemic areas of North and South America [3]. The infection results from the inhalation of airborne conidia which usually results in subclinical primary infections of the lungs or causes only mild pneumonitis in immunocompetent hosts. Clinical manifestation following primary infection is a consequence of agent–host interaction imbalance. Patients with chronic obstructive pulmonary disease can develop chronic pulmonary histoplasmosis. Extrapulmonary manifestations, localized or systemic, can occur either as a progression of the initial lymphohematogenous dissemination or as a reactivation of quiescent foci of past infections, or exceptionally, as a consequence of direct transmission from an infected graft [3–5]. Progressive disseminated histoplasmosis is a severe, life-threatening, systemic disease, usually involving many organs, particularly those of the reticuloendothelial system, such as lymph nodes, liver, spleen and bone marrow. It is commonly associated with fever, weight loss and malaise [6–8]. In such circumstances cutaneous compromise shows multiple acneiforme lesions which can progress to nodules, ulcers or vegetations. Progressive disseminated histoplasmosis is associated with cell-mediated immunosuppression, frequently HIV-induced or even, iatrogenic-induced, as observed among individuals under cancer therapy or immunosuppressive therapy used in solid organ transplantation [4,6]. Recently this form of the disease was reported following immunotherapy with anti-TNF α agents when treating rheumatoid
arthritis, psoriatic arthritis or Crohn’s disease [9]. Histoplasmosis seems to occur from 84 days to 14 years after organ transplantation [10]. We report the case of a 49-year-old woman presenting an uncommon cutaneous clinical picture of histoplasmosis diagnosed 18 years after a renal allograft transplant.

Case report

A 49-year-old woman who had undergone a living-related renal transplantation years before her presentation, developed a progressive and infiltrative skin lesion on her left arm associated with fever and malaise one week before being seen. There was no local trauma or previous skin disease and it was initially diagnosed as a presumed bacterial cutaneous infection and treated with oral antibiotics. Ten days later with worsening and extension of her lesion she was hospitalized, submitted to a general investigation and put under IV ceftriaxone. As there was no improvement, a dermatological opinion was requested. Past medical history was significant for an allogenic renal transplantation 18 years before the occurrence of the skin lesion. Transplantation occurred following a chronic diffuse glomerulonephritis, under immunosuppressive therapy with prednisone (10 mg/day) and azathioprine (150 mg/day) from 1988 to 2006 and since then, prednisone (10 mg/d) and mycophenolate sodium (1080 mg/day). Upon physical examination, the patient presented good general condition and showed a 25 cm erythematous, warm, infiltrative plaque with a central necrotic area on her left arm (Figs. 1 and 2). There were few additional erythematous nodular lesions scattered over the thorax and abdomen. Mouth, chest and abdomen inspections were normal. A preliminary diagnosis of cellulitis due to fungal etiology was suggested and skin biopsies for histopathological study and culture were performed.

Chest radiograph, thorax CT scan and sputum examination, serologic investigation for paracoccidioidomycosis, HIV, HBV and HCV-infection, PPD and paracoccidioidin skin test and blood laboratory investigations were either normal or negative. Histopathological examination showed an epithelial hyperplasia, lymphohistiocytic and granulomatous inflammatory infiltrate with multinucleated giant cells containing small oval bodies, surrounded by discrete refractile halo within the cytoplasm (Fig. 2). These intracellular structures tested positive with methenamine silver stain. Cultures of biopsy specimens were positive for *Histoplasma capsulatum* in all Mycosel tube seeded with portions of the biopsy tissue. Initially, colonies were grown at room temperature, as well as at 37°C to induce the formation of the yeast form of the organism.

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**Fig. 1** A large, 25 cm, erythematous, infiltrative lesion with a central necrotic area on the left arm.

**Fig. 2** Histological skin section showing yeasts (arrows). Gomori-Grocott silver stain (×400).

**Fig. 3** Slide culture of *Histoplasma capsulatum* stained with cotton blue showing many typical tuberculate conidia (×400).
Pre-treatment, specific antibodies to *H. capsulatum* were detected in immunodiffusion assay.

Despite the diagnosis of disseminated histoplasmosis, based on the presence of specific cutaneous lesions distant from that of the left arm and due to her good general condition, the patient was treated with itraconazole 200 mg/daily. The immunosuppressive therapy was not modified during treatment with itraconazole. Healing of all lesions could be observed by the fourth month of 12-month course treatment. During this period hepatic enzymes and renal function remained within pre-treatment range. After more than 12 months of follow-up, the patient had no manifestations of fungal recurrence.

**Discussion**

Although it has been considered as an opportunistic disease in the case definition for AIDS, histoplasmosis seems to be very uncommon among patients who have received solid organ transplantation. Some inquiries have tried to determine the incidence of mycosis or, specifically, the incidence of histoplasmosis, in cohorts of transplant recipients. In a hyperendemic area of the state of Indiana in the USA, the incidence of histoplasmosis was estimated to be 2.1% in a 39-month study, a period coincident with a large urban outbreak of the disease in the area [11]. However, more recently, a 36 month study in the same area, did not reveal any cases of histoplasmosis among 137 patients who underwent allogenic bone marrow transplant and 449 patients who underwent solid organ transplant [12]. In another similar endemic area, Cincinnati, Ohio the reported incidence was 0.5% among 1,074 renal transplant recipients over 25 years [10]. In Brazil, histoplasmosis was diagnosed in six patients (1.2%) of 502 renal transplanted recipients followed for up to 20 years [13]. In the same country, among 100 heart transplanted patients followed for three to 90 months, the incidence of histoplasmosis was 1%. In this one case, the diagnosis was made only upon post-mortem examination, with just one case being reported since then [14,15]. These data suggest that histoplasmosis is a rare infection following iatrogenic immunosuppression which, together with possible uncommon clinical presentation, made it difficult to formulate conclusive diagnoses.

Clinical manifestations of progressive disseminated histoplasmosis depend on the extent of the associated immunosuppression and usually are associated with prodromic events like fever, weakness and malaise or fatigue. Symptoms pointing to a specific organ involvement are variable and can include cough and dyspnea or lymph nodes augmentation plus hepatic and splenomegaly or oral or cutaneous lesions. In sum, a combination of multiple organ involvement, sometimes including the central nervous system and gastrointestinal system have been observed [7,8]. In some reports, cutaneous histoplasmosis lesions appear to be common in patients with HIV/AIDS [16–19]. In these circumstances the lesions resulting from the hematogenous dissemination and initially manifesting as acniforme which can evolve to more severe lesions. However, mucocutaneous lesions of histoplasmosis are uncommon among solid organ transplant recipients and are usually associated with pulmonary or other organic diseases [20]. In addition, cellulitis as a dominant picture of histoplasmosis related to iatrogenic immunosuppression is very uncommon and has been reported once and, like in this present case, was initially treated as a bacterial infection [21]. As there was no systemic evidence of histoplasmosis we could speculate on direct cutaneous inoculation of the agent. The size and the aspect of the lesion, reproduced on Fig. 1 reinforced such reasoning. However, since previous trauma was denied by the patient, this remains only as a theoretical possibility. On the other hand, cellulitis can be a primary cutaneous expression of cryptococcosis, with a similar picture in immunocompetent and immunosuppressed patients [22,23]. Upon the clinical suspicion the most useful diagnostic procedure is tissue biopsy and examination of the specimen using metanemine silver stain or periodic acid of Schiff for *H. capsulatum* and mucicarime stain for *Cryptococcus* spp. Etiologic confirmation can be provided by culture or through molecular approaches.

Without treatment progressive disseminated histoplasmosis is a fatal disease in 80% of the cases [21]. In immunocompromised patients or patients with severe disease, the classic amphotericin B 0.75 to 1.0 mg/kg/day is recommended. Liposomal amphotericin B can be a suitable choice for patients unable to receive classic amphotericin B. Both forms of this antifungal agent can be used as a single drug or as an induction therapy followed by itraconazole [24]. This latter procedure can be regarded as particularly suitable for renal transplanted patients. Itraconazole was chosen based on our successful experience in treating histoplasmosis in HIV-immunosuppressed patients and has been suggested before for moderate clinical cases of the disease [24]. Fluconazole can be an option for patients who do not tolerate itraconazole or when there is drug interaction between itraconazole and cyclosporine or with other essential drugs. If applicable, fluconazole must be used in high doses (>400 to 800 mg/d) [21,24]. Among the new antifungal drugs there are some reports indicating

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that posaconazole, a triazole with an extended antifungal spectrum, has excellent in vitro activity against *H. capsulatum*, as well as superior efficacy in murine model when compared with itraconazole and amphotericin B [25,26]. Lately, posaconazole proved to be very useful as salvage treatment in severe cases of disseminated histoplasmosis which were non-responsive to previous treatment with standard drugs [27]. In this present report, itraconazole, 200 mg/daily for 12 months was very effective and after another 12 months of follow up there was no recurrence.

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**References**