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Chronic progressive disseminated histoplasmosis in a renal transplant recipient

Farah Tanveer[a,*], Mariam Younas[a], Leonard B. Johnson[a,b]

[a] Division of Infectious Disease, Department of Internal Medicine, St. John Hospital and Medical Center, 19251 Mack Avenue, Suite 340, Detroit 48236, MI, United States of America

[b] Wayne State University School of Medicine, Detroit 48202, MI, United States of America

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ABSTRACT

Hematopoietic and solid organ transplant recipients are at increased risk of opportunistic infections and infections usually are severe due to impaired cell mediated immunity. We report an unusual case of disseminated histoplasmosis in a renal transplant recipient manifesting with a chronic progressive course over several years. After starting treatment with itraconazole, the patient showed marked improvement in his symptoms and had clinical resolution

1. Introduction

Histoplasmosis is an endemic mycosis caused by a dimorphic fungus. In USA, the disease is due to *H. capsulatum* which is endemic in the Mississippi and Ohio river valley areas [1]. Most of the infected individuals remain asymptomatic or have very mild illness that does not get diagnosed as histoplasmosis. Significant symptoms develop in less than 1% of patients and most frequently present as pulmonary or disseminated histoplasmosis [2]. Immunocompromised individuals, including patients with AIDS, hematologic malignancies, transplant recipients, and patients receiving prolonged steroids, are at higher risk of developing acute disseminated disease with a rapid and aggressive course. Chronic progressive disseminated histoplasmosis has been mostly described in the older but otherwise immunocompetent patients [1,2,3,4].

2. Case

The patient is a 58-year-old male with a medical history of coronary artery disease, hypertension, hypothyroidism, polycystic kidney disease, and a living-related donor renal transplant in 2003. He developed graft failure in 2015 and restarted hemodialysis three times a week. His immunosuppressive medications including tacrolimus 2 mg twice daily, mycophenolate mofetil 1000 mg twice daily and prednisone 5 mg daily were tapered down in January 2016 to tacrolimus 2 mg daily and prednisone 5 mg daily; mycophenolate mofetil was discontinued. He presented to our facility in November 2016 with complains of fever up to 38.8 °C, generalized weakness, malaise, and body aches for three days. He denied any concomitant respiratory, abdominal, or genitourinary complaints, but reported similar febrile episodes intermittently for the past seven years. He also complained of fatigue, night sweats, poor appetite, and unintentional weight loss over the same period of time. The patient denied sick contacts, animal exposure or travel outside of Michigan. He reported working as a registered nurse in the past, currently unemployed.

His vital signs on presentation (day 0) were reported as a temperature of 37.2 °C, pulse 59 beats per minute, blood pressure 111/61 mm of Hg, and respiratory rate 18/ minutes with oxygen saturation of 98% on room air. Physical examination, including the arteriovenous fistula site, was unremarkable. Complete blood count revealed pancytopenia with a white blood cell (WBC) count of 3600/cu mm, hemoglobin 7.7 gm/dL, and platelet count of 108,000/cu mm. The complete metabolic panel was normal except for elevated creatinine, and urinalysis was unremarkable for an infectious process. The patient was started on vancomycin for a suspected bloodstream infection related to dialysis access. Review of his previous medical records revealed recurrent hospital admissions in the past six years with fever of unknown origin as well as progressive pancytopenia. Laboratory data from previous admissions revealed negative HIV antibody screen, hepatitis B and C serology, tuberculin skin test, antinuclear antibody, and rheumatoid factor. Peripheral blood smear showed normal morphology but reduced number of WBC, RBC, and platelets. Over the next 48 h, the

* Corresponding author.
E-mail address: farah.tanveer@ascension.org (F. Tanveer).

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patient had a maximum temperature of 38 °C. Blood and urine cultures did not show any growth, computed tomography of the chest/abdomen/pelvis with contrast was unremarkable, rapid influenza screen was negative, serum cytomegalovirus was undetectable by polymerase chain reaction and thyroid stimulating hormone level was within normal limits. He was discharged home on day 4 with a presumed diagnosis of a non-specific viral illness. During outpatient follow up, the patient reported ongoing fatigue and night sweats. Urine Histoplasma Galactomannan antigen was tested which came back positive at a level of 6.7 ng/ml (cut off < 0.4). The patient was started on oral itraconazole (200 mg twice daily), tacrolimus was discontinued, while patient continued to receive prednisone 5 mg daily. Follow up urine Histoplasma Galactomannan antigen testing after three weeks showed a level of 4.7 ng/ml and became undetectable after two months of treatment. He completed a twelve-month course of treatment with itraconazole, with no recurrence of unexplained fever, and resolution of pancytopenia. Follow up urinary Histoplasma antigen after completion of treatment was undetectable.

3. Discussion

Histoplasma capsulatum is found as a mold in soil and grows as yeast in host tissues. In endemic areas, 50–80% of people are seropositive [1]. Soil is the natural environmental reservoir and can yield the organism for years after getting contaminated [2]. Humans acquire infection through inhalation of microconidia. Most infected persons experience a hematogenous spread of organism to reticuloendothelial organs such as liver, spleen, bone marrow and lymph nodes, via macrophages [2]. In most cases the host is able to control the infection by cell mediated immunity and remains asymptomatic. However, the organism stays latent in the host and can reactivate many years later, resulting in disseminated disease [2,3]. Disseminated histoplasmosis can involve various organs, including reticuloendothelial organs, gastrointestinal tract, adrenal glands, central nervous system, endovascular structures, kidney, and skin [3,4]. It typically presents with systemic symptoms like fever, generalized fatigue, night sweats, weight loss, and the symptoms related to the specific organ involved. Severe disseminated disease can manifest as septic shock, multi organ failure, and ARDS [5].

The manifestations and outcome of disseminated disease vary depending upon the host immune response. Immunocompromised patients usually manifest disease during early dissemination. In these individuals, the disease progresses aggressively within a few days and it is rapidly fatal if left untreated. In contrast, a chronic, progressive course is seen in older adults who are not overtly immunocompromised [1,2,3,4]. The course of disease in these patients may last months but is uniformly fatal if not treated [4,5]. This case is unique because despite being immunocompromised, the patient manifested a chronic, progressive course of disseminated histoplasmosis. It is not entirely clear as to when the patient actually acquired this infection, but he had been symptomatic for at least six years before the diagnosis was made. His renal allograft biopsy performed in 2014 had shown chronic rejection, however fungal stains were not performed on the tissue; hence it is uncertain if there was involvement of allograft by histoplasma. There has been one previously reported case of chronic disseminated histoplasmosis involving tongue, bone marrow, liver, spleen, and lungs in a patient who continued low dose immunosuppression after failure of a renal transplant. The patient had presumably acquired histoplasmosis two to three years prior to diagnosis. His case was complicated by acute CMV infection as well as Pseudomonas aeruginosa sepsis and resulted in a fatal outcome. [6]. This case emphasizes the importance of considering histoplasmosis in the differential diagnosis of fever of unknown origin, especially in endemic areas and immunocompromised individuals.

Detection of *H. capsulatum* polysaccharide antigen in urine, serum, and other body fluids is being increasingly used to help establish a diagnosis in immunosuppressed patients suspected to have disseminated histoplasmosis and is commercially available. Urine antigen test is more sensitive than serum testing [5,7]. Antigen levels decline with effective treatment and increase with relapse, making it a useful marker to monitor response to the treatment [8].

All patients with disseminated disease should be treated with antifungals. Amphotericin B is the recommended drug for severe disseminated disease. In patients with mild to moderate disease, oral itraconazole for 6–18 months is the preferred treatment [9].

Conflict of interest

There are none.

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