Clinical Report

A difficult diagnosis: acute histoplasmosis

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Abstract

A 43-year-old male with deceased donor kidney transplantation presented with fever of unknown etiology and underwent an extensive workup. The diagnosis of histoplasmosis was made after biopsy of a positron emission tomography-positive subcarinal lymph node showed non-caseating granulomas with a positive stain for yeast. The diagnosis was confirmed when fevers remitted with initiation of appropriate anti-fungal therapy.

Keywords: fever of unknown origin; histoplasmosis; kidney transplant

Background

Histoplasmosis is the most common endemic mycosis in North America, especially in the Midwestern states in the USA. Although relatively rare, even after solid organ transplant [1, 2], post-transplant histoplasmosis can present with a myriad of clinical manifestations, and its diagnosis requires a high index of suspicion and use of appropriate diagnostic tests [3, 4]. We report a case of histoplasmosis presenting as fever of unknown origin in a kidney transplant recipient where the diagnosis required pathological examination of a lymph node that was positive on positron emission tomography (PET) scan.

Case

A 43-year-old male, a resident of Ohio with a history of deceased donor kidney transplantation 2 years previously due to hypertensive end-stage renal disease, presented with fever, night sweats and malaise of several weeks duration. He denied any sick contacts, recent travel or any significant outdoor exposure. He had no localizing symptoms other than mild cough on presentation. Post-transplant, the patient had no rejection episodes and he was maintained on a stable immunosuppressive regimen that included mycophenolate mofetil 1 g twice a day and sirolimus 6 mg daily. On admission, the patient appeared well and was in no acute distress. The physical examination was unremarkable except for the elevated temperature of 102.7°F. Laboratory data revealed a slightly increased white blood cell (WBC) count of 10 400/μL (differential: 81.7% granulocytes, 12.2% monocytes and 2.9% lymphocytes). A chest X-ray showed a small indistinct opacity in the right lung base. A computed tomography (CT) chest revealed right lower lobe airspace disease, a few bilateral pulmonary nodules, the largest being 7 mm, a 2.3 × 2.3 cm necrotic subcarinal

node and no other significant lymphadenopathy. The patient was started on empirical intravenous vancomycin and piperacillin/tazobactam on admission with a presumed diagnosis of community-acquired pneumonia but the fever persisted. The subsequent negative workup included a urinalysis, serum *Cytomegalovirus* polymerase chain reaction (PCR), BK virus PCR, Epstein-Barr virus PCR, respiratory viral panel PCR done on nasopharyngeal swab, serum cryptococcal antigen, serum *Aspergillus* galactomannan assay, urine *Histoplasma* antigen, serial blood and urine cultures, serologies for HIV, *Brucella*, *Rickettsiae*, Q fever, *Bartonella* and endemic fungi (*Histoplasma*, *Coccidioides*, *Blastomyces*), Tuberculosis interferon-gamma release assay, rapid plasma reagin, rheumatoid factor, anti-nuclear antibody, serum cryoglobulin and serum and urine protein electrophoresis.

Based on the findings on chest imaging, a bronchoscopy and bronchoalveolar lavage (BAL) were performed and sent for cell count, bacterial culture, respiratory viral pathogen nucleic acid testing and general viral culture and fungal and acid-fast bacillus analysis. Cytology of the BAL fluid showed 71% macrophages, 12% neutrophils and 16% lymphocytes but other tests were reported to be negative. Other negative diagnostic workup included a CT scan of abdomen and pelvis, whole body WBC scan and a bone marrow biopsy. As fever continued, we also entertained the possibility of malignancy or lymphoma. It was important to figure out whether the single large necrotic-looking subcarinal lymph node seen on chest CT scan in absence of other lymphadenopathy was significant or not and whether we were dealing with a more systemic process. A PET scan (Figure 1) was subsequently obtained. It showed increased [18F]-fluorodeoxyglucose (FDG) uptake in mediastinal, hilar, supraclavicular, retroclavicular and periaortic lymph nodes. Thus, the PET scan confirmed the systemic disease and showed that necrotic-looking subcarinal lymph node enlargement was significant. A mediastinoscopy with subcarinal lymph node biopsy was then performed to better characterize the etiology of lymphadenopathy. Pathology revealed

Fig. 1. The PET scan shows a lymph node in the subcarinal area (circle). Please see the additional color image as Supplementary material online.

non-caseating granulomas (Figure 2) with small yeast forms suggestive of *Histoplasma capsulatum* (Figure 3). The patient was initiated on itraconazole capsule 200 mg bid but as the serum itraconazole level 10 days later was detected to be low at 0.6 mcg/mL, he was switched to the liquid formulation (to allow better absorption) at the same dose. With the liquid form, the patient achieved a target level of ~1 mcg/mL, and hence, he was continued on the same regimen. The patient defervesced within a week after initiation of itraconazole. Cultures of the nodes confirmed the diagnosis of histoplasmosis. So far, the patient has completed 8 months of itraconazole for a total of 12 months and has remained afebrile. He required reduction in the dose of sirolimus at the beginning of the therapy because the drug-drug interaction between itraconazole and sirolimus resulted in a significant increase in the drug level of the sirolimus. The patient has maintained a stable graft function till the time of last follow-up.

Discussion

The evaluation of infection in the transplant recipient can be challenging. The immunocompromised host can have falsely negative serologic studies (using the immunodiffusion and complement fixation methods) owing to ineffective and/or impaired antibody responses to infection. The advent of fungal antigen testing by enzyme immunoassay has facilitated the diagnosis in these patients and should be done routinely in febrile transplant patients. However, such tests are currently available for a limited set of pathogens. Such limitations often lead clinicians to approach management of such cases with empiric therapy. In the absence of clinical response, the diagnosis may require surgical pathology specimens.

This case illustrates that histoplasmosis in the solid organ transplant recipient may cause a major diagnostic dilemma. In the patient presenting with fever of unknown origin, the difficulty lies in differentiating it from other fungal infections, tuberculosis, sarcoidosis, lymphoma and malignancy.

Fig. 2. The epithelioid non-necrotizing granulomas with giant cells (arrows) in the lymph node. Please see the additional color image (hematoxylin & eosin stain) as Supplementary material online.

Fig. 3. The lymph node stain reveals the fungi (*Histoplasma*) in black. Please see the additional color image (Gomori's methenamine-silver stain) as Supplementary material online.

In the above patient, the diagnosis of histoplasmosis remained elusive due to an absence of significant pulmonary symptoms and chest imaging findings, negative blood cultures and a negative BAL. The histoplasma serology was negative in our patient, as the test is known to have a poor sensitivity in solid organ transplant recipients, especially in acute cases [4]. Although urinary Histoplasma antigen testing has been reported to be up to 90–95% sensitive in making a diagnosis of histoplasmosis [5, 6], the test remained negative in this case on several occasions, likely reflecting a lack of wide dissemination of disease. The sensitivity of antigen detection in acute disseminated histoplasmosis is reported to be higher in immunocompromised patients than in immunocompetent patients and in patients with more severe disease [4]. In contrast, the false-negative histoplasmosis antigen results have been reported in patients with mild disease, pulmonary versus disseminated disease and in those with negative blood cultures [4] and may occur in up to 10–20% of disseminated cases in immunocompromised individuals, including those with organ transplantation but without AIDS [4, 7]. The Histoplasma antigen testing of BAL may provide rapid diagnosis in some instances [8] but was not done in our patient. The nucleic acid PCR

testing for histoplasmosis is not offered at our center. Moreover, this test is not widely available, and its role in the diagnosis of histoplasmosis remains unclear [7, 9]. Fungal stains and cultures of the bone marrow aspirate and the bone marrow biopsy were also unrevealing for *Histoplasma* infection; this result was not surprising given a lack of significant cytopenia. In previously reported series of histoplasmosis in solid organ transplant recipients, the diagnosis was aided by a positive antigen test, culture or serology in all the patients [1, 10, 11]. In our patient, these tests were unrevealing and ultimately, PET scan was helpful in focusing attention on metabolically active tissue. PET scan has been reported to be helpful in the diagnosis and staging of invasive fungal infections, especially when lesions are unapparent on the corresponding CT [12]. Indeed, biopsy of the PET-avid nodes finally established the diagnosis.

In summary, the diagnosis of post-transplant histoplasmosis can be challenging due to poor sensitivity of serological tests in solid organ transplant recipients, uncertain role of molecular diagnostic methods (PCR) and falsely negative results obtained with antigen tests in less severe cases. PET scan may aid in the detection of small but metabolically active lymph nodes when lymphadenopathy is not yet conspicuous on the CT in the early and less severe cases of post-transplant histoplasmosis.

Supplementary data

Supplementary data are available online at <http://ckj.oxfordjournals.org>.

Conflict of interest statement. None declared.

References

1. Grim SA, Proia L, Miller R et al. A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. *Transpl Infect Dis* 2012; 14: 17–23.
2. Vail GM, Young RS, Wheat LJ et al. Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area. *Transpl Infect Dis* 2002; 4: 148–151.
3. Knox KS, Hage CA. Histoplasmosis. *Proc Am Thorac Soc* 2010; 7: 169–172.
4. Hage CA, Ribes JA, Wengenack NL et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. *Clin Infect Dis* 2011; 53: 448–454.
5. Connolly PA, Durkin MM, Lemonte AM et al. Detection of histoplasma antigen by a quantitative enzyme immunoassay. *Clin Vaccine Immunol* 2007; 14: 1587–1591.
6. Wheat LJ, Freifeld AG, Kleiman MB et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2007; 45: 807–825.
7. Kauffman CA. Diagnosis of histoplasmosis in immunosuppressed patients. *Curr Opin Infect Dis* 2008; 21: 421–425.
8. Hage CA, Davis TE, Egan L et al. Diagnosis of pulmonary histoplasmosis and blastomycosis by detection of antigen in bronchoalveolar lavage fluid using an improved second-generation enzyme-linked immunoassay. *Respir Med* 2007; 101: 43–47.
9. Tang YW, Li H, Durkin MM et al. Urine polymerase chain reaction is not as sensitive as urine antigen for the diagnosis of disseminated histoplasmosis. *Diagn Microbiol Infect Dis* 2006; 54: 283–287.
10. Cuellar-Rodriguez J, Avery RK, Lard M et al. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. *Clin Infect Dis* 2009; 49: 710–716.
11. Freifeld AG, Iwen PC, Lesiak BL et al. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. *Transpl Infect Dis* 2005; 7: 109–115.
12. Hot A, Maunoury C, Poiree S et al. Diagnostic contribution of positron emission tomography with [18F]fluorodeoxyglucose for invasive fungal infections. *Clin Microbiol Infect* 2011; 17: 409–417.

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