

Pulmonary *Histoplasma* Infection After Allogeneic Hematopoietic Stem Cell Transplantation: Case Report and Review of the Literature

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Histoplasmosis causes a wide spectrum of clinical illness, including disseminated infection in the immunocompromised. We report a case of pulmonary histoplasmosis in an allogeneic stem cell transplant recipient and review the literature on this topic. Histoplasmosis in this patient population is uncommon, but it is associated with poor outcome.

Keywords. allogeneic; *Histoplasma*; histoplasmosis; pulmonary; transplantation.

Histoplasmosis can range in spectrum from a localized pulmonary to a disseminated infection and can affect both immunocompetent and immunocompromised hosts. However, only a few cases of histoplasmosis have been reported in the allogeneic hematopoietic stem cell transplant (HSCT) population [1–5]. In this study, we report an allogeneic HSCT recipient from an endemic country in Central America who developed pulmonary histoplasmosis, review the literature of histoplasmosis in this patient population, and highlight the use of positron-emission tomography (PET) imaging and pan-fungal polymerase chain reaction (PCR), which were helpful in making the diagnosis.

CASE PRESENTATION

A 21-year-old man returned to the National Institutes of Health (NIH) in March 2014 for 1-year follow up after an allogeneic HSCT. He was initially diagnosed with pre-B cell acute

lymphoblastic leukemia in 2011 in El Salvador. In November 2011, he received induction chemotherapy with cyclophosphamide, vincristine, doxorubicin, dexamethasone, and 1 cycle of intrathecal methotrexate, followed by 5 cycles of maintenance chemotherapy with bendamustine, methotrexate, and 5-fluorouracil between December 2011 and May 2012. A bone marrow biopsy in May 2012 showed recurrent disease, prompting treatment with 3 cycles of high-dose cytarabine and mitoxantrone. A repeat bone marrow biopsy showed morphologic complete remission. After that, he received continuous maintenance therapy with methotrexate, 6-mercaptopurine, and monthly intrathecal methotrexate. He presented to the NIH in February 2013 for a human leukocyte antigen-identical sibling HSCT. The patient gave informed consent under an institutional review board-approved protocol (National Heart, Lung, and Blood Institute; 12-H-0028). He received myeloablative conditioning with fludarabine, cyclophosphamide and 1200 cGy total body irradiation (lungs shielded to 600 cGy), a CD3 and CD19 depleted graft, and graft-versus-host disease (GvHD) prophylaxis with cyclosporine followed by full engraftment. The immediate posttransplant course was complicated by an *Escherichia coli* urinary tract infection, *Clostridium difficile* colitis, and respiratory syncytial virus infection. He developed grade 1 acute GvHD of the skin, a brief episode of cytomegalovirus (CMV) viremia without end-organ disease, and a parainfluenza upper respiratory tract infection. He received continued prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) and acyclovir. Antifungal prophylaxis with voriconazole was discontinued 2 weeks posttransplant secondary to elevated liver enzymes. He had a follow-up visit at NIH in October 2013; he was asymptomatic and had 100% donor chimerism in CD3 and myeloid cells. In January 2014, while in El Salvador, he developed nonbloody diarrhea and was treated empirically by his local physicians with a 2-week course of prednisone with resolution of the diarrhea. When he was seen at NIH in March 2014 for routine follow up, he was asymptomatic and denied fevers, chills, cough, dyspnea, nausea, vomiting, abdominal pain, diarrhea, urinary symptoms, or rash. Aside from the aforementioned resolved diarrheal episode, he did not have other events in the previous months. His only medications were prophylactic TMP-SMX and acyclovir.

His vital signs and physical examination were unremarkable. His only additional medical history was asthma and hypothyroidism. He lived in a small, inland town in El Salvador. He did not travel outside of his hometown and Bethesda, Maryland during the year posttransplantation. He had no pets and denied tobacco, alcohol, or illicit drug use. His laboratory results were as follows: creatinine 0.81 mg/dL, alanine aminotransferase 123 U/L, aspartate aminotransferase 63 U/L, alkaline phosphatase 124

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U/L, total bilirubin 0.3 mg/dL, white blood cell count 5.6 K/ μ L (neutrophils 51.8%, lymphocytes 32.5%, monocytes 8.0%, eosinophils 7.0%), hemoglobin 14.2 g/dL, platelets 292 K/ μ L. His CD4 count was 353 cells/ μ L (22.6% of total lymphocytes), and his total T cells were 680 cells/ μ L. His chimerism showed 100% donor lineages.

A routine chest x-ray revealed a solitary right upper lobe nodule measuring 1.4 cm, which was not seen on prior x-ray performed in October 2013. A computed tomography (CT) scan of the chest revealed a right upper lobe lung lesion, measuring 2.1 cm in its longest dimension, associated with

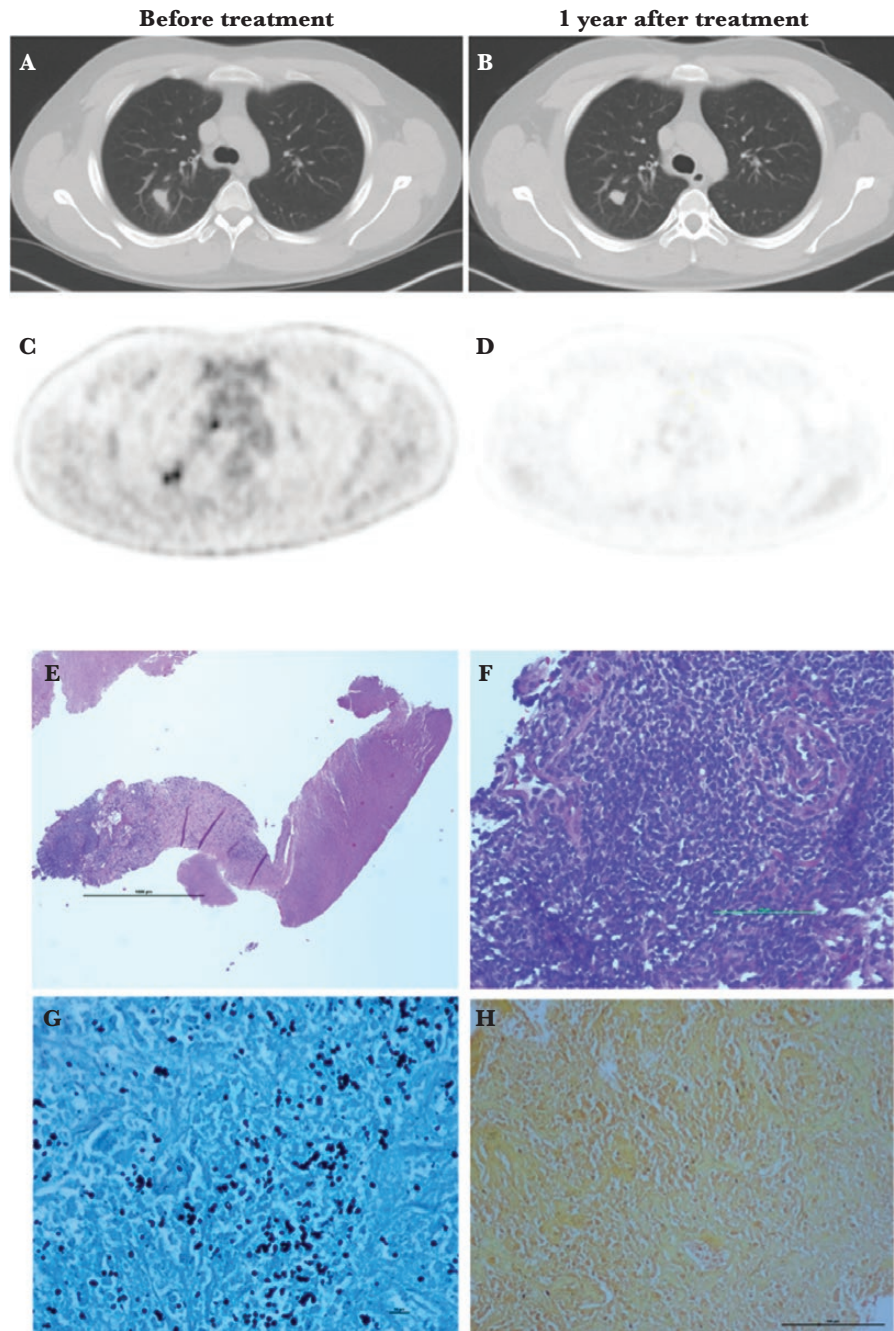


Figure 1. Radiographic and histopathologic presentation of a pulmonary histoplasmosis. (A) A chest computed tomography in March 2014, 1 year post-allogeneic hematopoietic stem cell transplant, revealed a 1.6 \times 1 \times 2.1 cm right upper lobe lung lesion, associated with surrounding ground-glass opacity. (C) A positron-emission tomography (PET) scan showed a hypermetabolic right upper lung nodule with activity of 4.4 maximum (max) standardized uptake value (SUV). Focal hypermetabolism was also noted in the right hilum associated with mildly hypermetabolic mediastinal nodes, including in the subcarina, where the activity measured 3.6 max SUV. (B and D) In April 2015, approximately 1 year after the prior scan, and after completion of a 12-week course of voriconazole treatment, a repeat chest computed tomography showed a decrease in the size of the right upper lobe nodule, which measured 1.4 cm in its longest dimension (B), and was negative by PET examination (D). Hematoxylin and eosin stains of the biopsy of the lung nodule showed areas of necrosis (E) and chronic inflammation (E and F). Grocott's methenamine silver stain revealed numerous yeast cells with narrow budding (G), which were negative by mucicarmine stain (H). Magnification, \times 20 (E); \times 200 (F and H); \times 400 (G). Scale bars, 1000 μ m (E); 100 μ m (F and H); 10 μ m (G).

ground-glass opacity. No other lung nodules, lesions, or pleural effusions were seen. A PET scan revealed a 1.6-cm, right upper lung nodule with hypermetabolic activity of 4.4 maximum (max) standardized uptake value (SUV). There was also focal hypermetabolism in the right hilum, associated with non-enlarged mildly hypermetabolic mediastinal nodes, including in the subcarina, where the activity measured 3.6 max SUV (Figure 1A and C).

The patient underwent a bronchoscopy with bronchoalveolar lavage (BAL) and brushings. The study did not reveal any endobronchial lesions, plaques, ulcers, or abnormal secretions. A Gram stain revealed moderate mononuclear cells but no neutrophils or organisms. Routine bacterial culture grew oropharyngeal flora. Fungal wet mount, modified acid-fast bacilli, and acid-fast bacilli stains were negative. A respiratory viral panel detected coronavirus. *Pneumocystis jirovecii* direct fluorescent antibody and PCR were negative. *Legionella pneumophila* PCR and *Legionella* culture were negative, as well as fungal, mycobacterial, and *Nocardia* cultures. Polymerase chain reactions for Epstein-Barr virus (EBV), CMV, and herpes simplex virus were negative in the BAL, as were PCRs for EBV, CMV, and adenovirus in blood. A BAL galactomannan antigen was negative.

The patient underwent a CT-guided biopsy of the lung nodule. The hematoxylin and eosin stain showed areas of necrosis and chronic inflammation with mononuclear cells; neutrophils or granulomas were not seen (Figure 1E–F). A Grocott-Gomori's methenamine silver stain revealed small, narrow-budding yeast cells (Figure 1G), which stained negative by mucicarmine (Figure 1H). Bacterial and fungal cultures of the nodule were negative. Deoxyribonucleic

acid (DNA) was extracted from the formalin-fixed paraffin-embedded tissue block of the lung biopsy as described previously [6]. The extracted DNA was amplified using pan-fungal primers targeting the internal transcribed spacer region, and the PCR product was sequenced. The sequence results were searched against the National Center for Biotechnology Information database and exhibited 100% identity to *Histoplasma capsulatum* (GenBank accession no. AF322379). A urine and serum *Histoplasma* antigen were negative.

The patient was treated with oral voriconazole at a dose of 200 mg every 12 hours for 12 weeks with trough levels between 1 and 2 µg/mL. He tolerated treatment without complications. A CT scan in El Salvador approximately 4 months after the completion of his treatment course revealed a decrease in the size of the lung nodule to 1.4 cm. He returned to the NIH in April 2015, approximately 1 year after his diagnosis of pulmonary histoplasmosis. He was asymptomatic and his physical examination was unremarkable. His CD4 count was 564 cells/µL (28.8% of total lymphocytes) and his total T cells were 992 cells/µL. He had chimerism of 100% donor lineages. A repeat CT chest scan revealed a decrease in the size of the right upper lobe nodule to 1.4 cm in its longest dimension (Figure 1B). A PET scan showed that the lesion was not hypermetabolic (Figure 1D).

DISCUSSION

Histoplasma capsulatum var. *capsulatum* is a dimorphic fungus found worldwide with areas of highest endemicity in North America and Central America. In endemic areas, the majority of infections are asymptomatic. There is a wide spectrum of clinical

Table 1. Reported Cases of Histoplasmosis in Allogeneic Hematopoietic Stem Cell Transplant Recipients

Age	Clinical Presentation	Organ Involvement	Time Posttransplant	GvHD	Steroid and Other Immunosuppression Within 3 Months of Diagnosis (Daily Dose Where Applicable)	Endemic Area Resident	Treatment	Outcome	Author, Year of Publication
42 yrs	Fever, chills, night sweats, hypotension	Disseminated (bone marrow)	70 days	Skin	Prednisone (140 mg)	Yes (Indiana, chicken farmer)	None (diagnosed post mortem)	Death	Walsh et al, 1983
20 yrs	Fever	Lung	35 days	Skin	Methylprednisolone (80 mg)	Yes (Iowa)	Amphotericin B	Death	Peterson et al, 1987
46 yrs	N/A	Lung	N/A	Yes ^b	N/A	N/A	N/A	N/A	Hot et al, 2011
60 yrs	Fever, confusion, cough	Disseminated (blood culture, brain)	3 months	GI	Prednisone ^a	No, but visited Illinois 5 years prior	Amphotericin B	Death	Haydoura et al, 2014
45 yrs	Fever	Disseminated	18 months	Skin	Alemtuzumab ^a	Yes (Indiana)	Amphotericin B followed by voriconazole	Death	Honarpisheh et al, 2016
21 yrs	Asymptomatic	Lung	1 year	Skin, GI	Prednisone (75 mg)	Yes (El Salvador)	Voriconazole	Resolution	Current report

Abbreviations: GI, gastrointestinal; GvHD, graft-versus-host disease; N/A, not available.

^aDose not available.

^bInformation on affected tissues not reported.

illness, ranging from acute and chronic pulmonary infections to disseminated histoplasmosis. The incidence of histoplasmosis after HSCT is unknown but is believed to be rare. Vail et al [7] retrospectively reviewed 137 patients who received an allogeneic HSCT from 1994 to 1996 in an endemic area and found no cases of histoplasmosis with a mean follow up of 16.1 months. Assi et al [8] retrospectively reviewed 111 cases of systemic histoplasmosis at the Mayo Clinic from 1991 to 2005 and identified only 1 case in an autologous HSCT recipient. Most recently, Kauffman et al [9] prospectively enrolled solid organ transplant (SOT) and HSCT recipients diagnosed with endemic mycoses from March 2001 to September 2005. Of 16 200 HSCT recipients, 3 cases of histoplasmosis were identified (0.02%). In contrast, 23 cases of histoplasmosis were identified from 16 806 SOT recipients (0.14%) over the same time period.

We found 5 cases of histoplasmosis complicating an allogeneic HSCT in the English literature [1–5]. The pertinent case details are summarized in Table 1 along with our patient. Both disseminated and isolated pulmonary infections were reported between 5 weeks and 18 months posttransplantation. All 4 patients with reported outcomes died. A notable common feature of most cases including ours is the recent receipt of corticosteroids for GvHD treatment.

Our patient was diagnosed early on routine imaging and was asymptomatic without fever or respiratory symptoms. A PET scan demonstrated that the pulmonary nodule and an associated hilar lymph node were hypermetabolic indicative of a localized histoplasma with a reactive regional lymph node. Although it is not the usual standard of care, the use of PET imaging has been previously reported to assist in the diagnosis of histoplasmosis and invasive fungal infections in general [5, 10, 11]. Because culture and *Histoplasma* antigen testing were negative in our patient's case, the use of pan-fungal primers to amplify DNA from the organism for sequencing was vital in making the diagnosis.

Per the 2007 Infectious Diseases Society of America management guidelines for histoplasmosis, treatment is not recommended for asymptomatic pulmonary nodules [12]. However, we chose to treat in this case because there was evidence of active inflammation on histology and PET scan, because the patient had an altered immune system after HSCT, and because of the dismal prognosis of histoplasmosis in this patient population (Table 1). Because monitoring of itraconazole levels in the patient's home country was difficult, the choice of voriconazole treatment was made after establishing levels of 1–2 µg/mL before discharge.

CONCLUSIONS

Our review of the literature suggests that histoplasmosis is rare post-allogeneic HSCT. However, because the diagnosis of histoplasmosis is challenging and empiric or preemptive antifungal treatment is often administered post-HSCT, it is likely that the incidence of histoplasmosis is underestimated in the HSCT population. Therefore, the use of PET imaging and molecular diagnostics, as shown in this case, may lead to recognition of additional cases of histoplasmosis and reassessment of its incidence in allogeneic HSCT recipients.

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