Disseminated Histoplasmosis in a Renal Transplant Patient

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Practice Points

- Histoplasmosis is a common endemic fungus, especially along the Ohio and Mississippi River valleys, and usually is asymptomatic or causes a mild flulike illness.
- Disseminated histoplasmosis develops in rare cases, often in immunocompromised patients.
- Typical cutaneous findings of disseminated histoplasmosis include hyperpigmented papules or plaques located on the face or upper body; systemic symptoms are nonspecific and include fever, cough, elevated liver enzymes, and lymphadenopathy.
- Disseminated histoplasmosis is treated with systemic antifungal medications, such as amphotericin B or itraconazole.

Histoplasma capsulatum is a common endemic mycosis. Infection typically goes unnoticed by an individual, but in immunosuppressed patients, it may become disseminated. We report a case of disseminated histoplasmosis occurring 6 weeks after a kidney transplant. We discuss disseminated histoplasmosis and review its characteristic clinical, laboratory, and histologic manifestations, as well as current treatment modalities.

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Disseminated histoplasmosis is a relatively rare infection, often occurring in immunocompromised patients. In an immunocompetent state, the infection often causes mild respiratory symptoms and usually is unnoticed by the patient. Our case involves the dermatologic manifestations of disseminated histoplasmosis occurring 6 weeks after a kidney transplant. It illustrates a typical presentation and the importance of maintaining histoplasmosis in a differential for an immunosuppressed patient with fever of unknown origin, pneumonitis, and/or cutaneous lesions.

Case Report

A 47-year-old man who had previously received a kidney transplant was admitted to the hospital for recurrent fevers and development of facial lesions. The patient reported that the recurrent fevers began 20 days prior to admission. Lesions initially presented on the left side of the upper cutaneous lip and the right nasal ala (Figure 1). According to the patient, additional lesions erupted "overnight" with a "burning" sensation and were localized to the head and neck only. The lesions were primarily hyperpigmented enlarging papules with crusted central surfaces. At admission, his laboratory values were within reference range, including his white blood cell count (5500/μL), aspartate aminotransferase (14 IU/L), and alanine aminotransferase (29 IU/L) levels. Computed tomography of the chest demonstrated a 1.2-cm lower right paratracheal lymph node. His immunosuppressive therapy at admission was 10 mg of prednisone, 3.5 mg of tacrolimus twice daily, and 250 mg of mycophenolate mofetil twice daily.

His medical history was notable for a kidney transplant 2 months prior, which was secondary

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to stage VI chronic kidney disease due to hypertension. His medical history also was remarkable for secondary hyperparathyroidism and obstructive apnea. Surgical history included cholecystectomy and appendectomy.

The patient grew up in the suburbs of Atlanta, Georgia, and denied travel outside of the country or exposure to caves or construction sites. The patient remained in Tampa, Florida, following his transplant and reported no recent travel to the Ohio or Mississippi River valleys.

A skin biopsy with hematoxylin and eosin stain demonstrated a granulomatous reaction involving the superficial and deep dermis (Figure 2). On higher magnification, numerous parasitized organisms were visible with a surrounding clear halolike appearance; they were fairly evenly spaced within the macrophages (Figures 3 and 4). Pulmonary and bone marrow biopsy demonstrated similar findings of a parasitized organism. Gomori methenamine-silver stain highlighted the budding yeasts in the lung, bone marrow, and skin (Figure 5).

Figure 1. Initial lesions of disseminated histoplasmosis were present on the left side of the upper cutaneous lip and the right nasal ala.
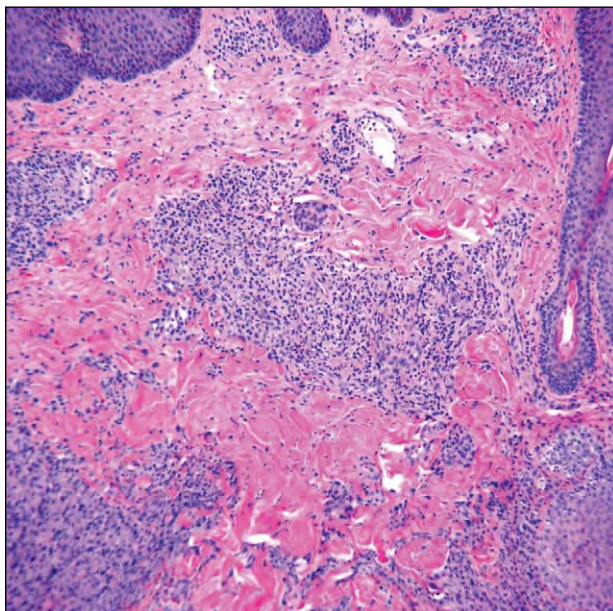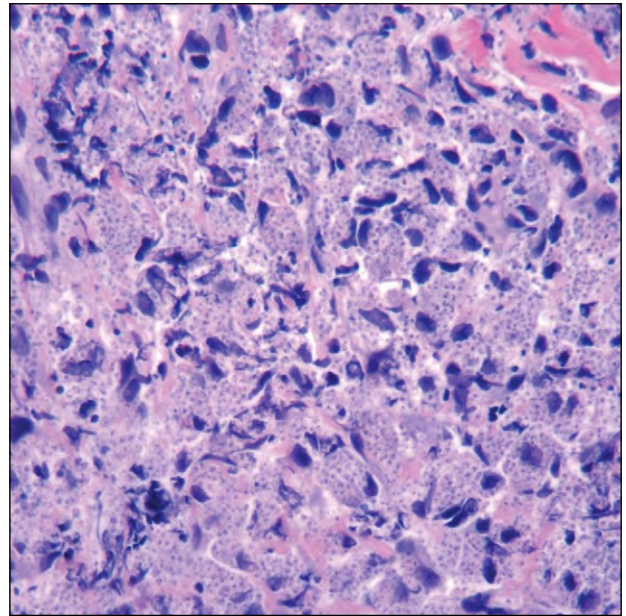

Figure 2. Numerous macrophages clumped in the dermis (H&E, original magnification ×10).

Figure 3. Parasitized *Histoplasma capsulatum* organisms were fairly evenly spaced within macrophages (H&E, original magnification ×20).
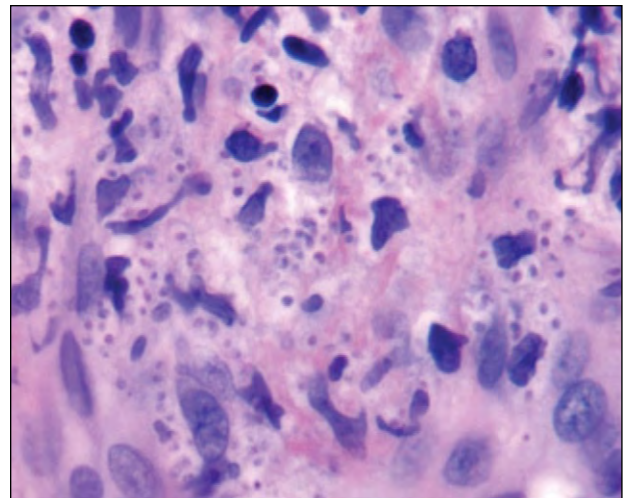

Figure 4. A clear halo or pseudocapsule was visible around the budding yeast in the macrophages (H&E, original magnification ×40).
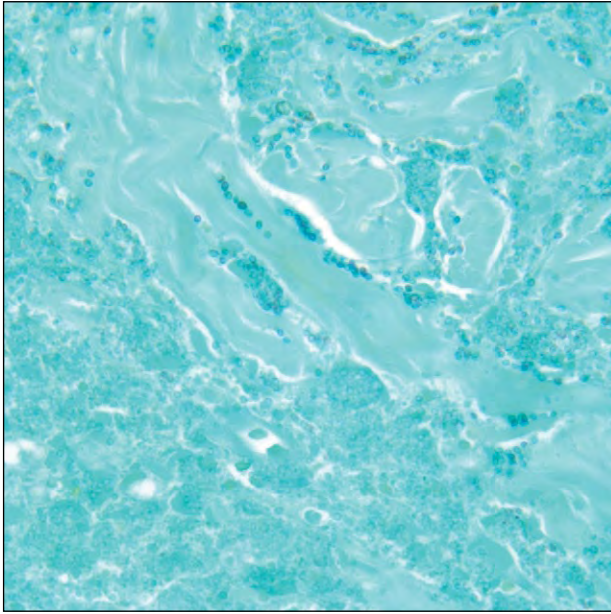
Figure 5. Gomori methenamine-silver stain highlighted the yeast form of *Histoplasma capsulatum* in the dermis and macrophages (original magnification ×60).

On admission, the patient was initially started on voriconazole due to his recent kidney transplant and concern regarding the potential nephrotoxic side effects of other systemic antifungals. After the fever was initially alleviated for several days, it returned periodically and reached 106°C. He was started on amphotericin B in combination with voriconazole. The skin lesions flattened slowly over the first 2 weeks, resolving with postinflammatory hyperpigmentation. After discharge, the patient was maintained on therapy with both agents and followed closely with slow improvement of his condition.

After admission, the patient's prednisone was tapered down to 5 mg daily, while both tacrolimus and mycophenolate mofetil were held. As the patient improved over the next 2 weeks and the month after discharge, both agents were reintroduced and the dosage of prednisone was increased to 20 mg daily. Twelve months following admission, the cutaneous lesions had resolved, leaving hyperpigmentation. The prednisone was reduced to 5 mg daily and the same dosages of both tacrolimus and mycophenolate mofetil were maintained.

Comment

Histoplasma capsulatum is the most common endemic mycosis.[1] It is endemic in states along the Ohio and Mississippi rivers, and more than 80% of young adults in this area demonstrate prior exposure.[2] The fungus is found in contaminated soil from bird or bat guano.[3] The highest concentration of the fungus often is in abandoned buildings and caves. Initial exposure is via inhalation, and spread occurs within macrophages through the reticuloendothelial system.[1] The fungus may remain latent in the body and reactivate years later, possibly in a nonendemic region.[3] In transplant recipients, the donor tissue can transfer *H capsulatum*, with the infection often occurring less than 9 months after surgery.[4] Because the symptoms began within 6 weeks after transplantation and immunosuppression, our patient likely experienced secondary infection from the donor kidney or reactivation of a latent infection. On 6-month follow-up with 2 other organ recipients who had a kidney and liver from the same donor, no symptoms or diagnosis of histoplasmosis were noted, which reinforces the likelihood of reactivation in our patient. Nonetheless, cases of disseminated disease transmitted following a renal transplant are reported in the literature.[4]

Histoplasma capsulatum is a dimorphic fungus that exists as a mold in the environment and a yeast in tissue.[5] If cultured several weeks on Sabouraud dextrose agar (25°C–30°C), the mold phase is visible with tuberculated conidia (macroconidia) and 2- to 4-μm, smooth-walled microconidia. In tissue (37°C), the yeast phase appears as 2- to 4-μm budding yeasts with a clear zone or pseudocapsule and is easily visualized with Gomori methenamine-silver or periodic acid–Schiff stains. A tentative diagnosis is obtained by the characteristic tuberculated conidia on culture or the parasitized organism in tissue but should be verified to confirm the diagnosis. Similarly, leishmaniasis appears as a parasitized organism histologically but possesses a kinetoplast and often is more along the periphery within the macrophages. The clinical presentation of leishmaniasis also is substantially different.[5] In renal transplant patients with disseminated disease, *H capsulatum* usually is identified in the whole blood using colorimetric microtiter plate polymerase chain reaction analysis. Molecular assays such as polymerase chain reaction have proven useful in cases when blood fungal cultures have remained negative.[6] Other diagnostic modalities include urine antigen and computed tomography.[7]

Risk factors for disseminated histoplasmosis include age (<1 year), AIDS, hematologic malignancies, solid organ transplants, congenital T-cell deficiencies, and immunosuppressive agents.[5] In transplant recipients, only 0.35% of patients develop histoplasmosis following surgery.[7] However, constant vigilance is required because solid organ transplant patients commonly present with fever of unknown origin or nonspecific pulmonary symptoms. A

potential at-risk patient population includes patients receiving immunosuppressive agents from various specialties. Dermatologists and rheumatologists need to be aware of the increased risk for disseminated histoplasmosis due to immunosuppressive agents.[7-9]

The newer immunosuppressive agents, such as tumor necrosis factor α (TNF-α) inhibitors, actually have increased the risk for disseminated disease, with the most common presentation being pneumonitis. Prophylactic testing in high-risk patients or patients with a history of histoplasmosis may be appropriate.[1] Infliximab, a chimeric monoclonal antibody against TNF-α, depresses IFN-γ production in lymphocytes intubated with infected alveolar macrophages. In mice, the neutralization of endogenous TNF-α has led to overwhelming infection with histoplasmosis.[10] Of note, the majority of TNF-α inhibitor–related histoplasmosis cases involved patients with concomitant immunosuppressive agents who resided in an endemic area.[9] Currently, screening for *H capsulatum* with skin test reactivity or serology is not recommended due to the low incidence and the questionable predictive value of who will actually develop an active infection.[8]

Clinically, disseminated histoplasmosis presents with fever, cough, weight loss, and dyspnea, though physical examination typically shows hepatosplenomegaly and lymphadenopathy. In immunocompromised patients, the most common clinical sign is fever (54%–66%).[11,12] Elevated liver enzymes (alanine aminotransferase [41%]; aspartate aminotransferase [38%]) and alkaline phosphatase (55%) were the most frequent abnormal laboratory values; an abnormal chest radiograph was found in 70% of immunocompromised individuals.[11] Cutaneous lesions often present as hyperpigmented papules, pustules, or plaques with ulceration, mainly on the face, chest, and upper extremities.[12] Severe infection may result in sepsis, disseminated intravascular coagulation, renal failure, and acute respiratory distress.[5] Our patient presented with recurrent fevers and developed smooth and crusted facial papules after several weeks.

Posttransplant histoplasmosis remains a rare event with only 1 case per 1000 person-years.[13] Ceullar-Rodriguez et al[13] retrospectively studied 3436 patients receiving solid organ transplants between 1997 and 2007. Among these patients, 14 developed disseminated histoplasmosis after transplantation; only 3 were kidney transplant recipients. The study reported a median time from transplant to diagnosis of 17 months.[13] A similar report by Einollahi et al[14] retrospectively studied 2410 patients receiving kidney transplants from 1998 to 2008. A total of 21 patients developed invasive fungal infections; only 1 developed disseminated histoplasmosis.[14] Both studies demonstrate the rarity of disseminated disease following renal transplantation.

Classically, the treatment of disseminated histoplasmosis is amphotericin B or itraconazole.[15] Liposomal amphotericin B is used more often due to the less nephrotoxic effects.[16] Yet the newer triazoles, including voriconazole, ravuconazole, and posaconazole, have shown effectiveness.[17,18] Wheat et al[17] found that voriconazole may not be as effective in histoplasmosis as itraconazole, ravuconazole, or posaconazole, and it may be less effective if the patient previously was exposed to fluconazole.[18] In transplant patients, coordination with the transplant team and possible reduction of immunosuppressive agents often are essential.[15] It is imperative that patients receive appropriate therapy in a timely manner, as antifungal therapy for histoplasmosis has been reported to have a success rate of 95%.[7] Similarly, in patients receiving immunosuppressive agents such as TNF-α inhibitors, the medication should be withheld if possible during treatment with antifungal therapy.[8]

This case demonstrates the classic presentation of disseminated histoplasmosis following a solid organ transplant. Although rare, physicians must be aware of this potential risk in transplant patients to initiate therapy as soon as possible. With the increasing use of immunosuppressive therapies, often with longer half-lives, physicians must consider opportunistic infections such as histoplasmosis. There are no current guidelines outlining prophylactic screening or therapy regimens in high-risk patients outside of those with a prior history of infection. Careful evaluation, education, and monitoring of these patients are recommended. Due to the potentially fatal nature of the disease, physicians should consider screening patients from high-risk areas and those presenting with nonspecific pulmonary symptoms after solid organ transplants.

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