1. Introduction

A 66-year-old Caucasian woman with a past medical history of type II diabetes mellitus and cirrhosis secondary to hemochromatosis presented with symptoms of decompensation including dyspnea, worsening ascites, and lower extremity edema. Several days after admission, she developed a rash on the medial aspect of her right thigh. The patient was a Dallas County resident and had no history of recent travel, gardening, insect bites, unusual food consumption, or known sick contacts.

On admission, she was noted to have mild tachypnea with a respiratory rate of 18. All other vital signs were normal. Physical examination revealed stigmata of cirrhosis including scleral icterus and spider angiomata. She had a distended abdomen, a positive fluid wave, and bilateral lower extremity edema. A skin lesion present on her medial right thigh, measuring approximately 8 cm x 11 cm, had an area of central necrosis with slight purulent drainage surrounded by firm skin without crepitation (Figure 1).

Laboratory findings were consistent with impaired liver function including thrombocytopenia, hypoalbuminemia, and elevated total bilirubin and INR. Peritoneal fluid analysis was consistent with spontaneous bacterial peritonitis, and culture of the fluid grew *Pseudomonas aeruginosa*. Gram-stain of the purulent wound drainage showed many budding yeasts; tissue biopsy revealed numerous fungal elements (Figure 2) and the immunohistochemical stain was diffusely positive for *Histoplasma*. Her urine *Histoplasma* antigen was positive as well.

Per recommendations of the infectious disease physician, her spontaneous bacterial peritonitis was treated with intravenous piperacillin/tazobactam but was later switched to intravenous ceftazidime. For the cellulitis, intravenous vancomycin was added for presumed bacterial infection. Her regimen was changed to daptomycin and meropenem when both her leukocytosis and skin lesion worsened. Approximately 3 weeks after the rash was first noted, the tissue biopsy revealed findings consistent with histoplasmosis. Itraconazole was initiated with the recommendation to switch to amphotericin if therapeutic levels of serum itraconazole were not achieved. All other antibiotics were discontinued, and since adequate serum concentration was attained, treatment with itraconazole was continued.

After a month-long hospital admission, the patient was finally discharged. Unfortunately, over the next few weeks, despite appropriate treatment, the patient’s cellulitis worsened, and further decompensation of her cirrhosis occurred. Because of the persistent-disseminated fungal infection, she was not an appropriate liver transplant candidate. During a return admission for complications related to her cirrhosis, the patient and family eventually elected hospice and comfort measures. She died 4 days after entering hospice care.

2. Discussion

In the environment, *Histoplasma capsulatum* exists as a mold with hyphae, which produce spores that are aerosolized and dispersed. Once inhaled by the susceptible host, the spores transform into budding yeast in warmer climates. The yeast forms are then phagocytized...
by macrophages, which assist in spreading the organism to various parts of the body. Once host cellular immunity to Histoplasma develops, the macrophages become activated to kill the organism. In immunocompetent patients, these defense mechanisms are usually sufficient to control the infection. Patients who develop the progressive, disseminated form of histoplasmosis generally have an underlying condition impairing their ability to defend against these intracellular pathogens. Risk factors for the disseminated disease include extremes of age, diagnosis of AIDS, hematologic malignancy, history of transplantation, treatment with immunosuppressive agents, and congenital T-cell deficiencies [1]. In our case, the patient was immunocompromised by both diabetes mellitus and decompensated cirrhosis due to hemochromatosis.

The clinical presentation of disseminated histoplasmosis can vary widely with a multitude of organ systems affected. As in our patient, skin lesions are reported in 10–15% of disseminated histoplasmosis cases. Characteristic lesions include nodules, papules, plaques, ulcers, vesicles, pustules, abscesses, and generalized dermatitis. Less commonly, exfoliative erythroderma, necrotizing vasculitis, cellulitis, panniculitis, petechiae, purpura, and ecchymoses can be seen [1]. Our patient had characteristic skin lesions with components of less common forms reflected in her tissue pathology report (Figure 3).

Rapid methods of diagnosis of disseminated histoplasmosis include antigen detection and cytology/histopathology. Antigen detection in urine and serum should be performed in all patients suspected of having disseminated histoplasmosis. In our patient, the urine Histoplasma antigen was positive, supporting the diagnosis of disseminated disease. Biopsy of skin lesions, mucous membranes, bone marrow or other

Figure 1. Rash of right medial thigh with area of central necrosis and surrounding erythema.

Figure 2. Histopathology of rash revealing numerous fungal elements in the dermis and subcutis indicative of disseminated histoplasmosis.
tissues can reveal the typical 2–4-micrometer yeast structures of *Histoplasma capsulatum*. Diagnosis by biopsy can be challenging and can lead to diagnostic errors because yeasts can be located extracellularly, and pathologic findings can resemble leukocytoclastic vasculitis. Less rapid methods of detection include culture and serologic tests for antibody to *Histoplasma* [2]. Cultures of purulent drainage from our patient’s rash eventually grew *Histoplasma capsulatum* after incubation for a few weeks.

Treatment is indicated for everyone with a diagnosis of disseminated histoplasmosis. Recommended treatment for mild to moderate disease is a regimen of oral itraconazole. In moderate to severe disease, initial treatment is 1–2 weeks of intravenous liposomal amphotericin B followed by a course of oral itraconazole. To reduce the risk of relapse, the total duration of treatment is at least 1 year. Because *Histoplasma* antigen concentrations in urine and serum fall with effective therapy, patients should be monitored for therapeutic response with serum and/or urine antigen testing at 4 to 6-month intervals [3]. Our patient was scheduled for outpatient infectious diseases follow up to monitor therapeutic response. She was also referred for outpatient wound care. Overall mortality of progressive disseminated histoplasmosis is 85–100% without treatment and reduced to less than 25% with treatment [3].

3. Conclusion

The clinical presentation of disseminated histoplasmosis can be protean and may involve multiple organs. Immunocompromised patients are unable to mount immune response necessary to defend against its intracellular yeast forms. Rapid diagnosis can be made with antigen detection and histopathologic evaluation. If patients with the disseminated disease remain untreated, this condition can continue to progress and may lead to death in immunocompromised patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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