CASE REPORT

A 30-year delayed presentation of disseminated histoplasmosis in a heart transplant recipient: diagnostic challenges in a non-endemic area

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SUMMARY

A 70-year-old man with history of heart transplant performed in 1986, presented with altered mental status. CT scan of brain showed ring-enhancing lesions, raising suspicion for metastatic malignancy. Work-up revealed bilateral adrenal masses, biopsy showed granulomatous changes consistent with histoplasmosis. The possibility of histoplasmosis was less likely as the patient had no prior history of symptomatic disease and had lived in the endemic area 30 years prior to presentation. Brain biopsy confirmed central nervous system involvement. Amphotericin B was initiated for disseminated disease but his hospital course was complicated by renal failure and new liver hypodensities on follow-up imaging. Acute progressive disseminated histoplasmosis can manifest after decades of initial exposure and should always be in differential diagnosis even in non-endemic areas for prompt diagnosis and better clinical outcome.

BACKGROUND

Histoplasma capsulatum is prevalent in the Midwestern states of the USA located in the Ohio and Mississippi river valleys. According to Baddley *et al*, the incidence of histoplasmosis in adults aged 65 years and older was found to be 3.4 cases per 100 000. Rates were highest in the Midwest, with an estimated 6.1 cases per 100 000 population.¹ According to one analysis, mortality ranges from 0.1 to 0.15/100 000 population in the USA.² An estimated 60% to 90% of people who live in endemic areas have been exposed to the fungus at some point during their lifetime.³

Infection is acquired by inhalation of mycelial fragments and microconidia. Most individuals remain asymptomatic but the infection can be lethal in patients with impaired immune system or exposure to a high quantity of inoculum. Clinical presentations vary from asymptomatic to acute pulmonary disease, cavitary pulmonary disease and disseminated disease. Acute progressive disseminated histoplasmosis mostly develops by exposure to a large inoculum but reactivation from an endogenous foci or transplanted organ can occur.⁴ Antigen detection, serology, cultures and histochemical identification are the mainstay of diagnosis for histoplasmosis. Collecting the greater number of specimens can increase the sensitivity of positive culture. Antigen assay in serum and urine by ELISA testing has 80% yield in moderate to

severe disease.⁵ On histopathology, Gomori methenamine silver and Grocott silver are most useful stains for diagnosis. On histochemical evaluation, granulomas, lymphohistiocytic aggregates and diffuse mononuclear cell infiltrates are the frequent findings. According to latest guidelines, liposomal amphotericin B followed by oral itraconazole are recommended therapeutic antifungals.⁶ Isavuconazole, a new triazole, has shown efficacy in treatment of histoplasmosis in a recent phase III trial and might add to the arsenal of therapy against histoplasmosis.⁷

Despite high prevalence in endemic areas, estimated incidence of histoplasmosis is <0.5% in solid organ transplant (SOT) recipients with most reported cases in renal and liver transplant patients.^{8–13} Mortality rate ranges from 0% to 13% in SOT recipients with histoplasmosis.¹⁴ Histoplasmosis in non-endemic areas have been seen infrequently, while exact incidence is unknown.¹⁵ Even in disease endemic areas very few cases of delayed presentation (10–20 years) following renal transplant have been reported in the literature.^{16–18} We report first case of disseminated histoplasmosis in a heart transplant recipient from non-endemic area with delay of 30 years after exposure.

CASE PRESENTATION

A 70-year-old Caucasian man presented with a complaint of altered mental status for 4 days. His medical history was significant for heart transplantation in 1986 secondary to ischaemic cardiomyopathy, and chronic renal insufficiency. The patient was on long-term immunosuppression with cyclosporin, azathioprine and prednisone. His physical examination was unremarkable except for confusion with a mini mental state examination score of 22/30. A CT scan of head without contrast showed heterogeneous ring-enhancing lesions, which raised the suspicion for metastatic malignancy. MRI (figure 1) confirmed the findings found on CT scan. MRI of chest, abdomen and pelvis demonstrated bilateral adrenal masses measuring 18 and 30 mm on the right and left adrenal glands, respectively. Guided adrenal biopsy revealed necrotising granulomas consistent with diagnosis of histoplasmosis. Brain biopsy was deferred due to the close proximity of lesion to the cerebral vasculature. Suspicion for histoplasmosis was very low as the patient had not left Arizona for many years; therefore, a second

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Figure 1 MRI brain without contrast demonstrating 1.9 cm lesion within medial right temporal region.

opinion was requested on biopsy slides along with additional work-up. On further inquiry, he had no history of spelunking, prior exposure to birds or bats droppings but he reported a short visit to North Carolina 30 years ago. Meanwhile, the patient was started on liposomal amphotericin B. After 2 weeks, amphotericin B was discontinued due to worsening renal functions and itraconazole 200mg two times per day was initiated. At that point, he was transferred to our centre from outside hospital for further management. Given his immunosuppressed state, a biopsy of medial right temporal brain lesion was performed to rule out possibility of metastatic malignancy. Biopsy revealed necrotising granulomas with fungal organisms (figure 2). Additionally, second opinion on adrenal biopsy slides and histoplasma growth on fungal culture after 2 weeks, confirmed the

Figure 2 Brain lesion biopsy demonstrating macrophages containing round yeast cells in the cytoplasm on (A) Grocott-Gomori's methenamine silver stain and (B) periodic acid-Schiff stain.

diagnosis of disseminated histoplasmosis. Postoperative course was complicated by cerebrovascular accident, causing left-sided hemiparesis. After confirmation of diagnosis, liposomal amphotericin B was restarted with close monitoring of infusion-related side effects. Doses of immunosuppressive drugs were reduced. Follow-up CT scan of the abdomen and pelvis after 4 weeks revealed two new hypodense lesions in the liver.

INVESTIGATIONS

Laboratory parameters showed mild anaemia with haemoglobin of 11.0 g/dL, total leucocyte count of $4.3 \times 10^9/L$ and creatinine of 2.1 mg/dL. Liver function tests and serum electrolytes were within normal limits. Cerebrospinal fluid analysis (CSF) was within normal range (white cell count $0 \times 10^9/L$, glucose 59 mg/dL, protein 100 mg/dL, Gram stain and cultures were negative). CSF histoplasma antigen, CSF PCR for cytomegalovirus, Epstein-Barr virus, herpes simplex virus as well as histoplasma urine antigen, cryptococcus serum antigen and coccidioides serology were negative.

DIFFERENTIAL DIAGNOSIS

Due to low clinical suspicion of histoplasmosis, the brain and adrenal lesions were initially suspected to be secondary from metastasis. Other possibilities included coccidioidomycosis due to high prevalence in Arizona, other fungal infections, bacterial infections such as tuberculosis and sarcoidosis.

OUTCOME AND FOLLOW-UP

Due to the complicated post-biopsy course with clinical deterioration, family decided not to pursue aggressive treatment and diagnosis and liver hypodensities were not further evaluated. Patient was discharged home with palliative care and itraconazole was continued.

DISCUSSION

H. capsulatum is often under diagnosed in non-endemic areas.^{19 20} The diagnosis of histoplasmosis is often delayed among SOT recipients who may present with atypical presentations.⁹ In our case, histoplasmosis was not part of the initial differential diagnosis because of the unusual presentation and since the patient had not been in the endemic area for over 30 years. In patients with disseminated histoplasmosis, the central nervous system (CNS) is involved in 10%–20% of cases and is associated with a mortality rate of 20%–40%.²¹ Solid organ transplantation, haematopoietic stem cell transplantation (HSCT), HIV/AIDS, use of immunosuppressive drugs and genetic predisposition are associated with an increased risk of disseminated infection.²² Sarosi and Johnson found immunosuppression was the single most common risk factor for the development of progressive disseminated histoplasmosis.²³ In one prospective study, the risk of histoplasmosis increased as CD4+T cells dropped below 300/ μL .²² In a review of 154 SOT patients diagnosed with histoplasmosis, the median time of onset was 27 months.⁸

Our patient presented more than 30 years after his heart transplant. This case is unique in that he had not been diagnosed with histoplasmosis in the past and his presentation occurred 30 years after a short visit to an endemic area. After extensive database research of disseminated histoplasmosis, we found that most reported cases in non-endemic area were preceded by symptomatic infection in the past. Medline and Embase search revealed only one published report of disseminated histoplasmosis involving the CNS in Arizona by Hott *et al* in 2003, in which a 47-year-old immunocompetent woman, presented with

spinal histoplasmosis 2 years after the identification of colonic histoplasmosis.²⁴ In a retrospective review of 20 diagnosed cases of histoplasmosis at Yale New Haven Hospital, Azar *et al* found histoplasmosis may be more prevalent than previously known in non-endemic areas.²⁰ Only 11 out of 20 patients reported travel to an endemic area, constitutional symptoms were present in only 6 patients and other 6 patients were either discharged or died without a diagnosis. Despite involvement of multiple organs, histoplasma urine antigen testing was negative, which could be due to his suppressed immune status.²⁵ In one study, sensitivity of histoplasma urine antigen in disseminated disease was found to be 82%, in immunocompromised patients.⁹ Consequently, these factors can result in a delayed diagnosis leading to poor prognosis.

While charting patient history, emphasis should be placed on the detailed history of travel to the endemic areas. The diagnosis of histoplasmosis must be considered in immunocompromised patients residing in non-endemic areas, especially when they report a history of travel or residence in endemic areas.

Learning points

- ▶ Acute progressive disseminated histoplasmosis can manifest after decades.
- ▶ Histoplasmosis should always be in differentials while evaluating an immunocompromised patient even in the non-endemic area.
- ▶ Patient's geographical and travel history should be thoroughly inquired.
- ▶ Prior asymptomatic infection can lead to progressive disseminated disease in immunocompromised patients.

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