CASE REPORT

Disseminated histoplasmosis presenting as diabetic keto-acidosis in an immunocompetent patient

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SUMMARY

Histoplasma capsulatum causes a spectrum of manifestations from asymptomatic to fatal disseminated disease. Disseminated histoplasmosis is mostly seen in endemic areas among immunocompromised patients such as those with AIDS. Here, we present a patient living in a non-endemic area with previously undiagnosed diabetes mellitus, who presented with septic shock and diabetic ketoacidosis (DKA), and was ultimately diagnosed with disseminated histoplasmosis. The patient rapidly recovered on administration of intravenous liposomal amphotericin followed by oral itraconazole. Uncontrolled diabetes may be a risk factor for disseminated or severe histoplasmosis in otherwise immunocompetent patients.

BACKGROUND

Histoplasmosis is one of the most prevalent endemic mycoses and is found in temperate zones worldwide. Specific endemic areas include the Mississippi, Ohio, and St. Lawrence River valleys, the Caribbean, southern Mexico and certain parts of Central and South America, Africa and Asia. In these regions, the fungus is found in high concentrations in soil contaminated with bird or bat excreta.¹ Transmission occurs via inhalation of *Histoplasma capsulatum* spores from the soil. Pancytopenia, hepatosplenomegaly, hepatic enzyme elevation and oropharyngeal or gastrointestinal lesions are usually seen in chronic infections.

Host immune status and the degree of exposure affect the clinical manifestations of histoplasmosis, which can vary from self-limited infection in immunocompetent patients to disseminated histoplasmosis in patients with compromised cellular immunity. Patients with progressive disseminated histoplasmosis appear to have a failure in activating macrophage fungicidal capacity to *H. Capsulatum*.^{2–4} Patients with severe immunodeficiency such as in AIDS or those receiving immunosuppressive therapies can present with overwhelming infection, shock, respiratory distress, hepatic and renal failure, obtundation and coagulopathy with a mortality rate up to 50% despite intravenous amphotericin B treatment.^{5–7}

Diabetes mellitus is not well described as a risk factor for disseminated histoplasmosis. We describe an immunocompetent patient with uncontrolled diabetes who presented with disseminated histoplasmosis leading to diabetic ketoacidosis (DKA).

CASE PRESENTATION

A 29-year-old man with no medical history was brought to the emergency room after he was found unconscious on the floor. According to family members, the patient was not feeling well for several days. He reported of nausea, fatigue, polyuria and dry lips. He lived in New York City and travelled to Miami 1–2 weeks ago. He had no history of smoking, alcohol or drug abuse. He had a parakeet at home, though he did not usually clean the cage.

In the emergency room, his blood pressure was 95/74 mm Hg, heart rate was 154 bpm, respiratory rate was 38/min, oxygen saturation was 90% on room air and temperature was 98° F.

INVESTIGATIONS

The following were his initial laboratory values: serum sodium 162 mmol/L, potassium 6.8 mmol/L, bicarbonate 8 mmol/L, blood urea nitrogen (BUN) 72 mg/dL, creatinine 5.87 mg/dL, pH 6.9, lactate 7.9 mmol/dL, anion gap >50 mmol/L, alkaline phosphatase 135 U/L, aspartate aminotransferase (AST) 89 U/L, alanine aminotransferase (ALT) 17 U/L, glucose 1645 mg/dL and haemoglobin A1C 14.9%. The lactate dehydrogenase (LDH) level was 2065 U/L, and the ferritin level was 10 732 ng/mL. Chest X-ray was clear. He was admitted to the medical intensive care unit for DKA and was started on intravenous fluids and an insulin drip. However, the patient became febrile to 105°F and lethargic. He was intubated to protect his airway, which was complicated by emesis, prolonged hypoxia and cardiac arrest. Ultimately, he was paralysed and ventilated but continued to have high fevers despite broad-spectrum intravenous antibiotics (vancomycin and meropenem). Blood cultures and urine cultures were negative.

The chest CT after 3 days showed interlobular septal thickening with diffuse patchy opacities suggestive of pulmonary oedema and/or multifocal pneumonia (figure 1).

Given his exposure history and elevated LDH, a urine specimen was tested for *Histoplasma* antigen, which came back positive (Mayo Clinic Laboratories, Rochester, Minnesota, USA). The *Histoplasma capsulatum* yeast antibody and *Histoplasma capsulatum* mycelial antibody by complement fixation test (CFT) were negative with a titre of <1:8 (Quest Diagnostics Nichols Institute, Chantilly, Virginia, USA). HIV serology and cryptococcal antigen were also negative.

He underwent a bronchoscopy and lumbar puncture. The bronchial lavage was negative for acid-fast

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Figure 1 Chest CT showing interlobular septal thickening with diffuse patchy opacities.

bacilli and fungus, and the CSF had only 1 WCC/hpf, glucose was 123 mg/dL and protein was 22.5 mg/dL.

TREATMENT

After the urine histoplasma antigen came back positive, he was started on liposomal amphotericin B, 240 mg intravenous daily.

OUTCOME AND FOLLOW-UP

After only 3 days of liposomal amphotericin B, he was weaned off the ventilator and extubated with complete recovery of his mental status.

Liposomal amphotericin was continued for 2 weeks then transitioned to oral itraconazole. He continues to do well. The histoplasma yeast antibody which was initially negative was found to be positive with a titre of 1:16 on follow-up 4 weeks later.

The patient had no history of travelling to endemic areas and his only exposure was the parakeet, so it was believed to be the source of histoplasmosis.

He had a negative glutamic acid decarboxylase (GAD) antibody, and the newly diagnosed diabetes mellitus was considered type 2.

DISCUSSION

Most patients with disseminated histoplasmosis have underlying conditions that impair the ability to defend against intracellular pathogens. A variety of conditions have been found to predispose to disseminated histoplasmosis, including AIDS, primary immunodeficiency or other immunosuppressive disorders, use of immunosuppressive medications and extremes of age.^{4–8}

There appears to be a separate entity of chronic progressive histoplasmosis among middle-aged to older men who have no known underlying immunosuppression.² In these patients, unidentified defects in cellular immunity likely explain their inability to control the infection.

There have been two reported cases of disseminated histoplasmosis in patients with diabetes who were otherwise immunocompetent. In both cases, there was no strong exposure history or diagnosed immune deficit, similar to our case. The first case involved a HIV-negative patient known to have poorly controlled diabetes; this patient presented with a chronic tongue ulcer and was found to have a reticulonodular pattern on chest CT. He was diagnosed with histoplasmosis based on pathology from a tongue biopsy.

Jariwalla *et al* described a middle-aged man who presented with polyuria, fever, weight loss and a sublingual ulcer. He was

found to have hepatosplenomegaly and elevated blood glucose. Workup revealed a positive *Histoplasma* skin test, and a liver biopsy showed non-caseating granuloma. He was diagnosed with disseminated histoplasmosis and diabetes mellitus. However, unlike our patient, neither of these patients were septic or in DKA.^{9–10} A retrospective study in India showed that diabetes mellitus and HIV infection were the most common comorbid conditions with disseminated histoplasmosis.¹¹

As seen in our case, *Histoplasma* antibody assays may be falsely negative in immunosuppressed patients and antibodies usually appear during the second month after exposure and may thus be negative on initial presentation. Antibodies can remain positive for several years and therefore may not indicate disease activity. The conversion of a negative histoplasma antibody may indicate acute infection.¹²

Learning points

- ▶ Uncontrolled diabetes could be a risk factor for disseminated histoplasmosis.
- ▶ Astute history taking and attention to laboratory abnormalities are important clues to diagnose rare diseases.
- ▶ Liposomal amphotericin B and itraconazole are effective therapies for disseminated histoplasmosis as was illustrated by the rapid and complete recovery in this case.

Contributors PM involved in infectious diseases attending following up on the patient as outpatient and literature review. NN wrote the case report. AK involved in initial infectious attending on the case and editing of the case report. SK contributed to critical care attending on the case, editing and literature review.

Competing interests None declared.

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