Disseminated histoplasmosis in an immunocompetent patient from an endemic area
A case report
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Abstract
Rationale: Disseminated histoplasmosis is a rare fungal infection and most documented cases are in immunocompromised individuals such as those with acquired immunodeficiency syndrome. However, histoplasmosis easily goes unrecognized in immunocompetent populations.

Patient concerns: We report a rare case of histoplasmosis that was manifested as persistent fever and abnormal liver function in a 45-year-old immunocompetent female from Jiangsu Province.

Diagnoses: Investigations revealed anemia and thrombocytopenia. Giemsa-stained bone marrow aspirate showed yeast-like cells, suggestive of *Histoplasma capsulatum*. Wright-stained bone marrow aspirate confirmed the diagnosis.

Interventions: The patient was treated by amphotericin B (amphotericin B liposome) and itraconazole.

Outcomes: Our patient responded well to the treatment.

Lessons: Emphasizing histoplasmosis as a cause of fever of unknown origin in an immunocompetent patient, this case highlights the need for an index of suspicion and the importance of prompt diagnosis, as any delay of treatment can be life threatening.

Abbreviations: CT = computed tomography, HIV = human immunodeficiency virus, IDSA = Infectious Diseases Society of America.

Keywords: amphotericin B liposome, disseminated histoplasmosis, immunocompetent, itraconazole

1. Introduction

Endemic histoplasmosis which caused by dimorphic fungus *Histoplasma capsulatum* is commonly found in these areas such as midwestern United States, central America, and south America.[1–4] Humans may be infected with *H capsulatum* via inhaling microconidia and mycelial fragments of the organism. Patients with AIDS or receiving immunosuppressive agents are easy to infect with *H capsulatum*. Nevertheless, immunocompetent patients are also occasionally infected with *H capsulatum*, which is usually expressed through nonspecific clinical manifestations such as prolonged fever, weight loss, oropharyngeal ulcers, hepatosplenomegaly, and lymphadenopathy. Here we report a case of histoplasmosis exhibited as an intermittent fever in an immunocompetent female.

2. Case report

A previously healthy 45-year-old Chinese female from Jiangsu Province exhibited intermittent fever of 6 months’ duration. From March 1, 2009 to April 5, 2009, the patient showed low-grade fever and malaise without treatment. In mid-April 2009, the patient’s temperature rose to 39.7°C, following chills, general malaise, dizziness, and night sweats. She was evaluated by her native hospital physician and was given a diagnosis of viral syndrome (blood routine test was normal) without special treatment, excluding paracetamol. The fever and malaise persisted, and during the following week, a laboratory examination suggested leukocytosis (white blood count was 12.7 × 10^9/L) with 83% neutrophils, 6.5% lymphocytes, and 9.9% monocytes; C-reactive protein level was 129 mg/L (0–5 mg/L). A thick blood smear and quantified buffy coat test were both negative for malaria. Also, the blood culture was negative for bacteria and fungi infection. Then, moxifloxacin, azithromycin, linezolid, hydroxychloroquine, and levofloxacin were successively administered as empirical therapy. However, after 2 months, new symptoms such as jaundice, hepatalgia, and dark urine appeared, and the fever remained difficult to control. Subsequently, the patient arrived at our hospital for further treatment.

The first day the patient was hospitalized in our hospital, we made a detailed inquiry as to her personal history. We found that the female came from the northeastern part of Jiangsu Province, and she lived near the live bird market. She was a typical...
housewife and denied having a medical history of diabetes mellitus, liver diseases, kidney diseases, rheumatic disease, and tuberculosis. The patient’s vital signs were as follows: 39.6°C temperature, regular heart rate, and regular respiratory rate. The blood pressure was 104/64 mm Hg with an oxygen saturation of 99% in room air. On physical examination, the patient’s head, eyes, ears, nose, and throat were unremarkable except for pale conjunctiva. Warm, firm, and large (1–2 cm) supraclavicular, anterior cervical, and inguinal lymph nodes were noted bilaterally. The abdomen was tender mostly over the left and right upper quadrant. The liver edge was 4 to 5 cm below the right costal margin, and the spleen was enlarged and tender to palpation (below the level of navel).

The patient’s admission laboratory results demonstrated pancytopenia, a white blood cell count of 3.66 × 10^9/L (79.2% neutrophils, 11.2% lymphocytes, and 6.3% monocytes), hemoglobin level of 65 g/L, and platelet count of 58 × 10^9/L. The liver function test was abnormal: total bilirubin 125.2 μmol/L, conjugated bilirubin 89.1 μmol/L, alkaline phosphatase 216 U/L, and albumin 22 g/L (38–48). Aspartate and alanine aminotransferase levels were normal. Prothrombin time and international normalized ratio were prolonged (20.8 seconds and 1.79, respectively). Serologic tests for human immunodeficiency virus (HIV), syphilis, hepatitis A, B, and C, toxoplasma antibody, cryptococcal antigen, and QuantiFERON test for tuberculosis were negative. Three sputum samples stained for acid-fast bacilli were also negative. Three sets of blood cultures were negative for fungal, mycobacterial, and bacterial infection. Nevertheless, a computed tomography (CT) scan of the chest (Fig. 1A, B) showed increased bilateral lung markings, ground-glass opacification of the bilateral lungs, infiltration lesions of the lower lung field, and normal-size mediastinal lymph nodes. To treat bacterial and fungal infections, cefepime and caspofungin (100 mg once daily) were administered to the patient.

Two weeks later, the fever still persisted, ranging from 38°C to 40°C; the pancytopenia had progressed, and upper abdominal CT (Fig. 1C) confirmed hepatosplenomegaly. At last, bone marrow aspiration of the right iliac crest was performed. Wright-stained bone marrow aspirate revealed the presence of numerous intracellular oval and spherical encapsulated organisms, which is highly suggestive of H capsulatum (Fig. 2A). The cefepime and caspofungin treatment was stopped and intravenous itraconazole (200 mg, 2 times per day) treatment began. Then, the fever, neutropenia, and thrombocytopenia gradually resolved; yet, hepatomegaly and splenomegaly remained (itraconazole had been administered for 3 weeks) on upper abdominal CT scan (Fig. 1D). Reexamination of the bone marrow aspiration demonstrated that some intracellular yeast-like microorganisms...
As a yeast in tissues at 35°C to 37.8°C, H capsulatum can exist as a mold in the environment and as a yeast in tissues at 35°C to 37.8°C. H capsulatum var capsulatum and H capsulatum var duboisii are 2 varieties of H capsulatum pathogenic to humans. In China, most patients came from Yangtze River flows regions, especially patients from Yunnan, Jiangsu, Hunan, and Hubei Province approximately account for 50% of the total patients in China.

The female patient came from northeastern part of Jiangsu Province, situated in the subtropics. The humid environment with strong winds and low sunshine levels is suitable for H capsulatum growth. The patient in this case first expressed an intermittent fever, then exhibited nonspecific manifestations such as hepatosplenomegaly, jaundice, pancytopenia, and weight loss, which contributed to the difficulty of this diagnosis. Ultimately, the patient was diagnosed with disseminated histoplasmosis by a bone marrow aspiration smear. Generally speaking, based on the clinical symptoms and signs, fungal culture, histology, immunologic, and molecular methods are useful to diagnose disseminated histoplasmosis, but these methods have different sensitivities and specificities. Isolating H capsulatum from culture is the golden standard for diagnosis of disseminated histoplasmosis. However, we made the diagnosis only based on the bone marrow aspiration smear without isolating H capsulatum.

The reasons for identifying the patient as infected with H capsulatum are as follows: as an inhabitant of Jiangsu Province, which is suitable for H capsulatum growth in China, the patient is easily exposed to H capsulatum; during the disease course, the manifestations were mostly prolonged fever, hepatosplenomegaly, and pancytopenia, which are the common features of disseminated histoplasmosis; bone marrow aspiration smear showed a large amount of intracellular oval and spherical encapsulated organisms, which is highly suggestive of H capsulatum; the fever was not controlled by previous use of antibiotics such as azithromycin, levofloxacin, linezolid, and cefepime. In addition, after administering itraconazole and amphotericin B liposome, the patient’s symptoms and signs resolved rapidly; the patient lived near a live bird market, and highly infectious soil can be found around this area. Disseminated histoplasmosis cannot be transmitted by birds themselves, but soils can be contaminated by their excrements, making H capsulatum easy to grow in these soils.

The potential for a false positive diagnosis based on bone marrow aspiration smear or histopathology alone must be noted. Because Penicillium marneffei morphologically also looks like intracellular microorganism and oval shape, sometimes penicilliosis caused by P marneffei may be easily confused with histoplasmosis. Additionally, antigen and antibody detections in urine and serum can be an important way for the rapid diagnosis of histoplasmosis, but these methods are still unavailable in China. Molecular identification such as real-time polymerase chain reaction assay is a fast and accurate method, but the application is challenging to carry out widely due to its high cost.

Immunocompromised patients usually are ease to have disseminated histoplasmosis; however, the patient from this case was not infected with HIV or received immunosuppressive agents and was still diagnosed with disseminated histoplasmosis. Therefore, we speculated that this immunocompetent woman perhaps inhaled a large quantity of H capsulatum or possibly exposed to a highly virulent strain of H capsulatum. In addition, the patient’s admission chest CT scan was described as patchy pneumonia and bilateral diffuse pulmonary infiltrates (Fig. 1),
although mediastinal lymph nodes were of a normal size, which was similar to the imaging of pulmonary histoplasmosis.

Guideline from Infectious Diseases Society of America (IDSA) played an important role in the treatment of this case. The female was identified with disseminated histoplasmosis, her body temperature ranged from 38°C to 39.6°C, but her blood pressure, respiratory rate, oxygen saturation, and heart rate appeared normal. Therefore, the patient’s condition was considered as mild to moderate at that time, and according to the IDSA guideline, itraconazole was the first choice for her therapy. Then, itraconazole 200mg twice daily was intravenously initiated. However, 3 weeks later, the symptoms and signs still progressed, which indicated that the disease was hardly controlled by administering itraconazole alone. Ultimately, substituting for itraconazole, the liposomal amphotericin B 150mg once daily (recommended dose 3.0mg/kg daily, the female’s weight was 50kg) was intravenously administered. After 2 months treatment with liposomal amphotericin B, the patient recovered and was discharged. Hence, patient’s condition and guidelines should be considered in unison when treating disseminated histoplasmosis.

One study showed caspofungin (dose was 5–10mg/kg/d) to be an effective treatment for histoplasmosis (H capsulatum in mold phase). Another study demonstrated that caspofungin at 5 to 10mg/kg twice daily did not reduce the burden of H capsulatum in yeast phase. Thereby, the phase of H capsulatum might explain the differences observed between the 2 studies. In this case, the patient was treated with caspofungin for a period of time, but the symptoms and signs still progressed. In our opinion, the H capsulatum in this patient remained in yeast phase (the yeast phase had been demonstrated by the bone marrow aspiration smear) and caspofungin was not effective to the yeast phase.

4. Conclusion

Although an indigenous case of disseminated histoplasmosis is challenging to diagnose, it should be considered in patients exhibiting fever and hepatosplenomegaly. Although isolation of H capsulatum from culture is golden standard for diagnosing disseminated histoplasmosis, bone marrow aspiration can also provide diagnostic value when the leukocyte, erythrocyte, and platelet levels simultaneously descend. The patient’s actual condition and guidelines should be simultaneously considered when determining the therapeutic regimen for disseminated histoplasmosis. In this case, we report our experience to increase clinicians’ awareness of disseminated histoplasmosis.

Author contributions

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References

[1] Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev 2007;20:115–32.
[2] Ge L, Zhou C, Song Z, et al. Primary localized histoplasmosis with lesions restricted to the mouth in a Chinese HIV-negative patient. Int J Infect Dis 2010;14(Suppl 3):e325–8.
[3] Cao C, Bulmer G, Li J, et al. Indigenous case of disseminated histoplasmosis from the Penicillium marneffei endemic area of China. Mycopathologia 2010;170:47–50.
[4] Pan B, Chen M, Pan W, et al. Histoplasmosis: a new endemic fungal infection in China? Review and analysis of cases. Mycoses 2013;56:212–21.
[5] Doughan A. Disseminated histoplasmosis: case report and brief review. Travel Med Infect Di 2006;4:332–5.
[6] Cao MV, Hajjeh RA. The epidemiology of histoplasmosis: a review. Semin Respir Infect 2003;16:109–18.
[7] Joseph WL. Current diagnosis of histoplasmosis. Trends Microbiol 2003;11:488–94.
[8] Hage CA, Ribes JA, Wengenack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis 2011;53:448–54.
[9] Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007;45:807–25.
[10] Graybill JR, Najvar LK, Montalbo EM, et al. Treatment of histoplasmosis with MK-991 (L-743,872). Antimicrob Agents Chemother 1998;42:151–3.
[11] Kohler S, Wheat LJ, Connolly P, et al. Comparison of the echinocandin caspofungin with amphotericin B for treatment of histoplasmosis following pulmonary challenge in a murine model. Antimicrob Agents Chemother 2000;44:1850–4.