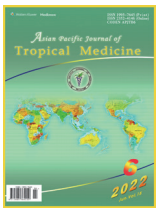

Case Report

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Disseminated histoplasmosis in a 17-year-old Nigerian male patient: A case report

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ABSTRACT

Rationale: Disseminated histoplasmosis is the most severe form of histoplasmosis and often associated with fatal outcomes. Both pulmonary and disseminated forms mimics tuberculosis (TB) and may be misdiagnosed.

Patient concerns: A 17-year-old male patient compliant with anti-tuberculosis therapy with complaints of fever, cough productive of thick yellowish sputum, fast breathing, abdominal pain, swelling and jaundice. HIV status was negative.

Diagnosis: Disseminated histoplasmosis.

Interventions: Antimicrobials including anti-TB therapy, ceftriaxone, gentamicin, azithromycin and ciprofloxacin.

Outcomes: He was responding to anti-TB drugs until about 4 and a half months on treatment when he fell ill. Peripheral blood film done 2 days prior to his demise revealed florid yeast like organisms in monocytes with eccentric chromatin suggestive of *Histoplasma capsulatum*.

Lessons: Histoplasmosis can both mimic and coexist with TB and so a high index of suspicion is needed for its diagnosis.

KEYWORDS: Histoplasmosis; Disseminated; Tuberculosis; Sepsis; Case report

1. Introduction

Histoplasmosis is an invasive fungal infection found worldwide but endemic in the United States of America and Central and South America[1]. Several case reports have also been reported in Africa and Asia, and in immigrants in Europe[1,2]. *Histoplasma* (*H.*) *capsulatum* and *H. duboisii* are the species that are known to cause infections in humans[1,2]. The former causes classical histoplasmosis while the latter causes African histoplasmosis[1,2]. *Histoplasma* infection is primarily acquired by inhalation but perinatal, congenital and gastro-intestinal mode of transmission have also been reported[1]. Histoplasmosis is an acquired immunodeficiency syndrome (AIDS) defining illness commonly seen in the immunocompromised patients but can also occur in the immunocompetent individuals[2,3], even though rare. A review by Ekeng *et al*. identified several factors predisposing to histoplasmosis in the pediatric population including HIV/AIDS, childhood malignancies and their treatment, lung diseases, environmental exposures and toxins, autoimmune diseases, organ transplants, long-term steroid therapy, the use of immunosuppressive drugs such as TNF-alpha inhibitors, malnutrition, histiocytosis, hyperimmunoglobulin M and E syndromes, pancytopaenias, diabetes mellitus and T-cell deficiency besides HIV/AIDS. About 97.1% of the cases were in the non-HIV population[1]. In addition, cases of histoplasmosis misdiagnosed as tuberculosis as well as histoplasmosis and tuberculosis co-infections have also been reported in the pediatric population[1,2,4]. This report highlights the fact that histoplasmosis can either be confused with or co-exist with tuberculosis (TB).

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2. Patient and observation

Informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images.

A 17-year-old male patient admitted into the children's emergency unit of the University of Calabar Teaching Hospital with complaints of abdominal pain and swelling, and jaundice for one month, associated with fever, cough productive of thick yellowish sputum and fast breathing of 6-day duration. He was on his 5th month of anti-TB therapy. HIV status was negative. On examination, he was acute on chronically ill-looking, dyspneic, moderately pale, moderately icteric, febrile (38.6 ℃), with generalized lymphadenopathy (axillary and cervical: 1.5 cm×2.0 cm; inguinal: 1 cm×2 cm), grade 3 finger clubbing with wide spread hypopigmented macular rashes, wasted, pitting pedal edema, with oxygen saturation of 96%-97% in room air. His weight was 44 kg (less than 3rd centile). His respiratory rate was 43 cycles per minute with stony dull percussion notes and reduced air entry in the right middle and lower lung zone. The abdomen was uniformly distended, moved with respiration with tenderness over the right hypochondrial region, hepatomegaly of 8 cm below the right costal margin and ascites. His pulse rate was 128 beats per minute, regular with moderate pulse volume. Blood pressure was 100/70 mm/Hg which was appropriate for his height for age centile. There were normal first and second heart sounds with no added sounds. His central nervous system was essentially normal. The working diagnosis was right lobar pneumonia with pleural effusion with pulmonary tuberculosis. Oxygen was commenced at 2 L/minute with intravenous ceftriaxone, azithromycin and gentamicin. Packed cell volume result was 17% and he was transfused with whole blood prior to transfer to the respiratory and infectious disease unit in the pediatric ward on day 3 of admission. Results of investigations showed leukocytosis of 21.67×10^9/L, absolute neutrophilia with a differential count of 96%, lymphocytes of 2.4%, monocytes 1.4%, eosinophils 0.1%, basophils 0.1%, and platelet count 151×10^9/L with toxic granulations and hypersegmented neutrophils on the peripheral blood film. Abdominal ultrasound scan showed hepatosplenomegaly with ascites and grade 2 renal parenchymal disease. Ascitic fluid Xpert MTB/Rif assay for tuberculosis yielded no *Mycobacterium* (*M.*) *tuberculosis*. Liver function test showed total bilirubin of 93.3 μmol/L (normal range: 2-17 μmol/L), conjugated bilirubin 86.3 μmol/L (normal range: 2-7 μmol/L), AST 4 IU/L (normal range: 5-40 IU/L), ALT 3 IU/L (normal range: 5-40 IU/L), ALP 88 IU/L (normal range: 22-92 IU/L). Urinalysis was positive for nitrites with a specific gravity of 1.020 and PH of 6. Temperature had remained unstable with alternating febrile episodes and hypothermia. Electrolytes, urea and creatinine showed a sodium level of 134 mmol/L (normal range: 135-144 mmol/L), potassium 3.0 mmol/L (normal range: 3.5-5.0 mmol/L), chloride 100 mmol/L (normal range: 98-106 mmol/L), urea 3.2 mmol/L (normal range: 2.6-6.7 mmol/L), bicarbonate 18 mmol/L (normal range: 22-28 mmol/L), creatinine 82.5 μmol/L (normal range: 80-160 μmol/L). An additional diagnosis of urinary tract infection was also considered following the urinalysis result but urine cultures could not be done. Antibiotic was switched to intravenous ciprofloxacin.

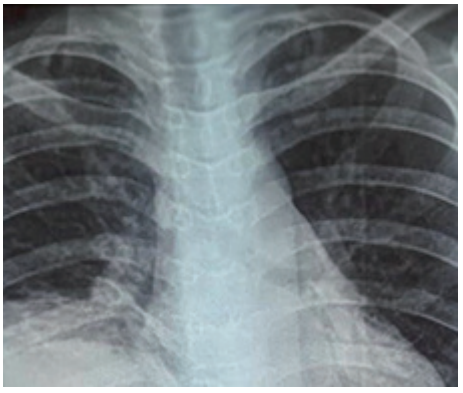

Figure 1. Chest X-ray showing homogenous opacity in the right middle lung zones and obliteration of the costophrenic and cardiophrenic angles in a 17-year-old Nigerian male patient with disseminated histoplasmosis.

He improved after three days of intravenous ciprofloxacin with reduction in temperature instability and regression of pedal edema. Chest X ray done on day 13 showed a homogenous opacity in the right middle lung zones with a meniscus sign and obliteration of the costo-phrenic and cardio-phrenic angles consistent with pleural effusion (Figure 1). Screening for hepatitis B and C viruses, and HIV were negative. Packed cell volume dropped to 18% and he received another unit of whole blood prior to insertion of a chest tube for drainage of the pleural effusion which yielded 750 mL of purulent blood-stained effluent on the first day. *M. tuberculosis* was also not detected in the pleural fluid. Drainage of the chest tube continued until day 20 of admission. Effluent subsequently reduced to 250 mL and 100 mL per day. The haemato-oncology teams of the hospital were invited to review the child due to consistently low hematocrit after a third blood transfusion was given post chest tube insertion. Peripheral blood film was suggestive of septicemia with marked neutrophilia, and lymphopenia and toxic granulations also seen with poikilocytosis and anisocytosis. Clinical microbiologists were also invited who reviewed the child by day 28 of admission and blood samples taken for peripheral blood film. The child continued to show worsening of symptoms with continuous fever over ensuing days up to the 30th day of admission despite the initial improvement on intravenous ciprofloxacin. Caregivers were unable to afford blood culture or further change in antibiotic cover by this time. However, peripheral blood film showed numerous extracellular

and intracellular yeast-like organisms, with eccentric chromatin in monocytes, features diagnostic of *H. capsulatum* (Figure 2) but the child died before anti-fungal medication could be commenced. Also, further confirmatory diagnosis for histoplasmosis wasn't done due to the unavailability of test kits for *Histoplasma* antigen detection. Terminally, he developed severe respiratory distress with saturation at 66%-70%. Intensive care was activated but patient died before this could be instituted. Autopsy was declined by the relatives.

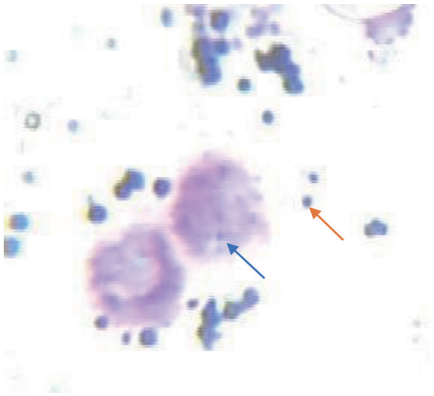

Figure 2. Giemsa-stained smear showing numerous intracellular yeast-like organisms, with eccentric chromatin in monocytes and extracellular forms in a 17-year-old Nigerian male patient with disseminated histoplasmosis. (Blue and orange arrows indicating intracellular and extracellular yeast cells; 100× magnification).

3. Discussion

Disseminated histoplasmosis (DH) results from the hematogenous spread of infection from the lungs. Clinical manifestations include malaise, fever, cough, dyspnea, weight loss, diarrhea, abdominal pain, peripheral edema, angina, headache, seizures, abnormal gait and altered consciousness[4]. Our case presented with similar features including fever, cough, abdominal pain, swelling and fast breathing. Symptoms of DH are non-specific and can mimic many other clinical conditions including malaria, tuberculosis, sepsis, hepatic failure, hematologic disorders and malignancies[2]. In areas highly endemic for TB, it can be misdiagnosed as these diseases[1,2,4]. In our case, even when GeneXpert was negative for *M. tuberculosis*, some clinicians still thought it was a TB treatment failure which caused a delay in diagnosis of histoplasmosis. This has also been documented in other case reports and reviews on histoplasmosis[2,4].

Commonly affected sites in DH include liver, spleen, bone marrow, gastrointestinal tract, heart, adrenal glands, central nervous system, eyes, and skin[2,4]. Our index case had jaundice with hepatomegaly, recurrent anemia with bone marrow suppression not responding to repeated transfusions, ascites with very high protein level, among others.

Chest radiograph in DH may be normal, or it may reveal interstitial, reticulonodular or miliary infiltrates or consolidation[4,5]. The chest radiograph of our case showed homogenous opacity in the right middle lung zones and obliteration of the costophrenic angle, corresponding with stony dull percussion notes in the right middle and lower lung zones and reduced air entry. This showed right lobar consolidation with pleural effusion.

In addition, because DH is presumed to be uncommon in our environment, it is rarely considered or ruled out as a differential diagnosis when patients with close mimics present[2,4]. In most cases, diagnosis is made at the latter stage of the disease and in some at autopsy[4]. This is not unconnected with the poor awareness and the low index of suspicion on the part of the clinicians[4]. Our index patient was bacteriologically diagnosed with XpertMTB/Rif assay as MTB detected and Rif resistant not detected. He was compliant and responded to his anti-TB regimen for about 4 and a half months before the above symptoms occurred and persisted with deterioration in clinical state until his demise. Histoplasma infection was only considered terminally 2 days prior to patients demise after inputs from the clinical microbiologist. Unfortunately, patients' sudden demise didn't allow room for more definitive investigations like Histoplasma antigen assay and lymph node histology. Also, autopsy was not done. However, the diagnosis of Histoplasma infection on peripheral blood film has been reported several times with confirmation using other diagnostic methods including histopathology, culture, antigen detection and serology[6–8]. We presume that our index case had a co-existing *M. tuberculosis* and *H. capsulatum* infection, even though he presented with a bacteriologically positive tuberculosis that was responding to treatment, he also acquired histoplasmosis concurrently or simultaneously during the course of the treatment.

4. Conclusions

The need for awareness creation and increased index of suspicion on the path of clinicians cannot be overemphasized. Histoplasmosis mimics TB and should be considered or ruled out when patients present with symptoms suggestive of TB, especially when they don't respond to anti-TB treatment. Although endemic in the United States of America, histoplasmosis is increasingly being reported in Africa and is no longer a rare clinical condition in this region.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the case report, authorship, and/or publication of this article.

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Authors' contributions

AUE: Conceptualization, data curation, resources, review, and editing, BEE: Conceptualization, data curation, resources, literature review and writing-original draft, review, and editing, GEB, EUA, AOA and LNN: Conceptualization, data curation, resources, review and editing.

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