Uncommon Infection Mimicking Common Disease

Case Report: Disseminated Histoplasmosis Mimicking Tuberculosis in a Non- Endemic Country

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Abstract

Progressive disseminated histoplasmosis is very rare in immunocompetent individuals and is usually associated with high mortality if not treated promptly. There is a wide range of symptoms that often mimic mycobacterium tuberculosis which is a more prevalent infection in Sri Lanka. Hence, misdiagnosis of histoplasmosis is common especially, in non – endemic countries.

We present a case of disseminated histoplasmosis in an immunocompetent 47 – year – old male, who was admitted to the respiratory unit of National Hospital Kandy Sri Lanka, with symptoms of adrenal insufficiency preceded by chronic non-productive cough, low grade fever and constitutional symptoms. The chest radiography revealed bilateral miliary mottling. Initial investigations were negative for Mycobacterium tuberculosis, fungal infections, other atypical infections and sarcoidosis. Histological analysis of an enlarged axillary lymph node revealed granulomatous infection with caseation. Based on this as well as the clinical and radiographic presentation, the patient was commenced on anti-tuberculosis treatment (ATT) with systemic steroids as a trial. However, the clinical response to treatment was not adequate and the patient readmitted with new onset diarrhea and a painful oral ulcer. The histological examination of the oral ulcer confirmed the diagnosis of histoplasmosis. He was subsequently started on oral itraconazole and adrenal replacement therapy following which a dramatic improvement was observed

Key words : Histoplasma capsulatum*, Histoplasmosis, Tuberculosis*

Introduction

Histoplasmosis is a slowly progressing, opportunistic intracellular fungal disease caused by *Histoplama capsulatum.* It is endemic to North and Central America, but exists in many other parts of the world including Europe and Asia. (1) However, it is rarely found in Sri Lanka and only few cases have been reported in the published literature so far. The clinical presentation of histoplasmosis may vary from asymptomatic or self-limiting flu like illness in most cases to progressive disseminated disease. (2) Symptomatic disease is mostly seen among patients with impaired cell mediated immunity such as those with AIDS, transplant recipients or following a large dose of inoculum. (1) However, disseminated histoplasmosis with concomitant involvement of pulmonary, oral and gastrointestinal tract, adrenals and bone marrow in an immunocompetent individual has only rarely been described. Here we report a case of disseminated histoplasmosis in a non- endemic area who presented with multi organ involvement and diagnosed by an oral biopsy.

Case report

A 47 – year – old previously healthy man was referred to respiratory disease treatment unit of National Hospital, Kandy, Sri Lanka with intermittent low-grade fever, non-productive cough, fatigue, malaise, and anorexia for 2 months duration. He also complained of a weight loss of 6kg over the preceding one-month. Since few weeks before the initial presentation, he developed frequent episodes of dizziness, which were mainly posture related and later admitted to a tertiary care hospital following an episode of loss of consciousness. He denied having any other respiratory symptoms such as hemoptysis, pleuritic chest pain or shortness of breath, and the systemic inquiry was negative. Past medical history was unremarkable and he was not on any long-term

medications. He was a non-smoker but had a significant long term occupational exposure to cement. Furthermore, the history did not reveal any foreign travel or social misbehavior.

On examination, he was emaciated (BMI 17 kg/m^2), mildly pale, afebrile and not dyspneic. He had generalized pigmentation which was more pronounced on the buccal mucosa and bilateral palms. There was a right-side axillary lymph node measuring 1.5 cm, firm and non-tender. His pulse rate was 100 bpm, regular and of low volume. Blood pressure was 90/ 50 Hg/mm (erect) with a postural drop of 20Hg/mm in systole. Respiratory system examination revealed diffuse bilateral coarse crepitations in all three zones of the lungs. The rest of the system examinations was normal.

The initial investigations performed at the referring unit revealed hypoglycemia (RBS of 54 mg/dl) which was managed with intravenous dextrose. Simultaneously the patient was resuscitated with intravenous fluids. The chest X ray revealed bilateral diffuse miliary mottling. (Figure 1)

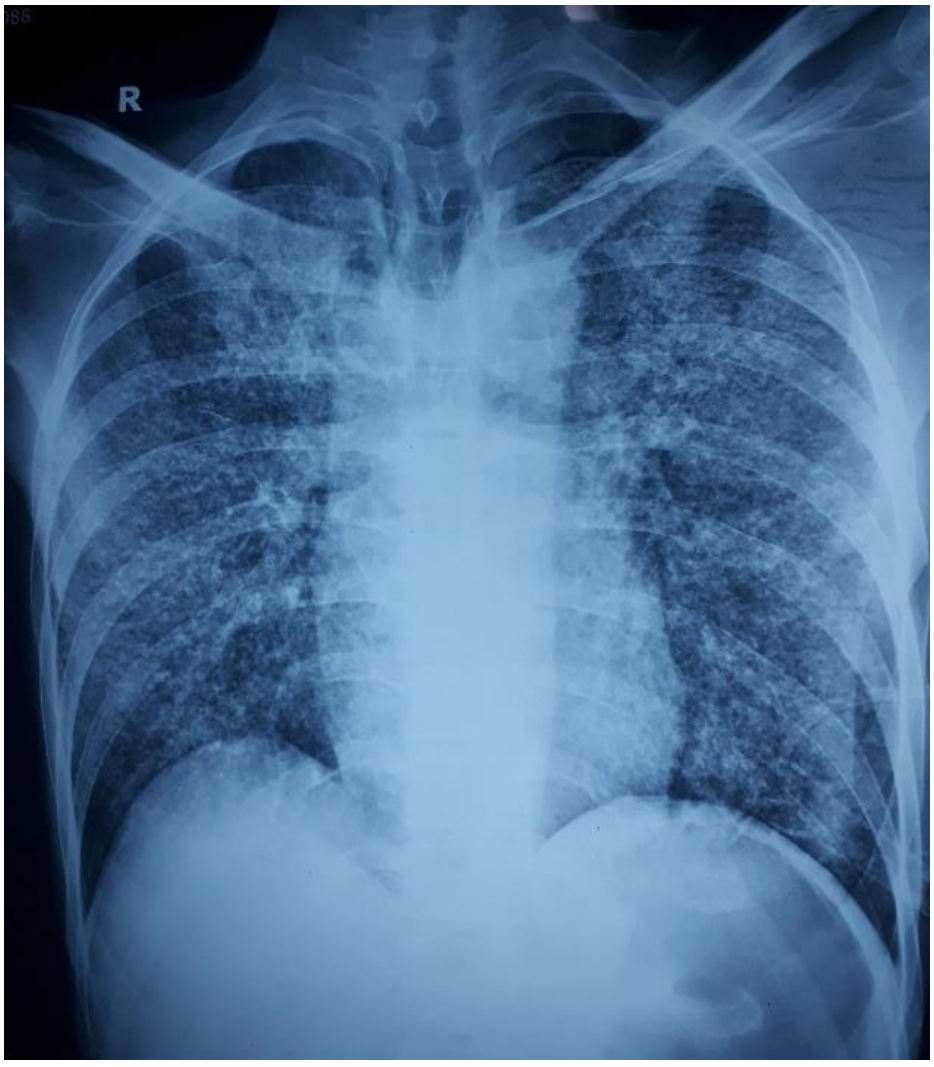

Figure 1 – Chest radiography showing bilateral diffuse miliary mottling

Based on the clinical presentation and chest radiographic appearance, the patient was commenced on anti-tuberculous (ATT) treatment for clinically diagnosed military tuberculosis. However, the patient was referred to our unit after one week of ATT due to poor clinical response.

The patient was re-evaluated and first line investigations were arranged. In the meantime, ATT was continued and he was started on intravenous hydrocortisone 200 mg followed by 50mg 6hourly as adrenal insufficiency was strongly suspected after obtaining venous blood for serum cortisol measurement.

The investigations performed on admission were as follows.

Investigations	**Results**
RBS	74 mg/dl
FBC (WBC, Hb, Platelets)	3.4×10^9/l, 10.4 g/dl, 104×10^6/l
Blood picture	Pancytopenia
Inflammatory markers (ESR, CRP)	30mm 1st hour/ 17.5 mg/l
SE (Na^+, K^+)	134 mmol/l, 5.5 mmol/l
Renal functions	Normal
Serum Albumin/Globulin)	2.9 g/dl, 3.4 g/dl
Liver enzymes	Normal
Serum calcium and phosphate	Normal
Random cortisol	10 mcg/dl

Three sets of early morning Sputum Acid Fast Bacilli (AFB)	Negative
Sputum GeneXpert	Negative
Mantoux	15mm
HIV 1,2 antibody	Repeatedly negative
VDRL	Non-reactive

However, the clinical and radiological improvement was not satisfactory after 2 weeks of ATT. Therefore, further investigations were performed in view of obtaining bacteriologic confirmation of tuberculosis as well as to exclude differential diagnosis.

Ultrasound abdomen did not show any organomegaly, lymphadenopathy or adrenal masses, 2D echocardiography was normal. Serum ACE level was 20nmol/ml/min. Serum total and ionized calcium levels and 24-hour urinary calcium excretion were normal.

CECT chest and abdomen revealed diffusely spread multiple small nodules with intervening fine reticular marking in bilateral lungs (Figure 02) There was no mediastinal lymphadenopathy. There were two hypodense lesions in the bilateral adrenal glands (right adrenal mass was 4.2 cm ×2.5 cm ×1.5 cm and left side was 4.4 cm × 1.5 cm × 1.6 cm) (Figure 03) without hepatosplenomegaly or para-aortic lymphadenopathy. Fiber-optic bronchoscopy and BAL revealed normal bronchial tree with mildly increased non-purulent secretions. BAL for Gram stain and pyogenic culture, fungal stain and culture, AFB smear, GeneXpert and AFB culture were negative. Trans-bronchial lung biopsy (TBLB) was performed however the specimens were unsatisfactory.

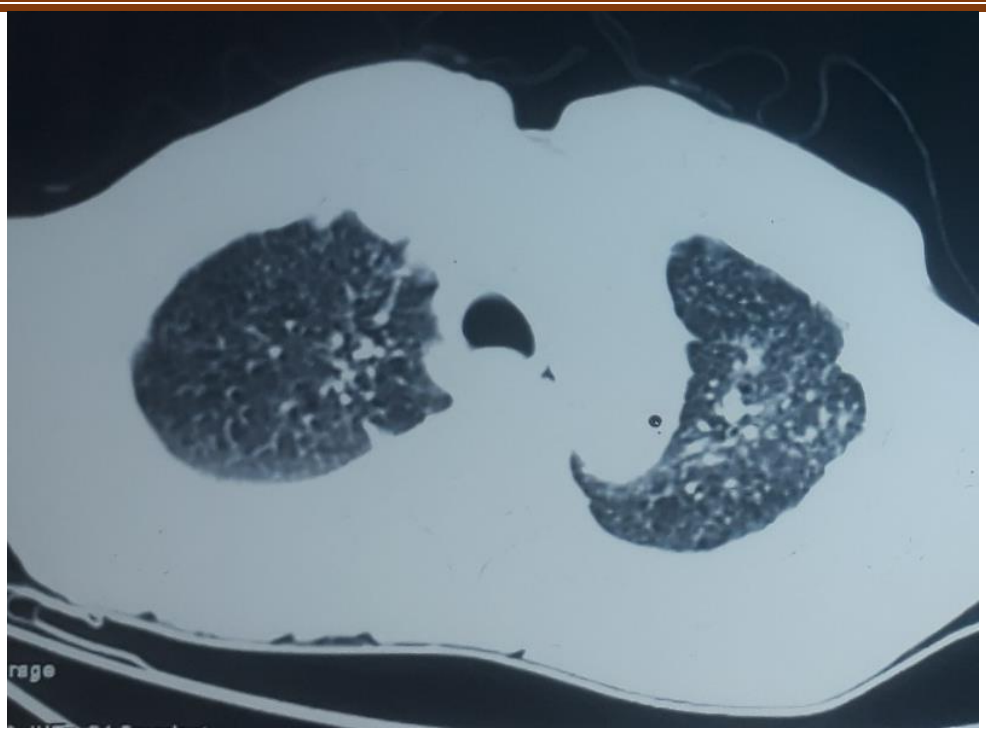

Figure 2 - CECT chest showing diffusely spread multiple small nodules in bilateral lung fields.

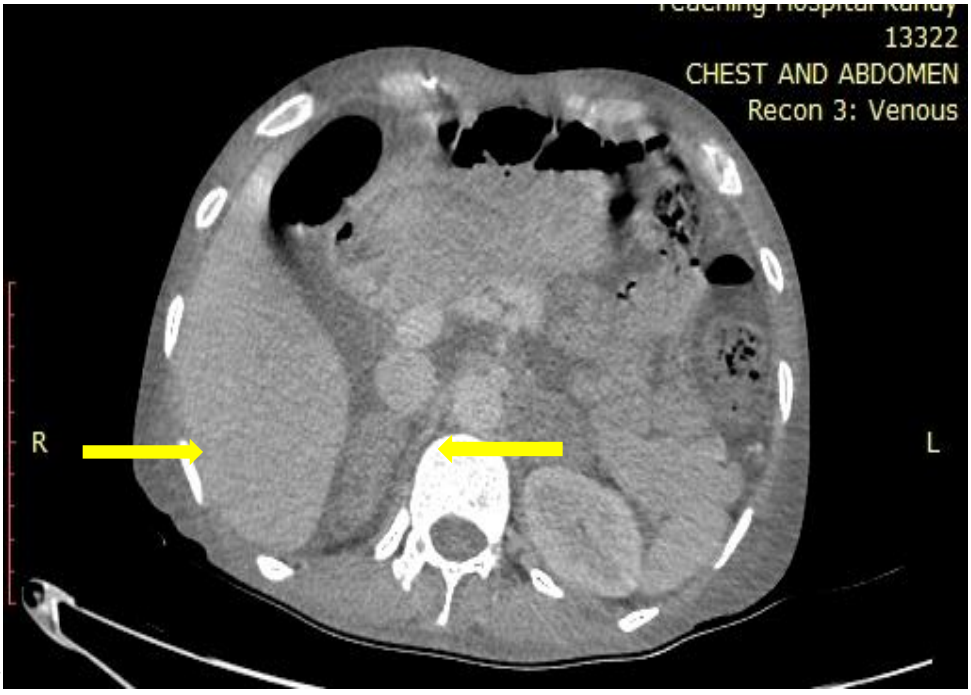

Figure 3 -CECT abdomen showing two hypodense lesions (arrows) in the bilateral adrenal glands (right adrenal mass was 4.2 cm ×2.5 cm ×1.5 cm and left side was 4.4 cm × 1.5 cm × 1.6 cm)

Adrenocorticotrophic hormone (ACTH) stimulation test was performed after converting hydrocortisone to oral dexamethasone and confirmed the diagnosis of Addison disease.

Bone marrow biopsy revealed reactive marrow with pancytopenia. AFB smear, AFB culture and fungal studies were negative. Histopathological analysis of right axillary lymph node was consistent with caseating

granulomatous necrosis. Based on the available investigations and in the absence of another definitive diagnosis the patient was discharged with ATT and oral steroids with a plan of review in two weeks.

Nevertheless, the patient readmitted after 10 days with persistent cough, constitutional symptoms, and adrenal insufficiency. In addition, he had developed a new onset painful oral ulcer on his right cheek and few episodes of watery diarrhea. Stool for calprotectin and lactoferrin were normal. Upper gastrointestinal endoscopy showed inflamed gastric mucosa and biopsy revealed infiltration of inflammatory cells, predominantly lymphocytes in the mucosa and lamina propria, without any evidence of granuloma formation. Colonoscopy revealed inflamed large bowel mucosa and biopsy was consistent with nonspecific colitis. Histopathological assessment of oral ulcer revealed diffuse infiltration of macrophages with small gray color spherical organisms containing clear cytoplasm suggestive of histoplasmosis. (Figure 4)

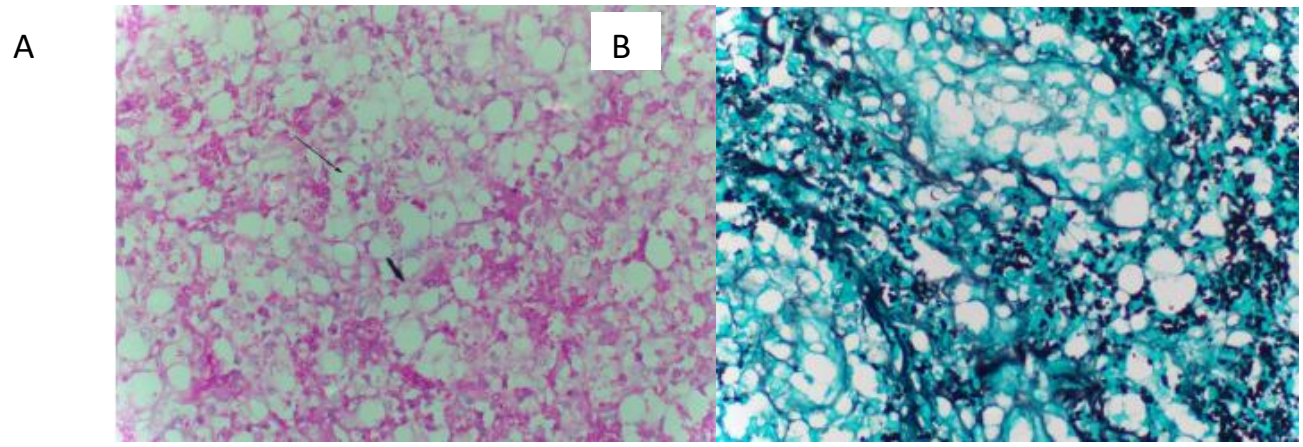

Figure 4 – Histopathological aspects of Histoplasmosis (A) diffuse infiltrate of epithelioid macrophages containing Histoplasmosis capsulatum (arrow) (B) GMS stain which confirms the presence of fungal spores consistent with Histoplasma capsulatum

A final diagnosis of disseminated histoplasmosis with pulmonary, adrenal, oral and gastrointestinal tract, and possible bone marrow involvement was made. Due to the unavailability Amphotericin B, which is the drug of choice in disseminated histoplasmosis, the patient was started on oral Itraconazole 200mg daily together with mineralocorticoid therapy (oral fludrocortisone 100mcg per day) and steroids (oral hydrocortisone 10mg at 6 am, 5mg at noon and 5 mg at 6pm). ATT was discontinued. The overall management of the patient involved input from multiple disciplines including endocrinology team, Oro-maxillary facial (OMF) surgical team, nutritionist, radiology team and the microbiology team. Two weeks after definitive treatment patient had remarkable response with healing of the oral ulcer, resolution of diarrhea and weight gain. Blood sugar levels, electrolytes and pancytopenia also improved gradually. Currently he is being followed up at respiratory clinic with a plan to continuing itraconazole for 1year and adrenal replacement therapy. A repeat CECT chest and abdomen is to be performed in 6 months to assess radiological improvement.

Discussion

Histoplasma capsulatum is a dimorphic fungus which exists as a mold in the environment and as a yeast in the tissues. It is a soil-based fungus which is especially found in river banks, birds and bats droppings. When these molds enter through inhalation, they grow as a yeast within alveolar macrophages and disseminate via reticular endothelium system throughout the body. (3)

Most of the primary infections are either asymptomatic or self-limiting (1). However, approximately 10% of patients may develop progressive disseminated disease (4,5). Acute disease is more common in immunocompromised individuals whereas progressive disseminated disease present as a chronic form in immunocompetent patients who present with fever, malaise, cough, weight loss and anorexia (5, 6) which

mimics tuberculosis and mislead the diagnosis of histoplasmosis especially as in Sri Lanka tuberculosis is endemic. Out of the many organs which can be affected in disseminated histoplasmosis, esophagus, colon, liver, spleen, adrenals and bone marrow are the most commonly affected (7). Oral ulcers also occur in 30% to 50% of disseminated form and can affect any area of the oral cavity including tongue, palate, oral mucosa, gingiva and pharynx (8, 9). Biopsy from the lesion is mandatory to rule out the possible differential diagnoses which include squamous cell carcinoma, tuberculosis, deep fungal infections and Crohn's disease. The adrenal insufficiency is commonly encountered in disseminated disease. However bilateral adrenal gland involvement is seen in many other disease conditions as well, such as tuberculosis, disseminated malignancies, other fungal infections like cryptococcosis and granulomatous conditions like sarcoidosis. (1,6,10,). The adrenal biopsy was another invasive investigation which could be used to confirm the diagnosis, nevertheless it was not required as the diagnosis was confirmed with oral biopsy.

The mild disease is usually self-limiting and do not require treatment (1, 10) whereas disseminated disease with multiorgan involvement warrants long term antifungal treatment (1). Intravenous Amphotericin B at a dosage of 0.7 – 1mg/Kg daily or liposomal Amphotericin B at a dosage of 3 – 5mg/Kg daily is recommended in severe disseminated infection (1). Generally, within few weeks almost all patients will show a good response and the therapy is switched to oral Itraconazole at a dosage of 200mg twice daily which is a less toxic antifungal medication (1,11). The duration of treatment depends on the severity of the infection and immunity status of the host. Generally, patients with chronic progressive disease respond slowly and often treatment may have to continue for a total of 18 to 24 months (1).

Since Intravenous Amphotericin is not freely available in our practice, we started oral itraconazole 200mg twice daily and planned to continue treatment for 18 months. Furthermore, antituberculosis treatment was discontinued.

Conclusion

In countries with tuberculosis endemicity, patients are often started on anti-tuberculous treatment when the clinical presentation is suggestive. This is important as delayed treatment of tuberculosis may result in detrimental effects. However, it is equally important to review the diagnosis when patients do not show satisfactory improvement for ATT and to exclude TB mimics such as histoplasmosis.

Contribution:

DM, SAL, IMN and BML, contributed to the manuscript preparation. DM supervised the all the aspects and was the supervising care physician. PW was involved in management.

Ethical statement:

Informed written consent was obtained from the patient for the publication of the case report and all the accompanying images.

Conflicts of interest:

All the authors have declared that they have no conflicts of interest.

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