Histoplasmosis in an apparently Immunocompetent Host – A perplexing Presentation as Submandibular Oedema

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ABSTRACT

Histoplasmosis is an endemic fungal infection with worldwide distribution and is caused by a dimorphic environmental fungus. This disease has a wide and varied spectrum of manifestations and severity. The non-invasive and rapid diagnostic assay with urine histoplasma antigen has revolutionised the field of diagnosis and treatment monitoring, despite its limitations of cross reactivity. The risk of dissemination is found commonly in those with deficient cell mediated immunity and elderly individuals. Here, we report an interesting case of pulmonary histoplasmosis. This case report is unique in literature, not only by its occurrence in an immunocompetent individual, but also by its puzzling rarity of presentation in the form of gross submandibular oedema and dysphagia.

KEY WORDS: **Histoplasmosis**
Urine histoplasma antigen
Immunocompetent host

Introduction

Histoplasmosis is the most common endemic mycosis in North America, Central America, and many countries of South America. It is also found in China, India, Southeast Asia, Africa, Australia, and Europe [1,2]. Nitrogen rich soil with large amounts of bird or bat guano supports profuse growth of the mold. The spectrum of disease manifestations are wide, ranging from acute to chronic, pulmonary to disseminated and a disease with spontaneous remission without treatment to that which requires prolonged antifungal treatment with still a high mortality risk [3]. No human to human transmission has been reported yet, till date [4].

Case Report

A 48-year-old lady, hailing from West Bengal, non-diabetic, a known hypertensive since 6 months on medication, with no other known co-morbidities and apparently normal 2 months ago, presented with complaints of facial puffiness and progressive breathlessness on exertion for 1 month, associated with a huge diffuse submandibular swelling. She had dysphagia more for liquids, intermittent retrosternal chest pain and nasal regurgitation of fluids for the past 20 days. Since 2 months ago, she had a sense of generalised weakness, loss of appetite, and a low grade intermittent fever with no weight loss.

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She was on regular ATT, started empirically in her hometown, 6 weeks ago. She was febrile and hypoxic on admission. On examination she was pale, had pedal oedema and a tense and tender submandibular oedema with erythematous facial puffiness. There was no focal neurological deficit. On auscultation, she had bilateral basal fine crepitations. Baseline blood investigations showed leucocytosis (14,600 cells /cu.mm.), anaemia (Hb: 8.9 g/dl) and an elevated ESR. LFT showed reduced Albumin levels at 2.4 gm, and A:G reversal. HbA1c was 6.8%. Urine routine showed trace proteinuria and her renal and hepatic functions were normal. Immunofixation electrophoresis showed polyclonal gammopathy. She was started on IV Albumin infusion. HBsAg, Anti HCV, and HIV were negative. USG W/A showed a bilateral trace pleural effusion and a grade 1 fatty liver with normal spleen. Chest X-ray showed bilateral lower zone opacities. CT chest showed patchy ground glass opacities and areas of dense consolidations in both lungs involving all lobes, more in both lower lobes. It also showed few sub centimetric mediastinal (subcarinal) nodes, some with calcification. Echocardiogram was

normal. She was started on empirical antibiotics. Blood cultures showed growth of probable commensals. The urine protein loss was not high enough to account for the hypoalbuminemia.

Figure 1. Bilateral lower zone opacities in chest X-ray.

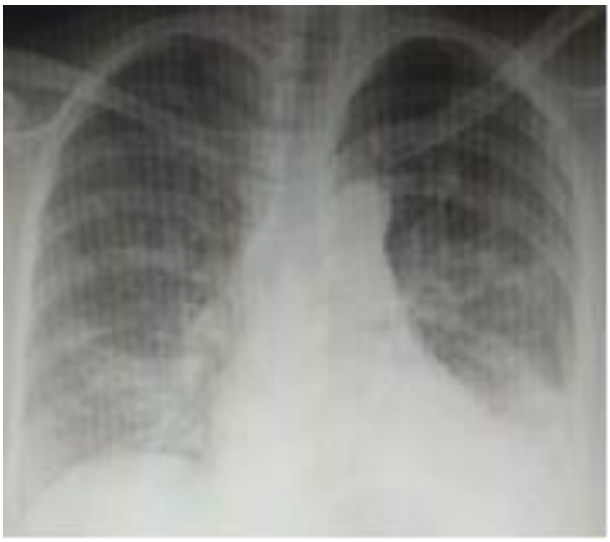

Figure 2. Patchy ground glass opacities and areas of dense consolidations predominantly in lower lobes, CT chest plain.

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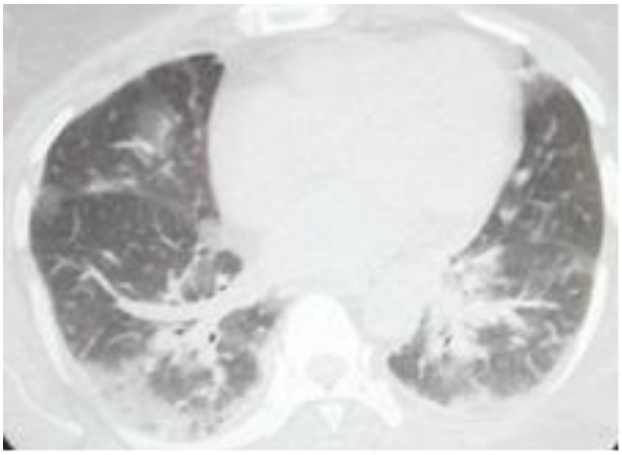

She had increasing dysphagia during the course of the hospital stay, and an ENT opinion was obtained in view of the persisting submandibular tense oedema. The possibility of Ludwig's angina was considered and was ruled out. USG Neck showed the presence of multiple sub centimetric lymph nodes. She had gross eye lids oedema, and mild blurring of vision. There was no papilledema in both eyes and extra ocular movements were full. Upper Gastro Intestinal (GI) endoscopy was normal. EUS (Endoscopic ultrasound) guided FNAC of subcarinal node was considered along with upper GI endoscopy but was not technically feasible as she was not fit enough to undergo the procedure. ANA was positive with high titres and with a speckled pattern. SLE, Wilson's disease, autoimmune hepatitis and other connective tissue disorders were ruled out by appropriate blood investigations. Fibroscan ruled out liver cirrhosis.

Sputum analysis showed No AFB, and Xpert MTB was negative with gram positive yeast with pseudohyphae. Sputum cultures grew several bacteria, which were also probable colonisers. Urine Histoplasma Antigen was sent on day 5 of admission, which was positive. ATT was stopped and she was started on conventional Amphotericin B which was switched over to Liposomal Amphotericin B in view of rising creatinine, and RFT was then normalised. Serum Cortisol and ACTH were within normal limits. Her facial oedema and erythema started resolving, and her dysphagia improved subsequently, and she showed definite clinical improvement for few days, subsequent to the initiation of antifungals. But after 4 days of apparent clinical improvement, she started deteriorating again, became tachycardic, tachypnoeic and had persistent fever spikes. Her total count increased further to 45,000 cells per cubic mm. Antibiotic was continued in view of a possible super-added bacterial pneumonia. Echocardiogram was repeated which showed no new changes. A repeat chest X-ray showed worsening of the pre-existent opacities. Repeated Sputum AFB Stains were done, which again were negative. She was not fit for a bronchoscopy. Amphotericin was continued and she was not initiated on any form of steroids. She developed features of coagulopathy, worsening respiratory failure and appeared drowsier with persisting dysphagia to liquids and nasal regurgitation. MRI brain with contrast was suggested during this time to rule out a dissemination of histoplasmosis to CNS, manifesting as dysphagia, but the same could not be done due to financial constraints. She has had 11 days of Liposomal Amphotericin B until now. In view of the partial response to Amphotericin, oral Itraconazole was started. Next day, she became unresponsive, was intubated in the ward, and was immediately shifted to ICU. Her GCS was 7T and she was on inotropic supports. She had persisting fever spikes. Hb fell to 6.9g, and total counts remained elevated. She progressively became auric, and was planned for CRRT in view of the acute renal shut down. Broad spectrum antibiotics was continued along with antifungals and other supportive measures. In view of financial constraints and request of the family members, she was discharged against medical advice in a state of septic shock with

MODS due to active histoplasmosis. She was taken to another hospital where she died after a few days.

Discussion

The accurate diagnosis of histoplasmosis requires a multifaceted approach. The Council of State and Territorial Epidemiologists (CSTE) has developed a consensus case definition for histoplasmosis. Confirmed and Probable cases are defined separately. A confirmed case is a clinically compatible case, that meets confirmatory laboratory criteria. A probable case is defined as: a clinically-compatible case that meets non-confirmatory laboratory criteria or a case that meets confirmatory laboratory criteria, but without available clinical information or a clinically-compatible case that does not meet laboratory criteria, but is epidemiologically linked to a confirmed case [4]. Isolation of the organism in culture from clinical specimens remains the gold standard for the diagnosis of histoplasmosis. Although not necessarily active infection, histopathological evidence of yeast cells consistent with Histoplasma capsulatum in tissue, supports the diagnosis of histoplasmosis [3]. Rapid diagnosis is of huge importance in patients with severe manifestations of acute pulmonary histoplasmosis, as early specific treatment could shorten the clinical course and disease severity [5]. A novel, highly sensitive and non-invasive diagnostic testing in the form of Histoplasma antigen assay was developed in the year 1986. This revolutionised the field by allowing physicians to make rapid and fairly accurate diagnosis [3]. Cross-reactivity of the Histoplasma urine antigen with some dimorphic and other fungal agents has been described in the past and remains a prominent limitation of this assay [6]. Cross-reactivity was more noted among patients with blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and aspergillosis, but was also found in patients with candidiasis and cryptococcosis [7]. In the latest third generation quantitative histoplasma antigen assay the sensitivity was 100% for antigenuria and 92.3% for antigenemia in AIDS patients with disseminated histoplasmosis and specificity was 99%. Cross-reactions occurred in 70% of other endemic mycoses, but not with aspergillosis [8].

Conclusion

Of late, we find various opportunistic microbes, affecting the apparently immunocompetent individuals in various published case reports and Histoplasmosis is one among these [9-11]. Above patient satisfied the clinical criteria (symptoms with radiological evidence) and non-confirmatory laboratory criterion and hence was a probable case of histoplasmosis. She was apparently immunocompetent, with no overt immunocompromised status. Her initial presentation was with huge and tense submandibular oedema along with facial puffiness and pedal oedema, with gross hypoalbuminemia probably reflecting the long-standing systemic disease process. The strong suspicion for histoplasmosis in view of the ongoing clinical picture rendered an accurate diagnosis and rapid initiation of specific management. But the active disease process which culminated in septic shock with multi-organ failure and the rapid deterioration despite accurate management, finally led to a poor outcome. This emphasises the need for early clinical suspicion and diagnosis of histoplasmosis. This is essential, in view of the possible rapid deterioration and poor outcome with delayed treatment initiation.

Conflict of Interest

We declare that we have no conflict of interest.

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