

# Non-resolving pneumonia: A rare presentation of progressive disseminated histoplasmosis

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## ABSTRACT

Histoplasmosis, a fungal disease caused by *Histoplasma capsulatum*, is endemic in North and South America. Except few scattered cases, the disease is considered to be a non-entity in India. Furthermore, disseminated histoplasmosis is rare in the immunocompetent individuals. We report an adolescent boy presenting as middle lobe consolidation which did not respond to antibiotics. His condition deteriorated with the development of mediastinal lymphadenopathy, pleural effusion and hepatosplenomegaly. A diagnosis of progressive disseminated histoplasmosis was established by his clinical findings as well as bronchoscopic biopsy, transbronchial needle aspiration cytology and bronchoalveolar lavage culture demonstrating *Histoplasma capsulatum*. The case represents a unique example of progressive disseminated histoplasmosis in an immunocompetent individual in India.

**KEY WORDS:** Disseminated, histoplasmosis, non-resolving pneumonia

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## INTRODUCTION

Clinical improvement in the community acquired pneumonia (CAP) should occur within 3 to 5 days.<sup>[1]</sup> Non-resolving pneumonia is defined as pneumonia with a slow resolution of radiologic infiltrates or clinical symptoms despite adequate antibiotic therapy.<sup>[2]</sup> Exclusion of an alternate diagnosis like tuberculosis, malignancies, pneumonia mimics etc., should be the first step in the approach to this problem. Next step will be to judge the adequacy of treatment and patients' compliance. Then we should exclude the associated factors causing the systemic or local immunodeficiency [intra-bronchial obstruction, smoking, diabetes, chronic obstructive pulmonary disease, malignancy, concomitant human immunodeficiency virus (HIV) infection, alcoholism or addictions, immunosuppressant therapy] and complications responsible for the delayed resolution

(empyema, necrotizing pneumonia, metastatic spread of infection and bacterial super-infection). However, we may rarely encounter some unexpected cause of a non-resolving pneumonia.

Histoplasmosis is a fungal disease caused by *Histoplasma capsulatum*, named after Darling who first described this clinical entity well in details. The endemic area includes the Ohio and Mississippi River valleys, Central and South America, and microfoci in the Eastern United States, southern Europe, Africa, and Southeast Asia.<sup>[3]</sup> Scattered cases of cutaneous, laryngeal and disseminated histoplasmosis in immunosuppressed persons have been reported from India.<sup>[4]</sup>

We herewith report, from eastern part of India, a geographically rare and unexpected case of progressive disseminated histoplasmosis (PDH) in a 17-year-old immunocompetent male patient that presented as non-resolving pneumonia.

## CASE REPORT

A 17-year-old male patient, student and nonsmoker, consulted a local physician at Murshidabad, West Bengal with high grade intermittent fever with chills but no rigors, cough with scanty mucoid expectoration, dull aching

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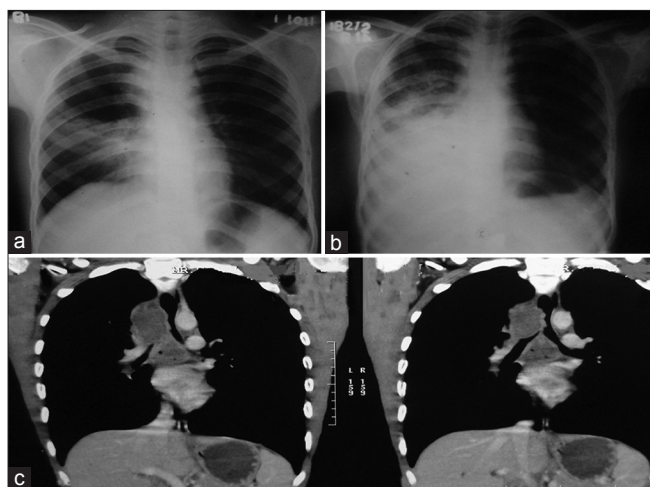
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chest pain, and generalized weakness for 5 days. The patient's chest X-ray postero-anterior (PA) view at that time showed middle lobe consolidation [Figure 1a]. The patient was treated as CAP with oral amoxicillin + clavulanic acid (625 mg) 8 hourly and levofloxacin (500 mg) daily was added afterwards. As the patient's condition deteriorated with documented weight loss of 5 Kg in 2 weeks, his father brought him to our hospital. On examination, the patient was very toxic with blood pressure 90/60 mmHg, pulse rate 130/min regular, respiratory rate 32/min with moderate pallor. Examination of the respiratory system revealed crepitations in the right mammary area. Examinations of other systems were normal. We treated the case as non-resolving pneumonia and did antibiotics adjustment with the intravenous cefoperazone-sulbactam (1.5 g) 8 hourly and oral clarithromycin (500 mg) twice daily along with the other supporting treatment. The investigations revealed hemoglobin 6.4 g%, total white cell count 15200/mm<sup>3</sup> with 94% neutrophils; fasting blood sugar 86 mg/dl, urea 45 mg/dl, creatinine 0.8 mg/dl, total bilirubin 0.96 mg/dl, alanine transaminase 78 U/L, aspartate transaminase 82 U/L and alkaline phosphatase 238 U/L. Routine urine examination was normal and culture revealed no growth after 72 h of incubation. Blood culture (two samples) was negative for bacteria. His sputum smear was negative for acid-fast bacilli for 3 consecutive days. Enzyme-linked immunosorbent assay (ELISA) for HIV 1 and 2 was non-reactive. Mantoux test with 5 T.U. was negative. HBsAg and anti-HCV were negative. USG whole abdomen showed hepatosplenomegaly. The patient's condition deteriorated further with appearance of right-sided pleural effusion [Figure 1b] and hepatosplenomegaly. Examination of pleural fluid showed cell count of 560/mm<sup>3</sup> with 70% lymphocytes, protein 3.4 gm/dl, sugar 46 mg/dl, lactate dehydrogenase 600 U/L and adenosine deaminase 36 U/L. The patient's contrast enhanced computed tomography (CECT) of thorax showed organization of right middle lobe consolidation

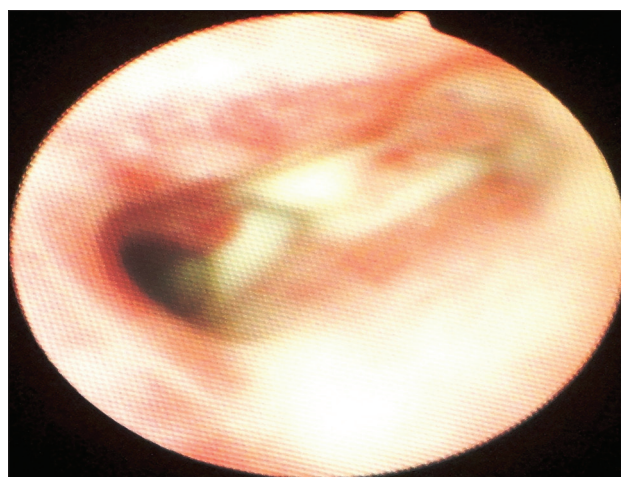


**Figure 1:** Chest X-ray PA view showing the right middle lobe consolidation (a) and the right sided pleural effusion with consolidation (b) CT scan thorax with contrast showing the necrotic lymph nodes in paratracheal and subcarinal sites (c)

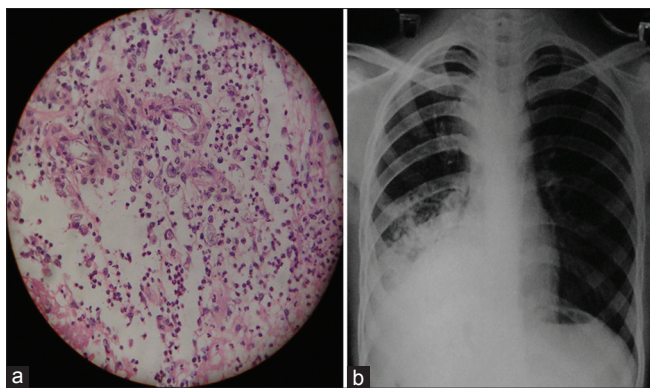
with enlargement of right paratracheal and subcarinal lymph nodes with central necrosis [Figure 1c]. Fibre-optic bronchoscopy revealed pus coming from the right main bronchus and a gelatinous mass in the posterior wall of trachea and a widened carina with constricted right main bronchus [Figure 2]. Bronchoscopic biopsy from the mass showed inflammatory granulation tissue with proliferation of capillaries and infiltration of a large number of inflammatory cells. Gomori's methenamine silver stain showed fungal spores morphologically resembling *Histoplasma capsulatum* [Figure 3a]. Bronchoalveolar lavage (BAL) and transbronchial needle aspiration (TBNA) from subcarinal lymph node also showed the presence of capsulated round microorganism on a background of inflammatory exudates compatible with *Histoplasma capsulatum*. Post-bronchoscopic sputum for fungal culture showed a growth of *Histoplasma capsulatum*. The patient did not have any past history suggestive of exposure to *Histoplasma capsulatum*. The patient was treated with intravenous amphotericin B 50 mg/day for 1 week followed by oral itraconazole 200 mg twice daily. Significant clinical improvement was noticed by 7 days and follow-up chest X-ray after one month showed a significant radiological resolution [Figure 3b].

## DISCUSSION

Non-resolving pneumonia is a challenging clinical problem. Incidence of non-resolving pneumonia was found to be 10% to 15% among hospitalized patients with CAP and of them 6% developed progressive pneumonia.<sup>[5]</sup> Mortality of un-resolving pneumonia ranges from 27 to 49%.<sup>[6]</sup> Approximately, 20% of presumed non-responding CAP had noninfectious etiology.<sup>[6]</sup> Old age, multilobar pneumonia, pneumonia severity index more than 90, Legionella pneumonia, gram negative pneumonia and discordant antimicrobial therapy were the common responsible for non-resolving pneumonia.<sup>[7]</sup> Non-resolving pneumonia was found to be responsible for 15% of inpatient pulmonary



**Figure 2:** Fibre-optic bronchoscopy showing the wide carina with constricted right main bronchus and pus coming out from the right main bronchus



**Figure 3:** Fungal stain of bronchial mucosal biopsy specimen showing the fungal elements suggestive of *Histoplasma capsulatum* (a) and follow-up chest X-ray PA view (b) after 1 month of treatment showing improvement of the right lung opacity in respect to pretreatment chest X-ray

consultations and 8% of bronchoscopies. In a recent study from south India tuberculosis (TB) was the cause of non-resolving pneumonia in 35.7% cases and malignancies were responsible for another 27% cases,<sup>[6]</sup> whereas Western literature has showed malignancies being responsible for up to 11% cases of non-resolving pneumonia.<sup>[5]</sup>

Histoplasmosis is caused by inhalation of the fungus *Histoplasma spp*, and the degree of infection and clinical presentation are determined by the size of inoculum, immune status of the individual and presence of underlying lung disease.<sup>[9]</sup> Like TB primary histoplasmosis heals spontaneously in about 99% of cases and only a few progress to PDH. PDH usually presents with high fever and weight loss. Hepatosplenomegaly, lymphadenopathy, anemia and leukopenia are the usual clinical findings. Adrenal gland involvement, lesions of oral mucosa, gastrointestinal tract and skin may be seen in 5 to 10% of cases.<sup>[10]</sup> Disseminated histoplasmosis usually occurs in immunocompromised host and is rare in immunocompetent host.

Histoplasmosis was once thought to be a nonentity in India. In Indian literature first case of histoplasmosis was reported by Panja and Sen in 1954.<sup>[11]</sup> Chronic pulmonary and progressive disseminated histoplasmosis are often fatal with reported mortality 83-100% in untreated cases and 7-23% in amphotericin B treated patients.<sup>[12]</sup> In case of appropriate clinical context, disseminated histoplasmosis

should be considered in both immunocompromised and immunocompetent patients, in endemic or non-endemic areas.

In our case the diagnosis of histoplasmosis was established by histopathological examination of tracheal lesion, BAL fluid and TBNA results, positive culture from sputum and therapeutic response to anti-fungal treatment. The case was more interesting because no factor responsible for immunosuppression could be demonstrated in the patient and PDH presenting as non-resolving pneumonia has not been reported in literature.

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