Presentations of chronic cavitary pulmonary histoplasmosis mimic infected cystic bronchiectasis in an immunocompetent host: A case report

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ABSTRACT

Background: Chronic cavitary pulmonary disease and laryngeal involvement are unusual manifestations of Histoplasmosis capsulatum infection, particularly in patients who are not immunocompromised. The presence of fibro-cavitary lesions has been reported as a radiologic presentation of chronic histoplasmosis in patients with pre-existing lung disease. However, there have been few reports of extensive basal predominant cavitary lesions that mimic cystic bronchiectasis.

Case presentation: A 65-year-old previously healthy Thai male presented with productive cough, hoarseness, low-grade fever, and weight loss for 6 months. There was no history of significant exposure to Histoplasmosis capsulatum. Tests for HIV and anti–IFN-γ antibody were negative. Chest CT revealed multifocal thick wall cavities, which were distributed in a peri-bronchial pattern, and some areas of consolidation in both basal lungs. Laryngoscopy revealed an ulcerative lesion of the false vocal cords. Histopathological study of false vocal cords and lung tissue showed granulomatous inflammation with mixed inflammatory cell infiltration and aggregation of histiocytes containing round intracytoplasmic organisms. GMS-staining was positive, but negative mucicarmine-staining was negative. A real-time PCR assay of the lung tissue was positive for Histoplasmosis capsulatum. The final diagnosis was chronic cavitary pulmonary histoplasmosis with laryngeal involvement.

Conclusion: Chronic cavitary pulmonary histoplasmosis is rare, as is laryngeal involvement. However, there have been such cases in endemic areas, even in immunocompetent patients. Chronic histoplasmosis should be considered in patients who present with the extensive basal predominant cavitary-pulmonary lesions that mimic cystic bronchiectasis.

1. Background

Histoplasmosis is a fungal infection that causes granulomatous inflammation and is transmitted through inhalation of soil contaminated with bird or bat excretion. The clinical manifestations of histoplasmosis vary greatly. Patients may be asymptomatic or may

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present with sub-clinical disease, chronic disease, or life-threatening conditions. Chronic cavitary pulmonary histoplasmosis has been reported primarily in immunocompromised patients, and extensive cavitary lesions and cystic bronchiectasis-like pulmonary lesions are rare. We report a case of histoplasmosis in an immunocompetent host who presented with chronic extensive cavitary pulmonary disease accompanied with laryngeal histoplasmosis.

2. Case presentation

A 65-year-old man presented with chronic productive cough for 6 months. He had progressive hoarseness without gross aspiration, weight loss of 10 kg, and low-grade fever. He was an former smoker (20 pack/year; quit 10 years previously) and was physically active without any known medical condition. He was a retired police officer living on a ranch in a rural area of Khon Kaen in northeast Thailand, a plateau area 187 m above sea level with a tropical climate for most of the year. He denied having traveled to any relevant areas or having any exposure to birds or bats. He had been admitted to another hospital for two weeks prior to this admission. Infected bronchiectasis had been the provisional diagnosis, and ceftazidime had been prescribed. However there had been no significant improvement to his persistent fever or respiratory symptoms.

At this admission, the patient was afebrile. Findings of a general examination were normal except for generalized rhonchi in both lungs. There was no physical sign that indicate the immunocompromised status of this patient. The results of a complete blood count and blood chemistry examination were normal, except for mild elevation of serum calcium and mild suppression of parathyroid hormone. HIV testing was negative. Chest radiography revealed thick irregular multifocal wall cavitary lesions with focal air-fluid level (Fig. 1). Computerized tomography (CT) of the chest revealed multifocal thick wall cavities distributed in a peri-bronchial pattern with some areas of consolidation in both basal lungs. Both adrenal glands were normal and the findings of the upper abdomen were unremarkable.

![Image A](image1.png) ![Image B](image2.png) ![Image C](image3.png) ![Image D](image4.png)

Fig. 1. A. Direct laryngoscopy revealed a yellowish inflamed lesion at the right false vocal cord B. Chest radiography revealed multifocal thick wall cavitary lesions and air-fluid level C. Chest CT at the upper trachea showed multiple irregular thick wall cavities D. Chest CT at the lower lung zone revealed multifocal cavitary lesions that connect to the bronchus and mimic cystic-bronchiectasis, multifocal consolidation, and ground-glass opacity and large pleural based cavities with air-fluid level at the posterior segment of the left lower lung.
Microbiological testing from sputum was negative for bacteria and mycobacteria. Bronchoscopy revealed multiple ulcerative laryngeal lesions and normal airway mucosa without endoluminal lesions or copious secretion. Transbronchial biopsy and bronchoalveolar lavage were performed, as well as direct laryngoscopic biopsy of the laryngeal lesion.

Histopathologic examination of the false vocal cord revealed granulomatous inflammation with several small lymphocytes and few neutrophil infiltration, as well as aggregation of histiocytes containing round intracytoplasmic organisms (Fig. 2). GMS staining of false vocal cord tissue revealed numerous uniform, intracellular budding fungal organisms. Bronchoalveolar lavage fluid cytology showed a small number of histiocytes containing intracytoplasmic organisms. Histopathological examination of the lung tissue also revealed aggregation of histiocytes with intracytoplasmic organisms. GMS-staining of the tissue was positive but mucicarmine-staining was negative. A real-time PCR assay of the lung tissue was positive for *Histoplasmosis capsulatum*.

The definite diagnosis was chronic-cavitary pulmonary histoplasmosis with laryngeal involvement. The patient was evaluated for acquired immunodeficiency, but no anti–IFN-γ antibody was detected. Amphotericin B (0.7 mg/kg/day) was administrated intravenously for 2 weeks and oral itraconazole (400 mg per day) was given consecutively. At 1 month of treatment, the patient’s fever, weight loss, cough, and chest radiography findings had significantly improved.

3. Discussion

*Histoplasmosis capsulatum* infection is commonly found in Thailand, which is an endemic area for the fungus. It has been reported most in immunocompromised hosts such as those living with HIV, solid-organ transplant recipients, and patients who receive immunosuppressive agents [1]. *Histoplasmosis capsulatum* infection occurs primarily through inhalation of soil contaminated with bird or bat excrement. When infectious *Histoplasmosis capsulatum* microconidia reach the lower airway, macrophages ingest the conidia, which are converted into yeast and multiply inside the macrophage. They then spread throughout the reticuloendothelial system. Dendritic cells recognize the organism and stimulate T-lymphocyte proliferation. T cell-mediated immune response plays a major role in organism clearance, which depends primarily on cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ, and interleukin-12 [2]. Accordingly, any defect or impairment in the cell-mediated immune pathway leads to *Histoplasmosis capsulatum* infection. A previous study reported neutralization of anti-interferon-γ autoantibodies in 96% of Asian adults who had multiple opportunistic infections including *Histoplasmosis capsulatum* [3]. Our patient was thoroughly examined for immunodeficiency, but blood cell count and testing for anti-HIV and anti-interferon-gamma autoantibodies were unremarkable. There was thus no evidence of cell-mediated immune deficiency.

The clinical manifestations of *Histoplasmosis capsulatum* infection vary depending on the intensity of inoculum exposure and host-immune status which can include asymptomatic or minimally symptomatic infection, acute pulmonary infection, chronic-cavitary

![Fig. 2. Biopsy of the larynx and lungs A. Histopathologic findings of tissue from the larynx revealed multinucleated giant cells (yellow circles), which contained intracellular organisms B. GMS staining of tissue from the larynx showed organisms 2–4 μm in diameter with internal septation C. PAS staining of tissue from the larynx showed numerous intracellular organisms D. H&E staining of lung tissue revealed histiocytes with numerous intracellular organisms E. GMS staining of the lung tissue was positive for yeasts. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)](image)
pulmonary infection, progressive disseminated infection, and mediastinal lymphadenitis [4]. Smokers with preexisting structural lung abnormalities, such as emphysema, are more likely to develop chronic-cavitary pulmonary histoplasmosis [5]. The typical presentations of which are productive cough, fever, night sweats, and weight loss that progresses chronically over one month and is rarely self-limiting [6]. Laryngeal histoplasmosis is a rare entity and difficult to diagnose. The symptoms of laryngeal histoplasmosis usually mimic malignancy and include hoarseness, sore throat, low-grade fever, and weight loss. On laryngoscopic imaging, laryngeal mucosa is commonly pearly white, inflamed, and edematous with visible ulcerative lesions, all of which are typical findings in malignancy. Histopathology of the laryngeal specimen will generally reveal granulomas, which should be differentiated from other pathogens such as tuberculosis or other fungi. Pseudo-epitheliomatous hyperplasia may also be visible, which may indicate squamous cell carcinoma [7,8]. In our case, the patient had never been diagnosed with chronic obstructive airway disease (despite his history of heavy smoking), and radiologic findings revealed no emphysematous features. Moreover, because of his immunocompetent status, he was considered to be at low risk for chronic-cavitary pulmonary histoplasmosis with laryngeal infection. Malignancy (such as squamous cell carcinoma of the larynx with cavitary-pulmonary metastasis) was the presumptive diagnosis based on his clinical presentation. However, this was eventually ruled out due to histopathological and microbiological confirmation of histoplasmosis.

Radiologic findings of pulmonary histoplasmosis vary and can mimic a number of pulmonary diseases. Consolidation or multiple pulmonary nodules are commonly found in cases of acute histoplasmosis, while a typical finding in chronic histoplasmosis is fibro-cavitary lesions that are predominantly distributed along the upper lobes. Mediastinal involvement, such as mediastinal lymphadenopathy, calcified mediastinal nodes, or fibrosing mediastinitis may also be visible [9]. In our case, radiologic examination revealed multiple cavitary lesions with peri-bronchovascular and lower lung distribution mimicking cystic bronchiectasis and multifocal consolidations, which are not typical findings in pulmonary histoplasmosis. Thus, pulmonary diseases other than histoplasmosis, such as malignancy, bacterial infection, and mycobacterium infection, were initially considered.

Due to its clinical rarity, there is lack of well-designed randomized controlled trials examining the treatment of chronic-cavitary pulmonary histoplasmosis. In out-patient setting, itraconazole at a dosage of 200 mg twice daily is generally recommended. The total duration of treatment ranges from 6 to 24 months with careful follow-up for failure or relapse. Without sufficient treatment, disease progression can lead to chronic respiratory failure and fatalty [4,10]. Nevertheless, in disseminated or severe disease, particularly in hospitalized patient, initial treatment with liposomal amphotericin B or amphotericin B deoxycholate in patients who are at a low risk for nephrotoxicity for 1–2 weeks followed by oral itraconazole for a total of at least 12 months has been recommended [11].

Here, we reported a patient without immunodeficiency or pre-existing pulmonary disease who had laryngeal involvement and chronic cavitary pulmonary disease as a manifestation of histoplasmosis infection. Radiological findings were also atypical, as there were multiple cavities and consolidations with lower lung predominance, which mimicked cystic bronchiectasis.

Declaration of competing interest
The authors declare that they have no competing interests.

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List of abbreviations
- anti–IFN–γ: anti-interferon-gamma
- CT: Computerized tomography
- GMS: Gomori methenamine silver stain
- HIV: Human immunodeficiency virus
- PCR: Polymerase chain reaction
- TNFa: Tumor necrosis factor-alpha

Ethics approval and consent to participate
The study has been approved by Center for Ethics in Human Research, Khon Kaen University, Thailand (HE641079).

Consent for publication
Written consent for publication of the clinical case details was obtained from the patient. Availability of data and materials. Not applicable.

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Authors' contributions

WC was a major contributor in writing a manuscript and primary physician. AS performed bronchoscopy and analyzed the data. WR, PR and IA reviewed the manuscript. AM reviewed the data regarding the infectious perspective. NC performed histological examination of larynx and lung specimen and reviewed the manuscript. All authors approved the manuscript.

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