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Case report

Update on the spectrum of histoplasmosis among hispanic patients presenting to a New York City municipal hospital: A contemporary case series

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ABSTRACT

Histoplasma capsulatum is the most common endemic mycosis worldwide. Although most of the globe's largest urban hubs fall outside this organism's regions of endemicity, clinicians practicing in a metropolis like New York City or Los Angeles must nevertheless remain vigilant for histoplasmosis because of the large immigrant population that is served by its hospitals. *H. capsulatum* infection ranges from asymptomatic pulmonary infection to life-threatening diffuse pneumonia with dissemination. The early years of the AIDS epidemic first introduced U.S. clinicians working in areas previously unfamiliar with histoplasmosis to newly immunocompromised patients from endemic regions presenting with disseminated *H. capsulatum* originally acquired in their home countries. Improvement in HIV prevention and therapeutics has reduced the frequency of such cases. Herein we report three cases of histoplasmosis encountered in our New York City institution over the last three years to emphasize that awareness of this infection remains mandatory for the frontline urban clinician.

1. Introduction

Elmhurst Hospital Center is located in Queens, NY, which is considered to be the city's most ethnically diverse borough. This public hospital straddles the Jackson Heights and Elmhurst neighborhoods, whose zip codes are home to one of the most diverse immigrant populations in the United States [1]. The unique patient mix treated at Elmhurst Hospital has been recognized as far back as 1982 in a *New York Times* article entitled "A Hospital Where Ethnic Change is Constant [2]." More recently, in May 2013, *the New Yorker* published an article about Elmhurst Hospital's famous pathology entitled "Every Disease on Earth." [3].

As a result of the demographic composition of their patients, Elmhurst Hospital clinicians must always be on alert for infectious agents not otherwise endemic to the New York City (NYC) area. One such pathogen is *Mycobacterium tuberculosis* (TB), for which there is always a high index of suspicion and with which there is broad familiarity. Another organism in this category—and a notorious, yet often overlooked, TB mimic—is *Histoplasma capsulatum*, a dimorphic fungus found primarily in the Ohio and Mississippi River valleys of the United States as well as across Mexico and Central and South America. Pulmonary involvement in histoplasmosis ranges from asymptomatic or minimally symptomatic disease to life-threatening pneumonitis with dissemination.

In the 1980s, three separate NYC hospitals published case series of disseminated histoplasmosis (DH), an entity essentially absent from NYC before that time [4–6]. Nearly all of the included cases occurred in the context of confirmed or suspected acquired immunodeficiency syndrome (AIDS) and had been born in South America or the Caribbean. Perhaps not surprisingly, two out of the three reporting institutions were, like Elmhurst Hospital, part of the municipal healthcare system. The prevailing theory that these immunocompromised DH cases represented reactivation of prior infection was later substantiated by mitochondrial deoxyribonucleic acid analysis that linked *H. capsulatum* isolates from five

Abbreviations: NYC, New York City; AIDS, Acquired immunodeficiency syndrome; DH, Disseminated Histoplasmosis; HIV, Human immunodeficiency virus; ED, Emergency department; CT, Computed tomography; L-AmB, Liposomal amphotericin B; AZA, Azathioprine; RES, Reticuloendothelial system; TB, Tuberculosis; ANCA, Anti-neutrophil cytoplasmic antibody; BAL, Bronchoalveolar lavage.

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AIDS patients residing in NYC to a Panamanian strain [7].

Advances in the treatment of the human immunodeficiency virus (HIV) coupled with increased use of therapeutic immunosuppression have almost certainly changed the face of pulmonary and DH in non-endemic areas since the aforementioned case series emerged nearly 30 years ago. Herein we describe three patients of Hispanic origin diagnosed with histoplasmosis at Elmhurst Hospital in the years 2012–2014 followed by a discussion that emphasizes concepts of relevance to the chest physician.

1.1. Case 1

A 47-year-old female, a resident of Mexico City, presented with fever, cough, and dyspnea. Her illness had started with a productive cough approximately 10 days prior during a family trip to the state of Chiapas, Mexico. At that time she was prescribed levofloxacin with no relief, followed by azithromycin and prednisone with temporary improvement of symptoms. Upon arrival to the USA, she became febrile and more dyspneic, which prompted her visit to the emergency department (ED). There was no personal history of TB.

Vital signs on admission were notable for a pulse of 108 beats/min, a temperature of 102 °F, and an oxygen saturation of 88% on room air that improved to 95% with 4 L/minute of oxygen via nasal cannula. Laboratory evaluation was significant for a mild leukocytosis (12 K/μL) and normal serum electrolytes. Liver function tests were unremarkable. Rapid testing for HIV was negative. Serial chest radiography revealed a rapidly progressive diffusely nodular infiltrate (Fig. 1A and B). Computed tomography (CT) of the chest confirmed the presence of innumerable nodules (Fig. 1C).

She was started on ceftriaxone for community-acquired pneumonia and on an empiric anti-tuberculous regimen. Blood cultures and sputum mycobacterial smears returned negative. Despite the aforementioned antimicrobial regimen, the patient remained febrile with a requirement for oxygen via 50% face mask. Bronchoscopic biopsies were performed but were non-diagnostic, described as interstitial lymphocytic infiltration without granulomas.

Upon further questioning, she mentioned entering Mayan ruins in Palenque during her visit to Chiapas. She likewise informed her clinicians that her children, who had accompanied her on that trip, were now ill in Mexico with “nodules in their lungs.” Liposomal amphotericin B (L-AmB) was started empirically for histoplasmosis, and the patient was referred for surgical lung biopsy, which revealed necrotizing granulomatous inflammation with fungal forms consistent with *H. capsulatum* (Fig. 2A and B). Subsequently her urine *Histoplasma* antigen assay returned positive (1.31 ng/ml, Quest Diagnostics, Inc., Teterboro, NJ, USA). She clinically improved after 8 days of L-AmB therapy and was discharged home to Mexico with instructions to complete a 12-week course of oral itraconazole 200 mg twice daily.

1.2. Case 2

A 77-year-old female, an immigrant from Peru 20 years earlier, with interferon-gamma release assay positivity for *M. tuberculosis*, presented with fevers and decreased oral intake due to poor appetite for the previous 3 weeks. Her review of systems on admission was otherwise negative, and she reported no recent travel. She had been diagnosed with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis approximately 1 year earlier and, after completing a 6-month course of cyclophosphamide, was taking 10 mg of prednisone and 100 mg of azathioprine (AZA) at the time of admission. Even prior to the diagnosis of vasculitis, her chest imaging had revealed fibrocystic and bronchiectatic changes.

Physical examination revealed a comfortable but undernourished woman with a temperature of 101.3 °F and dry crackles on lung auscultation. There were no other pertinent findings. Laboratory values were significant for serum sodium of 126 meq/L and normocytic anemia with a hemoglobin level of 11 gm/dL. Her admission chest radiograph (CXR) was unchanged from previous radiographs.

She was started on ceftriaxone and azithromycin for possible pneumonia. Her immunosuppressants were continued. Fevers persisted despite broadening of her antibiotic regimen first to cefepime and then to imipenem. Her subsequent CXR revealed subtle diffuse reticulonodular densities (Fig. 3A). Chest CT demonstrated a miliary pattern of involvement superimposed on chronic changes (Fig. 3B).

Due to concurrent worsening pancytopenia, AZA was discontinued, but the dose of prednisone was not changed. Despite the initiation of empiric anti-tuberculous therapy, she became progressively more hypoxemic and somnolent with a worsening CXR (Fig. 3C). Two sputum mycobacterial smears returned negative. Continued deterioration and pancytopenia prompted a bone marrow biopsy, which revealed rare aggregates of histiocytes (Fig. 4). Stains for acid-fast bacilli and fungi were negative. The patient expired just as she was about to receive the first dose of L-AmB for presumed DH. Post-mortem, her urine and serum *Histoplasma* antigen titers were reported as above the limit of quantification (>19 ng/ml, Quest Diagnostics, Inc., Teterboro, NJ, USA). Sputum and blood cultures ultimately revealed no growth. The family declined autopsy.

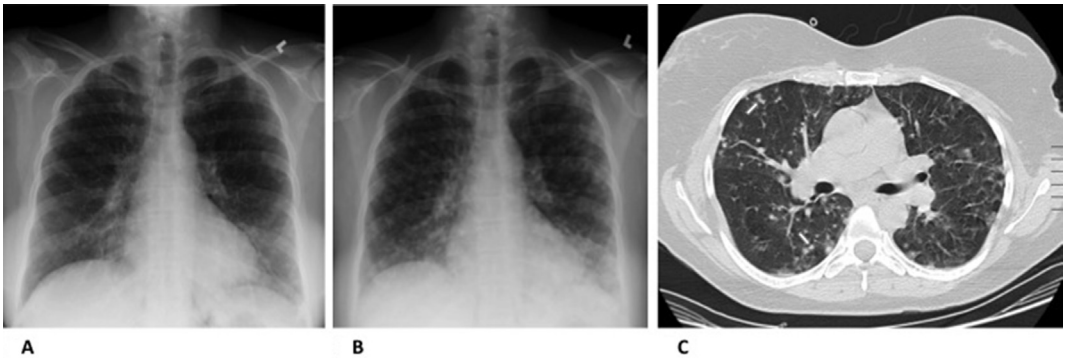

Fig. 1. A-B, Successive frontal chest radiographs showing progression of a diffuse nodular infiltrate. C, CT scan of the chest showing numerous ill-defined nodules in a centrilobular distribution (arrows).