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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.

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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/ μ L) 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.

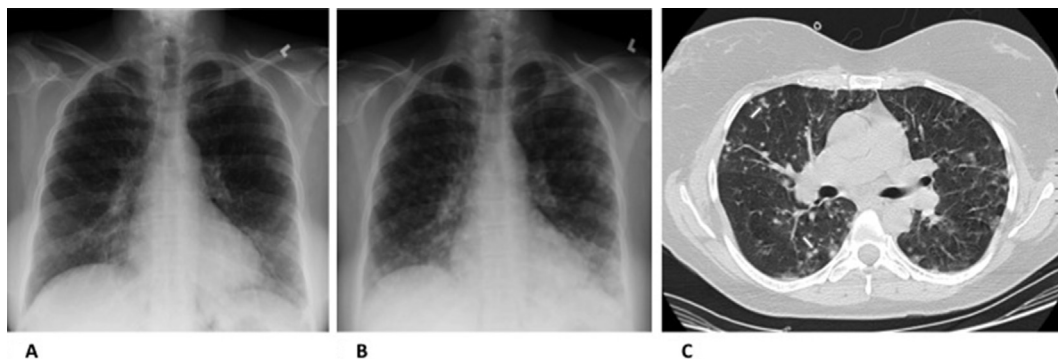


Fig. 1. A–B, Successive frontal chest radiographs showing progression of a diffuse nodular infiltrate. C, CT scan of the chest showing numerous ill-defined nodules in a centrilobular distribution (arrows).

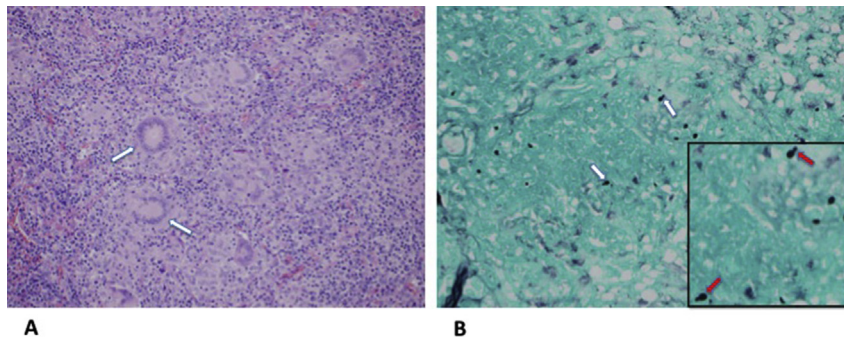


Fig. 2. A, Surgical lung biopsy specimen showing extensive necrotizing granulomatous inflammation (arrows) (H&E, original magnification $\times 100$). B, Methenamine silver stain highlighting numerous budding fungal organisms morphologically consistent with *H. capsulatum* (arrows) (original magnification $\times 100$). Inset: Closer look at the characteristic narrow-based budding of *H. capsulatum* (arrows).



Fig. 3. A, Frontal chest radiograph showing subtle reticulonodular densities bilaterally. B, Chest CT with innumerable tiny nodules in a miliary pattern. C, Subsequent frontal chest radiograph showing dramatic worsening of the previously subtle reticulonodular densities.

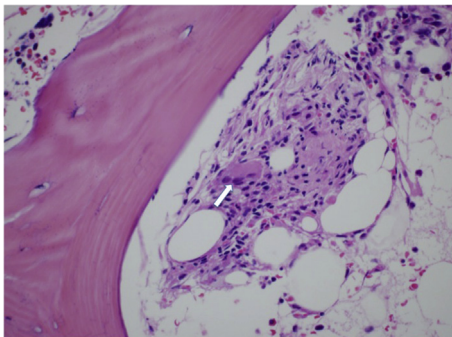


Fig. 4. Bone marrow aspirate showing a loose aggregate of histiocytes. In one area they have conglomerated into a multinucleated giant cell (arrow).

1.3. Case 3

A 27-year-old male construction worker who had emigrated from Ecuador 4 years earlier presented with 3 weeks of fevers, night sweats, productive cough, and progressive dyspnea. He was initially prescribed outpatient antibiotics with no relief. An HIV test was positive. Review of systems revealed recent weight loss and blood-streaked sputum. His risk factor for HIV was heterosexual contact.

On admission, he had a blood pressure of 102/48 mmHg with a pulse of 123 beats/min and a respiratory rate of 30 breaths/min. His temperature was 102 °F, and his oxygen saturation was 94% on room air. Physical examination revealed an ill-appearing undernourished male with hepatomegaly and bilateral crackles on lung

auscultation. There was no oral candidiasis, rash, or lymphadenopathy.

Initial laboratory evaluation yielded pancytopenia (leukocyte count 2800/ μ L, hemoglobin 6.5 gm/dL, platelet count 56,000/ μ L), AST 65 U/L, GGT 114 U/L with normal bilirubin, LDH 532 U/L, and serum sodium of 128 meq/L with normal serum potassium. CXR showed bilateral lower lobe streaky densities with probable cavitation on the left (Fig. 5A). Subsequent CT of the chest demonstrated a cavitary left lower lobe consolidation with an associated small pleural effusion (Fig. 5B). Abdominal CT revealed hepatosplenomegaly with an area of wedge-shaped hypoenhancement in the lateral aspect of the spleen compatible with infarct (Fig. 5C).

Ceftriaxone and azithromycin were started for community-acquired pneumonia as well as trimethoprim-sulfamethoxazole for empiric treatment of *Pneumocystis jirovecii* pneumonia. The CD4+ lymphocyte count was 5 cells/ μ L, and the serum cryptococcal antigen titer was 1:256. Treatment with L-AmB was initiated; lumbar puncture was negative for meningitis. The patient became afebrile on the second day of L-AmB therapy. Blood cultures revealed no growth, and multiple sputum smears returned negative for mycobacteria. Bronchoscopy with bronchoalveolar lavage (BAL) was negative for *Pneumocystis*, but lactophenol cotton blue preparation revealed budding yeast forms. Cultures yielded *Cryptococcus neoformans*, and the urine *Histoplasma antigen* assay was reported as above the limit of quantification (>19 ng/ml, Quest Diagnostics, Inc., Teterboro, NJ, USA).

The patient's clinical status improved, and therapy was switched from L-AmB to oral itraconazole after 14 days of treatment. He was discharged home to complete a prolonged course of oral itraconazole 200 mg twice daily for pulmonary cryptococcosis and DH. He

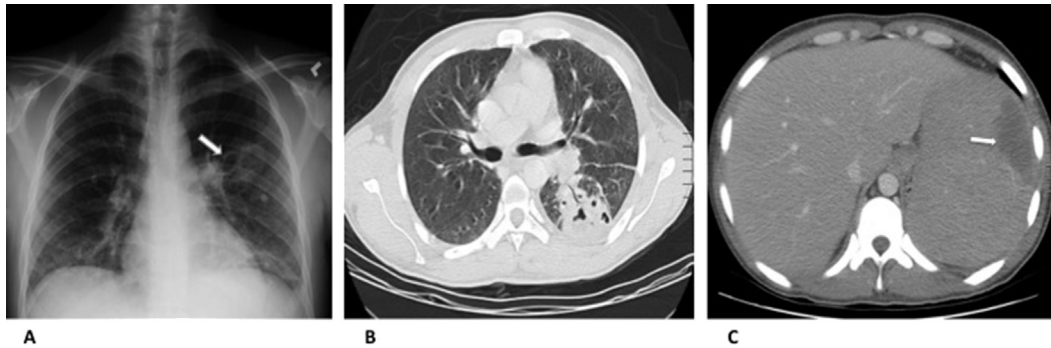


Fig. 5. A, Frontal chest radiograph showing bilateral lower lobe streaky densities and a left mid-lung field opacity with central radiolucency suggestive of cavitation (arrow). B, Chest CT confirms the presence of a cavitary consolidation in the superior segment of the left lower lobe. C, Abdominal CT showing hepatosplenomegaly with a peripheral hypodense area in the spleen likely representing infarct (arrow).

responded favorably to outpatient antifungal and antiretroviral therapy.

2. Discussion

Histoplasmosis is the most common endemic fungal infection worldwide. It was first described by the American pathologist Samuel Darling while working in the area of the Panama Canal. In 1906, he also published the first report of DH in a carpenter from Martinique, who was initially thought to have miliary tuberculosis [8]. It is now known that human acquisition of *H. capsulatum* occurs after inhalation of the mold form, which thrives in soil enriched with bird and bat excreta as well as in similarly contaminated caves. Conversion to the yeast form in the alveolar spaces gives rise to pulmonary disease that can vary in severity depending on host immunity and size of inoculum [9].

In endemic areas, the majority of the population exhibits *Histoplasma* skin test positivity, suggesting a high incidence of asymptomatic or undiagnosed mild infections. Usually discovered incidentally, these cases are characterized by minimal symptoms and the presence of focal air-space consolidation with intrathoracic lymphadenopathy on chest imaging [10]. Spontaneous resolution is the norm.

The classic scenario of an otherwise healthy young spelunker presenting with a rapidly progressive febrile pneumonitis illustrates the entity known as acute severe pulmonary histoplasmosis, which may likewise resolve without treatment and often leaves behind “buckshot” calcifications [11]. This influenza-like illness follows inhalation of a large fungal inoculum and manifests radiographically as diffuse nodularity, which can appear miliary.

Upon entry via the respiratory tract, *H. capsulatum* is engulfed by macrophages and is thereby spread throughout the reticuloendothelial system (RES) accompanied by a transient fungemia. Clinically overt dissemination is not universal because functional lymphocytes activate parasitized macrophages, which leads to containment of the organism. Subsequent evidence of this sub-clinical dissemination can be found incidentally in the form of splenic and lymph node calcifications. Impaired cell-mediated immunity predisposes to more severe pulmonary disease and to dissemination as a result of the failure of this defense mechanism.

DH has been classified as an AIDS-defining illness and has been described in association with various immunosuppressive agents, hematologic malignancies, and organ transplantation. [11,12] Histopathologically, the dissemination of *H. capsulatum* throughout the RES typically does not result in granulomatous inflammation at these extrapulmonary sites. Rather, the characteristic lesion of this process is histiocytosis, which in the case of DH represents either

the diffuse or focal aggregation of infected macrophages that displaces normal tissue and leads to organ enlargement and dysfunction [13].

Nearly all patients with acute or subacute DH (as opposed to chronic DH, which is a distinct clinical entity) present with a febrile illness. Other common presenting symptoms include malaise, weight loss, and cough. Abdominal complaints can arise from the often profound hepatosplenomegaly caused by macrophage infiltration. Central nervous system involvement in the form of meningitis and cerebritis is much more common at autopsy than in the clinical arena, which is also true of intestinal ulceration [13]. *H. capsulatum* endocarditis is a well-described albeit rare complication of fungemia. Cutaneous lesions, which take on many forms, occur more frequently in the AIDS population [14]. Altered hemodynamics directly related to DH can be seen with adrenal involvement and with catastrophic disease accompanied by multi-organ dysfunction syndrome.

The laboratory picture is reflective of dissemination to specific organs. Cytopenias and liver function test abnormalities, for example, point to involvement of the bone marrow and liver, respectively. When abnormal, chest radiography typically reveals a diffuse micro-nodular, sometimes miliary, pattern with or without accompanying reticular opacities [15]. Focal air-space disease is observed less commonly.

An international consensus conference has proposed defining the diagnosis of DH for research purposes by the presence of fungemia or antigenemia/antigenuria, although the question of whether the latter alone is sufficient to establish dissemination remains an open one [16]. Blood cultures are positive in approximately two-thirds of DH patients while *Histoplasma* antigen is detected in the urine of >90% of cases [9]. The sensitivity of the serum antigen had traditionally been inferior, especially in non-HIV patients, but has recently been shown to exceed that of urine after pretreatment of serum with ethylene diamine tetraacetic acid (EDTA) [17].

It is important to recall that latent dissemination is the norm in pulmonary histoplasmosis, whereby even a normal immune system may be initially overwhelmed. In fact, *H. capsulatum* can be isolated from extrapulmonary sites in up to a quarter of such immunocompetent hosts [10]. In some cases of DH, particularly catastrophic ones accompanied by shock and multi-organ failure, routine peripheral smears may reveal yeast forms within circulating neutrophils. Biopsy of any involved organ will generally reveal fungal organisms that, owing to their small size, can be missed on hematoxylin and eosin staining but are rendered readily apparent by methenamine silver [11]. Presumptive morphological diagnoses are confirmed by culture, the yield of

which is excellent from specimens of lung, bone marrow, and lymph nodes [18,19].

L-AmB is the accepted standard of care for the treatment of DH and is used in the majority of cases. Patients who improve on L-AmB are usually transitioned to itraconazole to complete 6–18 months of therapy. Itraconazole can be used to treat milder cases of DH and is also the preferred prophylactic agent [9].

Our first case illustrates the presentation of acute severe pulmonary histoplasmosis in a visitor to a non-endemic area. Her disease was acquired by massive inhalation of conidia in the Mayan ruins of Mexico. In parts of the globe unaccustomed to histoplasmosis, such cases have caused diagnostic confusion with miliary tuberculosis (TB), especially in the absence of CT imaging [20]. With the benefit of chest CT, one hopes to distinguish the typically centrilobular pattern of pulmonary nodules (with or without “tree-in-bud” appearance) in acute severe pulmonary histoplasmosis from the randomly distributed nodules of miliary TB, reflecting the endobronchial spread involved in the former versus the hematogenous spread that defines the latter. Progression of her disease was initially masked but ultimately promoted by the corticosteroid course prescribed by the patient’s physician.

The second case exemplifies DH due to endogenous reactivation in the setting of therapeutic immunosuppression. Both prednisone and azathioprine have been implicated in cases of DH, including those with underlying vasculitis [21–23]. This patient exhibited clinical evidence of dissemination in the form of progressive cytopenias and alteration of sensorium, findings attributable to bone marrow and CNS involvement, respectively. Of note, the chest CT pattern in this case was in fact miliary, raising the possibility of secondary hematogenous “seeding” of the lung. It is important to bear in mind that the rather bland bone marrow aspirate of this patient, including the absence of true granulomas, is indeed expected. The quantity of pathologic macrophages, whether visibly containing *H. capsulatum* or not, in bone marrow specimens has not shown meaningful correlation with abnormalities in peripheral blood counts [13]. The fact that empiric anti-tuberculous therapy was initiated significantly earlier than anti-fungal therapy in the first two cases highlights the typical delay in considering any endemic mycosis in a non-endemic region.

The third patient is reminiscent of DH cases in NYC from the early years of the AIDS epidemic and likewise presumably represents reactivation of prior infection acquired abroad. Dissemination was clinically prominent in this case, manifesting as constitutional symptoms, profound cytopenias, and hepatosplenomegaly with suspected splenic infarction. The ordinarily prevalent cutaneous lesions of DH in AIDS were absent. Our patient was concurrently diagnosed with another opportunistic infection (cryptococcal pneumonia with antigenemia), which was also true of the majority of cases from the largest series of DH in NYC’s AIDS population [6]. The combination of cryptococcosis and DH in advanced AIDS has been described previously [23]. The fact that our patient’s chest imaging was more consistent with cryptococcal pneumonia than DH and the failure of BAL fluid to yield *H. capsulatum* suggest the possibility of dissemination arising from an extrapulmonary site without any overt lung involvement. Interestingly, in an analogous co-infection case reported from France, respiratory fungal culture was positive for *C. neoformans* but negative for *H. capsulatum* despite unequivocal evidence of DH [24].

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Conflict of interest

None.

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