

Pulmonary Histoplasmosis in a patient with Cough, Dyspnea, Pulmonary Nodule and Rheumatologic Manifestations: Case Report and Review

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Abstract

In this case report we describe a case of pulmonary histoplasmosis in a healthy adult female living in Kentucky. The patient presented with two months history of poly-arthritis and myalgia, intermittent dry cough, chest tightness, exertional dyspnea, malaise, fatigue and one week history of skin rash. She did not respond to broad-spectrum antibiotic therapy and she also had extensive endocrine and rheumatologic work up that was negative. A diagnosis of histoplasmosis was established based on radiological findings as well as endobronchial ultrasound-guided transbronchial needle aspiration cytology (EBUS-TBNA) of mediastinal lymph nodes demonstrating necrotizing granuloma with fungal stains positive for *Histoplasma*. Patient showed significant clinical improvement on antifungal treatment. Since symptoms of histoplasmosis are often similar to the symptoms of community acquired pneumonia, other lung infections or malignancy, our case highlights the importance of maintaining a high index of suspicion and appropriate radiological, microbiology, and histologic evaluation especially in patients who live in or have traveled to areas endemic for histoplasmosis and are not responding to antibiotic therapy. Early diagnosis coupled with prompt initiation of antifungal treatment may lead to favorable outcomes.

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Introduction

Histoplasmosis has worldwide distribution, occurring most commonly in North, Central, and South America, as well as parts of Africa and Asia [1, 2]. Histoplasmosis is a granulomatous disease caused by a dimorphic fungus *Histoplasma capsulatum* (*H. capsulatum*). There are two varieties of *H. capsulatum* that are pathogenic to humans, *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*. *H. capsulatum* var. *capsulatum* is endemic in eastern United States and Latin America [3], and *H. capsulatum* var. *duboisii* is prevalent in Africa and South East Asia [4]. In the United States, *H. capsulatum* is primarily seen in Mississippi and Ohio River valleys. *H. capsulatum* grows best in soil contaminated with bird or bat droppings [5]. Transmission occurs via inhalation of *H. capsulatum* spores from the soil. Sites commonly associated with exposure to *H. capsulatum* include old buildings, caves, bridges, where birds have roosted [6, 7]. Infection may be acquired from exposure to outdoor activities such as exploring caves, construction, remodeling, demolition, bird handling, all of which can cause inhalation of the pathogen through the contaminated soil [8, 9]. The variation in clinical course due to histoplasmosis depends on the extent of the exposure to the organism. Histoplasmosis may remain asymptomatic in most healthy individuals following low-level exposure and asymptomatic pulmonary histoplasmosis is the most common syndrome following infection [10]. Fewer than five percent of exposed individuals develop symptomatic disease after a low level exposure to *H. capsulatum* [11]. Symptomatic

infection usually causes self-limited pulmonary illnesses, rheumatologic manifestations such as arthritis or arthralgia involving the large or small joints, dermatologic manifestations such as erythema nodosum and/or erythema multiforme or pericarditis. Exposure to heavy inoculum can cause diffuse pulmonary involvement [12]. Individuals at the extremes of age or with underlying immunosuppressive conditions can develop progressive disseminated disease. Histoplasmosis can involve every organ system during the course of dissemination [13]. Here, we describe a case of pulmonary histoplasmosis in a healthy adult female presenting with cough, dyspnea, pulmonary nodule and rheumatologic manifestations.

Case Report

A middle aged female, former smoker, outdoor worker with exposure to pigeons and their excreta, otherwise with no significant past medical history, presented to her primary care physician with two months history of poly-arthritis and myalgia, intermittent dry cough, chest tightness, exertional dyspnea, malaise, fatigue and one week history of skin rash consisting of multiple targetoid appearing erythematous papules of size 0.5-1.0 cm, on both of her hands as well as her thighs and lower legs. Photograph of the rash on both of her lower extremities is shown in (Figure 1).

Vital signs during her initial visit to primary care doctor were temperature 97.5° F, heart rate 82 beats per minute, respiratory rate 16 breaths per minute, blood pressure 132/78 mm Hg,

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and oxygen saturation 98% on room air. On physical exam, she had a skin rash with description as noted above, otherwise she had no respiratory distress, no lymphadenopathy, no joint swelling or tenderness. Examination of the respiratory system, cardiovascular system, abdomen, central nervous system was noted to be unremarkable.



Fig. 1 Skin rash consisting of multiple scattered targetoid appearing erythematous papules of size 0.5-1.0 cm on bilateral lower extremities.

Initial diagnostic laboratory work up showed leucocyte count of 9,100 cells/mm³ (no eosinophilia), hemoglobin 14.3 g/dl, hematocrit 44.3% and platelet count 295,000/mm³. Serum electrolytes, renal function, liver function tests, and lipid screen were normal. Urinalysis was negative for protein or blood. Rapid Streptococcus group A antigen test and Influenza test for A & B antigens were negative. Chest X-ray (CXR) showed new linear opacity best seen on the lateral view in the region of the lingula with differential of fluid or fat within the major fissure versus small infiltrate in the lingula (**Figure 2**).

High resolution chest computed tomographic (CT) scan was obtained revealing a linear density seen on the initial chest x-ray corresponding to a small amount of fat seen extending into the right major fissure, otherwise no residual infiltrate was noted. In the right lower lobe, posteriorly, there was a nonspecific sub-pleural nodule measuring about 8 mm in size. It was new since the prior chest computed tomographic (CT) scan obtained seven years ago. Remaining lungs were clear with no evidence of interstitial lung disease, ground-glass infiltrate, bronchiectasis, honeycombing or air trapping. Right para-tracheal node was present. No other mediastinal, hilar, or axillary nodes were seen. (**Figure 3**).

PET/CT skull base to mid-thigh was obtained that showed minimal level of metabolic activity at the site of the right lung pulmonary nodule, and hypermetabolic sub-carinal and right para-tracheal lymph nodes (**Figure 4**). An infectious process, including possible fungal disease, or malignancy were suspected.

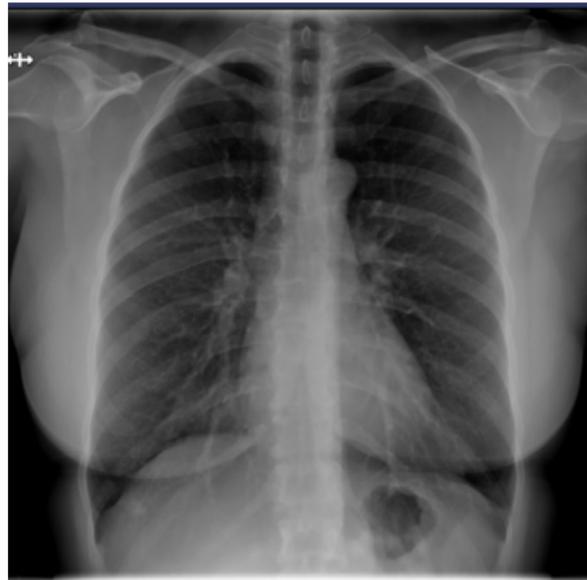


Fig. 2 Initial Chest X-ray (CXR) PA and Lateral showing linear opacity best seen on the lateral view in the region of the lingula with differential of fluid or fat within the major fissure versus small infiltrate in the lingula.

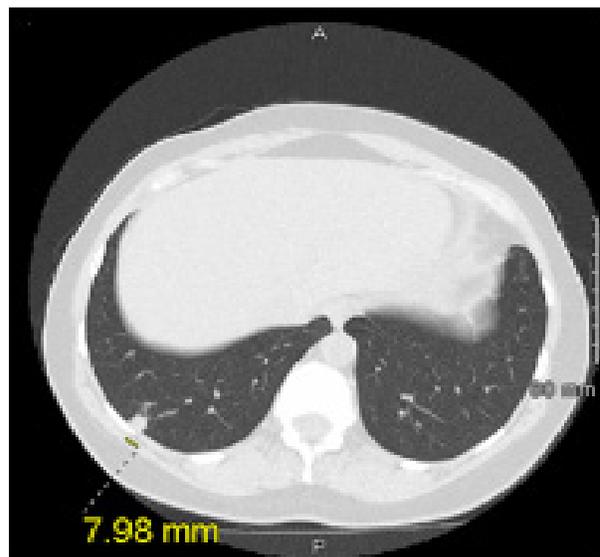


Fig. 3 Chest computed tomographic (CT) scan showing sub-pleural nodule measuring about 8 mm in size in the posterior aspect of right lower lobe.

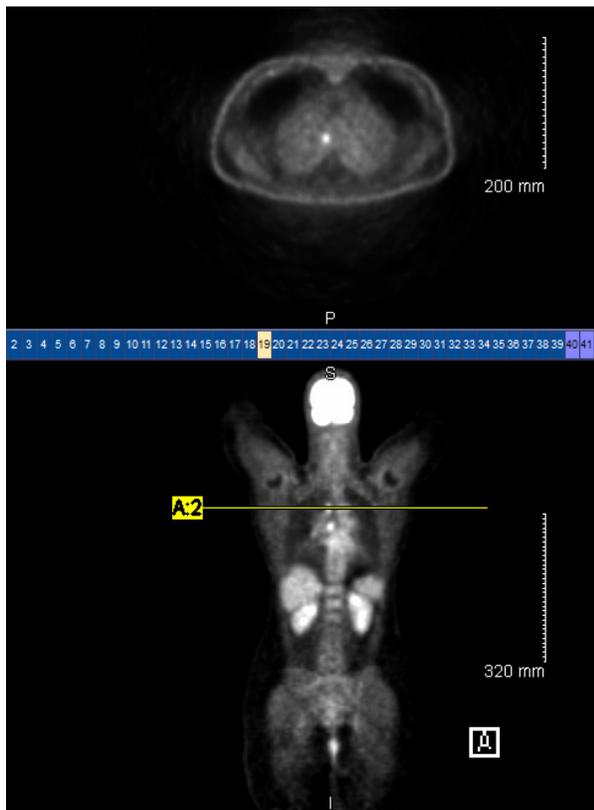


Fig. 4 PET/CT skull base to mid-thigh showing hypermetabolic sub-carinal and right para-tracheal lymph nodes.

A referral to dermatology was made and a punch biopsy of the skin rash from her right dorsal thigh was performed. Hematoxylin & Eosin (H & E) stained section of the specimen showed histiocytes in the dermis arranged in rings, and distributed in discrete foci throughout the dermis. Granular and fibrillary mucinous material was present in the foci of a histiocytic aggregation. In addition, there was superficial and deep perivascular lymphocytic infiltrate, with likely diagnosis of granuloma annulare. She was placed on five week course of a low dose oral prednisone taper with some improvement noted in her skin rash and joint symptoms.

During the subsequent weeks, due to non-resolution and persisting nature of her symptoms, she had several follow up visits with her primary care physician. She received several rounds of different oral antibiotics without significant improvement in her symptoms. In an effort to establish a diagnosis, extensive laboratory work up including rheumatologic/autoimmune and endocrine work up was performed which included CPK, aldolase, lactic acid, complement fixation tests, rheumatoid factor, antinuclear antibody, anti-neutrophil cytoplasmic antibody screen (MPO & PR3), SS-A/Ro and SS-B/La, ENA antibodies, Sm/RNP, dsDNA, CCP antibody, anti-glomerular basement membrane antibody, monoclonal protein, thyroid function panel, thyroid peroxidase (TPO), thyroglobulin antibody, parathyroid hormone (PTH intact), Insulin-Like Growth I (IGF-1), adrenocorticotrophic hormone (ACTH), serum cortisol, serum ferritin, iron/UIBC/transferrin saturation, vitamin B1, B6, B12 and Vitamin D (25-Hydroxy) levels and ACE level. All of the above laboratory work up was unremarkable. C-reactive protein (CRP) was mildly elevated at 6.44 (<5.0 mg/L is considered

normal), Erythrocyte Sedimentation Rate (ESR) was normal. Additional laboratory work up including human immunodeficiency virus serology, syphilis screen, acute hepatitis panel, urine Histoplasma antigen, serum (1→3)-β-D-glucan, serum fungal serology by immunodiffusion, fungal blood cultures, serum interferon gamma release assay, were also negative.

A bronchoscopy was performed and it did not reveal any endobronchial lesions. Endobronchial ultrasound (EBUS) scope was introduced and a systematic survey of the mediastinal lymph nodes was conducted. This revealed enlarged lymph nodes in stations 7 and 11R. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal lymph nodes was performed. The adequacy of the specimens was confirmed with rapid onsite pathology. Following this, endobronchial specimens, endobronchial brushing and bronchoalveolar lavage (BAL) were obtained from right lower lobe, right and left upper lobes.

Biopsy of the mediastinal lymph nodes, bronchial brushing & BAL cytology were negative for malignancy. Stains for acid-fast bacilli were negative. Stained section of mediastinal lymph node showed numerous lymphocytes, histiocytes, many multinucleated giant cells, forming necrotizing granuloma. Grocott's Methenamine Silver (GMS) stain also revealed the presence of small uniform black yeast forms of approximately 2 to 4 μm in size (**Figure 5**). Some of these yeast forms showed narrow-based budding, overall morphology was consistent with Histoplasma. Gram's stain of BAL and biopsy specimens showed rare white blood cells, no organisms. Aerobic, anaerobic, acid fast bacilli and fungal cultures were negative. BAL viral respiratory panel was negative.

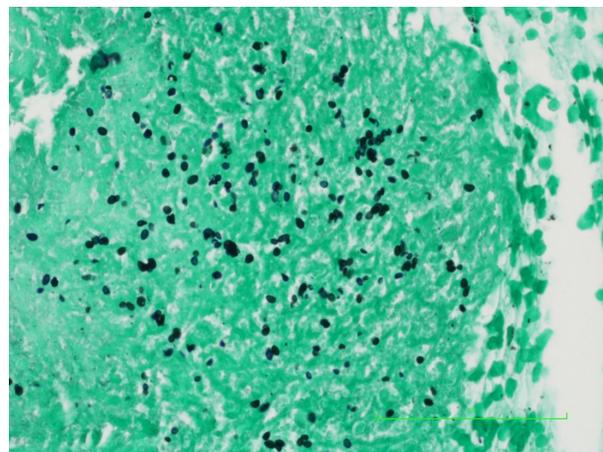


Fig. 5 Photomicrograph: Grocott's Methenamine Silver (GMS) stained section of mediastinal lymph node showing necrotizing granuloma containing small uniform black yeast forms of approximately 2 to 4 μm size with narrow based budding consistent with Histoplasma (GMS stain, 60X).

The patient was started on oral itraconazole for twelve weeks. She tolerated the treatment well and successfully completed her 12-week course of itraconazole for histoplasmosis with significant improvement in her symptoms.

Discussion

In this case report, we have described a case of pulmonary histoplasmosis in a healthy adult female living in Kentucky who presented with cough, dyspnea, pulmonary nodule and rheumatologic manifestations. This review focuses on the epidemiological, clinical, diagnostic, and therapeutic aspects of histoplasmosis.

Epidemiology

Histoplasmosis is a systemic mycotic infection caused by *Histoplasma capsulatum* [14]. It has two distinct pathogenic forms *H. capsulatum* var. *capsulatum* which is endemic in eastern United States and Latin America [3], and *H. capsulatum* var. *duboisii* which is prevalent in Africa and South East Asia [4]. Histoplasmosis is among the most common endemic mycosis in the United States with the largest burden of disease occurring in mid-western states around the Ohio and upper Mississippi River Valleys [13]. In the United States, an estimated 60% to 90% of people who live in areas surrounding the Ohio and Mississippi River valleys (where *Histoplasma* is common in the environment) have been exposed to the fungus at some point during their lifetime [15]. State-specific annual incidence rates in the mid-west range from 0 to 4.3 cases/100,000 population [16]. Our case is a good example of pulmonary histoplasmosis in an immunocompetent individual living around the Ohio River Valley which is endemic for Histoplasmosis.

Mycology

Histoplasma capsulatum is a dimorphic fungus. The organism exists in the mold (mycelial) form in the soil and switches to the yeast form at normal human body temperatures. It finds a natural habitat in soil with high nitrogen content such as areas contaminated by bird or bat excrements. Birds do not transmit the disease; however, bird excretions contaminate the soil, thereby enriching the growth medium for the mycelium. Contaminated soil can be potentially infective for years [17].

Pathogenesis

During outdoor activities, *H. capsulatum* enters the human host by inhalation of fungal conidia or mycelia fragment. Once inhaled these fungal elements convert to the yeast form and replicate within the macrophages, and then spread to the regional lymph nodes, and throughout the reticuloendothelial system via parasitized macrophages [18]. Macrophages initially are able to ingest but not kill the fungi [19, 20]. The infected macrophages induce inflammatory response and recruit more macrophages, lymphocytes and plasma cells to destroy the organism and arrest infection. These coalesce together to form granulomas consisting of giant cells with central caseous necrosis, which further undergoes fibrosis and calcification [21]. Even with the development of cell-mediated immunity, patients can have remaining foci of viable *H. capsulatum* in various organs, similar to tuberculosis. These organisms are held in check by the immune response but are not completely killed, and thus, reactivation of infection years later is possible [13].

Clinical Manifestations

Clinical findings of histoplasmosis are varied, and the disease should be considered in the following clinical presentations, particularly in the appropriate epidemiologic setting: Pneumonia with mediastinal or hilar lymphadenopathy, mediastinal or hilar masses suggestive of malignancy or

tuberculosis, pulmonary nodule suggestive of malignancy, cavitary lung disease suggestive of tuberculosis, pericarditis with mediastinal lymphadenopathy, pulmonary manifestations with arthritis or arthralgia plus erythema nodosum, and suspected sarcoidosis [22].

In most healthy individuals, the most common outcome after low-level exposure is asymptomatic pulmonary histoplasmosis [10]. Asymptomatic cases are usually identified based upon incidental chest imaging findings such as abnormal radiographs or computed tomographic (CT) scans showing enlarged mediastinal or hilar lymphadenopathy or pulmonary nodules. Less than five percent of exposed individuals develop symptomatic disease after a low-level exposure to *H. capsulatum* [11]. Symptomatic pulmonary histoplasmosis, as noted in our case report, presents as a subacute pulmonary infection weeks to months following exposure. Symptoms are usually mild, and may be accompanied by rheumatologic and/or dermatologic manifestations or pericarditis in approximately 5% of patients [13]. Myalgia and arthralgia are common symptoms during acute infection and appear to be more common in women [23]. The arthritis is poly-articular and usually symmetric and involves large or small joints [23]. Joint symptoms usually resolve spontaneously over several weeks and respond to nonsteroidal anti-inflammatory agents. About fifty percent of the patients with joint symptoms develop skin lesions. Erythema nodosum and erythema multiforme are the most common skin manifestations [24, 25]. They occur most frequently in women and are thought to be associated with a hypersensitivity response to the antigens of *H. capsulatum* [24-26]. Our patient presented with cough, dyspnea and pulmonary nodule accompanied with rheumatologic manifestations. Patients who live in endemic area and present with above clinical features, histoplasmosis should be strongly considered in the differential diagnosis, and appropriate diagnostic work up should be performed.

Patients who inhale a large inoculum can develop a severe and potentially fatal acute diffuse pulmonary infection [10, 27-30]. The onset of illness is abrupt, symptomatic infection can occur within a week or two [31-33], presenting with fever, chills, malaise, dyspnea, cough, and chest pain. Chest radiographs show diffuse reticulo-nodular or miliary pulmonary infiltrates. Disease can progress to respiratory failure or progressive extrapulmonary dissemination [28, 34-35]. Acute respiratory distress syndrome can occur within a few days [28-29].

Mediastinal granuloma or granulomatous mediastinitis is a rare complication of pulmonary histoplasmosis. Mediastinal lymphadenopathy is common in acute histoplasmosis. However, instead of enlargement of a few nodes that eventually recede and ultimately calcify as the host handles the infection, mediastinal granuloma is characterized by enlarging, encapsulated, caseous mediastinal lymph nodes which can remain enlarged for months to even years. Yeast forms of *H. capsulatum* can sometimes be seen in the midst of necrotic material that is obtained by needle aspiration or tissue biopsy [13].

Many patients are asymptomatic, and the nodes are discovered on a chest radiograph or computed tomographic (CT) scan of the chest. Radiographs show enlarged hilar, sub-carinal, or para-tracheal lymph nodes. However, others may experience variety of symptoms including chest pain, cough, hemoptysis, and dyspnea due to encroachment of this mass of nodes around

mediastinal structures such as esophagus, pulmonary vessels and superior vena cava [10, 36-39]. Rarely, the nodes may drain spontaneously into the adjacent soft tissues of neck or airways causing broncho-esophageal or trachea-esophageal fistula or even the pericardium [10, 37, 40-41]. Chest imaging findings in our patient showed mediastinal lymphadenopathy but no characteristic findings of granulomatous mediastinitis mentioned above were noted.

The development of disease associated with the initial dissemination of *H. capsulatum* is dependent on the host. Patients who are immunosuppressed and are unable to develop effective cell-mediated immunity against the organism are likely to manifest symptomatic disease during the period of acute dissemination. Progressive, clinically evident dissemination occurs primarily in patients with underlying immunosuppressive disorders. This includes patients with AIDS, hematologic malignancies, organ transplant recipients, or those who are on medications such as corticosteroids [8, 42-46].

Differential Diagnosis

Differential diagnosis of acute pulmonary histoplasmosis includes acute pulmonary blastomycosis, coccidioidomycosis, and atypical community-acquired pneumonias, such as those due to *Mycoplasma*, *Legionella*, and *Chlamydia*. Our patient's initial clinical presentation was thought to be due to bacterial community acquired pneumonia, however our patient failed to respond to multiple courses of different oral antibiotic therapy. Hilar or mediastinal lymphadenopathy is common with histoplasmosis and can be seen with blastomycosis but would be extremely uncommon with community-acquired pneumonia caused by *Mycoplasma*, *Legionella* and *Chlamydia*. Other possibilities include conditions in which parasitized macrophages are seen, such as leishmaniasis and *Penicillium marneffei* infections [47]. The parasites in leishmaniasis lack the clear halo seen in *H. capsulatum* and tend to aggregate at the periphery of the macrophage (marquee sign). *Leishmania donovani* (LD) bodies can be distinguished by a nucleus and bar-shaped kinetoplast within each amastigote and it is negative for Periodic acid-Schiff (PAS) stain [47]. The *Penicillium marneffei* yeast forms replicate by binary division and have a septate appearance, whereas *H. capsulatum* divides by narrow-based budding [47]. In the case of histoplasmosis, as noted in our case report, numerous small 2–4 μm in diameter yeast-like microorganisms may be seen within macrophage, multinucleate giant cells, or within fibrous tissue [48]. Patients who have hilar lymphadenopathy, arthralgia, and erythema nodosum can be mistakenly given the diagnosis of sarcoidosis [49, 50]. Also, the early clinical manifestations of disseminated histoplasmosis are nonspecific, often leading to diagnostic difficulty and misdiagnosis as tuberculosis, lymphoma or metastatic malignancy [51]. Thus, in the appropriate epidemiologic setting, testing for histoplasmosis should be included for patients who are under evaluation for these aforementioned conditions.

Diagnosis

Health care providers must be aware of the clinical syndromes and a careful history of possible exposure to *H. capsulatum*, epidemiologic clues, namely activities of daily living, travel and occupations that expose the patient to sites contaminated with bat or bird droppings are crucial to arriving at the correct diagnosis. Also, clinicians must be familiar with the uses and limitations of the diagnostic tests for fungal diseases.

The clinical picture, chest radiographic findings and histopathology using stains for fungi, cultures, antigen detection, and serologic tests for *Histoplasma*-specific antibodies can all help make the diagnosis of pulmonary histoplasmosis [52].

Detection of polysaccharide antigen by enzyme immunoassay (EIA) in either the urine, blood, or bronchoalveolar lavage fluid is useful in clinically ill patients in need of a quick diagnosis. Most studies have been performed using a commercial test that is currently available in the United States. In these studies, an *H. capsulatum* galactomannan can be detected in 60 to 83 percent of patients with acute pulmonary histoplasmosis [52, 53]. The highest sensitivity is obtained by testing both urine and serum [54]. Our patient had a negative urine *Histoplasma* antigen test.

False-positive reactions for *Histoplasma* antigen in urine are common among patients who have other endemic mycoses such as blastomycosis, penicilliosis, and paracoccidioidomycosis. In one study, 8 of 9 patients with paracoccidioidomycosis, 12 of 19 with blastomycosis, and 17 of 18 with penicilliosis had urine antigen tests that were positive for *Histoplasma* antigen [55]. In North America, there is little concern about this lack of specificity, except for those patients who have blastomycosis, because only the areas of endemicity of histoplasmosis and blastomycosis overlap [56].

Although not an antigen test, detection of (1 \rightarrow 3)- β -D-glucan (BG) in serum has been shown to be a useful adjunct for diagnosis of invasive fungal infections, especially candidiasis, aspergillosis, pneumocystosis, and histoplasmosis [57-59]. The sensitivity of the test was 87% in histoplasmosis cases and it had a specificity of 68% with controls. Histoplasmosis should be considered as a possible cause for a positive BG test, but such results may be found with many other conditions that are clinically similar to this fungal disease [60]. Our patient had a negative BG test.

Serologic tests for antibodies provide the basis for diagnosis in patients with mild infections, but require at least a month to appear after the initial exposure. Also, serologic testing may not be reliable in patients without a compatible clinical picture or epidemiologic risk factors. The standard assays are the complement fixation (CF) test that uses two separate antigens, yeast and mycelial (or histoplasmin), and the immunodiffusion (ID) assay. Less than 1 percent of residents in endemic areas are seropositive by the immunodiffusion test and less than five percent have positive complement fixation assays [61]. Diagnosis is based on a fourfold rise in CF antibody titer; a single titer of 1:32 is suggestive but not diagnostic. CF antibodies persist for years after infection; thus, the presence of a single low CF titer means little other than that the patient was exposed to *H. capsulatum* at some time [13]. The CF test appears to be less specific than the ID assay; False-positive CF tests occur in patients with lymphoma, tuberculosis, sarcoidosis, and other fungal infections, all of which may present as a mediastinal mass [13, 62-63]. Tissue biopsy is always required in these instances. Antibody assays may be falsely negative in immunosuppressed patients. Antibodies can remain positive for several years and thus may not indicate disease activity [61]. For those patients who have mediastinal lymphadenopathy, antibody assays may or may not be positive and cannot be relied upon to make a definitive diagnosis. Our patient had a negative serum *Histoplasma* antibody by immunodiffusion test.

The role of polymerase chain reaction (PCR) for diagnosis of histoplasmosis is uncertain. Several laboratories are working on developing PCR assays that might help with a more rapid identification of *H. capsulatum* [64-66]. In one study, PCR was less sensitive and was positive in only 8% of urine specimens from patients with histoplasmosis [67]. In another study, PCR was negative in one third of tissues in which yeast was seen by histopathology [68]. Currently there are no validated, and commercially available PCR methods for diagnosis of histoplasmosis.

Fungal cultures can be sent from infective material such as blood, bone marrow or sputum, and they should be observed for 6–8 weeks before they may be considered negative. They are useful in patients with chronic pulmonary histoplasmosis and submission of multiple sputum or bronchoalveolar lavage cultures produces a positive yield in the majority of cases [69]. The sensitivity of respiratory cultures is much lower in localized disease or acute disease [70]. Samples of tissue or body fluids sent to the laboratory for culture are plated onto Sabouraud's dextrose agar (SDA) and incubated at 25°C to allow for growth of the mycelial phase of *H. capsulatum*. After several weeks, and sometimes as long as 6 weeks, growth of a white to light tan mold occurs. Two types of conidia are produced on the hyphae. The macroconidia, or tuberculate conidia, are 8 to 15 μm in diameter and have distinctive projections on their surface; the microconidia are small (2 to 4 μm) and smooth walled. Identification of the tuberculate macroconidia allows a presumptive diagnosis of histoplasmosis. A definitive test to verify that the mold is *H. capsulatum* should always be performed. There is a commercially available chemiluminescent DNA probe which can be used for definitive identification of *H. capsulatum* [71].

Morphologic findings in biopsy specimens include granulomas, lymphohistiocytic aggregates, and diffuse mononuclear cell infiltrates. Histopathologic examination of lung or mediastinal lymph node tissue using special stains may show yeast-phase organisms of *Histoplasma*, measuring 2 to 4 micron in diameter, with narrow based budding (as noted in Figure 5 of our case report). Cultures are usually negative. Other organisms can mimic the appearance of *H. capsulatum* in tissues such as *Candida glabrata*, *Cryptococcus neoformans*, *Pneumocystis jirovecii* and *Leishmania*, but radiological and clinical picture will generally separate histoplasmosis from the others [13].

Treatment

Most infections caused by *H. capsulatum* are self-limited and require no therapy. However, patients who are exposed to a large inoculum of *Histoplasma* and those who are immunocompromised usually require antifungal therapy [22]

Amphotericin B, Itraconazole, voriconazole, posaconazole, isavuconazole and fluconazole, all have in vitro activity against *H. capsulatum*. Itraconazole is generally preferred for mild to moderate histoplasmosis, and amphotericin B has a role in the treatment of moderately severe and severe infections [72].

The Infectious Diseases Society of America (IDSA) has published clinical practice guidelines that are based upon open-label studies, case reports, and expert opinion [72]. According to a 2007 update by the Infectious Disease Society of America clinical practice guidelines for the management of

histoplasmosis, no treatment is recommended for patients with asymptomatic mediastinal granuloma as self-resolution may occur. The recommendation for symptomatic patients is medical management alone with 6–12 weeks of oral itraconazole [72].

For moderately severe to severe acute pulmonary histoplasmosis, lipid formulation of amphotericin B (3.0–5.0 mg/kg daily intravenously for 1–2 weeks) followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks) is recommended [72].

For mild-to-moderate acute pulmonary histoplasmosis, treatment is usually unnecessary. Oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for >1 month [72].

Treatment for asymptomatic pulmonary nodules (histoplasmosis) or mediastinal adenopathy is usually not indicated [51]. In the presence of persistent symptoms, accompanied by positive antigen tests, CF titers of 1:32 or higher, histopathology showing yeast resembling *H. capsulatum* or positive cultures, oral itraconazole treatment may be appropriate if no symptomatic improvement occurs after 1 month of observation [12]. Our patient had persisting symptoms for 2 months and histopathology of mediastinal lymph node showed necrotizing granuloma and Grocott's Methenamine Silver (GMS) stain also revealed the presence of yeast forms with narrow-based budding consistent with *Histoplasma*. She was treated with oral itraconazole for 12 weeks with significant improvement in her symptoms.

Arthritis or arthralgia with erythema nodosum occurs in 5%–10% of cases as a systemic inflammatory response to acute pulmonary histoplasmosis [24, 27]. These manifestations do not represent infection, and they respond to nonsteroidal anti-inflammatory agents without antifungal therapy. In some cases, the manifestations are moderately severe, requiring treatment with corticosteroids [27]. If corticosteroids are used, concurrent itraconazole treatment is recommended to reduce the risk of progressive infection.

Prevention

There is no vaccine against histoplasmosis. In areas where the fungus is common, it may not be possible to prevent infection. Pets, particularly cats & dogs, can get histoplasmosis, but it is not contagious between animals and people [73]. Birds don't appear to be able to get histoplasmosis. It may be difficult to avoid inhaling the spores of *Histoplasma* in the areas where it is endemic. Avoiding areas with bird and bat droppings may provide some protection. Wearing a respirator face mask can provide protection for workers in contaminated areas.

Conclusion

In conclusion, we report a case of pulmonary histoplasmosis in a patient presenting with cough, dyspnea, pulmonary nodule and rheumatologic manifestations. Our case highlights the fact that histoplasmosis can present with variable manifestations in immunocompetent individuals living in endemic region for histoplasmosis. Our patient presented with nonspecific symptoms with a vast differential diagnosis prompting a thorough work up and eventually leading to endobronchial ultrasound-

guided transbronchial needle aspiration cytology (EBUS-TBNA) of mediastinal lymph nodes demonstrating necrotizing granuloma with fungal stains positive for *Histoplasma*. Patient was treated with antifungal therapy and showed significant clinical improvement. This fungal disease accounts for a good number of cases of nonspecific flulike illness especially in endemic areas, but its inconsistent clinical manifestations often hinder a straightforward diagnosis. Thus, a high degree of suspicion and epidemiological reasoning on the part of the health care providers is required to consider histoplasmosis in differential diagnosis. In this context, our case report illustrates the following points: 1) cough, dyspnea and pulmonary nodule (accompanied with rheumatologic and/or skin manifestations) in patients especially living in the endemic areas should always alert the clinician of the possibility of histoplasmosis. 2) Starting oral antifungal therapy (Itraconazole) may lead to favorable outcomes in patients presenting with pulmonary nodule and/or mediastinal lymphadenopathy with persisting symptoms for more than one month and histopathology showing yeast resembling *H. capsulatum*.

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