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Acute pulmonary histoplasmosis following cave exploration in Ecuador

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Abstract

Pulmonary histoplasmosis poses a challenge to clinicians from both clinical and diagnostic perspectives. Epidemiologic clues and a careful exposure history, as well as patterns on chest imaging, may raise appropriate suspicion for the diagnosis. Proper interpretation of serologic and antigen-based testing is also critical for more rapid recognition and treatment of pulmonary histoplasmosis. We present an illustrative case of acute pulmonary histoplasmosis in a traveler returning to the United States from a remote area of Ecuador following a significant exposure to bat guano. Computed tomography of the chest revealed an unusual lung pattern – cannonball lesions – which prompted consideration of alternative diagnoses rather than a sole focus on the standard treatment of community-acquired pneumonia. Results of endemic fungal serologies and antigen-based testing required careful interpretation and ultimately led to the diagnosis of acute pulmonary histoplasmosis. Initiation of antifungal treatment led to a full recovery.

Keywords: Histoplasma; Pneumonia; Cannonball lesions; Bat guano.

Introduction

Pulmonary histoplasmosis poses a challenge to clinicians given the variety of presentations and need for careful interpretation of diagnostic tests. We present a case of acute pulmonary histoplasmosis in a traveler returning to the United States from a remote area of Ecuador where he had significant exposure to bat guano while spelunking.

Case report

A 67 year-old man with past medical history of bipolar disorder (receiving escitalopram oxalate) and obstructive sleep apnea traveled to Ecuador over a one-month period from February to March. He spent time on the beach and in rural areas, interacting with indigenous residents of remote villages. He traveled with his wife and a friend, staying in hostels where he drank and bathed using locally sourced water. He reported exposure to sand fleas on the beach and mosquitos in numerous locations. About one week prior to his return to the U.S., he and his traveling companions drove to a remote village in south central Ecuador on the Peruvian border. They boarded a river boat and paddled downstream where they docked before climbing a hill to reach a large cave. His companions declined to enter the cave upon seeing a large number of bats flying near the entrance. The patient entered the cave, hiking to the far side and returning after spending about 30 minutes inside. A large colony of bats was noted inside the cave, and although he suffered no known bites, scratches, or other trauma through direct contact, bats were flying close enough to his head that he could feel them routinely brush through his hair. The cave was dark,

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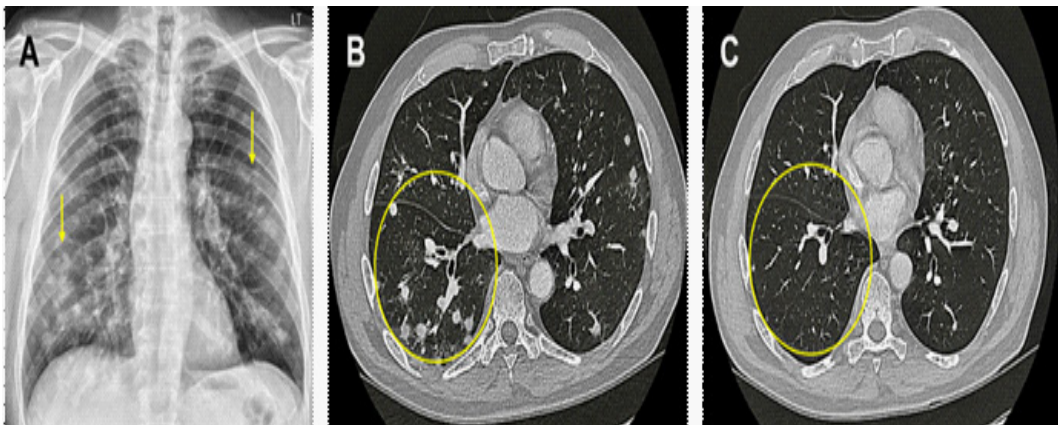

Figure 1: Cannonball lung lesions with acute pulmonary histoplasmosis.
Chest radiograph **(A)** revealed scattered, nodular opacities predominant within the right lower lobe and inferior portion of the left upper lobe (arrows). Computed tomography (CT) performed prior to antifungal therapy **(B)** revealed discrete, rounded "cannonball" lesions bilaterally. Representative lesions are noted within highlighted field of the right lower lobe (yellow circle). Repeat CT following 11 weeks of antifungal therapy **(C)** revealed resolution of the majority of lesions.

with walls encased in bat guano such that the patient's hands and clothes were covered with guano by the time he exited. After returning to the village, the patient used available running water in the shower to wash a thick layer of bat guano from his upper extremities and clothing. While doing so, aerosolized water containing bat guano repeatedly splashed in his face.

He returned to the U.S. about 1 week after spelunking, and he began to feel poorly about 2 days later with new onset of fatigue, fever, chills and night sweats. His recorded temperature was as high as 1050 Fahrenheit using an oral thermometer and remained elevated over the ensuing 48-72 hours. He sought medical attention at an urgent care facility 3 days after symptom onset, having suffered emesis and diarrhea just prior to the visit, but denying respiratory symptoms, rash, headache, or neck stiffness. A nasopharyngeal swab was collected for COVID, influenza A/B, and RSV PCR testing with negative results. Urinalysis revealed only mild proteinuria, and no hematuria or pyuria. A diagnosis of viral gastroenteritis was made, and robust fluid intake was recommended.

His fever seemed to abate within 72 hours following the urgent care visit, although he continued to suffer chills. He returned to the same clinic about 1 week later (10 days after symptom onset, 19 days after spelunking) where he reported interval development of pain in his lower chest bilaterally with deep inspiration and a non-productive cough. He also reported progressive drenching night sweats, ongoing fatigue and anorexia, and an occipital headache attributed to neck muscle soreness. He denied diarrhea, abdominal pain, rash, joint pain, neck stiffness, red eyes or photophobia. He was afebrile and without hypoxia. Examination revealed clear lungs to auscultation, no meningeal signs, no conjunctival suffusion, and no abdominal pain, adenopathy, or hepatosplenomegaly. He reported his spelunking activity to providers at this visit, prompting additional testing. Laboratory assessment revealed a peripheral white blood cell count of 7,200 x 10^6 cells/L, normal renal function, elevated total protein level of 8.8 g/dL, normal albumin level of 4.0 g/dL, mild elevations of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) at 45 U/L and 83 U/L, respectively, and a normal serum alkaline phosphatase level of 109 U/L. Qualitative assays for both Histidine-Rich Protein II (HRP2) specific to Plasmodium falciparum, and a pan-malarial antigen shared by all malaria species, were negative. Chest radiography revealed scattered bilateral nodular opacities predominant in the right lower lobe and the inferior portion of the left upper lobe. (Figure 1A) Given initial concern for bacterial pneumonia, he was prescribed amoxicillin/clavulanate 875/125 mg twice daily for a 7-day course, as well as a single dose of azithromycin 500 mg followed by 250 mg daily for an additional four days.

Following three days of antibacterial therapy with no clinical improvement, Chest Tomography (CT) was ordered. This revealed innumerable discrete, rounded "cannonball" lesions scattered throughout both lungs and located more peripherally, with each nodule measuring about 1 cm in average diameter. (Figure 1B) A QuantiFERON Gold assay and urine antigen testing for Streptococcus pneumoniae and Legionella pneumophila were negative. Qualitative serum Histoplasma and Blastomyces antigen assays also yielded negative results, but urine Histoplasma antigen was detectable. With these results, he was referred to an infectious disease specialist.

On further questioning in the infectious disease clinic two weeks after initiation of antibacterial therapy (and 33 days after spelunking), he reported no noticeable improvement with ongoing fatigue, drenching night sweats, dyspnea on exertion and relatively severe pleurisy. In reviewing his medical history, he had not been diagnosed with any form of immune compromise and was not receiving immunosuppressive treatment including systemic or inhaled corticosteroids. He reported having been tested for HIV on several occasions with negative results, and he had been in a monogamous relationship with his wife of several years. On examination, he was not diaphoretic and appeared comfortable at rest. Scattered expiratory wheezing was noted on auscultation of his chest. There were a few small, scattered, red, nodular, pruritic lesions on his left index finger and dorsum of his right hand. He had no discernable lymphadenopathy, oral lesions, or hepatosplenomegaly. A 4th generation antibody assay and p24 antigen testing for HIV-1 and HIV-2 yielded negative results. Coccidioides immunodiffusion and complement fixation

assays for antibody detection were negative. A screening enzyme immunoassay (EIA) for Blastomyces antibodies was positive, but both confirmatory Blastomyces ID antibody and quantitative tests for Blastomyces antigens in serum and urine were negative. A complement fixation assay revealed detectable Histoplasma antibodies with a titer of 1:16, while Histoplasma antibodies were not detected using an immunodiffusion assay.

Given detection of both Histoplasma urine antigen and antibodies, coupled with his extensive exposure to bat guano and his chest imaging results, he was diagnosed with acute pulmonary histoplasmosis. Antibacterial therapy was discontinued, and he was initiated on oral itraconazole solution using 200 mg three times daily for the first 3 days, followed by 200mg twice daily. Peripheral blood was collected 4 weeks after initiating itraconazole and revealed a normal peripheral white blood cell count, as well as normalization of total protein, AST, and ALT levels. Serum itraconazole and hydroxyitraconazole levels were 2.1 ug/mL and 3.2 ug/mL, respectively (composite itraconazole level of 5.3 ug/mL). He was experiencing mild nausea, and given his composite itraconazole level >5 ug/ml, his dose was reduced to 100 mg twice daily. About 7 weeks after initiating itraconazole, he reported substantial improvement with resolution of fever, chills, and muscle aches, and disappearance of the nodular skin lesions on his hands. He also reported significant reduction in dyspnea with only an intermittent non-productive cough. 11 weeks after initiating therapy, he had no audible wheezing on examination and reported only a rare, intermittent non-productive cough along with complete resolution of dyspnea and resumption of normal activity. A repeat Histoplasma urine antigen test was negative, and chest CT revealed resolution of the majority of cannonball lesions. (Figure 1C) With these results, itraconazole was discontinued. 5 months after completing antifungal therapy, he reported no residual fever, shortness of breath, or cough.

Discussion

Our patient's presentation of fever, progressive shortness of breath, pleurisy and cough beginning about 9 days after significant bat guano exposure. Coupled with lack of response to antibacterial therapy, his presentation was consistent with acute pulmonary histoplasmosis. Exposure to Histoplasma is well-documented following cave exploration, and specifically bat caves, with a direct correlation between time spent in these caves and symptomatic Histoplasma infection [1,2]. Symptomatic infection in immune competent individuals following exposure is relatively uncommon, occurring in only 5% or fewer cases [3,4]. Symptomatic infection in this case and the relatively short incubation period, in contrast to the typical incubation period of several weeks, was likely related to his more extreme exposure to Histoplasma in the cave in Ecuador [4]. Clinical presentations of histoplasmosis include acute and usually self-limited pneumonia, chronic cavitary pneumonia, lymph node calcification and endobronchial lesions mimicking malignancy, or mediastinal lymphadenitis with progression to granuloma formation and local complications. Rare presentations with immune-mediated pathogenesis (not amenable to antifungal therapy) include fibrosing mediastinitis with compression of vasculature or other structures. Disseminated disease with multiorgan involvement is seen more commonly with immune deficiency [4,5]. Of note, our patient also presented with relatively small erythematous, pruritic nodules on the dorsi of his hands which seemed to resolve following antifungal therapy. Among the protean dermatologic manifestations of Histoplasma infection include small papulopustular lesions, although these are probably more common with disseminated disease in immune compromised hosts [6]. It was possible that the patient's rash related instead to antibacterial therapy or other medications taken while he was ill since the lesions had not been recognized at the onset of his respiratory illness.

Chest imaging in this case revealed bilateral, discrete, rounded infiltrates within the lungs referred to as cannonball lesions (Figure 1). Histoplasma infection has been recognized, albeit only rarely, as a cause of cannonball lesions [7]. More common radiographic manifestations include focal infiltrates (occasionally with mass-like appearance), cavitary lesions, and mediastinal or hilar adenopathy [8]. In some cases, with acute illness following extensive exposure, more diffuse reticulonodular infiltrates with miliary pattern are observed, occasionally with progression to acute respiratory distress syndrome [9]. While consensus size criteria for cannonball lesions have not been defined, larger lesions are classically associated with lung metastases from pancreatic and endometrial cancer, renal cell carcinoma, testicular choriocarcinoma, and other gastrointestinal malignancies [10-12]. Other infectious etiologies associated with similar-appearing lesions of varying sizes include Mycobacterium tuberculosis (MTb), Aspergillus, other endemic fungi including Cryptococcus and Blastomyces, and non-tuberculous mycobacteria. Non-infectious etiologies of cannonball lesions include extramedullary hematopoiesis with advanced myelodysplastic syndromes [13], vasculitis [14], and cryptogenic organizing pneumonia [15]. With no clear etiology and lack of clinical or radiographic response to treatment, direct sampling of cannonball lesions for histopathologic assessment and culture is important. Their relation in this case to Histoplasma infection was implied with their virtual disappearance with itraconazole.

Positive results for both Histoplasma antibodies and urine Histoplasma antigen testing, coupled with clinical and radiographic response to antifungal therapy, confirmed the diagnosis in this case. Histoplasma antibodies are detectable in the vast majority of acutely infected patients (up to 96%) beginning around 4 weeks after symptom onset, with maximal titers noted within 2-3 months [16]. Of note, the sensitivity of antibody detection is greater with the use of complement fixation relative to immunodiffusion assays (about 90% versus about 80%, respectively), although specificity is greater with immunodiffusion assays [16]. Complement fixation titers >1:32 are generally considered diagnostic of acute infection, although titers >1:8 are suggestive of acute infection, with about one-third of patients with acute presentations exhibiting complement fixation titers between 1:8 and 1:16 [17]. It was possible that the complement fixation titer of 1:16 in this case (and negative result for the immunodiffusion assay) reflected the timing of serologic testing (about 3 weeks following symptom onset). Higher titers would have been anticipated with convalescent testing which was not performed at the patient's discretion. Other limitations of complement fixation testing include cross-reactivity with antibodies recognizing other fungi including Coccidioides and Blastomyces, as well as false-positive results seen with pulmonary tuberculosis and sarcoidosis [18]. In fact, false-positive rates of around 15% have been documented for the complement fixation assay [19]. A screening EIA for Blastomyces antibodies was also positive, but not confirmed by either Blastomyces-specific immunodiffusion antibody or antigen detection. EIA is often paired with immunodiffusion testing for Blastomyces antibody detection since EIA is more sensitive but carries a higher false-positive rate, and with cross-reactivity with Histoplasma antibodies. In

contrast, the specificity of the Blastomyces immunodiffusion assay approaches 100% [20,21]. Blastomyces infection was unlikely in this case with lack of detection of antibodies using the immunodiffusion assay, as well as lack of urine or serum antigen detection. This was consistent with available data suggesting that the fraction of bats which harbor Blastomyces is very small relative to Histoplasma [22], whereas Histoplasma colonization of bats in Ecuador, and human infections associated with bat exposure there, is well-documented [23].

Histoplasma antigen testing should be performed if acute histoplasmosis is suspected. The sensitivity of serum Histoplasma antigen testing is higher for disseminated disease in immune compromised patients (>90%) and generally ranges from 60-88% in cases of pulmonary histoplasmosis although could be as low as 30-40%. There is also potential value in performing both urine and serum antigen testing, with the possibility that only one or the other may be positive and with collective sensitivity >80% [24]. Combining antigen and antibody testing is helpful, with sensitivity of the combination potentially as high as 96% [25]. With negative results for non-invasive testing, bronchoalveolar lavage (BAL) may be helpful for confirming the diagnosis. The sensitivity of BAL Histoplasma antigen testing (>90%) likely exceeds that of serum or urine testing in cases of pulmonary histoplasmosis [26] and can be complemented by cytopathology and fungal culture of BAL fluid. Of note, Blastomyces antigen testing might reveal a false-positive result in about 60% of cases of histoplasmosis [27]. These issues highlight the challenge of interpreting diagnostic tests in these cases, and antibody testing should be accompanied by antigen testing and fungal cultures of respiratory specimens (ideally BAL) as well as cytopathology whenever possible and if epidemiologic clues and exposure history are less compelling.

Our patient received itraconazole for 11 weeks and made a full clinical recovery, and with significant reduction in the number of cannonball lesions on repeat CT performed at the conclusion of treatment. Of note, radiographic abnormalities may persist for several months, and calcification within small lung nodules or lymph nodes may persist for years [4]. Whether immune competent patients with acute pulmonary histoplasmosis require antifungal therapy is also a matter of debate, since some acute presentations may represent immune-mediated hypersensitivity to the organism and with the self-limited nature of more mild forms of the illness [28]. Given his more extreme exposure with diffuse bilateral cannonball lesions on CT, ongoing fever and dyspnea 1 month after symptom onset, and case reports of otherwise healthy individuals developing acute respiratory distress syndrome following bat guano exposure and spelunking [29,30], we opted to proceed with antifungal therapy. Itraconazole provides effective therapy for many forms of pulmonary histoplasmosis, and a duration of 6-12 weeks is recommended for acute pulmonary infection [28]. The liquid formulation is preferred given its superior bioavailability, and it should be taken on an empty stomach one hour before or two hours after meals since food intake will reduce absorption. The most common side effects are diarrhea and nausea, and serum itraconazole levels should be checked periodically. Combining itraconazole and hydroxyitraconazole levels is recommended, with composite target levels in the 1-5 ug/ml range commensurate with both treatment success and minimal toxicity [28]. With disseminated disease or ongoing respiratory distress and radiographic progression with pulmonary histoplasmosis, liposomal amphotericin preparations should be used.

Conclusion

This case highlights the clinical and diagnostic challenges related to pulmonary histoplasmosis. Patients with progressive respiratory illness or fever, developing over a more prolonged timeframe, unresponsive to standard antibacterial therapy, and especially following a compelling epidemiologic exposure, should be evaluated for Histoplasma infection. Clinicians should become familiar with the various radiographic presentations of pulmonary histoplasmosis which would aid in recognition of the disease, as well as proper interpretation of serologic and antigen-based testing.

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