Traveler to Uganda

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A 25-year-old, otherwise healthy female who traveled to Uganda 2 weeks prior to presentation complained of dyspnea on exertion and cough productive of clear sputum. Notably, she was concerned that several colleagues who traveled with her were displaying similar symptoms.

The patient was a graduate student who studied malaria in birds and mammals and had undertaken a research project in the rainforest of western Uganda near Fort Portal for the previous 2 months. The goal of the expedition was to collect and test the blood of various animals. She reported coming into contact with rats, mice, shrews, civets, bats, other small mammals, and various birds. She took part in capturing, drawing blood from, and skinning these animals. She did not use contact precautions consistently and did not use airborne precautions. Her team entered a large, hollow tree (Fig. 1.1) that housed insect-eating bats. In the cavity of the tree, she collected bats and bat droppings. Her team also placed traps for fruit-eating bats, and she drew their blood without the use of gloves. She did not skin any fruit-eating bats. Bat genera that she encountered on the trip included Hipposideros, Epomops, and Epomophorus.

There was a variety of monkeys inhabiting the area around the town where she lived, but she did not have direct contact with any of them.

The patient and her team swam in flowing streams but did not swim in ponds or other bodies of standing water. The patient reported that she took atovaquone/proguanil for malaria prophylaxis for only 6 weeks of the 8-week trip, and she recalled suffering from numerous mosquito bites. She consumed local dishes, which included meat from chickens and goats butchered by her research team. She also ate local fish dishes. All meat and fish she consumed were cooked. She denied any sexual activity during the trip. She was not aware of contact with anyone ill with tuberculosis.

Several weeks into the trip, the patient and the other members of her team developed high fevers, chills, malaise, and cough. The team was
empirically treated for possible leptospirosis with a 12-day course of oral doxycycline. While on doxycycline, the patient discontinued taking the atovaquone/proguanil because she was concerned for toxicity and drug interactions. After starting doxycycline, she reported that the headaches, fevers, and chills resolved but the cough persisted. When she returned to Chicago from her trip, two of her colleagues fell ill. A Ugandan collaborator was diagnosed with pulmonary tuberculosis based on a chest x-ray (CXR) and was being empirically treated. A coworker from the United States developed shortness of breath and cough, and his physicians suspected that he had tuberculosis.

The patient had no significant past medical or surgical history. Her family history was not remarkable. She was a daily smoker and drank alcohol socially, but she did not use illicit drugs. Her only regular medication was oral contraceptive pills. She was up to date with her childhood vaccines, had a rabies vaccine 5 years prior to presentation, and had received the influenza vaccine within the year. She was allergic to penicillin, which caused anaphylaxis.

On physical examination, the temperature was 96.8 °F, heart rate was 75 beats per minute, blood pressure was 122/80 mmHg, respiratory rate was 16 breaths per minute, and oxygen saturation was 99% breathing room air. She was in no acute distress and breathing comfortably. She had no rash, no conjunctival pallor or injection, and no nasal discharge. Her oropharynx was without lesions or abnormality, and she had no lymphadenopathy. The heart demonstrated a regular rhythm with no murmur, and the lungs were clear to auscultation bilaterally. The abdomen was benign, and she had no edema in the lower extremities. The neurologic exam was nonfocal, and her thought process was clear.

The complete blood count and complete metabolic panel were normal. Her CXR (Fig. 1.2) revealed a diffuse miliary pattern throughout the lungs without pleural effusion or pneumothorax.

The differential diagnosis is presented in Tables 1.1 and 1.2. The differential diagnosis for a miliary pattern on CXR includes tuberculosis; endemic fungal pathogens; bacterial infections including psittacosis, tularemia, bartonellosis, and brucellosis; parasitic diseases including

Table 1.1 Differential diagnosis for miliary infiltrates on chest x-ray

| No. | Diagnosis |
|-----|-----------|
| 1.  | Micronodules can be seen in multiple infectious and noninfectious diseases |
| 2.  | Miliary infiltrates refer to the presence of multiple pulmonary micronodules of millet-seed size (about 2 mm) |
| 3.  | The distribution of micronodules can point to a range of diagnoses: |
|   (a) | Random distribution (diffuse and uniform distribution) of micronodules is most often indicative of miliary tuberculosis, miliary fungal infection (histoplasmosis, coccidioidomycosis, blastomycosis, or cryptococcosis), hematogenous metastases, extensive sarcoidosis, or rarely Langerhans cell histiocytosis |
|   (b) | Perilymphatic distribution (subpleural, peribronchovascular) of micronodules is most often indicative of sarcoidosis, silicosis, coal worker's pneumoconiosis, lymphangitic spread of carcinoma, or rarely lymphoid interstitial pneumonitis and amyloidosis |
|   (c) | Centrilobular distribution (no pleural nodules) of micronodules is most often indicative of hypersensitivity pneumonitis, respiratory bronchiolitis, bronchoalveolar carcinoma, or infections with endobronchial spread (tuberculosis, nontuberculous mycobacterial infection, bacterial bronchopneumonia due to Staphylococcus aureus, beta-hemolytic streptococci, or Mycoplasma pneumoniae) |
| 4.  | Also consider viral pneumonia (influenza, measles), psittacosis, Q fever (Coxiella burnetii), leptospirosis (Leptospira spp.), bartonellosis (Bartonella spp.), brucellosis (Brucella spp.), strongyloidiasis (Strongyloides stercoralis), and toxoplasmosis (Toxoplasma gondii) |
of education and the development of vocational skills. A systematic approach to the treatment of these complaints should involve identifying the root cause and addressing individual needs. This chapter will discuss various strategies for managing mental health issues among students and workers as they return to school or work.

**Table 1.2** Bat-associated infections

| No. | Infection                                                                 | Description                                                                                                                                 |
|-----|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | Rabies                                                                    | Bite or direct contact of bat saliva with the mouth, eyes, nose, or fresh wound.                                                            |
| 2   | Histoplasmosis                                                            | Grows in bat guano with pulmonary inhalation from aerosols generated when the soil and guano are disturbed.                                 |
| 3   | Filovirus hemorrhagic fevers present in Africa:                           | (a) Marburg hemorrhagic fever has a fruit bat reservoir (*Rousettus aegyptiacus*)                                                         |
|     |                                                                           | (b) Ebola hemorrhagic fever may have a bat reservoir, likely fruit and insect-eating bats                                                  |
| 4   | Henipavirus encephalitis                                                 | (a) Nipah virus encephalitis associated with *Pteropus* fruit bats (flying foxes) in parts of Asia (documented human outbreaks in Malaysia, Singapore, India, and Bangladesh), with risk of person-to-person droplet transmission in the case of respiratory infections |
|     |                                                                           | (b) Hendra virus encephalitis associated with fruit bats (flying foxes) in Australia; humans are infected only when exposed to Hendra virus-infected horses, without bat-to-human or human-to-human infection |
| 5   | Some human coronavirus have originated from bats                          | (a) The SARS (severe acute respiratory syndrome) coronavirus originated in Chinese horseshoe bats; person-to-person transmission is the major mode of infection |
|     |                                                                           | (b) The MERS (Middle East respiratory syndrome) coronavirus may have originated from Saudi Arabian bats; however, human infections have been associated with direct exposure to camels |

- Toxoplasmosis, strongyloidiasis, and schistosomiasis; and noninfectious etiologies including malignancy, sarcoidosis, hypersensitivity pneumonitis, and pneumaticosis. On interviewing the patient, we provided her with a case series of biology students who entered into a bat-infested hollow tree in Uganda and who developed histoplasmosis [1]. The patient recognized the tree pictured in a figure in the manuscript and stated that it was the same tree that her team had entered. Further laboratory work-up included an interferon gamma release assay (IGRA), sputum culture for acid fast bacteria, fungal sputum culture, *Histoplasma* urine antigen, *Histoplasma* serum antibody, and *Blastomyces* serum antibody. Results from further work-up are shown in Table 1.3. The *Histoplasma* urine antigen was positive, confirming the diagnosis of histoplasmosis.

**Table 1.3** Laboratory results in the present case

| Test                        | Result               |
|-----------------------------|----------------------|
| Interferon gamma release assay | Negative              |
| AFB sputum culture × 2       | Negative              |
| Fungal sputum culture        | Negative              |
| Serum *Histoplasma* antibody | Negative initially, then positive |
| Serum *Blastomyces* antibody | Negative              |
| Urine *Histoplasma* antigen  | Positive              |

This patient had a large number of exposures during her travels, but initially the most worrying among them was the patient’s dissection without wearing gloves of fruit-eating bats, specifically the genus *Epomops*. The *Epomops* fruit-eating bat has tested positive for Ebola virus IgG and is considered a potential reservoir of Ebola virus [2, 3]. Furthermore, Ebola outbreaks were previously reported in Uganda in 2000 and 2007 [4, 5]. Ebola was not a likely diagnosis, however, given that our patient and her fellow team members did not display any of the typical signs and symptoms of a hemorrhagic fever syndrome. Her case was part of a larger outbreak initially suspected to be tuberculosis because of dyspnea and a miliary pattern on CXR. However, arguing against this diagnosis was the lack of known specific exposures to tuberculosis.

Instead, with the common exposure of ill travelers within the bat-infested hollow tree, the outbreak was most consistent with histoplasmosis. This was particularly suggested by the typical pulmonary findings and the incubation period. The initial symptoms of headache, fever, chills, and malaise (initially empirically diagnosed as leptospirosis) most likely represented the initial symptoms of histoplasmosis after exposure inside the hollow tree. Our patient first developed symptoms 4 weeks prior to presentation, when the *Histoplasma* serology test was positive only at the lower limit of positivity, while subsequent serologic testing revealed high-level positivity, confirming the diagnosis. The patient’s symptoms resolved completely with oral itraconazole therapy. This case demonstrates how an extensive history is vital in the returning traveler who has multiple high-risk exposures.

Interestingly, it appears that a similar histoplasmosis outbreak affecting 13 of 24 students on a biology field trip occurred when another group entered the hollow cavity of the very same tree.
Histoplasmosis has been visited by the patient in the present case. In that earlier outbreak, histoplasmosis was ultimately confirmed serologically but was also initially mistaken for tuberculosis.

1.1 Histoplasmosis

*Histoplasma capsulatum* var. *capsulatum* is a dimorphic fungus that displays characteristic narrow-based budding (Fig. 1.3). *Histoplasma* grows as a mold in the soil and proliferates best in soil contaminated with bird or bat droppings, which favors sporulation. Exposure occurs when soil or droppings with a high concentration of spores are disturbed as in a cave, in an attic or basement, or at a construction site [6].

Of note, there are two varieties of *Histoplasma capsulatum* pathogenic to humans, *Histoplasma capsulatum* var. *duboisii* (African histoplasmosis) and *Histoplasma capsulatum* var. *capsulatum* (classic histoplasmosis). African histoplasmosis is a rare, deep mycosis that usually occurs in the tropical belt of Africa and can involve the skin, subcutaneous tissues, lymph nodes, and bones [7]. It rarely affects the lungs and is rarely reported outside of Africa. Classic histoplasmosis is found worldwide, including Africa, and can cause pulmonary infection or disseminated infections.

Pulmonary histoplasmosis has a broad spectrum of presentations, from asymptomatic infection to life-threatening pneumonia. Disseminated disease can involve many different organ systems including the skin, central nervous system, gastrointestinal tract, joints, and adrenal glands. It can also cause endocarditis, prostatitis, osteomyelitis, pancreatitis, cholecystitis, pericarditis, and chorioretinitis.

Acute pulmonary histoplasmosis typically occurs within 1–3 weeks of exposure and is usually self-limited. For patients with impaired cellular immunity, dissemination may occur and may be fatal. Diagnosis is made by *Histoplasma* polysaccharide antigen test in the urine or in the blood [8]. The antigen test peaks 4–6 weeks after infection but is usually negative in the first 4 weeks. For patients who are symptomatic, therapy is warranted as per Infectious Diseases Society of America guidelines [9]. Antifungal therapy with itraconazole is recommended in patients who have symptoms for longer than a month. Intravenous liposomal amphotericin B followed by oral itraconazole is recommended for patients with moderately severe to severe acute pulmonary histoplasmosis.

**Key Points**

- Histoplasmosis is an endemic dimorphic fungus with a worldwide distribution and is on the differential for a returning traveler with lower respiratory symptoms.
- Activities associated with histoplasmosis exposure include cleaning attics, barns and chicken coops, caving, construction, and demolition.
- An outbreak with the same exposure may point to the diagnosis.
- *Histoplasma* polysaccharide antigen testing may be negative within 4 weeks of onset of infection in acute pulmonary histoplasmosis, so a repeat test may be necessary to confirm the diagnosis.
- Symptomatic patients and patients with moderate to severe disease warrant antifungal therapy.

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Fig. 1.3 Methenamine silver stain reveals *Histoplasma capsulatum* var. *capsulatum* fungi. Source: CDC. Available at [https://phil.cdc.gov/phil/details.asp](https://phil.cdc.gov/phil/details.asp) (Image ID#4220; Accessed on-line, June 21, 2017)
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