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A Multinational Outbreak of Histoplasmosis Following a Biology Field Trip in the Ugandan Rainforest

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Background:. Outbreaks of histoplasmosis have been increasingly reported in association with travel to endemic areas. Multiple outbreaks have been reported following travel to the Americas, but reports of pulmonary histoplasmosis in short-term immunocompetent travelers to Africa are rare.
Methods:. A biology student was referred to our unit with suspected pulmonary histoplasmosis following her return from a field trip in the Ugandan rainforest. The patient informed us that several of her multinational student colleagues on the same expedition had developed a similar illness. Using an alert in ProMED-mail and a questionnaire forwarded to each of the symptomatic students, we accumulated data on the other cases involved in this apparent outbreak of pulmonary histoplasmosis.
Results:. Thirteen of 24 students developed respiratory symptoms following the expedition. Chest X-ray appearances were often suggestive of miliary tuberculosis but in most cases a final diagnosis of histoplasmosis was made (confirmed with serology in five cases, clinically diagnosed in six, and retrospectively suspected in two). Detailed questioning indicated that the likely source was a large hollow bat-infested tree within the rainforest.
Conclusions:. This is an unusual outbreak of histoplasmosis following short-term travel to Africa. Pulmonary histoplasmosis should always be considered in the differential diagnosis of an acute febrile respiratory illness in travelers returning from endemic areas or reporting activities suggesting exposure.

Pulmonary histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic fungus that is endemic in the Americas and parts of Asia and Africa.[1] It grows as a mold in soil enriched with bird or bat guano and human infection occurs after inhalation of the dust generated when such soil is disturbed.[2] Exposure can therefore occur during activities such as construction, renovation, demolition, excavation, and caving.

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Histoplasmosis has emerged as a health concern for travelers to endemic areas, particularly for those engaging in recreational or occupational activities that disrupt contaminated soil. Multiple outbreaks have been reported among travelers to the Americas.[2] In contrast, there are few reports of infection occurring in immunocompetent persons after short-term travel to Africa. In this article we report an unusual outbreak of pulmonary histoplasmosis in travelers to Uganda.

Methods

In September 2011, an outbreak of histoplasmosis in travelers to Uganda came to our attention when one of the cases was referred to our hospital (case 1). The patient had developed a respiratory illness following her return from a biology field trip in Uganda. This field trip undertaken by a multinational group of biology students involved researching insects and primates for 1 month

in a rainforest near Fort Portal in western Uganda. Through the use of online social networks, the patient was aware that some of her colleagues on the field trip had developed a similar respiratory illness. With her assistance and that of physicians who responded to an alert in ProMED-mail, we were able to accumulate data on the other symptomatic students, one of whom presented with more severe illness requiring admission to an intensive care unit (case 2). A questionnaire was e-mailed to each of the affected students to ascertain the clinical details of their illness and any exposure to potential sources of histoplasmosis infection during the field trip.

Results

Case 1

A 22-year-old biology graduate developed fever (38.8°C) and flu-like symptoms, 12 days after returning from the rainforest in Uganda. Figure 1 shows the patient peering out from inside the hollow trunk of the second largest tree in the forest, during the last week of the field trip. A number of her fellow students ventured into the same tree, which was infested with bats.

The patient went on to develop a dry cough, chest pain, and shortness of breath on exertion. She initially sought health advice in Quebec, Canada, during a subsequent field trip. A chest X-ray showed diffuse bilateral miliary shadowing and induced sputum was negative on staining for acid-fast bacilli. The patient expedited her return home and was reviewed at a district general hospital in the UK with ongoing chest pain and exertional dyspnoea, 3 weeks after symptom onset. Physical examination was normal, oxygen saturation was 93% on air, and a repeat chest X-ray showed persistent bilateral miliary shadowing (Figure 2). She was referred to the Tropical and Infectious Disease Unit at the Royal Liverpool University Hospital in Liverpool, UK, with suspected pulmonary histoplasmosis. Serum antibodies to *H capsulatum* were detected by complement fixation test and double diffusion at the Mycology Reference Centre in Leeds, UK. She made a gradual recovery over the ensuing weeks without medication.

Case 2

A 21-year-old male presented to Addenbrooke's Hospital in Cambridge, UK, 2 weeks after the same field trip, with a productive cough and shortness of breath for 5 days and night sweats for 2 days. X-ray and computerized tomography imaging indicated mediastinal lymphadenopathy, bilateral pulmonary micronodules, bibasal consolidation, tiny effusions, and an enlarged spleen at 14 cm. He required admission to the intensive care unit for noninvasive ventilation and was treated with intravenous amoxicillin/clavulanic acid plus clarithromycin. Bronchoalveolar lavage fluid was negative on fungal staining and culture. He made rapid recovery and was discharged from the hospital

Figure 1 Suspected source of histoplasmosis outbreak: hollow, bat-infested tree in Uganda.

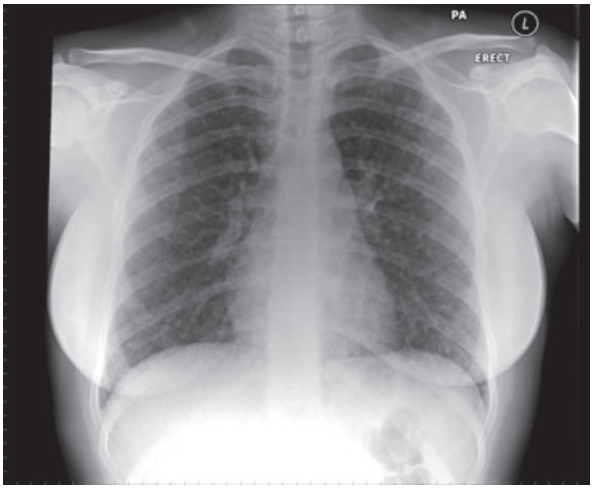

Figure 2 Chest X-ray showing miliary shadowing throughout both lung fields.

6 days after admission. Serum antibodies to *H capsulatum* were detected by complement fixation test during convalescence.

Overview of the Outbreak

Out of 24 taking part in the field trip, 13 students from 10 different countries (including the cases above) developed an acute respiratory illness (Table 1). Details for each case were obtained with the assistance of the first patient and from individual questionnaire responses. Questionnaires were returned by 10 of 13 affected students. Although there were reports of bats flying around the field station at dusk and birds nesting in the shower blocks, the most likely source of histoplasmosis infection was thought to be the hollow bat-infested tree, which the students explored in the last week of the field trip. There were no other reports of close contact with bats or exploration of caves during the field trip. One student with serologically confirmed

histoplasmosis had merely peered into the tree through the window in its trunk.

Nine of the 13 students developed symptoms in the first 15 days after leaving the rainforest (symptom onset was 40 days in one case; unknown in three). The students left the rainforest on July 20, 2011. Seven students specified a date between July 26 and August 4, 2011, when their symptoms began, supporting the likelihood of a common source. Six were not in their country of residence when they first needed medical attention (two still in Uganda, two in Kenya, one in Indonesia, and one in Canada). At least three were hospitalized for further investigation. Not all the cases were diagnosed as acute pulmonary histoplasmosis, but in each case the clinical picture was highly suggestive of this diagnosis retrospectively. In five cases the diagnosis of histoplasmosis was confirmed with positive serology. At least six students were initially thought to have miliary tuberculosis and two commenced antituberculous medication.

Discussion

This is the largest outbreak of pulmonary histoplasmosis reported in short-term travelers to Africa, with an intriguing source, a hollow bat-infested tree trunk in the Ugandan rainforest. The presentation and diagnosis of pulmonary histoplasmosis in travelers are discussed below.

Histoplasma capsulatum is a dimorphic fungus. There are two varieties that are pathogenic to humans, var. *duboisii* and var. *capsulatum*. The former exists only in Africa, while var. *capsulatum* is most prevalent in regions of North, Central, and South America but has also been reported from parts of Africa, Southern and Eastern Europe, Eastern Asia, and Australia.[1,2] Histoplasmosis grows as a mold in soil enriched with large amounts of bird or bat guano.[1] Humans become infected when such soil is disturbed, allowing aerosolization and inhalation of the infectious microconidia. Activities associated with exposure include cleaning chicken coops, bird roosts, attics, and barns; caving; excavation; construction, renovation, and demolition.[3]

Histoplasma capsulatum var. *duboisii* mainly involves the skin, subcutaneous tissues, lymph nodes, and bones. It rarely affects the lungs and appears to pose less of a risk to travelers.[4] The clinical features of the outbreak described in this article are much more consistent with infection caused by *H capsulatum* var. *capsulatum*. Its clinical manifestations vary according to host immunity and exposure intensity, ranging from asymptomatic infection (in most healthy persons exposed to a low inoculum) to life-threatening pneumonia with respiratory failure.[3,4] Between these extremes, clinical presentations include acute or subacute pulmonary disease, pericarditis, rheumatological syndromes with erythema nodosum, progressive disseminated disease, and mediastinal complications.[4] Acute pulmonary histoplasmosis (APH) in returning travelers typically presents as a flu-like illness with high-grade fever, chills, headache, nonproductive cough, pleuritic chest pain, and fatigue.[2] Chest radiographs often show diffuse reticulonodular infiltrates and mediastinal lymphadenopathy. Symptom onset is usually 1–3 weeks following exposure and most individuals recover spontaneously within 3 weeks.[2] Disseminated disease is a rare complication, more likely to occur in persons with severely impaired cellular immunity.

The diagnosis of APH in returning travelers is usually made by serology.[2] Complement fixation and immunodiffusion are the most widely used methods. Serology tests peak approximately 4–6 weeks after the onset of infection and are typically negative in the first month, thus it is important to obtain paired acute and convalescent samples.[3] The sensitivity for acute pneumonia with diffuse infiltrates is 40%–80%.[3] Serological tests are less useful in immunosuppressed patients, of whom up to 40% do not mount a measurable antibody response.[3] Antibodies may persist for several years after acute infection and low false-positive complement fixation titers are attributed to previous asymptomatic infection in endemic areas.[3]

Histoplasma polysaccharide antigen can be detected in urine, serum, cerebrospinal fluid, or bronchoalveolar lavage fluid, but antigen tests are not available in all countries. The diagnostic yield is highest when both urine and serum are tested.[5] In a recent evaluation of 130 patients with APH, antigen detection was 82.8% in the subset in whom both urine and serum were tested.[5] As with serological tests, cross-reactivity can occur with other endemic mycoses such as blastomycosis and coccidioidomycosis.[4]

Culture (on Sabouraud's dextrose agar) provides the strongest evidence for diagnosis but requires invasive sampling and has low sensitivity in mild disease.[3,4] Typical histopathological appearances in biopsied lung are caseating granulomas and characteristic budding yeast forms.[3]

The Infectious Diseases Society of America has developed guidelines for the treatment of histoplasmosis.[6] Antifungal treatment is not usually indicated for mild to moderate APH in immunocompetent persons. For patients who continue to have symptoms for >1 month, itraconazole is recommended.[6] Patients with moderately severe to severe APH should receive liposomal amphotericin B followed by itraconazole.[6] Methylprednisolone is advised during the first 1–2 weeks if there are respiratory complications, including hypoxemia or significant respiratory distress.[6] Patients with disseminated disease and those with underlying immunosuppression should receive a longer duration of therapy.[2,6]

Outbreaks of histoplasmosis have been increasingly reported in association with travel to endemic areas. Multiple outbreaks have been reported following travel to the Americas, frequently in association with activities such as exploring caves or reconstruction of old buildings.[7–14] In contrast, our literature search

Table 1 Clinical features, diagnosis, and treatment of students seeking medical advice following field work in the Ugandan rainforest

Country of origin	M/F	Age	Symptoms	Abnormal chest X-ray	Initial diagnosis of miliary TB	Final diagnosis by local healthcare provider	Antimicrobials received	Recovery
Netherlands	F	24	Dyspnoea, weight loss	Yes	Yes	Histoplasmosis*	Amoxicillin/ clavulanic acid, HRZE	Yes
UK (case 2)	M	21	Dyspnoea	Yes	Yes	Histoplasmosis*	Amoxicillin/ clavulanic acid, clarithromycin	Yes
Switzerland	F	24	Dyspnoea	Yes	No	Histoplasmosis*	Antimalarials, antibiotics, itraconazole	Yes
Ireland	F	23	Dyspnoea, cough, chest pain	Yes	No	Histoplasmosis	Amoxicillin	Yes
UK	F	28	Dyspnoea, fever, dry cough, fatigue	Not done	No	Upper respiratory tract infection (bacterial)	Amoxicillin/ clavulanic acid	Yes
Sweden	M	25	Dyspnoea, fever	Yes	Yes	Histoplasmosis*	Amoxicillin/ clavulanic acid, HRZE	Yes
Austria	M	31	Cough	Yes	NK	Histoplasmosis	Itraconazole	Yes
Poland	M	24	Cough, chest pain, fever	Yes	No	Malaria and unconfirmed respiratory illness, possible histoplasmosis	Antimalarials, ketoconazole, amoxicillin	Yes
UK (case 1)	F	22	Dyspnoea, chest pain, fever	Yes	Yes	Histoplasmosis*	Nil	Yes
Netherlands	M	NK	Dyspnoea, fever	Yes	Yes	Histoplasmosis	NK	NK
Kenya	F	27	Dry cough, chest pain, headache, fever, running nose	Not done	No	Unconfirmed	Ampicillin/ cloxacillin	Yes
Madagascar	M	24	Fever, night sweats, headache, fatigue, dyspnoea, cough, chest pain	Yes	No	Histoplasmosis	Tetracycline, amoxicillin, itraconazole	Yes, occasional chest pain on heavy exertion persists
South Africa	F	23	Dyspnoea, fever, dry cough, fatigue, night sweats	Yes	Yes	Histoplasmosis	Azithromycin, itraconazole	Yes

TB = tuberculosis; NK = not known; HRZE = isoniazid, rifampicin, pyrazinamide, ethambutol; M = male; F = female.
*Confirmed with positive serology.

highlighted only three articles reporting a definite association of pulmonary histoplasmosis with short-term travel to Africa in immunocompetent persons.[15–17]

Diagnosis of histoplasmosis in returning travelers can be difficult because of its nonspecific presentation. Furthermore, the differential diagnosis of an acute febrile respiratory illness in adventure travelers is broad and may include, in addition to histoplasmosis, *Streptococcus pneumoniae* pneumonia, legionellosis, mycoplasma, Q fever, leptospirosis, tuberculosis, schistosomiasis, Loeffler's syndrome, coccidioidomycosis, paracoccidioidomycosis, influenza, measles, hantavirus pulmonary syndrome, and malaria.[9,18] In the outbreak of histoplasmosis described here, a number of cases had

been misdiagnosed as miliary tuberculosis. Four out of 13 (31%) received antifungals and 10 out of 13 (77%) received other antimicrobial agents including antituberculous therapy and antimalarial treatment. Similarly, in a large outbreak of APH in American travelers vacationing in Acapulco, Mexico, in 2001, 25% of symptomatic, laboratory-confirmed cases received antifungal treatment and 56% received other antimicrobials.[10] Reporting "sentinel" cases on ProMED-mail can alert other physicians to possible outbreaks of pulmonary histoplasmosis, facilitating diagnosis and management.

Conclusions

This is an unusual outbreak of APH following short-term travel to Africa. Histoplasmosis is an important consideration in the differential diagnosis of an acute febrile respiratory illness in travelers reporting risk factors for exposure in endemic areas. Recognition of outbreaks such as this, affecting individuals in multiple nations, can be hugely assisted by on-line e-alerts such as ProMED-mail.

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Declaration of Interests

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