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# *Breath-taking contacts... a hollow tree in Uganda*

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A group of young students fall ill during a field trip to Uganda. As they are from different countries, they are admitted to various hospitals all over the world upon their return. Many of them are initially suspected of having tuberculosis, but intensive contacts between the affected students through social media repeatedly reveal 'errors' in the differential diagnoses established by some of the specialists. In the end, everything can be traced back to a literally breath-taking large hollow tree. One of the two Dutch students in the group later turns out to have benefitted from her size ...

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**BY: JEROEN VERHEUL, PULMONOLOGIST**

**I**n 2012, a 26-year-old biology student of Wageningen University (The Netherlands) went on several field trips to Africa. During his last visit to Uganda, where he stayed for a month and a half this time, he fell ill one week before his return to the Netherlands. He had high spiking fever, general malaise, pain in the joints and a dry cough. He had a gradually worsening feeling of not being able to breathe properly, both when at rest and during exertion. He also had diarrhoea and was sweating profusely, though there was no significant nocturnal perspiration. He had no relevant medical history of disease and was not immune-compromised. The doctors in Uganda suspected malaria, and prescribed proguanil, which gave some clinical improvement.

Some days after his return to the Netherlands his clinical condition worsened and he visited our hospital

in the town of Ede. At that time he suffered from non-productive cough with progressive dyspnoea, and the night before his admission to hospital he felt as if he was suffocating. He also had poor appetite, general malaise and weakness of the legs. He smoked sporadically, drank no alcohol and did not use any recreational drugs. In view of his frequent travels to Africa, he had had enough vaccinations against yellow fever, hepatitis A and B, cholera, typhus, meningitis and rabies to be protected against these diseases. Physical examination revealed a slender, athletically built but ill patient with some purpura on the thorax. Auscultation revealed bilateral basal crackles. Lab tests on admission showed mild hypoxia despite hyperventilation: pCO<sub>2</sub> 3.9 kPa; pO<sub>2</sub> 9.0 kPa; O<sub>2</sub>-saturation 94%; Hb 9.4 mmol/L; Leukocytes 8.8x10<sup>9</sup>/L; Thrombocytes 316x10<sup>9</sup>/L; Gamma GT 213 IU/L; Alkaline phosphatase 203 IU/L; ASAT 78 IU/L; ALAT 103 IU/L and CRP 221 mg/L. Supplementary diagnostics for infections were

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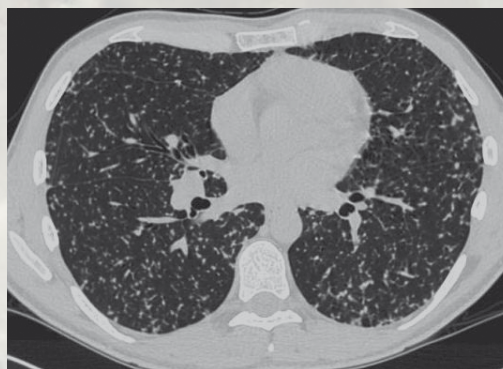
initiated, on serum and urine. A TB skin test was done and three thick blood smears to test for malaria. The chest radiograph showed an extensive diffuse interstitial pattern of a miliary nature, without signs of enlarged hilar glands (see figure 1).



**Figure 1.** Chest radiograph showing diffuse interstitial pattern. On the left is a clavicular fracture, which is well consolidated.

The patient was admitted to the pulmonology department in view of the pronounced miliary pattern in the lungs and hypoxia with O<sub>2</sub> demand. In view of the chest radiograph findings and the fact that the patient had frequently visited Africa, miliary tuberculosis was suspected. A bronchoscopy was performed and samples were taken for culturing, after which tuberculostatics were started. The supplementary

diagnostics showed that all three thick smears were negative, the TB skin test was negative, the Quantiferon test was negative, the HIV test was negative, the Mycoplasma serology was negative, and a bone marrow biopsy showed no signs of tuberculosis. The treatment that was started failed to improve the patient's condition. He deteriorated and was in danger of respiratory failure. In view of the increasing O<sub>2</sub> deficiency, the differential diagnosis was extended and an HRCT scan of the lungs was made (figure 2) to get a better overview of the state of the lungs.



**Figure 2.** HRCT scan of the chest, showing numerous small nodules in both lungs, with a diffuse distribution pattern, both intraparenchymatous and peripherally against the pleural membranes. There are no signs of ground glass opacifications or bronchiectasis. No pleural fluid.

The scan revealed a bilaterally extensive miliary pattern without signs of enlarged glands. In view of a possible paradoxical reaction to tuberculostatics which can

occur in an active tuberculosis infection, and after consultation with a TB consultant, the patient was given a brief course of steroids 50 mg once daily. Eventually he recovered somewhat, but the diagnosis of TB was not confirmed, despite extensive examinations. As his clinical condition improved, he was able to contact the others in the international group, located all over the world. Intensive exchange of email and text messages between the students soon revealed that many of the group had also fallen ill. It was especially those who had visited the Kibale National Forest who had similar symptoms. Those who had fallen seriously ill had been admitted to various hospitals after returning to their home countries. A striking finding was that those who had climbed into a hollow tree to take soil samples were the ones with the most severe symptoms. The tree was inhabited by hundreds of bats.

Based on the reports about possible contacts with (and inhalation of) bat droppings, as well as the chest radiograph and the fact that tuberculostatics did not improve the patient's condition, the differential diagnosis was extended to include histoplasmosis. A Histoplasma serology test proved weakly positive, as was a test for the histoplasmosis antigen in his urine. Since the other hospitals had also admitted seriously ill group members, the patient sent emails and text messages to inform the rest of the group of this alternative diagnosis. It turned out that he was the first of the group with serologically proven Histoplasma infection.

Since the patient continued to show considerable abnormalities on a chest radiograph and had very low exercise tolerance, it was decided to start a course of antifungal medication: 100 mg itraconazole suspension, orally, twice daily (after initial treatment with 100 mg thrice daily). This therapy resulted in rapid recovery,

and the chest radiograph also showed pronounced reduction of the abnormalities (figure 3).



*Figure 3. The interstitial pattern has diminished compared to the previous radiograph (figure 1). The aspect has virtually returned to normal.*

### **Role of social media**

In the meantime, another Dutch student who was part of the same group had contacted our patient. She was staying in Nairobi, Kenya, at the time. She also felt ill and had symptoms of fever and non-productive cough, but she was not really dyspnoeic. Because of these symptoms, she visited the outpatient clinic for infectious diseases at a hospital in Nairobi. A chest radiograph and CT scan showed that her lungs also presented a finely nodular spotted miliary pattern. The local doctor in attendance concluded that she must have miliary TBC, despite the fact that she mentioned the Histoplasma infection with which her colleague and fellow traveller had been diagnosed. She was put on tuberculostatics.

In the meantime the patient hospitalised in our clinic in Ede had given me the email address of this second

patient in Nairobi. This enabled me to invite her by email to make an appointment at our pulmonology outpatient clinic for further analysis. The email exchange also led to discontinuation of the tuberculostatics. A few weeks later the student had completed her field trip and visited our outpatient clinic. At that stage, her symptoms had clearly diminished, though she still complained of a tickly cough and poor physical condition. In all, she had lost 15 kg of body weight. The patient reported that she had also tried to climb into the hollow tree, like the others, but she could not pass through the narrow crack in the tree, as was also the case with some of the other students. Hence, she had merely taken some pictures near the tree (figure 4).



*Figure 4. The Group of students examining a 'breath-taking' hollow tree in the Kibale National Forest in Uganda.*

Physical examination showed an overweight patient with a height of 1.75 m and a body weight of 91 kg. The examination revealed no abnormalities. Lab tests showed a normal blood count with low infection parameters, negative Quantiferon but positive

Histoplasma serology with negative Histoplasma antigen in the urine. A new chest radiograph made in the Netherlands showed virtual normalisation of the bilateral pulmonary condition.

This clustering of patients had meanwhile been reported both in the Netherlands and worldwide, again using modern media such as online e-alerts on web pages to send out an international alert.

### **The fate of the other group members**

At the European Conference on Clinical Microbiology and Infectious Diseases, held in London in April 2012, a number of other cases were presented by doctors from Liverpool, Cambridge and Dublin. One of the cases concerned a 22-year-old student who had fallen ill on a trip to Uganda. She had been on a field trip to study insects, monkeys and bats. She had a fever and flu-like symptoms, was dyspnoeic, with reduced exercise tolerance, dry cough and chest pain. The chest radiograph showed a diffuse miliary pattern. She still had symptoms at the time of her return to England. Supplementary examinations showed hypoxia (saturation 93%), and the abnormalities on the chest radiograph were still present.

Histoplasma serology was positive. She gradually recovered without antifungal medication. In the meantime it had become known that some of her colleagues had developed similar clinical symptoms after visiting the rainforest. Social media had enabled the doctors to contact them and exchange findings. One seriously ill fellow traveller had been admitted to an intensive care unit in Cambridge (England), and had been put on antifungal medication. Another colleague had been hospitalised in Dublin (Ireland) with milder symptoms. Thirteen of the 24 students who had taken part in the project in Uganda, from 10 different countries, eventually developed respiratory symptoms.

Eight of them were ultimately diagnosed with pulmonary histoplasmosis, including the two patients we saw at our hospital in Ede. The remaining five were not in their native country when they developed their first symptoms and required medical assistance. Two of them were in Kenya at that time, the others in Uganda, Indonesia and Canada, respectively. At least six of the patients were initially suspected of having miliary tuberculosis, and two were treated with tuberculostatics.

## Histoplasmosis

Histoplasmosis is an infection caused by the fungus *Histoplasma capsulatum*, which mostly affects the lungs but can sometimes spread throughout the body. Histoplasmosis occurs throughout the world, but is endemic in the central and eastern parts of the United States and Africa. The spores can survive for several years in moist soil, especially if it is mixed with bird or bat droppings. The fungus is particularly prevalent in caves where many bats roost, and many people have been infected (sometimes with serious consequences) in such caves. The droppings of starlings, which collect in large groups, also frequently contain *Histoplasma*. Spores may be found in soil and sometimes also in organic waste bins. Farmers and other people who work with soil run the highest risk of inhaling the spores, and it has also been reported that treasure hunters have been infected while digging in the soil to take samples. Cases of histoplasmosis are rare in the Netherlands.

People generally become infected by inhaling the spores, particularly from the dust of dried bat or bird droppings. After 3 to 17 days, there may be a flu-like clinical picture, as patients feel unwell and complain of chest pain and coughing, sometimes dry cough. The disease can become severe when large numbers of spores are inhaled. Immune-compromised persons run a higher risk of contracting histoplasmosis when they

visit high-risk areas, especially the disseminated form (the form that spreads throughout the body). This was probably what happened to the patients described above, as it is unusual for immunocompetent young people to show this course of histoplasmosis. Being inside or near the hollow tree will have caused them to inhale many spores, and it was this high *Histoplasma capsulatum* load that caused the severe clinical picture in this group of people. Sometimes there is a characteristic pattern on radiograph. The infection is in most cases self-limiting. If necessary, patients can be treated with fungistatics like itraconazole or amphotericin B. If the infection spreads, the outcome is usually fatal unless suitable treatment is started timely. Going through an infection provides some degree of immunity against reinfection.

## Practice recommendations

Outbreaks of histoplasmosis among travellers are uncommon, with cases occurring especially in Africa, but it is usually possible to identify a suspected source. In the cases described here, the infection most probably occurred when the patients entered a hollow tree which housed bats. It was the third largest tree in the forest, and was very popular with visitors, who climbed inside it and/or took pictures. Histoplasmosis should be included in the differential diagnosis of patients who have recently returned from a journey and show a miliary pattern on chest radiographs and who have risk factors and may have been exposed. On-line e-alerts (ProMED mail) and the ever expanding social media represent a highly valuable additional option when such outbreaks are detected, and help to decide on suitable management.