The accuracy of the identifications made by VITEK 2 (63%–81%), Phoenix (0%–28%), and API 20NE (37%–99%) systems varied substantially (7,8). Zakharova et al. found that commercially available biochemical identification systems commonly misidentified B. pseudomallei as Chromobacterium violaceum or B. cepacia complex (9). We found that although the isolate in this study was misidentified by multiple systems, most systems accurately identified the genus. MALDI-TOF mass spectrometry is a rapid, accurate, and highly reproducible technique for bacterial identification. Several studies have explored the potential of MALDI-TOF mass spectrometry for the identification of B. pseudomallei. We prefer the Bruker Biotyper system, which is more accurate because the VITEK databases lack reference spectra for B. pseudomallei (10). In conclusion, scientists must be aware of the potential misidentification of B. pseudomallei by automated identification systems, especially those in regions to which B. pseudomallei is not endemic.

About the Author

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Autochthonous Case of Pulmonary Histoplasmosis, Switzerland

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A 48-year-old man in Switzerland sought treatment for a 1-year history of progressive dyspnea, cough, 20-kg weight loss, and increased sweating; he was receiving oxygen therapy. Results of previous consultations had been inconclusive. An HIV screening test was negative. Medical history included hyperreflexia, depression, and chronic hepatitis B. The man had stopped cocaine inhalation and heroin consumption 20 years earlier but continued smoking cigarettes and cannabis. Regular medications included omeprazole and trimipramine. Except for a short trip to Greece and Italy many years before, the patient reported no foreign travel.

In the absence of travel history to an endemic area, histoplasmosis was not initially considered at the time this patient sought treatment. A prolonged diagnostic process and delayed treatment initiation had meanwhile resulted in significant deterioration of health, including need for home oxygen therapy, and loss of ability to work. Meanwhile, the patient was cachectic and had clubbing on his fingers and toes. Spirometry revealed nearly normal dynamic lung volumes. Forced expiratory volume was 3 L (75%) and forced vital capacity 4.1 L (83%), but diffusion capacity was severely impaired; diffusing capacity for carbon monoxide was 20%. A 6-minute walking test was limited to 400 m (59% predicted), initial oxygen saturation dropping from 90% to 78%. A chest computed tomography (CT) scan showed a diffuse reticulonodular pattern with predominantly upper lung opacifications and bronchiectases indicating fibrotic lung disease (Figure, panels A, B). Reversed halo signs and right upper lobe nodules were found. Bronchoscopy results including bronchoalveolar lavage were unremarkable. Initial sampling with microbiological screening was negative.

Differential diagnoses included toxic lung damage or other interstitial lung disease, (e.g. atypical presentation of Langerhans cell histiocytosis or sarcoidosis). A wedge biopsy showed predominantly upper-lobe fibrosis and multiple, confluent, necrotizing granulomas harboring yeasts, establishing the diagnosis of pulmonary histoplasmosis (Appendix Figure, https://wwwnc.cdc.gov/EID/article/27/3/19-1831-App1.pdf).

A qualitative immunodiffusion test (IMMY, https://www.immy.com) was positive for antibodies in plasma, but an antigen immunosassay for Histoplasma in urine (IMMY) was negative; a beta-1,3-D glucan test (Fungitell, https://www.fungitell.com) was highly positive (>500 pg/mL; limit <80 pg/mL). At
prolonged incubation (14 days, 30°C), a fungal culture on BD Difco dehydrated culture media Sabouraud brain heart infusion agar base (with chloramphenicol and cycloheximide) showed flat, floccose to powdery, whitish growth. We found microscopically large, tuberculated macroconidia (7–12 µM) and small round microconidia on short, lateral pegs consistent with *Histoplasma capsulatum*. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI Biotyper, https://www.bruker.com) results confirmed the diagnosis. Molecular identification was done using an in-house panfungal PCR assay with consecutive sequence analysis. We used the internal transcribed spacer region as target and internal transcribe sequences 1 and 2 for amplification primers (1,2). Microsynth AG (https://www.microsynth.ch) performed DNA sequencing. Sequences produced alignments of *H. capsulatum* in BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi) and CBS (Centraalbureau voor Schimmelcultures; Westerdijk Institute, https://wi.knaw.nl) databases.

Some radiologic features were unusual. There was no cavity formation (3), and the reverse halo sign has rarely been described in chronic pulmonary histoplasmosis (4). However, bullae seen on the scan, previously observed in patients with heavy tobacco use and underlying lung disease, were compatible with the diagnosis. Despite slow growth, cultures for histoplasmosis together with histopathology remain the diagnostic standard (1). Panfungal PCR is sensitive, but its performance depends on internal validation processes (2). Immunocompetence and lack of dissemination could explain repeatedly negative urine antigen testing (1).

Underlying lung disease likely predisposed this patient for severe disease. However, his clinical response to treatment was remarkable. We initiated antifungal treatment with liposomal amphotericin B and oral prednisolone. After a few days, the patient improved substantially, and oxygen supplementation was stopped. At 10 days, therapy was switched to oral itraconazole. Steroid treatment was continued at a tapered dosage over 3 months, with prolonged incubation (14 days, 30°C), a fungal culture on BD Difco dehydrated culture media Sabouraud brain heart infusion agar base (with chloramphenicol and cycloheximide) (https://www.bd.com) showed flat, floccose to powdery, whitish growth. We found microscopically large, tuberculated macroconidia (7–12 µM) and small round microconidia on short, lateral pegs consistent with *Histoplasma capsulatum*. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI Biotyper, https://www.bruker.com) results confirmed the diagnosis. Molecular identification was done using an in-house panfungal PCR assay with consecutive sequence analysis. We used the internal transcribed spacer region as target and internal transcribe sequences 1 and 2 for amplification primers (1,2). Microsynth AG (https://www.microsynth.ch) performed DNA sequencing. Sequences produced alignments of *H. capsulatum* in BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi) and CBS (Centraalbureau voor Schimmelcultures; Westerdijk Institute, https://wi.knaw.nl) databases.

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The source of infection for this patient remains speculative. However, possible risk exposures were guano from flying bats in the garden (6), previous use of organic fertilizer possibly containing histoplasma (7), and regular work-related unpacking of fruits and spices from straw-filled boxes from West Africa, although *H. capsulatum* var. *capsulatum* is less common in that region (8).

In addition to previous findings of histoplasmosis in badgers (9), this case confirms the likely environmental occurrence of *H. capsulatum* in Switzerland. Although diagnoses of autochthonous histoplasmosis have been rare, and few autochthonous cases have been described (10), our finding of a probable autochthonous case of chronic pulmonary histoplasmosis in an immunocompetent male in Switzerland highlights the incomplete understanding of histoplasmosis endemicity and indicates that it has likely been underestimated in Europe.

**About the Author**

Ms. Schmiedel has a masters degree in epidemiology and a diploma in tropical medicine from Cayetano Heredia Universidad in Lima, Peru, and has completed specialized training in infectious diseases and internal medicine. She currently works as a senior infectious disease consultant at Hôpital du Jura (affiliated with Basel University Hospital) and has a strong interest in infection control and tropical medicine. Ms. Büchi has a masters degree in immunology and microbiology from Bern University in Switzerland and is studying to become an internist at the Inselspital in Bern. She has a primary research interest in bloodstream infection.

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etymologia

Histoplasma capsulatum [his’tə-plā’z’mə kāp’sə-lā’təm]

Monika Mahajan

In 1905, Samuel Taylor Darling serendipitously identified a protozoan-like microorganism in an autopsy specimen while trying to understand malaria, which was prevalent during the construction of the Panama Canal. He named this microorganism Histoplasma capsulatum because it invaded the cytoplasm (plasma) of histocyte-like cells (Histo) and had a refractive halo mimicking a capsule (capsulatum), a misnomer.

Histoplasma capsulatum, a dimorphic fungus, now belongs to Kingdom Fungi and causes histoplasmosis (Darling’s disease) through inhalation of spores found in soil and bird droppings. The fungus thrives in the central and eastern parts of United States, especially around the Ohio and Mississippi River valleys, and in South America, Africa, Asia, and Australia. Three varieties exist globally: H. capsulatum var. capsulatum, H. capsulatum var. duboisii, and H. capsulatum var. farciminosum.

Sources

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Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 27, No. 3, March 2021 969
Autochthonous Case of Pulmonary Histoplasmosis, Switzerland

Appendix

Appendix Figure. Diagnostic wedge-biopsy establishing diagnosis of pulmonary histoplasmosis. A) (hematoxylin and eosin staining; 20× magnification) Overview of the diagnostic wedge-biopsy showing emphysema, fibrosis, and necrotizing granulomas. B) Higher magnification (hematoxylin and eosin staining; 400×) highlights the necrosis and the surrounding histiocytic wall. C) (400× magnification) Grocott silver staining discloses the ovoid histoplasma organisms (black staining).