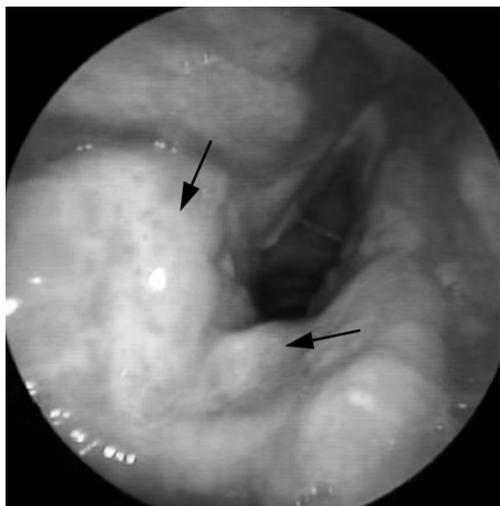


## ANSWER TO THE PHOTO QUIZ

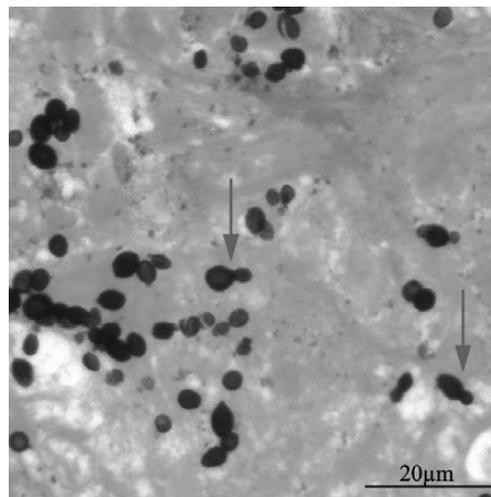
Philip A. Mackowiak, Section Editor

## A Well-Preserved Culprit

(See page 704 for the Photo Quiz.)



**Figure 1.** Yellowish, edematous mucosal changes in the interarytenoid region involving the posterior part of the vocal cords (arrows). Along with Addison's disease, mucous membrane lesions are a characteristic manifestation of *H. capsulatum* infection.



**Figure 2.** Grocott–Gomori methenamine silver stain (magnification  $\times 400$ ) showing blastoconidia of *H. capsulatum* and the typical narrow-necked budding (arrows).

Diagnosis: reactivated, disseminated histoplasmosis.

Histological examination of laryngeal biopsy specimens showed the presence of budding yeast cells (Figures 1 and 2). Based on this observation, laryngeal histoplasmosis with underlying iatrogenic hypercortisolism, steroid-induced hypertension, and diabetes mellitus was suspected. Histopathological reexamination of the adrenal glands, which had been removed in 1996, also raised suspicion of adrenal histoplasmosis instead of the previously suspected culture-negative tuberculosis. The presence of *Histoplasma capsulatum* in both the laryngeal and adrenal gland tissues was demonstrated by broad-spectrum polymerase chain reaction (PCR) targeting the fungal internal transcribed spacer (ITS) region, followed by sequence homology analysis of the PCR product [1]. *H. capsulatum* genotyping using 4 targets of sufficient intraspecies variability (*arf*, *h-anti*, *ole*, and *tub1*) [2, 3] provided proof that reactivation, not reinfection, took place. Interestingly, tests for specific antibodies remained negative twice, but *H. capsulatum* antigen detection from a urine sample obtained

after 2 weeks of antifungal therapy was positive. After 6 weeks of incubation, *H. capsulatum* was also cultivated from the patient's urine (Figure 3).

Treatment with itraconazole was initiated according to the current Infectious Diseases Society of America guidelines [4]. The hoarseness disappeared almost completely, but hospitalization became necessary due to progressive asthenia. Cranial computed tomography (CT) scan was not indicative of cerebral histoplasmosis, but CT scans of the chest and abdomen suggested bilateral pulmonary involvement. The patient, who always had sufficient capacity of discernment, chose to discontinue any treatment, including hydrocortisone substitution, and died from hypocortisolism 2 months after the diagnosis of disseminated histoplasmosis was made. The development of diabetes mellitus and immunological changes as a result of advancing age may have contributed to the reemergence of the pathogen 15 years after the initial manifestation.

Only <1% of individuals infected with *H. capsulatum* develop symptomatic disease. The severity of symptoms depends on the degree of exposure and the immune status of



**Figure 3.** White to buff-brown mould form of *H. capsulatum* grown at 25°C on Sabouraud's dextrose agar. Large numbers of infectious conidia may be released by the mere lifting of the culture plate lid.

the host, and can range anywhere from mild pulmonary affection to severe disseminated disease. Disseminated disease mostly occurs in patients with impaired cell-mediated immunity [5]. In this context, it is remarkable that invasive fungal infections are not consistently recognized in patients treated with immunosuppressants like corticosteroids and tumor necrosis factor- $\alpha$  blockers [6, 7].

Disseminated histoplasmosis can affect every organ system. Involvement of mucous membrane tissue in combination with Addison's disease due to the destruction of both adrenal glands are particularly indicative of histoplasmosis compared to other systemic mycoses. Reactivation of a silent focus can occur decades after the initial exposure [6, 8].

*H. capsulatum* is highly prevalent in the central and south-eastern parts of the United States as well as in Central and South America and parts of Africa. However, our case shows that, due to increasing international travel activity, infection needs to be ruled out in a wide variety of clinical scenarios, not only within endemic regions. In addition to traditional diagnostic techniques (histopathology, serology, and culture), broad-spectrum PCR targeting the fungal ITS region is a valuable tool for the detection of this potentially fatal pathogen, not least in settings where reliable histopathological identification may be difficult to obtain.

## Notes

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Florian P. Maurer,<sup>1</sup> Ewerton Marques Maggio,<sup>2</sup> Thomas N. Roth,<sup>3</sup> Stefan P. Kuster,<sup>4</sup> and Guido V. Bloemberg<sup>1</sup>**

Institutes of <sup>1</sup>Medical Microbiology and <sup>2</sup>Surgical Pathology, Divisions of <sup>3</sup>Otorhinolaryngology, and <sup>4</sup>Infectious Diseases and Hospital Epidemiology, University Hospital Zürich, Switzerland

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Correspondence: Florian P. Maurer, MD, Institute of Medical Microbiology, University of Zürich, Gloriastr. 30/32, 8006 Zürich, Switzerland (florian.maurer@imm.uzh.ch).

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