Answer to Photo Quiz: Yeast Forms Consistent with *Blastomyces* Species

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This case illustrates the challenge of interpreting a Gram stain when fungal elements are present. The initial impression was that white blood cells or other debris were present rather than a fungal organism. A fungal stain using calcofluor white demonstrated more clearly the presence of budding yeasts resembling *Blastomyces* species. Review of the cytologic stain also raised the possibility of *Blastomyces* species. Twenty-four hours after collection of the BAL fluid, creamy, smooth colonies were noted on the inhibitory mold agar plate, which is abnormally fast for this organism and suggestive of high organism burden. The organism was definitively identified as *Blastomyces dermatitidis*/*Blastomyces gilchristii* using matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics Biotyper research-use-only [RUO] database), with a score of 1.93 (cutoff acceptability score, ≥ 1.70). The results for a *Blastomyces* total antibody enzyme immunoassay (Omega) and immunodiffusion (in-house assay) were both positive.

The patient's condition declined rapidly, and he required intubation for respiratory support within 16 h of admission. Following the report of *Blastomyces* species from the fungal smear, the patient was started on liposomal amphotericin B. Unfortunately, 2 days later, his renal and liver function declined and he developed embolic infarcts in the kidneys. The patient continued to decompensate and passed away 6 days after admission and 5 days after initiation of antifungal therapy.

Blastomycosis typically presents as a pulmonary infection following inhalation of conidia (1). This dimorphic pathogen is endemic in regions surrounding the Ohio and Mississippi River Valleys and the Great Lakes region, particularly near waterways. Clinical manifestations are often varied and subtle, with symptoms including low-grade fever, productive cough, shortness of breath, chest pain, and/or progressive weight loss. Radiography of the chest typically reveals infiltrates or a mass lesion (1, 2).

Although systemic disease is most common in immunocompromised patients, blastomycosis has high mortality rates in all populations. Due to disease rarity and syndromic overlap, blastomycosis can often be misdiagnosed clinically as community-acquired pneumonia, resulting in patients receiving multiple antibacterial therapy courses before a diagnosis is established (3, 4). Mortality rates can reach 90 percent, even if patients are receiving appropriate therapy (1, 4).

Direct staining of respiratory specimens containing *Blastomyces* species with a fungal stain often demonstrates distinctive thick-walled, spherical, and broad-based budding yeasts between 8 to 15 μm in diameter. Microbiologic culture of the organism is considered the gold standard for diagnosis. Various methods may be used to identify the organisms from colonial growth, including rapid nucleic acid hybridization probes, MALDI-TOF mass spectrometry, laboratory-developed PCR assays, and DNA sequencing. Conversion of the organism from the mold to the yeast phase with growth at a

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higher temperature (37°C) was historically used as a method of identification, but this is not often done currently, due to the time required for conversion and due to safety concerns for the laboratory staff. The number of recognized *Blastomyces* species is growing and includes several (*B. dermatitidis*, *B. gilchristii*, and *B. helicus*) that have been reported to cause human disease. Careful microscopic examination of morphology can sometimes be used to differentiate species, but often, molecular methods such as sequencing are required for definitive identification. Differences in susceptibility to the various antifungal agents are not yet well defined for the newest species, since the number of isolates available for study is limited. Serologic testing can also be useful in establishing diagnosis but should not be the sole method, due to low sensitivity and the potential for cross-reactivity with *Histoplasma capsulatum* and other endemic fungal organisms (5).

This case serves as a reminder to carefully examine the Gram stain not only for bacteria but also for fungal forms that can be rapidly recognized by the astute eye of a trained microbiologist. Gram staining is often the first test performed by the microbiology laboratory on a specimen, and presumptive identification of fungi such as *Blastomyces* species can assist physicians with timely initiation of antifungal therapy.

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