An Unusual Presentation of Blastomycosis

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ABSTRACT

Introduction: Blastomycosis is a rare pyogranulomatous infection that most commonly involves the lungs and sometimes the skin. Other manifestations are much less common. Diagnosis relies on biopsy, histopathology, and culture of suspicious lesions.

Case Presentation: In this case, a healthy 42-year-old male from Wisconsin presented to the emergency department with a chief complaint of 2 weeks of knee pain without a clear mechanism of injury. Upon further examination, he was found to have lesions on his abdomen, which he had first noticed over 3 years prior and had been treated with antibiotics as cellulitis for nearly 18 months. Biopsy of these lesions was consistent with blastomycosis infection, and further work-up and examination was notable for brain and laryngeal lesions without any pulmonary involvement. Intense anti-fungal treatment was immediately initiated with dramatic improvement in his symptoms.

Discussion: This case highlights the importance of a thorough physical exam and consideration of rare infections in cases without clear answers. To our knowledge, this is the first published example of a blastomycosis infection involving brain, laryngeal, skin, and knee lesions without pulmonary infection.

INTRODUCTION

Blastomycosis is a pyogranulomatous infection caused by the organism *Blastomyces dermatitidis* that typically arises after inhalation of fungus conidia. It is endemic to the Ohio and Mississippi River valleys, the Great Lakes area, and the southeastern United States.[1] Even in the most commonly infected areas of Wisconsin, Arkansas, Mississippi, and Tennessee, incidence is less than 1 per 100,000 people.[1]

Up to 91% of cases of blastomycosis involve the lungs, with skin, bone, and other sites of infection being much less common.[2] In cases without pulmonary involvement, infection is likely a result of direct inoculation, and several case reports have been published with examples of skin or joint infection in isolation, usually following trauma. We have been unable to find any reported cases of multi-organ infection without pulmonary involvement. In Wisconsin, pulmonary infection is the sole manifestation in 77% of patients.[3] After *Blastomycosis dermatitidis* conidia are inhaled, they are susceptible to phagocytosis by pulmonary monocytes, typically resulting in an asymptomatic infection. However, if allowed to convert to the yeast form, *B dermatitidis* becomes more resistant to immune destruction and can proliferate.[4] Subcutaneous granulomatous nodules are possible following hematogenous spread from a primary lung infection; however, laryngeal and soft tissue involvement is rare. Skin involvement typically involves a verrucous lesion with irregular borders and colors ranging from gray to violet. Central nervous system (CNS) infection is present in 5% to 10% of cases and can include meningitis and intracranial or epidural abscesses.[4]

While many other deep fungal infections occur predominantly in immunocompromised patients, blastomycosis can occur in immunocompetent hosts.[5] Diagnosis relies primarily on histopathology and culture, although recently, antigen testing also has proven useful and expedient, despite exhibiting significant cross-reactivity between *B dermatitidis* and *Histoplasma capsulatum*.[6]

Samples for histopathology and culture can be obtained via sputum or, more reliably, bronchoalveolar lavage (BAL) for patients with lung involvement, skin biopsy for patients with skin involvement, cerebrospinal fluid (CSF) from patients with CNS

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involvement (although yield in this case is low), and even other sites of dissemination, including prostate and bone.[6] Samples for antigen testing can be obtained from urine, serum, CSF, or BAL.[6] At this time, the currently available standard immunodiffusion and complement fixation assays used for the diagnosis of other fungal infections are neither sensitive nor specific enough to diagnose blastomycosis.[6]

For most cases of disseminated blastomycosis, recommended treatment differs based on whether the disease is mild to moderate versus moderately severe to severe.[7] For mild to moderate disease, the recommended treatment is 200 mg oral itraconazole 3 times/day for 3 days, followed by 200 mg oral itraconazole 1 to 2 times/day for 6 to 12 months.[7] For moderately severe to severe disease, the recommended treatment is 3-5 mg/kg per day of lipid formulation amphotericin B, or 0.7-1 mg/kg per day of amphotericin B deoxycholate, for 1 to 2 weeks or until the patient improves clinically, followed by 200 mg oral itraconazole 3 times/day for 3 days and then 200 mg oral itraconazole 2 times/day for at least 12 months total.[7] In all cases, serum itraconazole levels should be monitored after at least 2 weeks of treatment to ensure adequate dosage.[7] For patients with blastomycosis that has disseminated to the CNS, the recommended treatment is 5 mg/kg per day of lipid formulation amphotericin B for 4 to 6 weeks followed by an oral azole for at least 12 months and until resolution of CSF abnormalities.[7] The oral azole can be 800 mg/day of fluconazole, 200 mg 2 to 3 times/day of itraconazole, or 200-400 mg 2 times/day of voriconazole.[7]

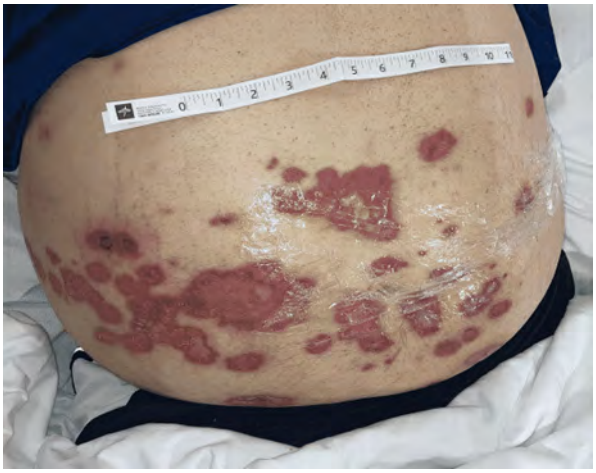
CASE PRESENTATION

A 42-year-old immunocompetent male from northern Wisconsin with a history of hypertension and obesity presented to our hospital with a chief complaint of right knee and thigh pain and abdominal rash.

His clinical course began about 3 years prior. He initially noted a nonpainful, approximate 2-cm lump beneath the skin of his abdomen. The lump persisted for 2 years before becoming tender and inflamed in 2020. In October 2020, he was seen by an outpatient gastroenterology advanced practice nurse prescriber (APNP), who diagnosed him with cellulitis and prescribed cephalexin. At a follow-up visit 2 weeks later, the lump had ruptured, draining blood and pus. Antibiotic coverage was thus changed to trimethoprim sulfamethoxazole (TMP-SMX). Symptoms did not improve following a 10-day course of TMP-SMX, so his course of treatment was extended for 5 days.

Although his symptoms did not resolve and he continued to experience abdominal lesions that grew beneath the skin before rupturing and draining, the patient did not follow up with a clinician until May 2021, at which time he presented with left lower extremity pain. He also continued to have an abdominal rash. He was diagnosed with cellulitis of the left lower extremity and prescribed a 14-day course of TMP-SMX. At this visit, he also was told that his body mass index was likely the predisposing factor to his repeated infections and counseled to lose weight.

Figure 1. Cutaneous Findings on Patient



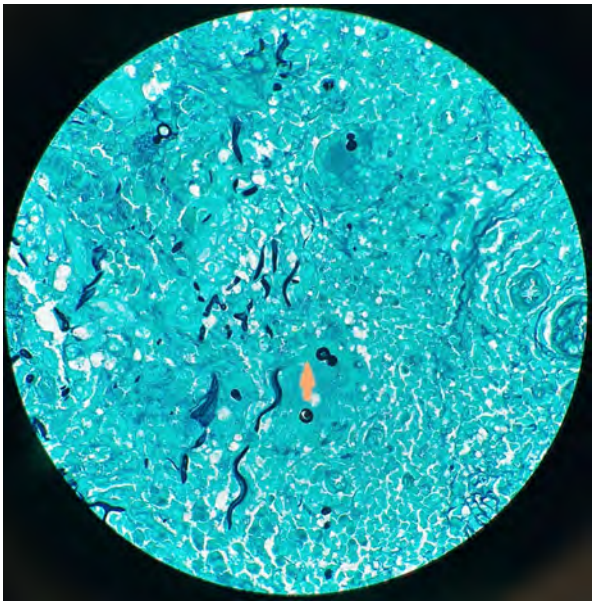
Lesions were present for years prior to diagnosis.

Several months later in 2021 at his annual physical exam, his persistent abdominal lesions were noted, and he was diagnosed with abdominal cellulitis. He was prescribed a 14-day course of doxycycline and counseled to lose weight.

In March 2022, he began to experience right lower extremity pain, contralateral to his previously treated left lower extremity pain. He first noticed this pain as a slight limp before palpating a small lump under the skin on his right thigh. Two days after he noticed these symptoms, he awoke with a very tender, swollen, warm knee that was exquisitely painful to movement and palpation. He described the pain as sharp, stabbing, "like a muscle constantly contracting," nonradiating, and 10/10 in severity. His abdominal symptoms persisted as well, although on presentation his knee pain was his primary concern. He presented to an outside emergency department on April 6, 2022, where he was admitted for extensive workup. Magnetic resonance imaging (MRI) demonstrated signal concerning for myositis and knee effusion. Further workup, including creatine kinase, arthrocentesis, antinuclear antibodies, myeloperoxidase, proteinase 3, anti-neutrophil cytoplasmic antibodies, and inflammatory bowel disease differentiation, was ultimately negative.

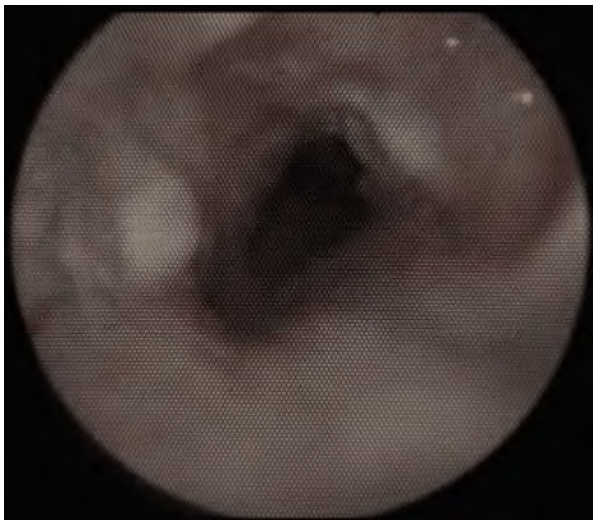
The patient was discharged with supportive measures and referred to our hospital. On admission, in addition to his lower extremity symptoms, he also complained of an abdominal rash that involved 30-40 mm, nonpainful lesions that grew beneath the skin of the abdomen and would eventually rupture and release pus and fluid. After rupturing, these lesions would slowly heal and crust over. Exam was notable for numerous red, ovoid, confluent lesions of varying sizes and stages of healing spread diffusely across the abdomen (Figure 1). Several had crusting around the edges.

Figure 2. Skin Punch Biopsy Sample



Gomori's methenamine silver stain x 400 showing broad-based budding yeast (yellow arrow) consistent with blastomycosis.

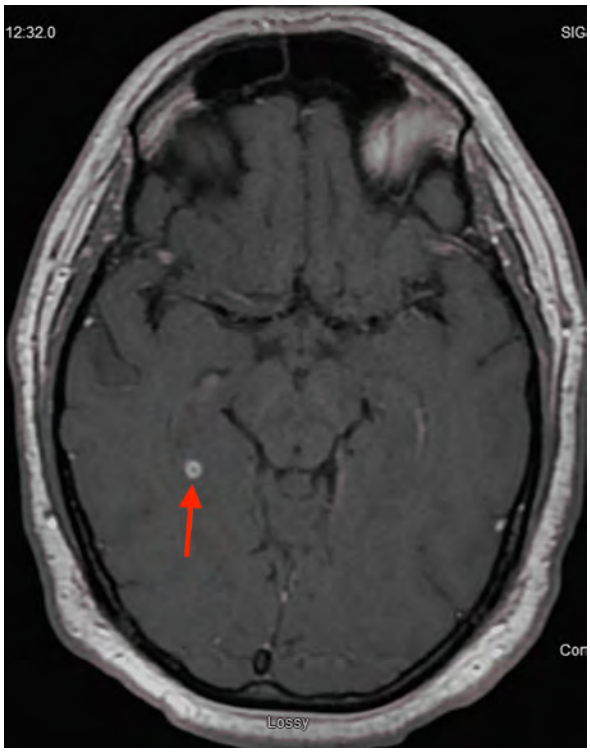
Figure 3. Transnasal Laryngoscopy Findings



Two 1x1-cm punched-out lesions appeared to be in an earlier stage of healing.

After extensive workup demonstrated mild leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate and C-reactive protein, and unremarkable chest x-ray, a skin biopsy revealed broad-based yeast forms (Figure 2) with surrounding inflammation and pseudoepitheliomatous hyperplasia consistent with blastomycosis infection. Urine blastomycosis antigen was positive as well. Computed tomography (CT) of the chest was remarkable for

Figure 4. Magnetic Resonance Imaging Brain From Patient With an Example of One of the Small Ring-Enhancing Lesions (red arrow)



no pulmonary consolidation or nodule. Head/neck CT was concerning for tracheal narrowing, and transnasal laryngoscopy was notable for vocal cord lesions consistent with disseminated blastomycosis (Figure 3). MRI brain demonstrated 3 small ring-enhancing lesions also consistent with disseminated blastomycosis (Figure 4). Interestingly, the patient denied any neurological symptoms throughout his clinical course, and exams were consistently negative for any abnormal neurological findings.

He was started on intravenous amphotericin B, with progressive symptomatic improvement of his knee pain reported as early as the following morning. His rash remained stable, and repeated laryngoscopy after 10 days showed complete resolution of vocal cord lesions and healthy-appearing mucosa. He was discharged after an 11-day hospital course with plans to take voriconazole 400mg twice daily for 1 year with close follow-up with infectious disease specialists. At his 1-month follow-up, he reported "substantial improvement in energy level, thigh pain, and skin lesions."

DISCUSSION

We report a case of disseminated blastomycosis with atypical presentation in a patient without evidence of pulmonary involvement but with widespread CNS, skin, and soft tissue pathology. Blastomycosis is endemic to the Great Lakes area, the Ohio and

Mississippi River valleys, and the southeastern United States. The patient described resides in Green Bay, Wisconsin, and presented to us in Milwaukee, Wis.

This case highlights several important points. First, it demonstrates the importance of a thorough physical exam on all patients. Knee pain and inconclusive MRI findings in isolation would never have been sufficient to lead to a diagnosis of blastomycosis. Despite a 3-year gap between the onset of this patient's abdominal rash and knee pain, the two were ultimately linked to the same underlying pathology.

Second, this case highlights an important bias often seen in medicine: anchoring on a common or initial diagnosis. When this patient was first evaluated, a diagnosis of cellulitis was not unreasonable; however, when repeated courses of antibiotics failed to resolve his symptoms, an alternative diagnosis should have been considered. By the time of admission, he had been evaluated by at least 4 clinicians, among whom only one broadened their differential beyond cellulitis in their assessment. Each of these clinicians prescribed antibiotics, despite historical inefficacy. In April 2022, a full 18 months and 6 office visits after his first evaluation, the patient was referred to a dermatologist for further examination and workup. Several factors, including clinician time constraints, easy and convenient alternative diagnosis, and multiple previous visits documenting cellulitis, likely played a role in this failure of the medical system.

Finally, this case records a highly unusual manifestation of blastomycosis with CNS, cutaneous, laryngeal, and muscular involvement completely free of respiratory symptoms and without pulmonary abnormality on chest CT. Most instances of a fungal infection of this etiology will involve the lungs exclusively; however, this case demonstrates an example of widespread infection that seemingly spares the lungs. Blastomycosis is typically transmitted through inhalation of spores leading to pulmonary disease and possible subsequent hematogenous dissemination,[8] but direct cutaneous inoculation is also possible. Several published cases report widespread cutaneous lesions without pulmonary involvement, including a case in 2022 describing a similar patient with knee pain who was diagnosed with cutaneous blastomycosis and treated successfully with itraconazole.[9] However, this patient did not have evidence of infection in any other organ system.

To our knowledge, we provide the first reported case of nonpulmonary multiorgan blastomycosis. This case highlights the fact that even if a patient does not have pulmonary blastomycosis, they may still have widely disseminated blastomycosis with involvement of multiple organ systems. A lack of pulmonary infection does not rule out disseminated blastomycosis infection altogether. This case also highlights the importance of expansion of a differential when a patient presents with persistent, atypical, or repeated cutaneous infection unresponsive to antibiotics, particularly in an area where blastomycosis is endemic.

CONCLUSIONS

In this case, we highlight an unusual presentation of disseminated blastomycosis in an immunocompetent host to increase awareness among clinicians. This case also highlights the importance of considering the diagnosis of blastomycosis in patients who are not responding to therapy like antibiotics. This case demonstrates the importance of involving specialists early on in cases where patients present with unexplained refractory signs and symptoms of disease after treatment, as specialists can aid in the identification of more rare diseases, such as blastomycosis. Early detection and treatment can prevent morbidity and mortality.

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REFERENCES

1. Castillo CG, Kauffman CA, Miceli MH. Blastomycosis. *Infect Dis Clin North Am.* 2016;30(1):247-264. doi:10.1016/j.idc.2015.10.002

2. Chapman SW, Lin AC, Hendricks KA, et al. Endemic blastomycosis in Mississippi: epidemiological and clinical studies. *Semin Respir Infect.* 1997;12(3):219-228.

3. Baumgardner DJ, Buggy BP, Mattson BJ, Burdick JS, Ludwig D. Epidemiology of blastomycosis in a region of high endemicity in north central Wisconsin. *Clin Infect Dis.* 1992;15(4):629-635. doi:10.1093/clind/15.4.629

4. Miceli A, Krishnamurthy K. Blastomycosis. In: *StatPearls.* StatPearls Publishing; 2021. Accessed April 26, 2023. https://www.ncbi.nlm.nih.gov/books/NBK441987/

5. Gray NA, Baddour LM. Cutaneous inoculation blastomycosis. *Clin Infect Dis.* 2002;34(10):E44-E49. doi:10.1086/339957

6. Linder KA, Kauffman CA. Current and new perspectives in the diagnosis of blastomycosis and histoplasmosis. *J Fungi (Basel).* 2020;7(1):12. doi:10.3390/jof7010012

7. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;46(12):1801-1812. doi:10.1086/588300

8. Musial CE, Wilson WR, Sinkeldam IR, Roberts GD. Recovery of Blastomyces dermatitidis from blood of a patient with disseminated blastomycosis. *J Clin Microbiol.* 1987;25(8):1421-1423. doi:10.1128/jcm.25.8.1421-1423.1987

9. Caldito EG, Antia C, Petronic-Rosic V. Cutaneous blastomycosis. *JAMA Dermatol.* 2022;158(9):1064. doi:10.1001/jamadermatol.2022.3151

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