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ID TEACHING CASES

Blastomycosis Presenting With Acute Airway Obstruction From a Retropharyngeal Abscess and Complicated by Severe Hypokalemia During Posaconazole Therapy: A Case Report and Review of Literature

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We report a case of cervical blastomycosis with associated paravertebral involvement and severe spinal canal stenosis in a 48-year-old patient presenting with acute airway obstruction from a retropharyngeal abscess. Our case was also complicated by severe hypokalemia that developed during the blastomycosis treatment course with posaconazole and which improved after discontinuation and replacement therapy. After 12 months of blastomycosis-targeted therapy, our patient had complete resolution of clinical, laboratory, and radiological findings of blastomycosis.

Keywords. abscess; blastomycosis; hypokalemia; posaconazole; retropharyngeal.

Seventy-six years after Thomas C. Gilchrist first described the North American blastomycosis in 1894 [1, 2], Gehweiler et al [3] summarized in 1970 the distribution of 89 osseous lesions among 45 reported cases of blastomycosis. The most common sites were long bones (particularly the tibia), ribs, short bones, and vertebrae except the cervical spine where no lesions were reported. In 1995, Nokes et al [4] reported their radiological case of the month in *The Journal of the Arkansas Medical Society*, describing the first blastomycosis cervical osteomyelitis case associated with epidural and retropharyngeal abscesses. Two years later, Saccente et al [5] described the clinical characteristics of 12 patients with vertebral blastomycosis associated with paravertebral abscess including Nokes' case and 8 other newly reported ones, among them, a case involving C2–C7. Most recently, in 2015, Patel et al [6] described another case of cervical blastomycosis involving C6 with associated prevertebral abscess and spinal cord compression. We report an unusual case of cervical blastomycosis associated with paravertebral involvement and retropharyngeal abscess. This case report was prepared in accordance with the CAse REport (CARE) guidelines [7].

CASE PRESENTATION

A 48-year-old immunocompetent man with a past medical history significant for obstructive sleep apnea and asthma presented with subacute onset of neck pain, left arm numbness and weakness, and a 60-pound weight loss over 2 months. In the 2 weeks prior to his presentation, he also described progressive difficulty breathing and with swallowing solid foods. He had no associated fever, chills, cough, lower back pain, or skin nodules. His past medical history also included benign prostatic hyperplasia and gastroesophageal reflux disease. He had no prior history of cancer, tuberculosis, immunosuppression, or neck trauma. His past surgical history included arthroscopic left subacromial decompression. He was allergic to shellfish with no known medication allergies. The patient spent his childhood in the southern United States (US) and described a residence for around 1 year in an urban location within the midwestern US before the onset of symptoms. He denied any exposure to construction or excavation sites, forests, camping, fishing, or hunting. He had never traveled outside of the country. He had no pets and recalled no exposure to any farm animals. He was an occasional cigar smoker, social alcohol drinker, and he never used any recreational drugs.

The physical examination revealed labored breathing and an absence of skin nodules but was otherwise unremarkable. White blood cell count was 8.0 K/μL; plasma C-reactive protein (CRP) was 1.59 mg/dL. Human immunodeficiency virus screening with a fourth-generation assay was nonreactive. Lateral radiographs of the cervical spine (Figure 1) demonstrated the interval development of marked, prevertebral soft tissue

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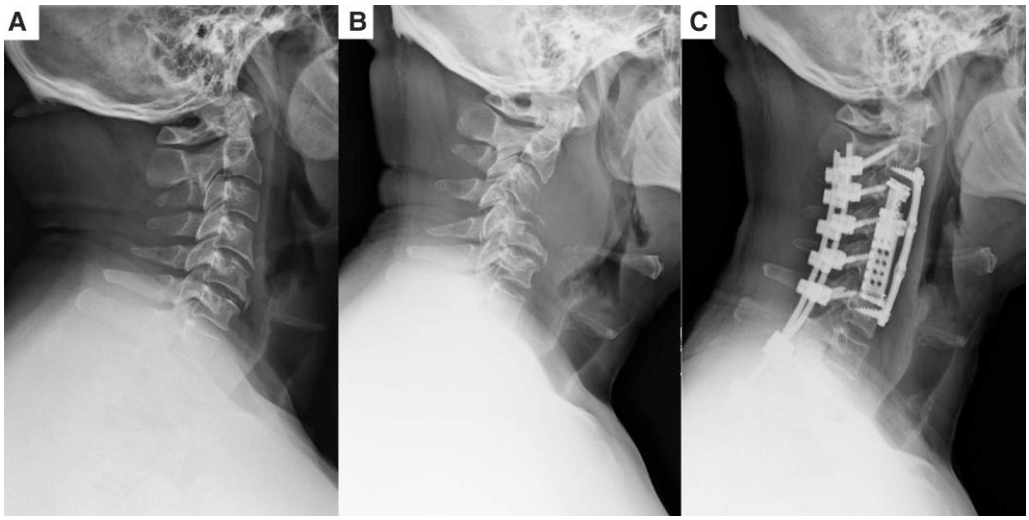

Figure 1. Lateral radiographs of the cervical spine. *A*, Fifteen months prior to admission, there is degenerative disc disease of C4–C6 with disc height loss and spurring. Prevertebral soft tissue thickness is normal. *B*, At time of admission, there is marked, prevertebral soft tissue swelling and osteolysis of the C3–C5 vertebral bodies, as well as pathologic collapse of the C4 vertebral body with gibbus deformity. *C*, Three months after admission, C3–C5 corpectomies, C2–C6 anterior fusion, and C2–T2 posterior fusion.

swelling and collapse of C4 in comparison to an examination 15 months earlier obtained as part of a routine evaluation for neck pain. Computed tomography (CT) (Figure 2) of the neck and chest demonstrated a large retropharyngeal collection, critical narrowing of the airway, and innumerable bilateral small pulmonary nodules. Bedside laryngoscopy demonstrated a large obstruction of the posterior pharynx. The patient was in respiratory distress and an emergent tracheotomy was performed. Biopsy of the posterior pharynx returned a copious amount of turbid fluid that was cultured and subsequently grew few *Streptococcus anginosus*, *Streptococcus salivarius/vestibularis*, *Rothia mucilaginosa*, *Streptococcus gordonii*, *and Haemophilus parainfluenzae.* Magnetic resonance imaging (Figure 3) of the cervical, thoracic, and lumbar spine demonstrated destruction of C4 with 6 mm retrolisthesis, severe spinal canal stenosis, and cord effacement. The patient was transferred to another facility for emergent C3–C5 corpectomies and cervical spine fusion and treated with intravenous vancomycin and ampicillin-sulbactam. Bone and tissue samples were submitted for cultures, and pathology (Figure 4) demonstrated acute necrotizing granulomatous inflammation, acute osteomyelitis, and budding yeast. Fungal serology was positive for *Blastomyces* by enzyme immunoassay (EIA), but negative by immunodiffusion and later by complement fixation. Intravenous liposomal amphotericin B was initiated, and the patient was transferred back to our institution. After continued clinical improvement and discontinuation of antibiotic therapy, he was discharged home on posaconazole delayed-release oral tablets 300 mg daily pending intraoperative cultures.

At the first clinic follow-up, surgical cultures were reviewed and notable for *Blastomyces dermatitidis* from both the pharyngeal biopsy and cervical fusion procedures. Laboratories were requested and remarkable for serum potassium of 2.3 mmol/L and posaconazole level of 3.4 μg/mL. The patient was referred to the emergency department where he complained of atypical chest pain but denied nausea, vomiting, or diarrhea. An electrocardiogram demonstrated U waves and he was readmitted for treatment of severe hypokalemia. On the first hospital day, elevated blood pressures were recorded but he did not require antihypertensive treatment. Posaconazole was discontinued due to suspicion that it was causing the hypokalemia, and the patient was discharged on itraconazole oral capsules 200 mg twice a day and potassium supplementation. Serum potassium levels were normal but declined to 3.0 mmol/L following discontinuation of potassium supplements 2 months later. Itraconazole was suspected as the cause of the hypokalemia, which, after switching to voriconazole oral tablets 200 mg twice a day, resolved on follow-up laboratory tests. Voriconazole levels were monitored (range, 2.7–4.2 μg/mL) throughout the duration of therapy. At 12 months of follow-up, the patient underwent a CT of the cervical spine that demonstrated stable postsurgical changes with no evidence of hardware failure. He had normalization of CRP and complete clinical resolution of symptoms. Accordingly, voriconazole was discontinued after 12 months of antifungal therapy was completed. At 15 months of follow-up, the patient experienced no recurrence of symptoms, and chest CT showed complete resolution of his lung nodules.

After 19 months of follow-up, the patient was invited to share his perspectives for this case report. He indicated that his neck pain and weight loss were resolved following the above-described treatments, but he described 1 month of difficulty swallowing solids and was referred for evaluation. A modified barium swallow

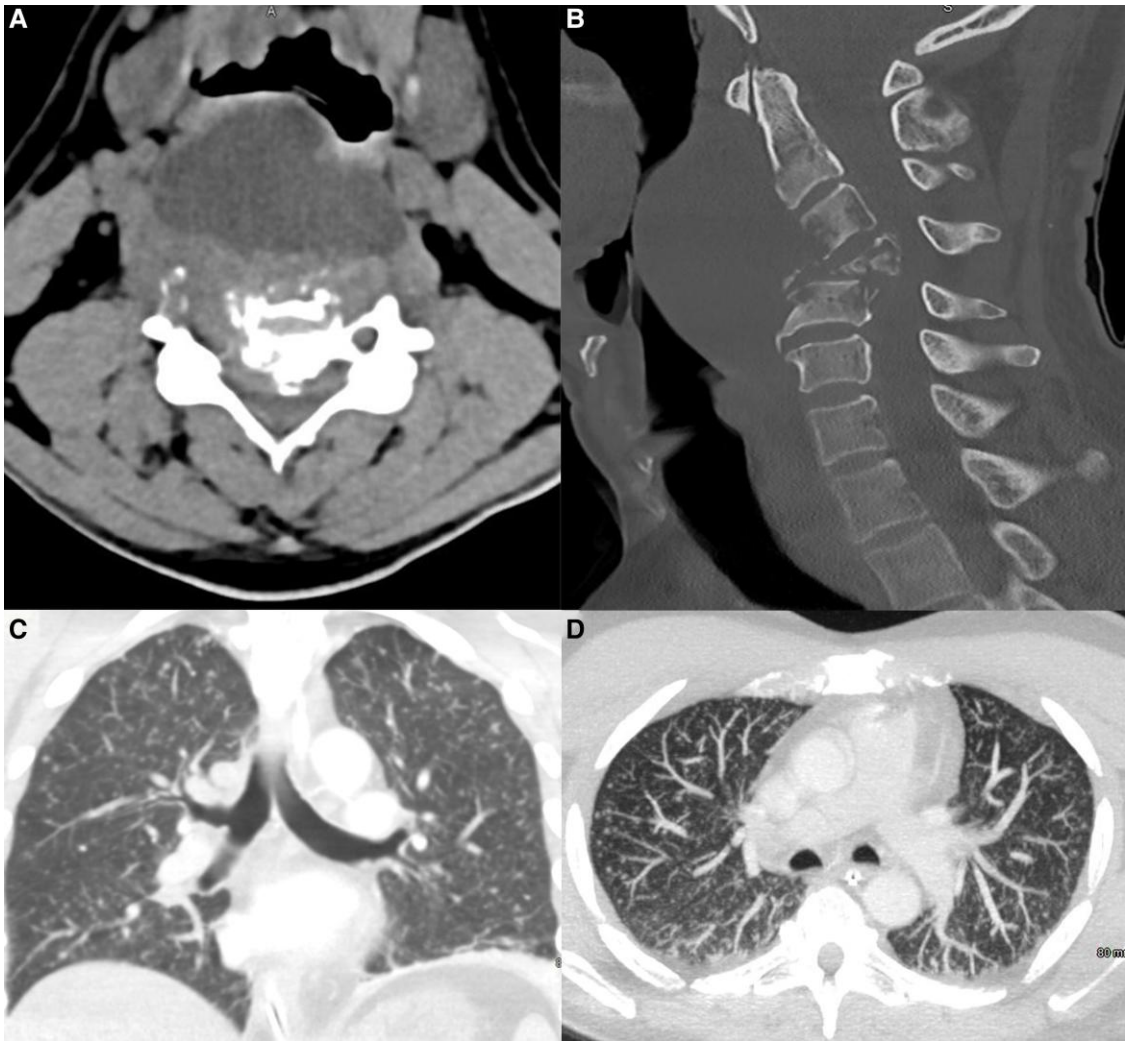

Figure 2. Computed tomographic images at the time of admission. Noncontrast axial (*A*) and sagittal (*B*) images of the cervical spine show a large, retropharyngeal abscess with critical narrowing of the supraglottic airway. There are destructive changes of the subjacent vertebral bodies with retropulsion and spinal stenosis. *C*, Coronal images through the chest show disseminated pulmonary nodules throughout both lungs. *D*, Corresponding axial maximal intensity projection chest images better illustrate extent of disease.

study was obtained and within normal limits. One month later, the symptoms had resolved.

DISCUSSION

Blastomycosis is the rarest of the endemic mycoses in the US with an annual incidence of approximately 1–2 cases per 100 000 population [8], compared with up to 6 for histoplasmosis [9] and 40 for coccidioidomycosis [10], in states reporting from within endemic regions. Most cases in the US occur in proximity to the Mississippi and Ohio rivers and the Great Lakes, and in Canada near the St Lawrence Seaway [2, 11, 12]. *Blastomyces dermatitidis* and *Blastomyces gilchristii* account for most infections, with the former more geographically widespread and both with similar clinical presentations [11]. Outbreaks have been associated with selected activities and exposures including beaver lodges, canoeing, construction, excavation, fishing, and hunting. Inhalation of aerosolized conidia from soil is considered the primary mechanism for transmission, and the usual incubation period is 3 weeks to 3 months. Pulmonary infection is reported in the majority of patients, spanning asymptomatic infection to acute respiratory distress syndrome, and including acute and chronic pneumonia [11]. *Blastomyces* is disseminated beyond the lungs in approximately 15%–48% of cases [11], with osseous involvement the second most common extrapulmonary manifestation, following cutaneous involvement [2, 12]. As discussed, osteomyelitis of vertebrae, long bones, and ribs is among the most frequently reported, although any bone can be affected [11]. Clinical manifestations in the series of 8 vertebral osteomyelitis patients

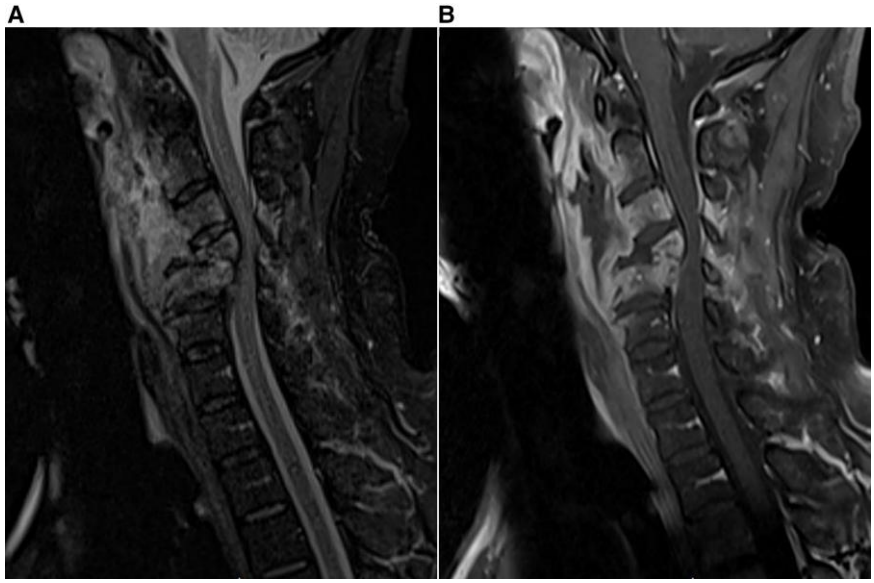

Figure 3. *A*, Sagittal short tau inversion recovery magnetic resonance image of the cervical spine shows pathologic collapse of the C4 vertebral body with gibbus deformity and severe spinal stenosis. Bone marrow edema spans C2–C6. There is extensive, heterogeneous, increased T2 signal of the prevertebral soft tissues. Abnormal signal is also present in the interspinous and paraspinal soft tissues. *B*, Sagittal T1 postcontrast magnetic resonance image of the cervical spine shows corresponding enhancement of the C2–C6 vertebrae consistent with osteomyelitis. There is a large, peripherally enhancing retropharyngeal abscess. Few foci of signal void within the abscess are attributed to air.

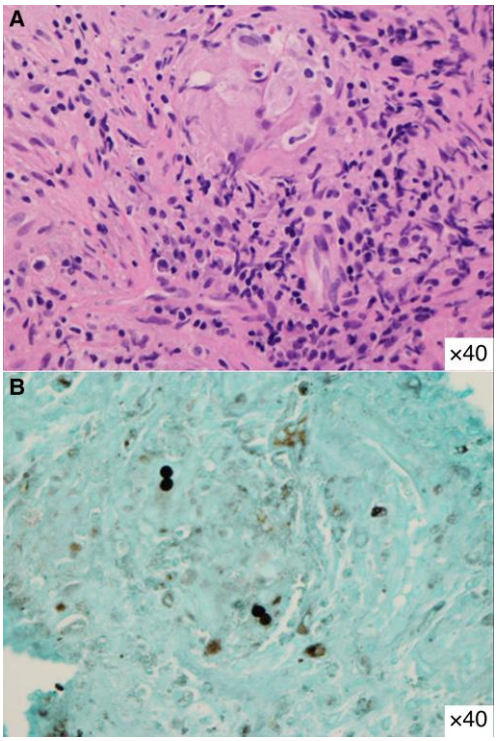

Figure 4. *A*, Representative hematoxylin and eosin–stained sections from biopsies of prevertebral tissue, C4 and C5 bone, and left longus muscle tissue that all demonstrate acute and granulomatous inflammation at ×40 magnification. *B*, Methenamine silver staining of sections from biopsies of prevertebral tissue; C4 and C5 bone also all demonstrate budding yeast forms at ×40 magnification.

reported by Saccente et al [5] were primarily constitutional symptoms or related to lytic bone destruction. In the same report, all patients had clinical or radiographic findings of contiguous abscesses, often psoas and paravertebral. Within the spine, blastomycosis typically affects the thoracolumbar vertebrae and can be difficult to distinguish radiographically from tuberculosis and coccidioidomycosis [13]. In our patient, both metastatic malignancy and infection including tuberculosis were considered in the differential diagnosis and were not excluded until pathology and culture results became available after surgery.

Retropharyngeal abscesses are reported in association with cervical epidural abscess and/or cervical vertebral osteomyelitis [14]. In this clinical scenario, the most common causative organism is *Staphylococcus aureus*, though cases involving β-hemolytic streptococci, anaerobes, and aerobic gram-negative organisms have also been reported. Among the atypical causes, in the presence of contiguous, cervical vertebral osteomyelitis, tuberculosis [15], blastomycosis [16], and coccidioidomycosis [17] have been reported. The recovery of *Blastomyces* from cultures of the fluid encountered during the retropharyngeal biopsy and cervical bone tissue supported a mechanism of contiguous spread of infection between the cervical vertebrae and retropharyngeal abscess in our patient. Furthermore, the initial findings of polymicrobial bacterial growth may have represented colonization by oropharyngeal flora.

Laboratory diagnosis of blastomycosis can be challenging; *Blastomyces* serology is considered unreliable due to

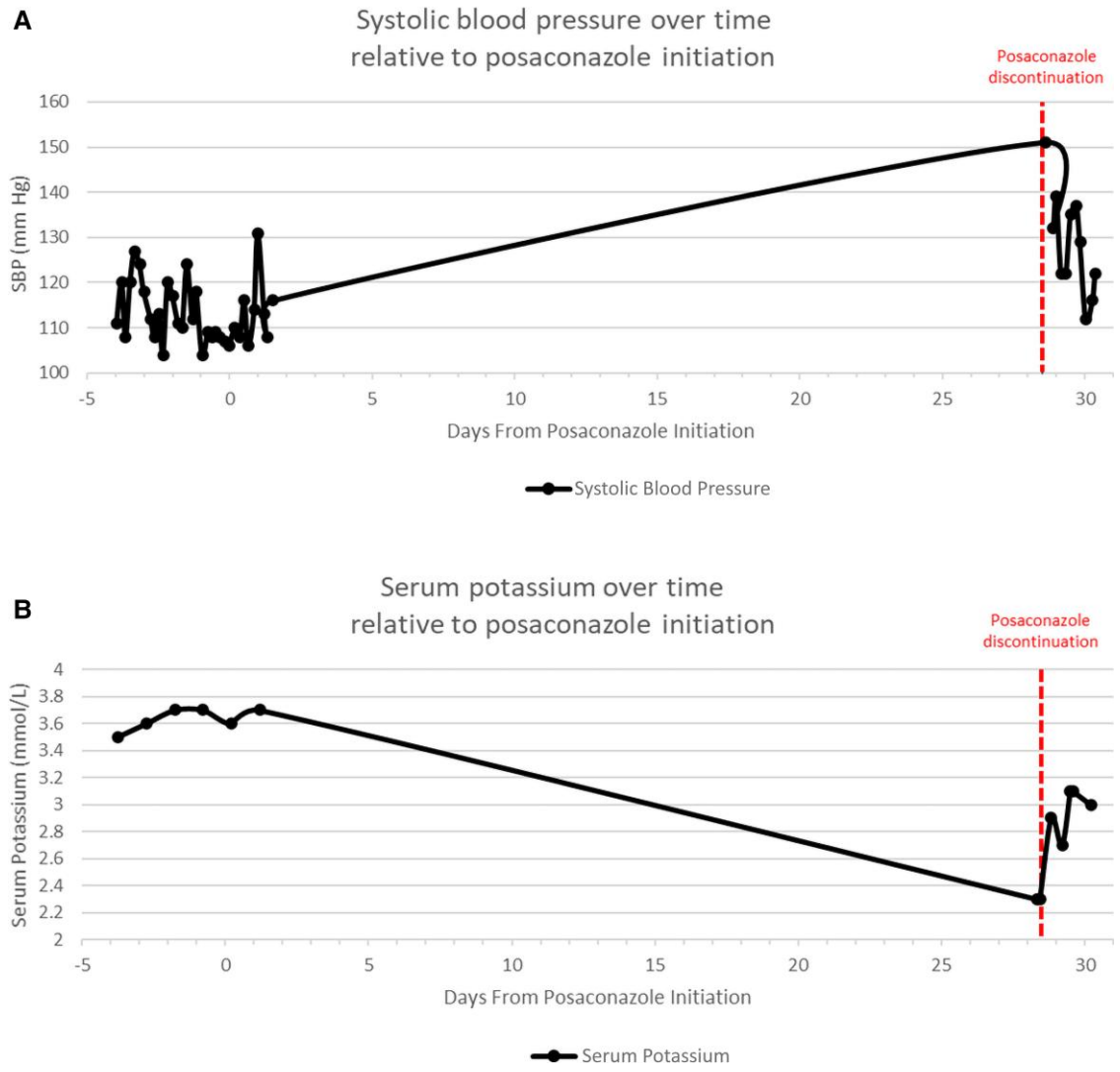

Figure 5. Systolic blood pressure (*A*) and serum potassium (*B*) plotted over time.

inadequate sensitivity and specificity including cross-reactivity of antibodies in patients with histoplasmosis [18]. A newer EIA assay with improved sensitivity and specificity targeting the BAD-1 antigen has been described but is not available for use in clinical care [19]. Antigen testing is available for blood, urine, bronchoalveolar lavage, and cerebrospinal fluid (CSF) samples, but cross-reactivity has been described between *B dermatitidis* and other dimorphic fungi such as *Histoplasma capsulatum* [18]. Unlike for coccidioidomycosis and histoplasmosis, the serum β-(1,3)-glucan test is unreliable for blastomycosis [11]. Clinical specimens can be stained with calcofluor, 10% potassium hydroxide, cytology specimens with Papanicolaou, and histopathologic tissue with methenamine silver or period acid-Schiff, while awaiting culture confirmation. Characteristic findings include pyogranulomatous inflammation with areas of necrosis, and broad-based budding yeasts with a thickened cell wall [11, 18, 20, 21].

Patients with life-threatening infection or central nervous system (CNS) involvement, those who are immunocompromised, and those who are pregnant are recommended to start therapy with amphotericin B (lipid formulations are preferable) followed by transition to an active azole, preferably itraconazole, which is the most studied agent against *Blastomyces* [22]. Posaconazole [23], isavuconazole [24], and voriconazole [25] are also reported to be effective, though clinical experience is limited. In mild-to-moderate blastomycosis, initial therapy with an active azole is the mainstay of therapy without need for intravenous induction with amphotericin B [22]. Voriconazole is recommended as step-down oral therapy for CNS blastomycosis including infections of the epidural space. Moreover, case reports of favorable outcomes for CNS blastomycosis [25] and CSF penetration [26] were factors in selecting voriconazole for our patient after intolerance to itraconazole.

Our patient was diagnosed with severe hypokalemia 28 days after initiating posaconazole. He also developed hypertension when blood pressure measurements were compared with pretreatment baseline measurements (Figure 5). We suspected that this may have occurred as the result of posaconazole-induced pseudohyperaldosteronism (PIPH). He did not have any symptoms to implicate gastrointestinal potassium losses as a cause of hypokalemia and he was not taking a diuretic, making renal losses less likely. PIPH is a recently described syndrome characterized by hypokalemia, hypertension, and occasionally metabolic alkalosis [27, 28] and is confirmed by elevated 11β-deoxycortisol with concurrently suppressed renin and aldosterone [29]. In the mechanism advanced, posaconazole inhibits 11β-hydroxylase and/or 11β-hydroxysteroid dehydrogenase 2 depending on the patient [30–32]. In a retrospective case-control study of 69 patients treated with posaconazole [29], 16 (23%) were diagnosed PIPH a median of 46 days (range, 14–96 days) after drug initiation; significant risk factors were older age, posaconazole level, and preexisting hypertension. Median posaconazole levels were 3.0 μg/mL compared to 1.2 μg/mL in the control group, and posaconazole levels positively correlated with 11β-deoxycortisol levels. Although we did not obtain confirmatory studies for PIPH in our patient, the timing of onset after starting therapy (28 days), the posaconazole level (3.4 μg/mL), and clinical improvement upon drug discontinuation were all consistent with this diagnosis. Patients with PIPH have been managed by posaconazole dose reduction, transition to another agent, or addition of a mineralocorticoid antagonist, but there is currently no consensus on optimal management [33]. Among the other azole antifungals, only itraconazole has similarly been associated with a syndrome of mineralocorticoid excess [34].

CONCLUSIONS

Cervical osseous involvement of blastomycosis is rare. We report an unusual case of blastomycosis cervical osteomyelitis that presented with a retropharyngeal abscess resulting in acute airway obstruction requiring emergent intervention. Clinicians should maintain a high index of suspicion for osseous blastomycosis, as clinical and radiographic findings can overlap with other infections and malignancy. They should also take a detailed history of any residence and/or travel through endemic areas to assess risk for exposure. In addition, they should consider early follow-up and monitoring of potassium levels in all patients initiated on posaconazole.

Notes

Author contributions. J. J. H., J. M. G., M. A. K., E. B. K., R. J. A., and D. F. S. contributed to the writing of the manuscript. J. J. H. and D. F. S. performed the literature review. J. M. G. and M. A. K. created figure 5.

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