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Successful Treatment of Osseous Blastomycosis without Pulmonary or Disseminated Disease and Review of the Literature

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Abstract

Blastomycosis commonly occurs following inhalation of *Blastomyces dermatitidis* conidia causing a pulmonary infection and can disseminate to extrapulmonary sites. Osseous involvement primarily results from hematogenous spread but in rare cases direct inoculation can occur. We describe a case of osseous blastomycosis without pulmonary or disseminated disease successfully treated with posaconazole.

Keywords

Blastomycosis; orthopedic infection; cutaneous inoculation

Case

A 49 year old healthy man with no significant past medical history suffered right tibial and fibular closed fractures in 2003 after falling from a 30-foot ladder while working indoors as a sprinkler fitter. The injury was repaired by intramedullary nail fixation without complications until March 2011 when he developed induration, swelling, erythema, and pain overlying the distal interlock screw surgical scar. He underwent distal interlock screw removal with negative operative bacterial cultures and was treated with several weeks of intravenous vancomycin. His drainage continued, so complete hardware removal was performed in April 2011. Bacterial cultures from intra-operative specimens remained sterile and he received another 6 weeks of intravenous vancomycin along with oral ciprofloxacin. Despite these interventions, drainage increased and an area of necrosis with surrounding

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erythema developed along the distal interlock screw incision. He denied systemic symptoms including fever, chills, shortness of breath, cough, or chest pain and remained ambulatory. He lived in Central Virginia near the Shenandoah Valley and worked as an indoor sprinkler fitter which required him to work on his hands and knees in older buildings at times. He spent time fishing and hiking at a Central Virginia lake known to have beaver dams but he stayed on the defined trails, had no animal exposures, and had no pets.

He was referred to our infectious diseases clinic in June 2011. At that time, laboratory evaluation revealed an erythrocyte sedimentation rate of 8 mm/h, C-reactive protein of 0.9 mg/dL, white blood cell count 7.7 k/μL (85% neutrophils, 7% lymphocytes, 3.6% monocytes, and 1.8% eosinophils), hematocrit 38.0%, platelet count of 220 k/μL, and normal electrolytes, renal, and liver function. An MRI of the right tibia and fibula showed edema over the distal medial ankle without abscess or osteomyelitis, myositis in the distal soleus muscle, and fluid in the tibial medullary canal. He was then referred to the Department of Orthopaedic Surgery for further debridement with a concern for ongoing fungal, mycobacterial, or atypical bacterial infection and/or an underlying nidus of infection.

He underwent debridement and washout and was found to have drainage around the medial malleolus and had fibrous tissue, but no sinus tract, abscess or fluid collection. Operative deep tissue and bone samples showed no bacteria on gram stain, no fungal elements on KOH preparations and no acid fast bacilli on concentrated AFB smear, but no samples were sent for pathology. After two weeks of incubation, fungal cultures from deep tissue and bone samples had moderate growth of mold. We then performed 26S ribosomal DNA sequencing by extracting DNA from the isolate using PrepMan® Ultra Sample Preparation reagent following the manufacturer's directions (Life Technologies/Applied Biosystems, Foster City, CA). The extracted DNA was subjected to DNA sequence analysis of the D2 26S rDNA region following the methods of Kurtzman and Robnnet (1997). The sequence was compared to the GenBank database using the NCBI Basic Local Alignment Search Tool (BLAST). The top nine hits were *Ajellomyces dermatitidis (Blastomyces dermatitidis)* with 100% sequence query coverage (725 base pairs) and 100% identity.

In follow-up, a urine *Blastomyces* antigen (MiraVista Diagnostics, Indianapolis, IN) was not detected, a chest X-ray was normal, and he was not infected with HIV. He initially received itraconazole 200 mg twice a day but the dose was increased to 300 mg twice a day due to a sub-therapeutic itraconazole concentration of <0.3 mcg/ml. Despite increasing the dose and taking the medication on an empty stomach, his serum itraconazole level remained <0.3 mcg/ml (>0.5 mcg/ml for localized infection; >1.0 mcg/ml for systemic infection). He was changed to voriconazole but this was stopped after 2 weeks of therapy due to hepatotoxicity with AST 85 (normal is <35 U/L) and ALT 151 (normal is <55 U/L). He then successfully completed 6 months of treatment with posaconazole 400 mg twice daily with a therapeutic posaconazole level of 1710 ng/mL (>700 ng/mL). He had complete resolution of his symptoms, returned to his normal functional status, and did not require any further surgery.

Discussion

The dimorphic fungus *Blastomyces dermatitidis* causes infection in humans when conidia are inhaled or directly inoculated into tissues followed by transition to a yeast form (Saccente and Woods, 2010). *B. dermatitidis* is primarily a disease of North America and is endemic in the Mississippi and Ohio River valleys and areas bordering the Great Lakes (Saccente and Woods, 2010). *B. dermatitidis* is saprobic and associated with outdoor exposures (Saccente and Woods, 2010). The clinical presentation of blastomycosis is variable, ranging from asymptomatic to severe disseminated infection and can mimic common diseases including bacterial pneumonia, malignancies, and tuberculosis. Pulmonary blastomycosis, either acute or chronic, is the most common clinical presentation while cutaneous blastomycosis is the most common extrapulmonary site followed by osseous and genitourinary infection (Saccente and Woods, 2010). Skeletal involvement has been described in 6-60% of blastomycosis cases and is generally the result of hematogenous spread (Oppenheimer et al., 2007; Saccente and Woods, 2010; Saiz et al., 2004). Infection can occur in any bone but is most frequently found in the vertebrae, skull, and long bones (Hamann and Marberry, 2010; Oppenheimer et al., 2007; Saccente et al., 1998; Saccente and Woods, 2010; Saiz et al., 2004; Veligandla et al., 2002). Rarely, direct cutaneous inoculation occurs through a penetrating wound or laboratory injury (Saccente and Woods, 2010; Veligandla et al., 2002).

This case of osseous blastomycosis occurred without evidence of pulmonary or systemic infection suggesting direct inoculation. The patient's initial injury was a closed fracture that occurred indoors and required surgical repair so we suspect the infection did not occur at the time of the initial injury. The source and timing of his infection with *Blastomyces* is unknown and he denied any subsequent trauma to the area. Although the actual inciting event is unknown, he spent time outdoors in Central Virginia and likely had an exposure that led to direct cutaneous inoculation in the area years after the initial injury. His outdoor exposures occurred in Central Virginia and the Shenandoah Valley where *Blastomyces* is known to be endemic but no detailed epidemiological data are available.

Direct inoculation of *Blastomyces* has been described as a cause of cutaneous blastomycosis but infection of the underlying osseous structures by this route is very rare (Farr et al., 1992; Gray and Baddour, 2002; Veligandla et al., 2002; Wagner et al 1985). We identified six additional cases of osseous blastomycosis without pulmonary or disseminated infection in the medical literature (Table 1) (Codifava et al., 2012; Saccente et al., 1998; Veligandla et al., 2002; Farr et al., 1992; Wagner et al., 1985). The majority of cases occurred in men between 25 and 50 years of age. Male predominance in blastomycosis cases is well described and believed secondary to increased risk of exposure rather than an increased susceptibility to infection (Bradsher, 1996; Saccente and Woods, 2010). However, we found two cases in women less than 25 years old and one in a 3 year-old child, although infection in children and adolescents is uncommon (Saccente and Woods, 2010). Four of the cases involved infection in the lower extremity including femur, knee and ankle and this location is consistent with direct inoculation from an environmental exposure. The primary symptom at presentation was pain and swelling of the adjacent joint. All patients had at least one month of symptoms before diagnosis and four patients had symptoms for a year or greater.

Such a significant delay in diagnosis and treatment of osseous blastomycosis suggests a lack of awareness of the diagnosis which may increase associated morbidity.

In the majority of cases, the diagnosis of osseous blastomycosis was made by growth of *B. dermatitidis* from tissue or fluid samples. All but one patient had a normal white blood cell (WBC) count but the erythrocyte sedimentation rate (ESR) was elevated in all patients where it was measured except in the case described here. Pulmonary imaging was normal in all patients except one case where no imaging was done but the patient was described as having no abnormalities on pulmonary exam (Veligandla et al., 2002). Several of the cases occurred in areas not considered endemic for blastomycosis including two cases in Nebraska and one in Europe (Veligandla et al., 2002; Codifava et al., 2012). Most cases were treated with amphotericin B and/or itraconazole for six to twelve months and all were considered cured without relapse. The case described here suggests osseous infection occurred after direct inoculation since there was no evidence of pulmonary and systemic infection, the infection was localized to the area of prior injury, and the findings are consistent with other cases of direct inoculation blastomycosis described here.

Diagnosis of cutaneous blastomycosis requires visualization of characteristic yeast forms on pathologic specimens or growth of the organism in culture (Saccente and Woods, 2010). *B. dermatitidis* are round to oval multinucleated yeast cells demonstrating single broad based budding (Saccente and Woods, 2010). Growth on fungal media occurs in about 1 to 3 weeks with the mold form showing branching hyphae with conidiophores at right angles or single terminal conidia (Saccente and Woods, 2010). A DNA probe, PCR, or nucleic acid sequencing can confirm the diagnosis (Saccente and Woods, 2010). Evaluation for disseminated disease is required when cutaneous blastomycosis is identified. *Blastomyces* urine antigen is detected in most cases of pulmonary and disseminated blastomycosis with a sensitivity of around 90% (Saccente and Woods, 2010).

Little information is available regarding the treatment of cutaneous inoculation blastomycosis. Early reported cases resolved without systemic antifungal therapy using various combinations of incision and drainage, surgical excision, potassium iodide and in one case radiation therapy (Gray and Baddour, 2002). Current guidelines for the treatment of extrapulmonary blastomycosis recommend 1 to 2 weeks of amphotericin B for moderate to severe disease followed by 6 to 12 months of itraconazole while mild to moderate disease can be treated with 6-12 months of itraconazole (Chapman et al., 2008). Osteoarticular blastomycosis is more difficult to treat with a higher concern for recurrence, so the recommended treatment duration is 1 year (Chapman et al., 2008). The duration of therapy is not clear for primary skin lesions without dissemination or osseous involvement (Gray and Baddour, 2002). In this report, the patient received 6 months of therapy despite having a positive bone culture for *B. dermatitidis* with complete symptom resolution and no relapse. Surgical debridement, removal of hardware and lack of disseminated infection likely contributed to the successful treatment of osseous blastomycosis with only 6 months of therapy. This is the first reported case of osseous blastomycosis involving orthopedic hardware and the removal of hardware may have been an important factor that allowed for shorter treatment duration.

Amphotericin and itraconazole are the first-line antifungals used for the treatment of blastomycosis but extended spectrum azoles voriconazole and posaconazle can be effective alternative agents (Chapman et al., 2008). Amphotericin B is no longer recommended as sole therapy due to toxicity with itraconazole having fewer side effects and an efficacy over 90% in non-life threatening blastomycosis (Bradsher, 1996; Chapman et al., 1997; Chapman et al., 2008; Dismukes et al., 1996). Voriconazole and posaconazole have *in vitro* activity against *B. dermatitidis* but are not well studied in the treatment of blastomycosis (Chapman et al., 2008; Li et al., 2000; Sugar and Liu, 1996). Voriconazole has been used to treat blastomycosis in the setting of itraconazole intolerance or sub-therapeutic drug levels and has been successful in the treatment of CNS blastomycosis (Borgia et al., 2006; Freifeld et al., 2009; Freifeld et al., 2010). There are two previously reported cases describing the successful treatment of blastomycosis using posaconazole (Proia and Harnisch 2012). Our report represents the third case of blastomycosis successfully treated with a prolonged course of posaconazole due to sub-therapeutic itraconazole levels and voriconazole hepatotoxicitiy with no relapse at one year.

Conclusion

We report a case of osseous blastomycosis secondary to direct cutaneous inoculation involving orthopedic hardware. In addition, this case demonstrates successful treatment of osseous infection with 6 months of antifungal therapy and supports the efficacy of posaconazle against blastomycosis. In endemic regions, osseous blastomycosis, with or without pulmonary or disseminated disease, should be considered in patients with chronic orthopedic infections even if there are no systemic symptoms.

References

Borgia SM, Fuller JD, Sarabia A, El-Helou P. Cerebral blastomycosis: a case series incorporating voriconazole in the treatment regimen. Med Mycol. 2006; 44(7):659–64. [PubMed: 17071562]

Bradsher RW. Histoplasmosis and blastomycosis. Clin Infect Dis. 1996; 22(Suppl 2):S102–11. [PubMed: 8722836]

Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, Kauffman CA. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008; 46(12):1801–12. [PubMed: 18462107]

Chapman SW, Lin AC, Hendricks KA, Nolan RL, Curriet MM, Morris KR, Turner HR. Endemic blastomycosis in Mississippi: epidemiological and clinical studies. Semin Respir Infect. 1997; 12(3):219–28. [PubMed: 9313293]

Codifava M, Guerra A, Rossi G, Paolucci P, Lughetti L. Unusual osseous presentation of blastomycosis in an immigrant child: a challenge for European pediatricians. Ital J Pediatr. 2012; 38(69):1–4. [PubMed: 22233935]

Dismukes WE, Bradsher RW, Cloud GC, Kauffman CA, Chapman SW, George RB, Stevens DA, Girard WM, Saag MS, Bowles-Patton C. Itraconazole therapy for blastomycosis and histoplasmosis. NIAID Mycoses Study Group. Am J Med. 1992; 93(5):489–97. [PubMed: 1332471]

Farr RC, Gardner G, Acker JD, Brint JM, Haglund LF, Land M, Schweitzer JB, West BC. Blastomycotic cranial osteomyelitis. Am J Otol. 1992; 13(6):582–6. [PubMed: 1449188]

Freifeld AG, Bariola JR, Andes D. The role of second-generation antifungal triazoles for treatment of the endemic mycoses. Curr Infect Dis Rep. 2010; 12(6):471–8. [PubMed: 21308557]

Freifeld A, Proia L, Andes D, Baddour LM, Blair J, Spellberg B, Arnold S, Lentnek A, Wheat LJ. Voriconazole use for endemic fungal infections. Antimicrob Agents Chemother. 2009; 53(4):1648–51. [PubMed: 19139290]

Gray NA, Baddour LM. Cutaneous inoculation blastomycosis. Clin Infect Dis. 2002; 34(10):E44–9. [PubMed: 11981746]

Hamann JC, Marberry K. Sentinel presentation of disseminated *Blastomyces dermatitidis* infection as hip pain in a young adult: a case report. J Bone Joint Surg Am. 2010; 92(2):469–72. [PubMed: 20124077]

Kurtzman CP, Robnett CJ. Identification of clinically important ascomycetous yeasts based on nucleotide divergence in the 5′ end of the large-subunit (26S) ribosomal DNA gene. J Clin Microbiol. 1997; 35:1216–23. [PubMed: 9114410]

Li RK, Ciblak MA, Nordoff N, Pasarell L, Warnock DW, McGinnis MR. *In vitro* activities of voriconazole, itraconazole, and amphotericin B against *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*. Antimicrob Agents Chemother. 2000; 44(6):1734–6. [PubMed: 10817743]

Oppenheimer M, Embil JM, Black B, Wiebe L, Limerick B, MacDonald K, Trepman E. Blastomycosis of bones and joints. South Med J. 2007; 100(6):570–8. [PubMed: 17591310]

Proia LA, Harnisch DO. Successful use of posaconazole for treatment of blastomycosis. Antimicrob Agents Chemother. 2012; 56(7):4029. [PubMed: 22564845]

Saccente M, Abernathy RS, Pappas PG, Shah HR, Bradsher RW. Vertebral blastomycosis with paravertebral abscess: report of eight cases and review of the literature. Clin Infect Dis. 1998; 26(2):413–8. [PubMed: 9502464]

Saccente M, Woods GL. Clinical and laboratory update on blastomycosis. Clin Microbiol Rev. 2010; 23(2):367–81. [PubMed: 20375357]

Saiz P, Gitelis S, Virkus W, Piasecki P, Bengana C, Templeton A. Blastomycosis of long bones. Clin Orthop Relat Res. 2004; 421:255–9. [PubMed: 15123956]

Sugar AM, Liu XP. *In vitro* and *in vivo* activities of SCH 56592 against Blastomyces dermatitidis. Antimicrob Agents Chemother. 1996; 40(5):1314–6. [PubMed: 8723494]

Veligandla SR, Hinrichs SH, Rupp ME, Lien EA, Neff JR, Iwen PC. Delayed diagnosis of osseous blastomycosis in two patients following environmental exposure in nonendemic areas. Am J Clin Pathol. 2002; 118(4):536–41. [PubMed: 12375640]

Wagner DK, Varkey B, Head MD. Blastomycotic osteomyelitis of the mandible: successful treatment with ketoconazole. Oral Surg Oral Med Oral Pathol. 1985; 60(4):370–1. [PubMed: 3864096]

Table 1

Cases of osseous blastomycosis without evidence of pulmonary or systemic involvement

Patient (yrs/sex)	Site	Symptoms	Symptom Duration[a] (mo)	Diagnosis	Specimen	WBC (k/μL)	ESR (mm/h)	CXR	Location/ Occupation	Therapy (dose)	Therapy Duration (mo)	Ref.
49/M	Right ankle	Ankle pain, swelling & drainage	5	Culture	Ankle tissue & bone	7.7	8	Normal	Virginia/sprinkler fitter	Posaconazole (400mg twice daily)	6	This report
3/UKN	Left femur	Left knee pain	UKN	Pathology	Purulent fluid adjacent to femur	Normal	N/D[b]	N/D[c]	Ghana & Italy/N/A	Lipid Amphotericin B (0.7mg/kg/day); Itraconazole (10mg/kg/day)	6	Codifava et al 2012
17/F	T12-L2	Back & left leg pain	15	Culture	Aspiration left psoas fluid	5.6	57	Normal	Alabama or Arkansas/UKN	Itraconazole (200mg twice daily)	6	Saccente et al 1998
29/M	Right knee	Knee pain & swelling	12	Culture	Patellar tissue	5	N/D	Normal	Nebraska/agronomist	Itraconazole (100mg twice daily)	12	Veligandla et al 2002
36/M	Right knee	Knee pain	1	Culture	Granulation tissue	8	N/D	N/D[d]	Nebraska/welder	Itraconazole (200mg daily)	12	Veligandla et al 2002
24/F	Left temporal	Headache & otitis	12+	Pathology	Tympanic membrane	13	30	Normal	Tennessee & Florida/UKN	Amphotericin B (total dose of 2.5g)	5	Farr et al 1992
40/M	Left mandible	Mandibular swelling & pain	3	Culture	Sinus tract drainage	10	84	Normal	Wisconsin/UKN	Ketoconazole (200mg daily)	26	Wagner et al 1985

[a] Duration of illness before diagnosis of osseous blastomycosis,

[b] C-Reactive Protein 13.22 mg/dl,

[c] Total body CT was negative,

[d] "No abnormalities noted on the pulmonary examination" (Veligandla et al 2002)

WBC = White Blood Cell, ESR = Erythrocyte Sedimentation Rate, CXR = Chest X-ray, UKN = Unknown, N/D = Not Done, N/A = Not Applicable