Cavitating lung nodule and lytic spinal lesions in an adolescent male

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A previously healthy 17-year-old boy from northern New Brunswick presented to his local physician with a six-week history of mid-thoracic back pain and a 4 kg weight loss. There was no history of trauma, fever or night sweats; the review of systems was otherwise normal. He had no recent travel outside of the province, no recent infectious contacts, took no medications and his immunizations were up to date. He was a nonsmoker and denied illicit drug use. A brief exposure to his grandfather with suspected tuberculosis 12 years earlier was noted.

Physical examination revealed a tall, thin and well-looking adolescent male. His vital signs, including temperature, were normal. His head and neck examinations were unremarkable. Tactile fremitus was noted over his left upper lung fields, but on auscultation, air entry was good bilaterally with no adventitious sounds. His cardiac and abdominal examinations were normal. There was no tenderness on palpation of the spine or paraspinal muscles. His neurological examination was normal.

Initial laboratory results included a normal complete blood cell count and an absolute neutrophil count. The erythrocyte sedimentation rate was elevated at 60 mm/h. Serology tests for antinuclear antibody, perinuclear anticytoplasmic antibody and circulating antineutrophil cytoplasmic antibody were negative.

A nuclear bone scan demonstrated an increased uptake in the sacrum and mid-thoracic spine, further defined on computed tomography (CT) scan as a lytic right-sided S1/S2 sacral lesion involving adjacent soft tissue. A large lytic lesion of T9 was also seen, as well as a cavitating 3 cm diameter lung lesion in the left upper lobe of the lung, surrounded by minimal alveolar infiltrate. No hilar adenopathy was present. The patient was referred to the IWK Health Centre (Halifax, Nova Scotia) for further evaluation. Over the course of investigations, a mild nonproductive cough developed.

Further studies noted normal serum quantitative immunoglobulin levels, a normal sweat chloride test and a negative tuberculin skin test. An oxidative burst assay of neutrophil function was normal.

An open sacral biopsy was performed revealing neutrophilic and eosinophilic infiltrates, but no dysplasia or malignancy. Gram, Kinyoun and Calcofluor stains for bacteria, mycobacteria and fungi were negative. Routine bacterial and mycobacterial cultures were negative. Pathology noted the rim of a granuloma in one section.

Two weeks later, a repeat CT scan documented rapid disease progression despite the indolent symptoms. The lytic T9 lesion had extended into T10 with increased soft tissue swelling and rim enhancement (Figure 1), and there were

Figure 1 Coronal computed tomography image before the computed tomography-guided vertebral biopsy and the thoracoscopic lung biopsy. An intermediate window-level setting depicts both the spine and lung lesions. The lytic T9 lesion, the left paraspinal soft tissue thickening and the T9-T10 disc height reduction are visible; the osteolysis involving the upper plateau of T10 is present on a more anterior image. The juxta-pleural thin-rimmed cavitating left upper lobe lesion is also appreciated. Foci of alveolar opacities are present on a more posterior plane

increased infiltrates around the pulmonary cavitation. Mycobacterial and fungal cultures of the biopsy material remained negative. Nucleic acid amplification tests for mycobacteria were negative from the biopsy.

In pursuit of a firm diagnosis, both a T9 CT-guided needle biopsy and thoracoscopic excisional lung biopsy of the cavitation were performed. Necrotizing granulomas were seen in the tissue from both sites. What is the diagnosis?

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DIAGNOSIS

Fungal cultures of both the lung and T9 biopsies were positive after two weeks incubation, with growth of *Blastomyces dermatitidis*. On Sabouraud dextrose agar at 30°C, white yeast-like colonies developed that later produced aerial mycelia. Microscopic examination revealed thin septate hyphae bearing pear-shaped conidia. Subculture to brain heart infusion agar at 37°C, in a biocontainment level III laboratory, demonstrated the characteristic thermal conversion to yeast-like cells with broad-based budding.

Initial reviews of tissue histology were negative for fungal elements. Periodic acid-Schiff stains of the tissue revealed extremely rare budding yeast, and only after extensive review. Serology for *B dermatitidis* performed at a reference laboratory was positive.

A diagnosis of disseminated blastomycosis was made, and therapy was initiated with itraconazole 300 mg/day. Within several weeks, an improvement in cough, appetite and weight was noted. Three months later, the pulmonary infection was no longer radiologically visible and bony reconstruction was present on the vertebral bodies.

DISCUSSION

Blastomycosis in Canada's Maritime provinces is an exceedingly rare, but potentially fatal disease. Our patient acquired blastomycosis in New Brunswick without recent travel to an endemic area, generally defined as the Mississippi and Ohio River basins, the Great Lakes and St Lawrence lowlands, northern Ontario and eastern Manitoba (1-5).

Only six Maritime cases have been reported since the 1960s, and four either omit relevant travel history (6) or followed travel to endemic areas (7). Of the remaining two, the case in 1960 (8) was the first report of blastomycosis in Nova Scotia, while the other described a cutaneous case in New Brunswick (9).

B dermatitidis, a thermally dimorphic fungus, causes a wide spectrum of disease. Inhalation of conidia, the typical exposure route, is followed by an incubation period averaging 30 to 45 days. Infection is subclinical (greater than 50% of cases), pulmonary or extrapulmonary. Disseminated, extrapulmonary

disease follows hematogenous spread, typically involving skin, bone (often axial skeleton), the genitourinary system or the central nervous system (10). Direct inoculation leading to cutaneous infection is described. Blastomycosis can be acute, mimicking bacterial pneumonia, or remarkably indolent and indistinguishable from tuberculosis, cancer or other endemic fungal diseases. In a recent Canadian case series (2), 38% of patients with disseminated infection had no constitutional symptoms.

Laboratory diagnosis can be challenging. On direct tissue microscopy, *B dermatitidis* appears as thick-walled spherical yeast cells (8 µm to 15 µm in diameter) with single broad-based budding. Granulomatous tissue reactions are typical, but the burden of organisms may be low, making microscopic diagnosis difficult. Serological assays for *B dermatitidis*, although positive in this case, have variable sensitivities.

Requesting appropriate fungal cultures and fungal stains during histopathology is critical for diagnosis, as well as alerting laboratory staff to take proper precautions. Commercially available molecular testing (ie, Accuprobe [Accuprobe Inc, USA]) can rapidly identify *B dermatitidis* colonies that appear in cultures, but manipulation of dimorphic fungi must be performed in appropriate biocontainment facilities.

Amphotericin is recommended for life-threatening infections, central nervous system disease, infection in immunocompromised hosts, infants and during pregnancy (10). For most other presentations, itraconazole therapy is appropriate. Bone infections are particularly prone to relapse and should be treated for a minimum of one year (10,11). A guideline (10) by the National Mycoses Study group and the Infectious Diseases Society of America provides detailed therapeutic recommendations.

CONCLUSION

Blastomycosis does occur in Canada's Maritime provinces. Establishing a diagnosis often requires invasive diagnostic measures. Symptoms may be indolent in the presence of extensive disease, and can mimic malignancy or mycobacterial infection. An index of suspicion is critical for obtaining a timely and accurate diagnosis.

REFERENCES

- Walsh CM, Morris SK, Brophy JC, Hiraki LT, Richardson SE, Allen UD. Disseminated blastomycosis in an infant. *Pediatric Infect Dis J* 2006;25:656-8.
- Morris SK, Brophy J, Richardson SE, et al. Blastomycosis in Ontario, 1994-2003. *Emerg Infect Dis* 2006;12:274-9.
- Dworkin MS, Duckro AN, Proia L, Semel JD, Huhn G. The epidemiology of blastomycosis in Illinois and factors associated with death. *Clin Infect Dis* 2005;41:e107-11.
- Dwight PJ, Naus M, Sarsfield P, Limerick B. An outbreak of human blastomycosis: The epidemiology of blastomycosis in the Kenora catchment region of Ontario, Canada. *Can Commun Dis Report* 2000;26:82-91.
- Crampton TL, Light BR, Berg GM, et al. Epidemiology and clinical spectrum of blastomycosis diagnosed at Manitoba hospitals. *Clin Infect Dis* 2002;34:1310-6.
- Grandbois J. La Blastomycose Nord-Americaine au Canada. *Laval Med* 1963;34:714-31.
- Nicoll LE, Rostein C, Bourgault AM, et al. Invasive fungal infections in Canada from 1992 to 1994. *Can J Infect Dis* 1998;9:347-52.
- Gordon CA, Stewart WB. Treatment of North American blastomycosis with amphotericin B. *CMAJ* 1960;82:471-3.
- Ross JJ, Keeling DN. Cutaneous blastomycosis in New Brunswick: Case report. *CMAJ* 2000;163:1303-5.
- Chapman SW, Bradsher RW, Campbell GD, Pappas PG, Kauffman CA. Practice guidelines for the management of patients with blastomycosis. *Infectious Diseases Society of America. Clin Infect Dis* 2000;30:679-83.
- Oppenheimer M, Embril JM, Black B, et al. Blastomycosis of bones and joints. *South Med J* 2007;100:570-8.