

CASE REPORT

PULMONARY BLASTOMYCOSIS DIAGNOSED IN HAWAI'I

Michael V Arnett¹, Susan L Fraser² and Vincent X Grbach¹

¹Tripler Army Medical Center, Honolulu, HI; ²Walter Reed Army Medical Center, Washington DC, USA

Abstract. Blastomycosis, a fungal infection caused by *Blastomyces dermatitidis*, was once thought to be endemic only to the Central and Great Lakes regions of the United States of America. We present the first reported case series of patients documenting the diagnosis of blastomycosis in the Pacific region. In both cases, exposure to endemic areas was retrospectively identified.

INTRODUCTION

Blastomycosis is a fungal infection caused by *Blastomyces dermatitidis*, a fungus once thought to be endemic only to the Central and Great Lakes regions of the United States of America. There is an increasing body of literature reporting cases of "North American" blastomycosis throughout the world among patients with no reported history of travel to endemic areas of the United States.

Infection occurs when the fungus is inhaled into the lungs. Pulmonary infection is the most common presentation, but several organs may also be infected, and multiple organ systems may be involved simultaneously. The clinical presentation of blastomycosis infection may mimic tuberculosis, influenza, other fungal infections or malignancy. Because of the insidious onset of disease, the vague-

ness of symptoms during clinical infection, and the normal self-limited course, diagnosis of infection is rare even in endemic areas. Clinical infections may be successfully treated with antifungal agents. Itraconazole can be used for moderate infections, but amphotericin B should be used for life-threatening disease and whenever central nervous system involvement occurs. We present a case series of patients who were diagnosed with pulmonary blastomycosis in Hawai'i. In both cases, we were able to retrospectively identify exposure to endemic areas of the United States.

CASE REPORTS

Case 1

A 30 year old African-American male sailor was evacuated from a United States Navy aircraft carrier to the military hospital in Honolulu, Hawai'i for evaluation of suspected pneumonia during a scheduled port call. He had a worsening non-productive cough, recurrent fevers and his physician also discovered an enlarging goiter. Shipboard laboratory values were significant for elevated blood glucose and hematuria. His past medical history was significant for impaired fasting glucose diagnosed ten years previously. Review of

Correspondence: Dr Michael Arnett, MCHK-DM, 1 Jarrett White Rd, Honolulu, HI 96859, USA.
Tel: 808-433-4049; Fax: 808-433-1555
E-mail: michael.arnett@amedd.army.mil

The views expressed in the manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

systems was significant for a 4.5 kg weight loss over two months, malaise, fatigue and erectile dysfunction. A travel history revealed, since enlisting in the Navy from his home in Chicago, Illinois, he had been stationed in San Diego, California and had participated in several tours of the South Pacific. Immediately prior to onset of symptoms, the patient had been in Alaskan waters and initially attributed his cough to exposure to the cold climate.

The physical examination revealed tachypnea, fever to 39°C, coarse rhonchi over the left upper lung field, a symmetric non-nodular goiter and no lymphadenopathy or abnormal skin findings. Laboratory studies included a white blood cell count of 16.8 ($\times 10^9/l$), microscopic hematuria, and thyroid function testing that revealed a free thyroxine (FT4) of 7.3 ng/dl and an undetectable thyroid stimulating hormone (TSH) level. A chest radiograph demonstrated left lung consolidation (Fig 1), and a thyroid uptake scan was performed which revealed diffuse homogeneous uptake. A bone scan demonstrated no evidence of focal disease.

Azithromycin was prescribed for community acquired pneumonia. Over the next 48 hours, the patient demonstrated worsening cough, persistent febrile episodes, and increased left lung consolidation on serial radiographs. Antibiotic coverage was broadened to clindamycin and cefepime without any improvement in fever, respiratory symptoms, or hematuria. He continued to have fevers to as high as 39°C, and his leukocytosis increased to 29.4 ($\times 10^9/l$). Purified protein derivative (PPD) skin testing was performed to evaluate for tuberculosis, which was negative. Serum markers of inflammation were measured: erythrocyte sedimentation rate (ESR) was elevated at 113 mm/hr and C-reactive protein (CRP) was elevated at 23.65 mg/dl.

A bronchoscopy was performed to further evaluate the patient's airways and to obtain samples for histological evaluation and cell



Fig 1—Chest radiograph demonstrating extensive consolidation within the left upper lobe and lingula.

culture. Gram staining, as well as staining for acid-fast bacteria and fungal organisms, was performed and no organisms were identified. Samples from bronchial lavage were submitted for bacterial and fungal cultures. Evaluation of the transbronchial biopsies demonstrated focal sheets of acute inflammation and necrosis with focal microabscesses and palisading histiocytes.

The patient's condition worsened clinically despite broad-spectrum antibiotics. The presence of hematuria and the absence of organisms on initial staining of bronchial samples led the primary team to suspect an underlying vasculitis. Corticosteroid treatment was initiated, and the patient demonstrated significant clinical improvement.

Three days after bronchoscopy, fungal cultures of the bronchial lavage demonstrated a broad-based budding yeast that was identified as *Blastomyces dermatitidis*. The patient was treated with itraconazole 200 mg twice daily and the corticosteroids were terminated. Urinary and serum *Blastomyces* antigen detection tests, performed by Miravista labs, were positive. The patient demonstrated marked clinical improvement throughout the remainder of his hospital course. He was transferred to his home station in California

with the recommendation to complete a six month course of itraconazole. Follow-up three months after discharge demonstrated complete resolution of respiratory symptoms. The patient received thyroid ablation for treatment of his Graves' disease, and follow-up thyroid testing demonstrated a TSH level of 0.77 mIU/ml and a FT4 level of 1.80 ng/dl. Repeat urinalysis demonstrated resolution of the hematuria, and the ESR and CRP levels returned to normal ranges.

Case 2

A 21-year old Caucasian male soldier, originally from Minnesota, was evacuated from Iraq for a facial cellulitis and mandibular abscess. He was returned to his duty station in Hawai'i for further recovery. Following resolution of the cellulitis, he presented for evaluation of chronic lower back pain. Radiography demonstrated an incidental finding of a right lower lobe infiltrate which appeared stable when compared to previous films. Review of pulmonary symptoms revealed a two-week history of non-productive cough and runny nose during his combat tour which were symptoms shared by several members of his unit. The patient denied any history of chronic cough before or after deployment. Physical examination revealed a well-healed scar at the mandibular abscess incision and drainage site and no lymphadenopathy.

Pulmonary examination demonstrated no abnormal findings. A CT-scan demonstrated a 2.8 cm by 2.3 cm cavitory lesion in the right lower lobe (Fig 2). The patient was tested for tuberculosis infection with a PPD skin test, which was negative. The patient was then evaluated by bronchoscopy assisted lavage. No organisms were isolated and histological evaluation demonstrated reactive alveolar macrophages and histiocytes without evidence malignant cells.

Video-assisted thoroscopic surgery was then obtained for further evaluation. Tissue from the lesion demonstrated an acute and



Fig 2—Computed tomography demonstrating a 2.8 x 2.3 cm thin-walled cavitory lesion in the right lower lobe.

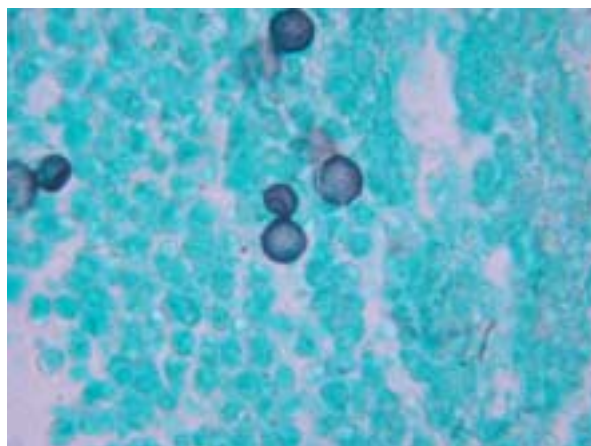


Fig 3—Gomori methanamine silver stain demonstrating *Blastomyces dermatitidis* in the budding phase.

chronically inflamed necrotic cavity with associated fibrosis and granulomatous inflammation without evidence of malignancy. Aerobic, anaerobic, and AFB cultures were negative for organisms. Fungal cultures demonstrated *Blastomyces dermatitidis* (Fig 3). Given the absence of pulmonary symptoms and the typical self-limited clinical course of blastomy-

cosis, the patient was not treated with anti-fungal medication.

DISCUSSION

Blastomyces dermatitidis is classically associated with the central region of the United States. Geographic distribution includes the states that border the Great Lakes as well as the Ohio and Mississippi River Valleys (Klein *et al*, 1986). Infection is caused by inhalation of the organism which is found in the soil throughout endemic areas. Interestingly, there are documented cases of clinical infection of *B. dermatitidis* in Africa (Anjorin *et al*, 1984), Italy (Rivasi *et al*, 2000), Israel (Kuttin *et al*, 1978), and India (Randhawa *et al*, 1983) among patients who have no history of travel to the United States.

The most common clinical presentation of blastomycosis is pneumonia with accompanying radiographic evidence of an infiltrate (Bradsher *et al*, 2003). Initial complaints may be vague and include malaise, fatigue, and fever. Clinically, blastomycosis infection is indistinguishable from tuberculosis, other fungal infections, or malignancy. The diagnosis of blastomycosis is often delayed secondary to the non-specificity of symptoms and the rarity of the diagnosis in clinical practice. Extra-pulmonary involvement is not uncommon. Lesions may occur in any organ system, but the most common extra-pulmonary sites, in descending order of frequency, are: cutaneous, osseous, genitourinary, and central nervous system.

Diagnosis is achieved via visualization of *B. dermatitidis* in tissue or exudate samples stained with Gomori methenamine silver stain (GMS) or periodic acid-Schiff stain (PAS) or by isolation on fungal culture, which is associated with a high diagnostic yield (Martynowicz and Parakash, 2002). The fungus appears as large, broad-based, unipolar budding yeast-like cells, 8-15 microns in diameter. New genera-

tion testing for specific cell wall antigens are available for clinical use. Radioimmunoassays, and utilization of Western blot techniques are being developed.

Itraconazole 200-400 mg daily is the primary agent of choice in the treatment of non-life threatening infections. Alternative regimens include ketaconazole 400-800 mg daily or fluconazole 400-800 mg daily. Patients who are not able to tolerate azoles or who do not respond to treatment should have their treatment changed to amphotericin B 0.5-0.7 mg/kg daily. Life threatening infection and central nervous system involvement should be treated with amphotericin B 0.7-1 mg/kg daily (Chapman *et al*, 2000). The Infectious Disease Society of America is expected to release an update on treatment guidelines in the summer of 2008.

Regarding the interesting overlap between systemic blastomycosis infection and the hyperthyroid state observed in the first patient, we postulate that his Grave's disease was worsened by his active pulmonary fungal infection which he had acquired months or years prior to presentation while in northern Illinois. We could find only one prior case of blastomycosis associated with goiter in a 15 year old boy reported from a Chicago hospital (DeLeon and Johnson, 2001).

The patient in the second case presented with a solitary thin-walled cavitary lesion on routine chest radiography. This is a rare radiographic finding in pulmonary blastomycosis; and it is especially rare in an asymptomatic patient. Several retrospective studies evaluated the radiographic patterns of patients presenting with pulmonary blastomycosis in endemic areas. Air-space disease is the most common presentation (44-61%) followed by mass-like infiltrates (22-26%) (Halvorsen *et al*, 1984; Patel *et al*, 1999). A review of 100 patients over a 15 year period demonstrated only one presentation with a cavitary lesion (Patel *et al*, 1999). A smaller study identified 3 of 27 patients with pulmonary blastomycosis who

presented with thick-walled cavitory lesions (Halvorsen *et al*, 1984).

In summary, blastomycosis is an endemic mycosis that presents as an insidious infection that may involve multiple organ systems. The absence of pathognomonic features and the low-suspicion for infection by the healthcare provider make the detection of blastomycosis infections particularly difficult. In both cases presented here, a history of exposure to endemic areas of the United States was identified; however, there is a growing body of evidence in the literature suggesting a much wider reservoir for *Blastomyces dermatitidis* than previously believed. Though the typical course of infection is self-limited, antifungal medications should be initiated if there is evidence of systemic illness or in patients with immunosuppressed states. Additionally, providers should include fungal infections in their differential when patients, especially those who are immunocompromised, present with pulmonary infections that do not respond to empiric antibiotics.

ACKNOWLEDGEMENTS

We acknowledge the help of Dr Judy Freeman who provided the pathology image of *Blastomyces dermatitidis* from the patient's fungal culture.

REFERENCES

- Anjorin FI, Kazmi R, Malu AO, Lawande RV, Fakunle YM. A case of blastomycosis from Zaria, Nigeria. *Trans R Soc Trop Med Hyg* 1984; 78: 577-80.
- Bradsher RW, Chapman SW, Pappas PG. Blastomycosis. *Infect Dis Clin North Am* 2003; 17: 21-40.
- Chapman SW, Bradsher RW, Campbell GD, Pappas PG, Kauffman CA. Practice guidelines for the management of patients with blastomycosis. *Clin Infect Dis* 2000; 30: 679-83.
- DeLeon MA, Johnson A. Pathological case of the month. *Arch Pediatr Adolesc Med* 2001; 155: 91-2.
- Halvorsen RA, Duncan JD, Merten DF, Gallis HA, Putman CE. Pulmonary blastomycosis: radiologic manifestations. *Radiology* 1984; 150: 1-5.
- Klein BS, Vergeront JM, Davis JP. Epidemiologic aspects of blastomycosis, the enigmatic systemic mycosis. *Semin Respir Infect* 1986; 1: 29-39.
- Kuttin ES, Beemer AM, Levij J, Ajello L, Kaplan W. Occurrence of *Blastomyces dermatitidis* in Israel. First autochthonous Middle Eastern case. *Am J Trop Med Hyg* 1978; 27: 1203-5.
- Martynowicz MA, Parakash UBS. Pulmonary blastomycosis: an appraisal of diagnostic technique. *Chest* 2002; 121: 768-73.
- Patel RG, Patel B, Petrini MF, Carter RR 3rd, Griffith J. Clinical presentation, radiographic findings, and diagnostic methods of pulmonary blastomycosis: a review of 100 consecutive cases. *South Med J* 1999; 92: 289-95.
- Randhawa HS, Khan ZU, Gaur SN. *Blastomyces dermatitidis* in India: first report of its isolation from clinical material. *Sabouraudia* 1983; 21: 215-21.
- Rivasi F, Nanetti A, Cesinaro AM, Mazzone A. Histopathological evidence of North American blastomycosis in Italy: report of two cases. *Acta Pathol Microbiol Immunol Scan* 2000; 108: 273-5.