Gallium-67-Citrate and Bone Scintigraphy in Disseminated North American Blastomycosis

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We present a patient with North American blastomycosis involving lung and bone. Chest radiographs and CT scan showed a mass in the lung. Bone scintigraphy detected a photon-deficient area in the sternum and ^{67}Ga SPECT showed uptake in the right upper lung and in the sternum. A diagnostic thoracotomy and needle biopsy from the sternal lesion revealed granulomatous infection due to *Blastomyces dermatitidis*. After 3 mo of antifugal therapy, the follow-up ^{67}Ga study showed no evidence of the original lesions but demonstrated a new, asymptomatic, unsuspected lesion in the left infraspinatous muscle. This case illustrates that North American blastomycosis should be included in the differential diagnosis in cases of atypical pulmonary disease with bone involvement, even in geographic regions that are not considered endemic for this microorganism. Gallium-67 and bone scintigraphy may be useful in determining the extent of dissemination, in detecting occult lesions and in the follow-up of response to therapy.

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North American blastomycosis (NAB) is a fungal infection caused by *Blastomyces dermatitidis* which, if untreated with specific antifungal chemotherapy, has a progressive course and may be associated with a high mortality rate. The diagnosis of NAB is difficult because clinical, laboratory and imaging findings are nonspecific. It is only when the infecting microorganism is isolated on cultures from tissue sections or body fluids that the diagnosis can be made (*1,2*).

We report a patient who presented with a lung mass and a destructive lesion in the sternum. Investigation included chest radiographs, computed tomography (CT) scan and ^{67}Ga-citrate and bone scintigraphy. At thoracotomy, granulomatous infection caused by *Blastomyces dermatitidis* was identified in the tissue removed. Follow-up ^{67}Ga scintigraphy was performed 3 mo later to evaluate the response to treatment.

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CASE REPORT

A 37-yr-old male tobacco smoker was admitted to the hospital with a 4-mo history of nonproductive cough, anorexia and weight loss of 6 kg, low grade fever and night sweats. Serial chest radiographs performed prior to admission showed volume loss and opacity of the right upper lobe with adjacent pleural thickening (Fig. 1A). These findings did not improve despite antibiotic and antituberculous therapy. Bronchoscopy as an outpatient showed narrowed right upper lobe bronchus. Smears and cultures of bronchial washings were negative for acid fast bacilli. Physical examination on admission revealed low grade fever and occasional wheezing over the right upper lung. Abnormal laboratory results included a white blood cell count of 14.9×10^9/liter with a normal differential count and microcytic hypochromic anemia of 121 g/liter. At this point, lung malignancy was strongly suspected and fiberoptic bronchoscopy was repeated. This showed a mass invading the right upper bronchus. Bronchial washings and biopsy of the mass were negative for malignancy. While in the hospital, the patient complained of a sharp pain in the midchest area and a tender swelling was palpated at the left 4th and 5th costochondral junction. Bone scintigraphy was performed for clinically suspected costochondritis. Images of the entire skeleton were obtained 3 hr after the injection of 25 mCi (925 MBq) ^{99m}Tc-imidodiphosphate (IDP), which detected a cold lesion with peripherally increased activity in the inferior aspect of the sternum (Fig. 2A). Because lymphoma was a possible diagnosis, ^{67}Ga scintigraphy was performed to search for other unsuspected foci of disease. Planar images and SPECT studies of the chest, abdomen and pelvis were performed 48 hr after the injection of 6 mCi (222 MBq) ^{67}Ga-citrate. Imaging was performed with a medium-energy collimator and 20% window over the three photopeaks of ^{67}Ga.

Planar images showed uptake in the right upper chest and in the midchest (Fig. 2B). SPECT studies included 64 stops, 20 seconds per stop. Data were reconstructed with a ramp filter and prefiltering with a Hanning window, cutoff of 0.6. The reconstructed images showed the uptake on the right to be in the lung and extending posteriorly. The uptake in the midchest was located in the sternum (Fig. 2C). Computed tomography confirmed the presence of opacification of the right upper lobe with narrowing of the posterior bronchi (Fig. 1B) and destruction of the lower sternum with associated soft-tissue swelling anteriorly and posteriorly (Fig. 1C). The presumptive diagnosis was bronchogenic carcinoma metastatic to the sternum.

Because lymphoma, other malignancies or atypical inflammatory or infectious processes could not be ruled out, a thoracotomy with right upper lobectomy and a needle biopsy of the

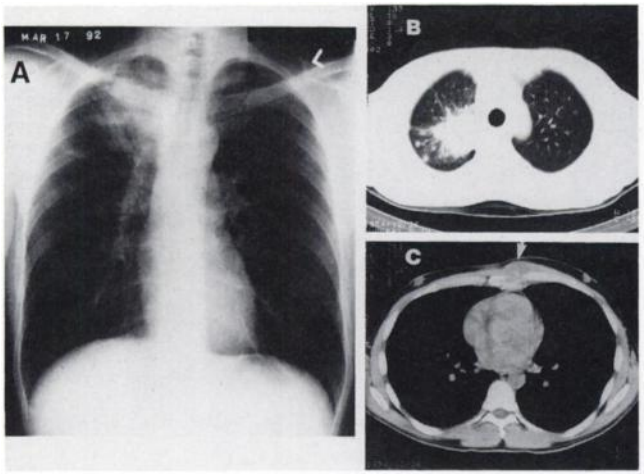

FIGURE 1. (A) Chest radiograph shows consolidation and volume loss in the right upper lung. (B) CT scan shows consolidation and narrowing of the bronchi. (C) CT scan shows destruction of the sternum and soft tissue swelling (arrow).

sternal lesion were performed for tissue diagnosis. Histology of the specimen showed replacement of the normal lung tissue by confluent suppurative and granulomatous inflammation. Numerous yeast cells were seen on hematoxylin eosin stain as well as on PAS and Gomori's methenamine silver stains. The majority of these yeast cells were within multinucleated giant cells (Fig. 3A). The yeast cells were 5–10 micron in diameter and thick walled with single broad budding (Fig. 3B). These morphologic details are typical of *Blastomyces dermatitidis*. Definite diagnosis of NAB was made by showing dimorphism on culture where the organisms converted from mycelial form at room temperature to yeast form at 37°C. Cultures of the sternal lesion also yielded *Blastomyces dermatitidis*. Treatment with intravenous Amphotericin B was initiated. When the patient had received a total dose of 800 mg of this agent, Itraconazole (200 mg p.o. per day) was substituted. The latter agent will be continued for 6 mo. Further history revealed that the patient, as part of his employment, travelled extensively across North America, including the southwestern Ontario region which is endemic for NAB. Three months after antifugal treatment was initiated, the patient seemed to be free of disease and ^{67}Ga scintigraphy was performed to confirm this clinical impression. No abnormal uptake was demonstrated in the original lung and sternal sites, but a new focus of increased uptake was detected in the left chest wall posteriorly. MRI imaging found this new lesion to be located in the infraspinatous muscle (Fig. 4).

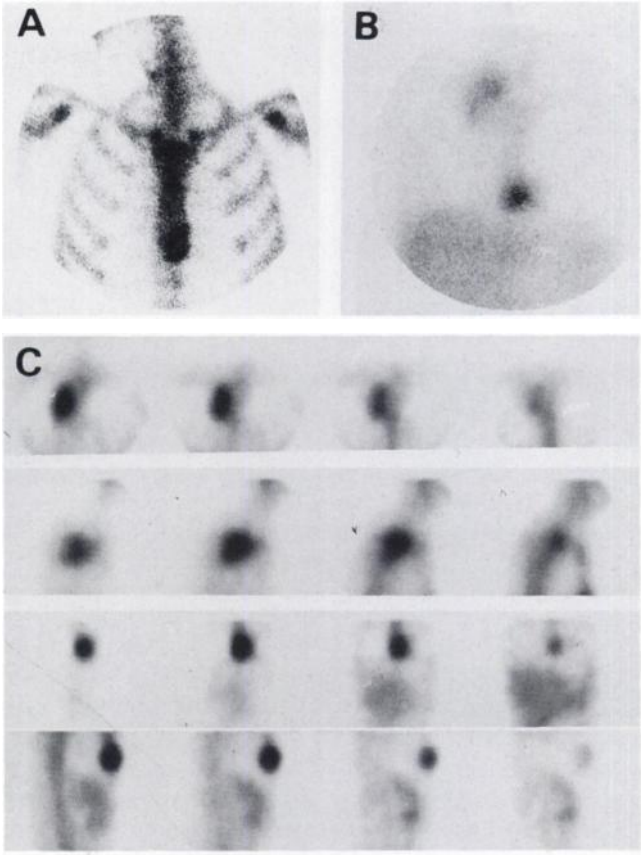

FIGURE 2. Radionuclide imaging. (A) Bone scintigraphy shows a cold lesion with peripheral increased activity in the inferior aspect of the sternum. (B) Planar ^{67}Ga imaging shows two foci of uptake, one in the right upper chest and the other in the midchest. (C) Gallium SPECT coronal and sagittal slices through the lesion in the right upper chest (top two rows) show the uptake to be in the lung and extend posteriorly. Sagittal and coronal slices through the midchest lesions (bottom two rows) show the uptake to be in the sternum.

DISCUSSION

The Maritime provinces of Canada, where this patient resides, are not considered endemic for *Blastomyces dermatitidis*. The last diagnosed case of NAB in Nova Scotia was in the late 1970s. The travelling history of our patient was such that it may well be that he was infected outside the province. Sporadic cases of this fungal infection, however, may occur throughout the United States and Canada (*1,2*).

North American blastomycosis is an uncommon disease. The accurate number of cases of *Blastomyces dermatitidis* infection is unknown since in some patients the infection is subclinical and in others it causes a mild self-limited disease. Because there is no sensitive screening test for NAB, diagnosis is made only in those patients with clinically overt disease, and even then diagnosis is difficult and requires isolation of the infecting microorganism from tissue or body fluids. The clinical manifestations are nonspecific and highly variable in both severity and duration. The lung is the portal of entry. Most patients seek medical aid for pulmonary symptomatology which is either acute and resembles an acute respiratory infection or insidious mimicking other pulmonary granulomatous diseases such as tuberculosis or lung carcinoma. The infection may disseminate, most commonly to the skin and bone and, in men, to the reproductive organs, causing a severe fulminating infection (*1,2*). Serologic tests utilizing yeast antigens are nonspecific and cross-react with other fungi. These tests are also insensitive since only 40% of patients with documented *Blas-*

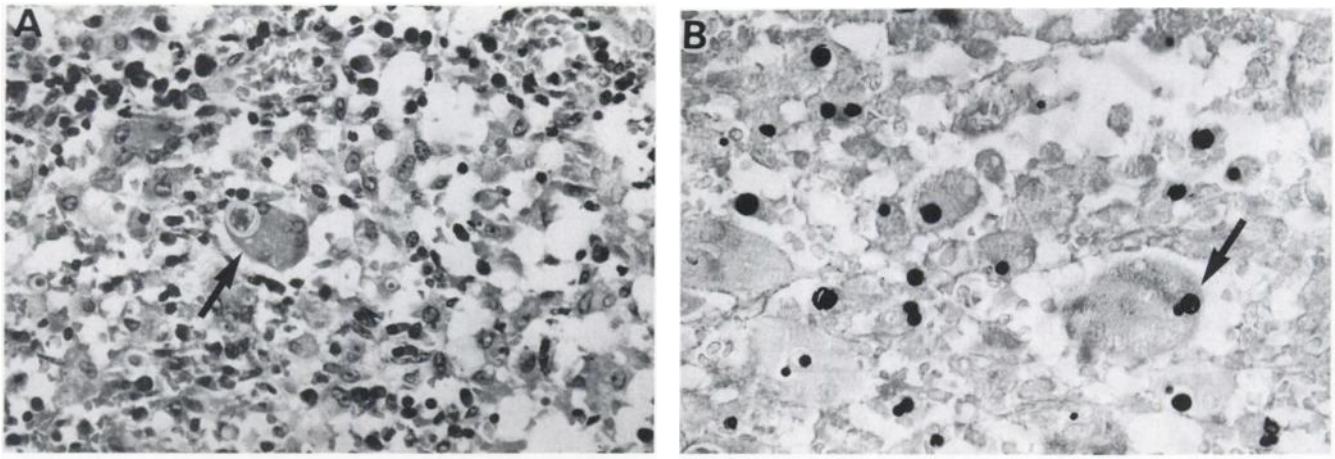

FIGURE 3. Histology. (A) Hematoxylin eosin stain. Granulomatous process with yeast cells, the majority of which are within multinucleated giant cells (arrow). (B) Gomori's methenamine silver stain. The yeast cells are stained black and show characteristic morphologic details for *Blastomyces dermatitidis*, including a thick wall and single broad based budding (arrow).

tomyces dermatitidis infection show positive tests (*3*). Pulmonary radiographic manifestations of NAB are nonspecific and include reticulonodular infiltration, consolidation or a lung mass with or without cavitation (*4,5*). It is not unusual for a mass to be removed from the lung with the preoperative impression of a lung malignancy only to have *Blastomyces dermatitidis* isolated in the removed tissue as was the case in our patient (*6*).

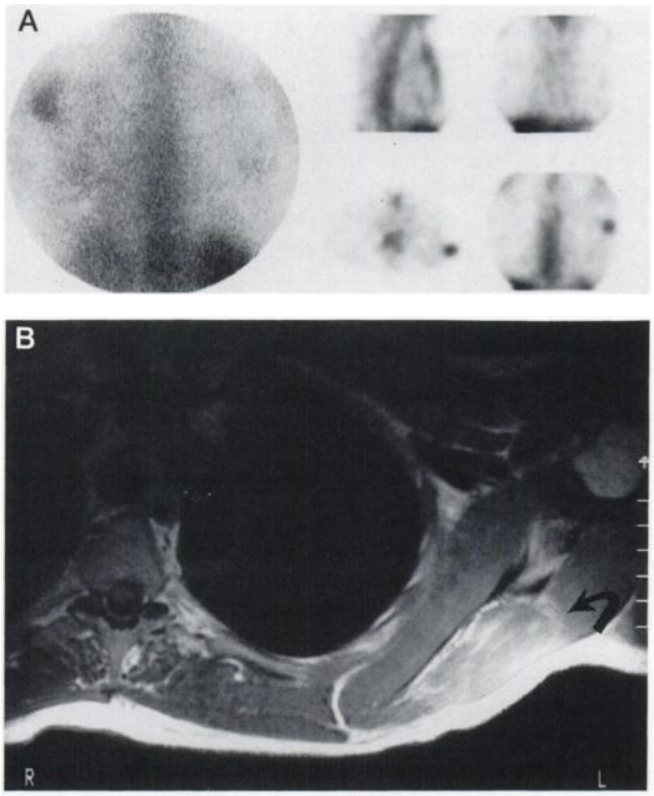

FIGURE 4. Follow-up. (A) ^{67}Ga scintigraphy shows a new focus of uptake in the left chest wall posteriorly. No lesions are detected in the lung or the sternum. (B) MRI image. The new lesion is located in the left infraspinatous muscle (arrow).

The presented case illustrates the role of radionuclide assessment in a patient with NAB presenting as an atypical pulmonary disease and a bone lesion. Accumulation of ^{67}Ga in a lung lesion is nonspecific and may occur in acute bacterial infections, active tuberculosis, fungal infection as well as neoplasms (*7–11*). Involvement of extrapulmonary sites by these disease processes is common, e.g., extrapulmonary tuberculosis may occur in over 10% of cases and in as high as 80% of cases with NAB. The role of ^{67}Ga scintigraphy is therefore not in the differential diagnosis of the pulmonary lesion but in determining the systemic extent of the disease. Gallium-67 scintigraphy is useful in identifying sites of disease which may be more readily available than the lung for simple biopsy. In our patient, although clinical judgment dictated performing a thoracotomy, a reasonable alternative approach would have been a biopsy of the sternal lesion for tissue diagnosis, possible sparing the patient from major surgery.

The introduction of Amphotericin B and several Imidazole drugs has achieved a marked reduction in the mortality rate from NAB. Relapse, however, may still occur in as high as 10% of the cases with disseminated disease (*1*). In the present case, follow-up ^{67}Ga scintigraphy was performed to confirm the clinical impression that the patient was cured but detected a new asymptomatic muscular lesion. This would suggest that baseline ^{67}Ga scintigraphy may also be indicated in those patients in whom the diagnosis of NAB has already been made, for purposes of comparison with follow-up ^{67}Ga scintigraphy, in order to evaluate the response to treatment. The sternal lesion detected on bone scintigraphy in our patient presenting with a lung mass was suspected to be a bony metastasis, since bronchogenic and breast carcinomas are the most common metastatic lesions to result in photon-deficient lesions (*12*). However, this finding eventually was found to be due to bony destruction by the fungal

infection. This scintigraphic appearance is in keeping with the typical bony lesions of blastomycosis which are well circumscribed and osteolytic (*1*).

In conclusion, NAB may simulate other infections or malignancy on clinical and radiologic assessment and therefore should be considered in the differential diagnosis of atypical pulmonary disease even when occurring in geographic regions which are not considered endemic for this organism. Scintigraphic assessment, although not showing a specific pattern of NAB, may be useful in determining the extent of dissemination and in detecting occult lesions. Because the rate of relapse is still significant, follow-up ^{67}Ga scintigraphy is indicated in patients with NAB, even when there are clinical indications that the antifugal therapy appears to have eradicated the disease.

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