Pulmonary Blastomycosis
An Appraisal of Diagnostic Techniques

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Objectives: Pulmonary blastomycosis often mimics bacterial pneumonia or bronchogenic carcinoma, which may result in delayed therapy or the performance of unnecessary diagnostic procedures. We have reviewed the utilization of diagnostic techniques in the workup of patients with pulmonary blastomycosis, defined their diagnostic yields, and proposed an optimal diagnostic approach for the patient in whom pulmonary blastomycosis is considered.

Design: Retrospective chart review of all patients with the diagnosis of blastomycosis at a major academic medical center.

Results: Of the 119 patients with blastomycosis, 56 (47%) had pulmonary involvement. A total of 92 specimens were obtained by noninvasive means (sputa, 72 specimens; tracheal secretions, 5 specimens; and gastric washings, 15 specimens) in 35 patients. KOH smears were prepared from 22 of those specimens (24%). The diagnostic yield from these culture specimens obtained by noninvasive means was 86% per patient, and 75% per single sample. The diagnostic yields from KOH smears were 46% and 36%, respectively. Flexible bronchoscopy was performed in 24 patients and yielded a diagnosis in 22 (92%). Cultures of bronchial secretions (19 patients) and BAL fluid (6 patients) were positive in 100% and 67% of patients, respectively. The corresponding yields of KOH preparations were 17% (1 of 6 preparations) and 50% (3 of 6 preparations), respectively. Pathology specimens including those from bronchoscopic lung biopsies (nine patients), bronchial brushings (two patients), and bronchoscopic needle aspiration (one patient) were positive in 22%, 50%, and 0% of cases, respectively. Cytology was usually performed to exclude malignancy and was positive for Blastomyces dermatitidis in five patients (sputum, three patients; bronchial washings, two patients). Thoracotomy was performed in 11 cases, and in all patients the procedure yielded a diagnosis. Serology results were available in 25 patients. Immunodiffusion was positive in 10 patients (40%), and complement fixation in 4 patients (16%).

Conclusions: In patients with pulmonary blastomycosis, the positive yield from respiratory specimen cultures is high, but the confirmation of a diagnosis may take up to 5 weeks. Wet smears and cytology examinations of respiratory specimens provide quicker diagnoses but are underutilized. Their routine use is recommended in endemic areas. Commonly used serologic assays are insensitive and are not useful for diagnostic screening.

Key words: Blastomyces dermatitidis; blastomycosis; bronchoscopy; cytology; lung surgery; sputum culture

Abbreviations: BLB = bronchoscopic lung biopsy; BNA = bronchoscopic needle aspiration; PCR = polymerase chain reaction

Pulmonary blastomycosis is a relatively rare but important and potentially lethal disease. Clinical manifestations range from asymptomatic infection to fulminant hypoxic respiratory failure and extrapulmonary dissemination. The disease often mimics others and may pose diagnostic challenges. On the one hand, it may resemble a bacterial pneumonia or cause respiratory distress syndrome leading to a delay in diagnosis, incorrect treatment, dissemination, and a poor outcome. On the other hand, it may imitate a bronchogenic carcinoma and may lead to the performance of an unnecessary thoracotomy.

In an effort to clarify the above concerns, we designed this study to accomplish the following:
(1) to review the utilization of various diagnostic techniques employed in the workup of patients with pulmonary blastomycosis at our institution; (2) to define the diagnostic yields of these techniques; and (3) to propose an optimal diagnostic approach to a patient in whom the differential diagnosis includes pulmonary blastomycosis.

**Materials and Methods**

We reviewed the medical records of patients who had received diagnoses of blastomycosis at the Mayo Clinic Rochester (Minnesota). The diagnosis of pulmonary blastomycosis was accepted if the following criteria were found: (1) *Blastomyces dermatitidis* was isolated from a respiratory specimen; or (2) the organism was isolated from an extrapulmonary site in the presence of a compatible clinical course and an abnormal finding on a chest radiograph; or (3) no organism was isolated, but the diagnosis was strongly suggested by the clinical course, an abnormal finding on a chest radiograph, and positive results of serology testing. All excluded patients had either (1) no microbiological, histologic, or serologic evidence of blastomycosis infection (pulmonary or extrapulmonary) or (2) documented extrapulmonary blastomycosis with no clinical indications of active pulmonary infection and normal findings on chest radiographs.

All pulmonary diagnostic specimens were included in the analysis except those that were collected > 2 weeks after the initiation of effective therapy (ie, surgery or the administration of antifungal agents) in order to avoid falsely negative results. The majority of the cytologic specimens that were reviewed had originally been obtained with an intention of finding malignant cells using Papanicolaou preparations. The use of specific fungal stains (eg, Gomori’s methenamine-silver stain, silver chromate stain, and periodic acid-Schiff stain) was seldom reported. For these reasons, we elected to report only positive cytology results, and a calculation of the diagnostic yield for cytologic tests was not performed.

**Results**

**Patients**

The medical records system identified 119 patients who had received a diagnosis of “blastomycosis.” Sixty-three patients (53%) were found to have pulmonary blastomycosis (using the criteria specified in the “Materials and Methods” section). Ten patients had documented extrapulmonary blastomycosis with no pulmonary involvement. Fourteen patients had a presumptive diagnosis of blastomycosis based on a highly suggestive clinical course but without microbiological, histologic, or serologic confirmation. No proof for the disease was identified in the remaining 32 patients.

Of the 63 patients with pulmonary blastomycosis, 7 had documented extrapulmonary disease with abnormal findings on chest radiographs, but without respiratory specimens collected, and were, therefore, not included in the respiratory specimens yield analysis. The remaining 56 patients were seen at the Mayo Clinic Rochester between May 1967 and November 1998. Fifty-two patients were residents of the midwestern United States, and 4 patients were from Ontario, Canada. The mean (± SD) age was 51 ± 17 years (range, 12 to 80 years). Forty-two patients were men or boys and 14 were women or girls.

In 51 patients, the diagnosis was made based on the isolation of *B dermatitidis* from a respiratory specimen. Four patients had an organism isolated from an extrapulmonary site (pretibial cellulitis, one patient; ankle cellulitis, one patient; tibial osteomyelitis, one patient; and a loculated pleural effusion, one patient) with an abnormal finding on a radiograph. One patient had acute pneumonia with a pulmonary infiltrate, a immunodiffusion assay positive for the *B dermatitidis*-directed antibody, and no bacterial organism isolated.

**Noninvasive Respiratory Specimens**

Table 1 details the use and diagnostic yields of noninvasive respiratory specimens. Overall, a total of 92 specimens were collected from 35 patients, averaging 2.6 specimens per patient. These specimens included 72 from sputa (78%), 5 from tracheal secretions (5%), and 15 from gastric washings (16%). In some instances, more than one type of specimen was collected from the same patient (ie, sputum and gastric washings). KOH smears were prepared from

**Table 1—Diagnostic Yield From Respiratory Specimens Obtained by Noninvasive Methods**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Culture</th>
<th>KOH Preparation</th>
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<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Samples</td>
</tr>
<tr>
<td>Sputum</td>
<td>25/31 (81)</td>
<td>54/72 (75)</td>
</tr>
<tr>
<td>TS</td>
<td>3/3 (100)</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>GW</td>
<td>7/10 (70)</td>
<td>10/15 (67)</td>
</tr>
<tr>
<td>Total</td>
<td>30/35 (86)</td>
<td>69/92 (75)</td>
</tr>
</tbody>
</table>

*Values given as No. of positive test results/total No. of patients or samples (% yield of the test). TS = tracheal secretions; GW = gastric washings.
†Data reflect cumulative positive yield of all samples collected per each patient.
‡Data reflect an average yield of a single specimen sample.
§Average no. of samples collected per patient.
22 of the 92 specimen samples that had been obtained by noninvasive means (24%).

The overall diagnostic yield of noninvasive respiratory specimen cultures was 86% per patient (ie, an average of 2.6 samples) and 75% per single sample. The diagnostic yields per specimen of sputum, tracheal secretions, and gastric washings were 75%, 100%, and 67%, respectively. Of the five patients in whom the evaluation of noninvasive respiratory specimens did not reveal the organism, four presented with the disease in an extrapulmonary site as the primary problem (skin, two patients; bone, one patient; and pleura, one patient), with none of them having acute respiratory symptoms or fever. One patient presented during the resolution phase of an acute episode of pneumonia that had been spontaneously resolving at the time of the evaluation.

A total of 16 KOH sputum preparations that were obtained from 12 patients yielded a diagnosis in 4 patients (25%). Five KOH preparations of tracheal secretions were examined in three patients and four of the five (80%) demonstrated _B dermatitidis_, aiding in the diagnosis in all three patients. One KOH preparation of gastric washings was examined and was negative for _B dermatitidis_. Of note, in one patient who had been treated with amphotericin B for several days, the KOH sputum preparation was positive for _B dermatitidis_. Of note, in one patient who had been treated with amphotericin B for several days, the KOH sputum preparation was positive for _B dermatitidis_, while a culture of the same specimen was negative.

Cytology results were positive in the sputum specimens of three patients. Sputum cultures were positive for _B dermatitidis_ in all three. In two patients, KOH preparations were tested, and the results of both were positive.

**Bronchoscopy**

Table 2 details the use and diagnostic yields of bronchoscopic specimens. Overall, 24 patients underwent bronchoscopy. Bronchial inspection was abnormal in 13 patients (54%). Mucosal abnormalities were present in seven patients and included mucosal “friability,” “thickening,” or “irregularity.” Extrinsic bronchial compression was noted in four patients, purulent secretions were noted in two patients, and a nodular endobronchial lesion was noted in one patient. Bronchoscopic procedures included bronchial washings in 19 patients (79%), bronchoscopic lung biopsy (BLB) in 9 patients (38%), BAL in 6 patients (25%), bronchial brushings in 2 patients (8%), and bronchoscopic needle aspiration (BNA) in one patient (4%). KOH smears were prepared from 12 of 25 microbiological specimens (48%) [ie, specimens taken from bronchial washings or BAL].

Overall, bronchoscopy yielded the diagnosis in 22 patients (92%). Cultures of specimens from bronchial washings and BAL fluid were positive in 100% and 67% of cases, respectively. KOH smears were prepared from 6 of the 19 bronchial washing specimens and 6 of 6 BAL fluid samples, and the results were positive in 17% and 50% of specimens, respectively. The results of testing pathologic specimens from BLB, bronchial brushings, and BNA were positive in 22%, 50%, and 0% of specimens, respectively. Cytology results were positive in specimens from bronchial washings taken from two patients. In both of these patients, specimen cultures were positive, and in one patient the KOH smear was positive.

In two patients, the bronchoscopic evaluation did not yield the diagnosis. One patient, in whom the wedge resection was diagnostic, had a patchy bilateral infiltrate with no acute respiratory symptoms or fever. The other patient had acute pneumonia caused by _Pneumocystis carinii_ that was diagnosed during the same bronchoscopic procedure. Even though the BAL did not yield the diagnosis of blastomycosis, a sputum culture from a specimen that was obtained on the same day did.

**Transthoracic Needle Aspiration**

Transthoracic needle aspiration was performed in three patients to evaluate a pulmonary nodule or mass. Lesions were 1.5 to 7 cm in maximal diameter. In one patient with a 1.5-cm subpleural nodule, the procedure yielded a positive result. Two of three patients who underwent transthoracic needle aspiration also had bronchoscopy. In both patients, cultures of bronchoscopic specimens eventually have turned positive.

**Surgery**

Eleven patients (20%) underwent thoracotomies. Indications for surgery included pulmonary no-
Hodgkin’s lymphoma in one patient (2%), and a known blastomycosis-related empyema in one patient (2%). Five lobectomies, five wedge resections, and one resection of empyema with decortication were performed. Thoracotomy yielded a diagnosis in all 11 patients (100%). Overall, histologic sections, specimen cultures, and KOH preparations had yields of 73%, 80%, and 50%, respectively.

Of seven thoracotomy patients with pulmonary nodules or masses, three had fungal cultures of either noninvasive or bronchoscopic specimens, and cultures for all three patients eventually turned positive (a KOH smear performed in one patient was negative). Of two patients with ARDS, one had a positive sputum culture (no KOH smear was performed), and no fungal diagnosis was pursued in the second. In a patient with non-Hodgkin’s lymphoma and pulmonary infiltrates, the findings of bronchoscopy with BAL and BLB were negative.

Serology

A serologic diagnosis was attempted in 25 patients (45%) and included immunodiffusion and complement fixation in all. The results of immunodiffusion were positive in 10 of 25 patients (40%), and the results of complement fixation were positive in 4 patients (16%). Results were positive in four patients with acute pneumonia, in two patients with solitary pulmonary nodules, in two patients with blastomycotic osteomyelitis, in one patient with a brain abscess, and in one patient with a blastomycosis-related pleural effusion.

Discussion

This study demonstrates that very high diagnostic yields can be expected from culture specimens in the diagnosis of pulmonary blastomycosis, regardless of the method of specimen collection, whether it be noninvasive (e.g., from sputum, tracheal secretions, or gastric lavage), bronchoscopic (e.g., from bronchial secretions or BAL), or surgical. The results indicate that specimens from more than one culture source may increase the diagnostic rate. For specimens obtained by noninvasive means, increasing the number of samples from 1 to an average of 2.6 resulted in a modest increase in the yield (from 75 to 86%). Bronchial washings tended to have a higher diagnostic yield than BAL (100% vs 67%), although the small number of patients evaluated with BAL may put the validity of the comparison in question.

The average time to respiratory specimen culture confirmation takes up to 5 weeks and therefore, contributes to the delay in making a clinical decision about the use of an antifungal agent or the need for a surgical excision of a pulmonary lesion. The immediate KOH stain technique may hasten the diagnosis. However, KOH smears were used in only 30% of all the microbiological specimens that were collected. Furthermore, they had a relatively low diagnostic yield (0 to 50%, depending on the type of specimen) and were comparable with the yields reported by others. Tracheal secretions were the exception (three of three positive results). That difference may be accounted for by the small number of subjects in this group and by a high organism burden, since all three patients had blastomycosis-related acute respiratory failure. Given the simplicity and low cost of the procedure as well as its potential for providing a rapid diagnosis, we suggest that a wet sputum preparation be used on all specimens collected.

Cytology contributed to the diagnosis in five of our patients (sputum specimen, three patients; bronchial washing specimens, two patients), and cytologic fungal stains were reported in only three of the cases. Johnston et al were the first to report a cytologic detection of B dermatitidis, followed by reports from two other smaller series. Trumbull and Chesney analyzed the usefulness of a cytologic sputum examination in 30 episodes of pulmonary blastomycosis among 29 patients and noted that the cytologic technique yielded a positive diagnosis in 93% of patients (70% on the first specimen) and that they compared favorably with wet smears from sputum (61% and 32%, respectively). The authors reported a decrease in the time to the initiation of effective chemotherapy and the incidence of major surgery at their institution after the introduction of routine cytologic testing of respiratory specimens in patients with pulmonary nodules or infection. They concluded that a cytologic evaluation should be adopted as a standard diagnostic tool in pulmonary lesions not otherwise diagnosed, especially in the eastern half of the United States where blastomycosis is endemic.

Bronchoscopic lung biopsies yielded a diagnosis in two of our nine patients. The numbers of patients evaluated using bronchial brushings, BNA, and transthoracic needle aspiration were too small to draw meaningful conclusions, although these methods tended to perform poorly. It is generally accepted that with flexible bronchoscopy, the yield of a specific benign diagnosis of a pulmonary nodule is poor, presumably because these lesions are not "bronchogenic" in location. The sensitivity of transthoracic needle aspiration for the diagnosis of benign lesions has been reported to be anywhere between 0% and 70% and seems highly variable depending on
the local experience and technique (eg, use of small biopsy needles vs large biopsy needles).13–16
Surgery yielded the diagnosis in all 11 thoracotomy patients in our series. Only five thoracotomy patients (45%) had noninvasive or bronchosopic specimen cultures, and one thoracotomy patient (9%) had a KOH smear prior to surgery. Four of five cultures were positive for B dermatitidis. Surgery was performed in all those patients within 6 to 8 days after nonsurgical specimens were obtained. If the organism were to be recovered prior to thoracotomy using a nonculture-based rapid technique, it could have affected the diagnostic evaluation and likely could have prevented the performance of a surgical procedure for a benign disease.7,17

In endemic mycoses, serology techniques have proven to be useful for the study of immune responses to fungi and epidemiologic investigations.18 They are also commonly used in the clinical practice in which a mycosis is a diagnostic consideration. In our study, the sensitivities of immunodiffusion and complement fixation for serum antibody detection were 40% and 16%, respectively. These rates are comparable to those reported by others.19–22 Although the antibody titer has been reported to depend on the disease activity,19 we and others8 have found positive serology results both in acutely ill patients (pneumonia, empyema, osteomyelitis, or brain abscess, seven patients) and in those with chronic disease (pulmonary nodules, three patients). Several groups have reported that enzyme immunoassay,19 Western blot analysis,20–24 and radioimmunoassay25,26 have significantly superior sensitivities and equal specificities when compared with immunodiffusion or complement fixation. However, these techniques are not used routinely in most institutions because they are technically more complex and expensive. For the detection of other endemic fungi, effective ways of identifying fungal antigens in serum27,28 and urine29 also have been developed. Overall, commonly used serologic assays have low sensitivity and are not useful for diagnostic screening, although they are relatively inexpensive and, when positive, may direct a diagnostic workup toward an identification of the offending organism.

The introduction of novel nonculture techniques to the armamentarium of diagnostic methodology should aid in a rapid diagnosis of blastomycosis as well as other endemic mycoses. Immunohistologic methods utilizing fluorescent antibody, immunoperoxidase, and gold-silver staining have proven applicable to formalin-fixed, paraffin-embedded tissues of patients infected with several fungal species, including B dermatitidis.30–32 The polymerase chain reaction (PCR) technique has been used in the epidemiologic study of blastomycosis.33,34 To our knowledge, PCR has not been applied to any clinical specimens in case of blastomycosis, although it has been successfully used for the detection of Paracoccidioides brasiliensis in isolates of human tissue.35 Molecular probing systems have been developed for the detection of gene products of several pathogenic fungi, including those causing systemic mycoses, and some of them have been tested successfully on human tissue specimens.36,37

Given the limitations of the many diagnostic techniques described in this article, the concomitant use of culture techniques and multiple nonculture techniques is necessary for an expeditious diagnosis of pulmonary blastomycosis.23,38 Novel serologic tests for serum antibody detection, antigen detection in body fluids, immunohistologic methods, PCR, and molecular-probing technology likely may enhance the rapid diagnosis of B dermatitidis and other endemic mycoses in the near future.39

In conclusion, the diagnosis of pulmonary blastomycosis is often challenging. A prompt clinical recognition of this disease may be crucial if a delay in effective therapy, the systemic dissemination of the disease, or the performance of an unnecessary diagnostic thoracotomy are to be avoided. Diagnostic yields from cultures of respiratory specimens are very high, but the average time to culture confirmation takes up to 5 weeks. Thus, the expeditious evaluation of pulmonary blastomycosis requires the concomitant use of culture and multiple nonculture techniques. Wet smears and the cytologic examination of respiratory specimens are underutilized, yet may be effective, and their routine use in endemic areas is recommended. Even though the commonly used serologic assays have low sensitivity and are not useful for “ruling out” B dermatitidis infection, they are relatively inexpensive and, when positive, they may aid in the diagnosis. Novel nonculture techniques, including serologic tests, immunohistologic methods, PCR, and molecular-probing technologies are being developed and are likely to help in the rapid diagnosis of B dermatitidis.

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