Primary Pulmonary Botryomycosis: Case Report and Review

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Botryomycosis is an uncommon bacterial disease characterized by the microscopic formation of eosinophilic granules that resemble those of infection by Actinomyces species. The diagnosis of botryomycosis can be made when microscopic inspection and culture of the granules reveal gram-positive cocci or gram-negative bacilli. Botryomycosis is caused by common bacterial pathogens including Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, yet the host and microbial factors that contribute to the pathobiology remain unknown. Pulmonary botryomycosis can resemble actinomycosis, tuberculosis, or invasive carcinoma by causing a mass lesion with constitutional symptoms. Radiographically, it invades bone and disrupts tissue planes. Successful treatment often requires a combination of both surgical debridement and long-term antimicrobial therapy. We report a case of primary pulmonary botryomycosis and review the literature on this unusual infectious process.

Botryomycosis is an uncommon bacterial disease that clinically and histologically mimics infection by Actinomyces species. It is defined by the histological presence of eosinophilic material surrounding densely packed microorganisms associated with a supplicative focus [1]. This unique but characteristic pattern became known as the Splendore-Hoeppli phenomenon after the two scientists who described it. The Splendore-Hoeppli phenomenon is not unique to botryomycosis and actinomycosis, however, and may be seen with other infections including those due to fungi and helminths [2]. In the case of botryomycosis, the granules resemble the sulfur granules of actinomycosis, but when these granules are cultured, common organisms like Staphylococcus aureus [3], Escherichia coli [4], and Pseudomonas aeruginosa [5] are recovered. Other organisms including Proteus vulgaris [1] and Streptococcus species [6] have also been reported to cause botryomycosis.

In 1870, Bollinger [7] was the first to describe this eosinophilic material, which he isolated from the lung of a horse. However, it was not until 1884, when Rivolta [8] noted the grapelike appearance of the granules, that the term botryomycosis was coined. Since Rivolta attributed the histological pattern to a fungal infection, the term botryomycosis was derived from the Greek words for ‘‘bunch of grapes’’ (botrys) and ‘‘fungus’’ (mycosis). In 1919, Magrou [3] firmly established the bacterial nature of the disease by isolating S. aureus from a pulmonary botryomycotic lesion in a horse and by reproducing the disease experimentally in guinea pigs.

Although first discovered as a disease of animals, there have been ~90 reported cases of human botryomycosis. Human disease occurs in two broad categories: cutaneous and visceral. Cutaneous botryomycosis is more common and accounts for ~75% [9] of the reported cases. Visceral disease, on the other hand, is rare and has been described mainly in patients with underlying diseases such as diabetes mellitus, cystic fibrosis, or HIV infection. We describe a case of primary pulmonary botryomycosis in a patient without any known underlying illness whose clinical course mimicked actinomycosis. We also review all other reported cases of primary pulmonary botryomycosis.

Case Report

A 67-year-old man was admitted to Barnes-Jewish Hospital (St. Louis) in late October 1996 for an open lung biopsy of a left pleural lung mass. The patient was first brought to medical attention in early August 1996 when he began experiencing progressive left posterior chest wall and back pain and a 20-lb weight loss. He denied cough, night sweats, or fevers. A chest roentgenogram revealed a 6-cm mass in the superior segment of the left lower lobe.

The patient was a retired road construction worker who recalled extensive exposure to inhaled cement dust for many years. He had no known exposure to tuberculosis but admitted to a history of cigarette smoking (110 packs per year) and multiple lower respiratory infections in recent years. Other medical history included hypothyroidism treated with levothyroxine sodium and asthma that was controlled with β-agonist and steroid inhalers. The patient’s surgical history was significant for hemigastrectomy and partial transverse colectomy for treatment of peptic ulcer disease 4 years before the present illness. His only known drug allergy was to a quinolone antibiotic, which had caused shortness of breath.

A CT scan obtained in September 1996 revealed a left posterior intrathoracic mass with bony invasion into the thoracic spine and the left posterior sixth and seventh ribs. The patient underwent CT-guided needle biopsy of the mass, and patholog-
The platelet count was 667,000/μl, and renal function. The patient’s absolute CD4 count was 147 cells/mm³. His HIV test was negative. The lab results were within normal ranges, including studies of liver and renal function. The patient recovered quickly; the lumbar drain was removed on the fourth postoperative day, and he was extubated the following day. He was discharged from the hospital 10 days after surgery, and was to continue a prolonged course of high-dose intravenous ceftazidime (2 g every 8 hours) was administered postoperatively. Postoperative blood cultures, urine cultures, and repeated cultures of CSF were negative. Cultures of the surgical specimen were negative for acid-fast bacilli, fungi, and Actinomyces species. Histopathologic examination of the surgical specimen revealed eosinophilic granules that were embedded in abscesses and surrounded by epithelioid histiocytes (figure 3).

Examination of the specimens of vertebral bone demonstrated osteomyelitis. Acid-fast, Grocott-Gomori methenamine–silver nitrate, and gram stainings were negative; however, Brown-Hopps gram staining revealed dense clusters of gram-negative rods within the granules. Brightly eosinophilic clubs at the periphery of the granules were identified as Splendore-Hoeppli material. The Splendore-Hoeppli phenomenon can be seen with several infectious processes including both actinomycosis and botryomycosis. A final diagnosis of pulmonary botryomycosis was made by pathological examination and was confirmed by culture.

The patient recovered quickly; the lumbar drain was removed on the third postoperative day, and he was extubated the following day. He was discharged from the hospital 10 days after surgery and was to continue a prolonged course of high-dose intravenous ceftazidime as an outpatient. The patient died 6 months later of respiratory insufficiency. At the time of death, there was no evidence of recurrence of the botryomycotic lesion.

Discussion

Since its initial description in humans in 1913 [11], the disease known as botryomycosis has been difficult to distinguish from actinomycosis. Pathologically, actinomycosis, like botryomycosis, can display the Splendore-Hoeppli phenomenon [12]. The two diseases are satisfactorily distinguished,
Figure 1. Preoperative posteroanterior (A) and lateral (B) chest radiographs of a man with primary pulmonary botryomycosis that show a 4 × 4-cm region of opacification in the superior segment of the left lower lobe; this region is best seen on the lateral view.

however, when Brown and Brenn gram staining (for gram-positive bacteria) and Grocott-Gomori methenamine–silver nitrate staining fail to identify the branching organisms of actinomycosis. Routine gram staining of the granules of botryomycosis may show the responsible organism. For our patient, Brown-Hopps gram staining (for gram-negative bacteria) revealed gram-negative rods consistent with growth in culture of \textit{P. aeruginosa}.

Flynn and Felson [13] and Neuhauser [14] reported that radiographic evidence of contiguous involvement of lung tissue, pleura, and bone is so strongly suggestive of actinomycosis that it should prompt the clinician to include this disease in the differential diagnosis. All three of these radiographic findings were demonstrated in our case. Furthermore, our patient’s clinical course resembled that of pulmonary actinomycosis: an indolent systemic syndrome dominated by several months of chest pain and weight loss.

Infection with \textit{Actinomyces} species usually requires disruption of a mucosal barrier. This disruption may be created iatrogenically, as in a surgical procedure [15], or by a foreign body such as an intrauterine device [16]. Pulmonary actinomycosis, however, is usually attributed to aspiration. The factors that induce the formation of the granules of botryomycosis have not been identified, but both bacterial and host factors have been implicated. Some of the earliest reports of botryomycosis

Figure 2. MRI of the thoracic spine of a man with primary pulmonary botryomycosis that shows destruction of both the sixth thoracic vertebral body (a) and the adjacent rib (b).
more, they found that most of the afflicted animals had foreign bodies associated with their lesions. Our patient had no evident foreign material in or around his lung mass, but perhaps his years in road construction led to inhalation of significant amounts of particulate matter that could act as a nidus for granule formation.

Although there is no direct evidence to suggest that the immune status of the host plays a role in actinomycosis, immune deficiency does seem to predispose patients to botryomycosis. A review of the literature by Brunken et al. [10] noted that many patients had immunologic abnormalities. Paz et al. [20] described one patient whose first manifestation of chronic granulomatous disease was pulmonary botryomycosis; they recommended that any patient for whom visceral botryomycosis is diagnosed should be evaluated for the presence of chronic granulomatous disease. Seven cases of primary pulmonary botryomycosis have been described in patients with cystic fibrosis [21], possibly implying a breakdown in local defenses. Our patient almost certainly had abnormal local immune defenses; he admitted to a long history of tobacco abuse that contributed to his chronic lung disease, and his treatment included inhaled steroids, which also serve to change the local immune environment. These factors, combined with the potential for serious malnutrition from weight loss, may have provided a suitable local environment for botryomycosis.

Some of the more recent cases of botryomycosis in immunocompromised hosts have been described in patients with HIV infection [9, 22]. As in most patients with botryomycosis, patients with HIV infection usually present with cutaneous disease. Perhaps the depletion of the CD4+ subset of T lymphocytes in some way permits this infection. Yet, botryomycosis remains rare even in this patient population. It is interesting that our patient was found to have a low CD4+ cell count and cutaneous anergy to delayed-type hypersensitivity skin testing. It is difficult to know whether this immune defect was present before his infection or was the result of chronic infection. In the study by Brunken et al. [10], most patients with botryomycosis were found to have defects in cellular immunity as evidenced by weak T cell proliferative responses to mitogen stimulation; these defects, however, resolved after excision of the lesion and treatment with antibiotics. Our patient’s CD4+ cell count rose to 451/mm3 after 4 weeks of intravenous antibiotic therapy.

Because botryomycosis is rare, we reviewed the literature for guidance on duration of therapy and expected clinical outcome. Our review of the English-language literature via MEDLINE (key words, “botryomycosis” and “pulmonary” or “visceral”), however, yielded only seven reports of cases of primary pulmonary botryomycosis. The organisms (when isolated), treatments, and outcomes in these cases are listed in table 1. As expected, nearly all patients received antibiotic therapy; five investigators treated their patients with surgery. When long-term follow-up was addressed, most patients were reported to have a clinical response to the chosen therapy.
### Table 1. Summary of data on all reported cases of primary pulmonary botryomycosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Risk factor</th>
<th>Microbiology</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[21]</td>
<td>66 y/F</td>
<td>None</td>
<td>Microscopy showed gram-positive coccal and bacillary colonies, cultures negative</td>
<td>Surgery and intravenous antibiotics for 2 w</td>
<td>Resolution</td>
</tr>
<tr>
<td>[20]</td>
<td>19 y/F</td>
<td>Chronic granulomatous disease</td>
<td>Staining with methylene blue showed curved rods, cultures negative</td>
<td>Intravenous gentamicin and nafcillin</td>
<td>Clinical response to therapy</td>
</tr>
<tr>
<td>[24]</td>
<td>28 y/M</td>
<td>Pulmonary sequestration</td>
<td>Gram-positive bacterial masses</td>
<td>Surgery only</td>
<td>Clinical response at 6 mo</td>
</tr>
<tr>
<td>[25]</td>
<td>53 y/F</td>
<td>Diabetes mellitus</td>
<td>Gram-positive bacterial filaments, cultures yielded <em>Bacillus</em> species</td>
<td>Surgery only</td>
<td>Not reported</td>
</tr>
<tr>
<td>[21]*</td>
<td>9 mo to 12 y/M (3 patients), F (4 patients)</td>
<td>Cystic fibrosis</td>
<td><em>Pseudomonas aeruginosa</em>, <em>M. pyogenes var. aureus</em></td>
<td>Surgery for 3 patients, intravenous chloramphenicol and erythromycin for 7 patients</td>
<td>5 patients died, 2 patients still living at time of report</td>
</tr>
<tr>
<td>[6]</td>
<td>47 y/M</td>
<td>None</td>
<td>Microaerophilic nonhemolytic <em>Streptococcus</em> species</td>
<td>Oral tetracycline, surgery</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

NOTE. Table lists all human cases of primary pulmonary botryomycosis identified by a MEDLINE search of the English-language literature. Other cases were subsequently identified in the references of certain articles. References are listed by publication date in reverse chronological order.

* Seven cases.

Botryomycosis is an unusual bacterial infection that may mimic infection by *Actinomyces* species. Although infrequently diagnosed, botryomycosis should be considered in the differential diagnosis of any lesion where there is disruption of tissue planes, erosion into bone, and granule formation.

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**References**