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Battling the breath-stealers: *Blastomyces* and *Pseudomonas* triggering acute respiratory distress syndrome (ARDS)

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ABSTRACT

Blastomycosis is an endemic disease in North America and commonly manifests with pulmonary symptoms. Blastomycosis should be consider when patients have persistent infiltrates on imaging in an endemic area. We present a case of a 46-year-old male who presented to the pulmonary clinic with fever, cough with production of yellowish-green sputum and culture of BAL-fluid showed growth of *Pseudomonas* spp. Antimicrobial therapy was started accordingly, but was not effective. A repeat bronchoscopy was performed and BAL-fluid culture was positive for *Blastomyces dermatitidis* and liposomal amphotericin B was initiated. Unfortunately, the patient died after withdrawing care.

1. Introduction

Blastomycosis, caused by the dimorphic fungus *Blastomyces dermatitidis*, is endemic to North America and commonly manifests with pulmonary symptoms. Blastomycosis should be considered as a differential diagnosis when patients do not respond to treatment for bacterial pneumonia [1]. Blastomycosis may also develop into cavitary lesions or as a severe complication resulting in acute respiratory distress syndrome (ARDS) [2]. Life-threatening blastomycosis should be treated with amphotericin B [1]. We present a case of a patient who failed outpatient antibacterial treatment and was admitted secondary to multi-focal pneumonia caused by *Pseudomonas* sp. then underwent bronchoscopy and bronchoalveolar lavage which identified concomitant blastomycosis. The objective of reporting this case is to raise awareness of bacterial-fungal-co-infection, presenting a diagnostic and therapeutic challenge.

2. Case report

A 46-year-old male with a past medical history of hypertension, poorly controlled diabetes, chronic obstructive pulmonary disease, current tobacco use, cellulitis and bursitis treated with intravenous (IV) antibiotics 3 months ago, now presented to the rural clinic with fever and productive cough with yellowish green sputum. The symptoms started 3–4 weeks prior to presentation with malaise and flu-like symptoms and self-resolving diarrhea and vomiting for 2 weeks. The patient had been treated with cephalexin for 7 days. Chest X-ray (Fig. 1) revealed bilateral perihilar upper lobe consolidation with extensive right middle lobe consolidation consistent with multifocal pneumonia.

The patient was admitted (day 0) for further evaluation and management after failing outpatient treatment. Pulmonology was consulted for further evaluation. Patient also endorsed 30-pound weight loss in the past three months. The patient was started on piperacillin-tazobactam, linezolid and azithromycin on day 0. Chest computed tomography (CT) scan done on day 0 (Fig. 2) revealed bilateral patchy areas of consolidation with an evolving right middle and lower lobe cavitary lesion.

On day 1, bronchoscopy with bronchoalveolar lavage (BAL) was performed, and supplemental oxygen was provided for hypoxia. BAL-fluid culture was positive for *Pseudomonas* sp. and the patient was de-escalated to IV piperacillin-tazobactam on day 4 with outpatient levofloxacin therapy on discharge based on sensitivities for 3 more days. During follow-up visit one week later (day 11), the patient was found to have worsening shortness of air at rest and uptrending leukocytosis and was re-admitted after failing outpatient treatment with differentials of bacterial reinfection, fungal infection, autoimmune disease, and

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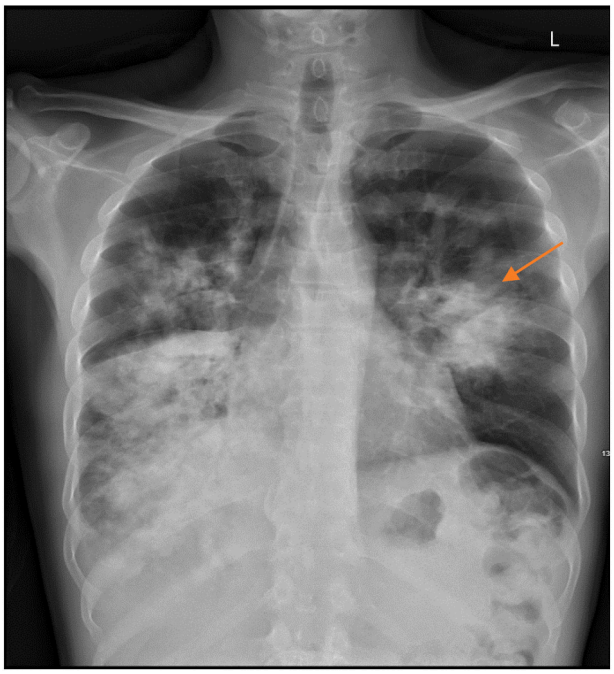

Fig. 1. Outpatient chest X-ray showing multifocal patchy infiltrate (orange arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

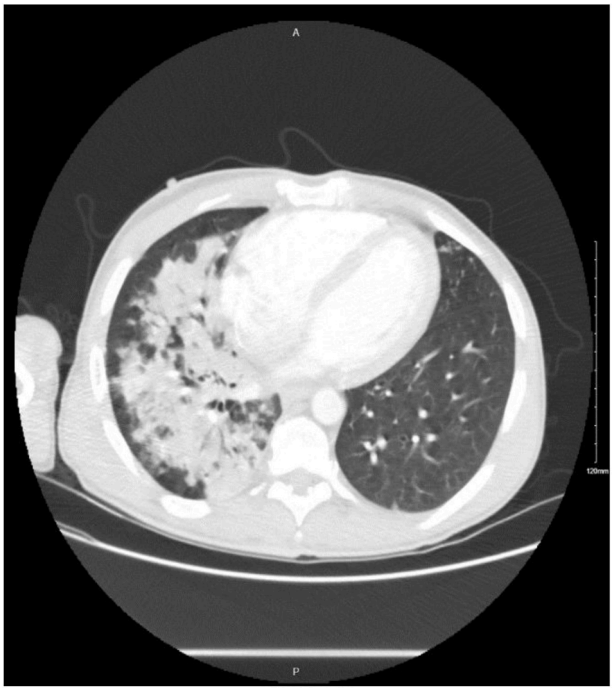

Fig. 2. Chest CT scan on first admission showing dense consolidation with air bronchograms.

malignancy. CT chest done on day 12(Fig. 3) revealed stable infiltrates at the time of re-admission.

Treatment was escalated to meropenem. Workup for fungal infection was ordered. Previous BAL-fluid cultures remained negative. Beta-D-glucan, histoplasmosis and blastomycosis antigens (serum and urine) were ordered. Repeat bronchoscopy was performed on day 14 during the second hospitalization with endobronchial ultrasound with fine needle aspiration of lymph nodes at station 7 and 11. On day 17,

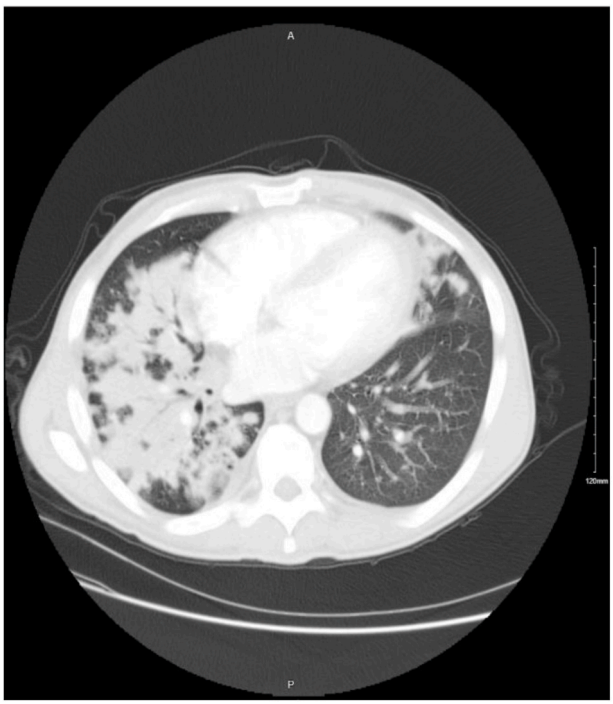

Fig. 3. CT chest (day 12) showing stable infiltrates.

Histoplasma antigen was positive in both serum and urine, Blastomyces antigen was detected in urine and serum [positive, below the limit of quantification]. ANA and Anti-U1-RNP antibodies were also positive, but there was low suspicion of mixed connective tissue disease or autoimmune etiology in the absence of clinical symptoms. Treatment was started with itraconazole 200mg three times a day. The next day, treatment was switched to liposomal amphotericin B 250mg (5mg/kg/day) daily based on the severity of the disease as per infectious diseases recommendation. BAL-fluid culture from initial hospitalization grew broad based budding yeast which was identified as *Blastomyces dermatitidis* after 3 weeks (day 21) from initial bronchoscopy, and in repeat BAL-fluid culture. The final needle biopsy and transbronchial biopsy showed no granulomas or malignancy. Susceptibility testing was not performed. The patient had worsening respiratory failure with worsening radiographic evidence of infiltrates suggestive of ARDS (Fig. 4), requiring intubation and mechanical ventilation.

The patient was transferred to a tertiary care center and continued on

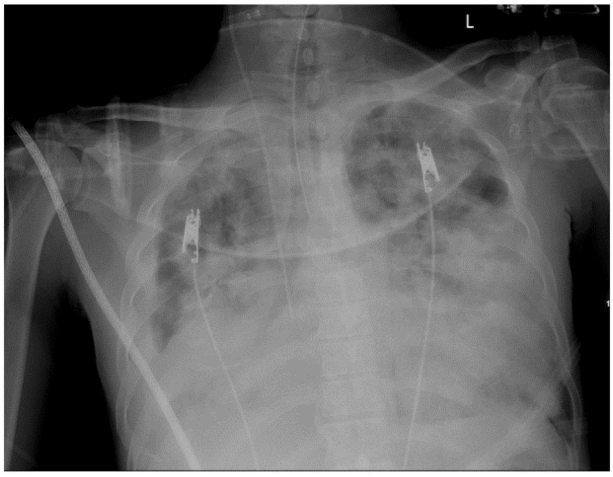

Fig. 4. X-ray chest showing bilateral diffuse patchy infiltrates consistent with ARDS.

IV liposomal amphotericin B 250mg daily(5mg/kg/day), did not receive steroids, Extracorporeal membrane oxygenation (ECMO) was needed for adequate oxygenation. Given the guarded prognosis, the family decided to withdraw care and the patient passed away.

3. Discussion

Blastomycosis is caused by *Blastomyces dermatitidis*, a thermally dimorphic fungus, growing as a mold in the environment and as a yeast in the tissues. It is mostly endemic to North America, Ohio and the Mississippi River Valleys [1]. *Blastomyces* spp. particularly live in moist soil and decomposing plant matter, like wood and leaves. When disruption of the soil matter occurs, the spores are released into the air and upon inhalation enter the lungs, the human body temperature allows the spores to transform into the yeast form. Dissemination to the bloodstream and other organs like skin, bones, joints and central nervous system, can occur [3]. Obesity, diabetes mellitus, immunosuppression and pulmonary multi-lobar disease are considered risk factors for the development of severe and disseminated blastomycosis [5]. Onset of symptoms occurs from three weeks to three months after infection [4]. Lung is the primary portal of entry and more than 79 % of patients have documented pulmonary blastomycosis [6]. Usually presenting as fever, dyspnea, productive or non-productive cough [7], acute pulmonary blastomycosis is frequently mistaken for bacterial community-acquired pneumonia (CAP). Chest radiography shows consolidation, indistinguishable from CAP [8]. It can also present as cavitary lung lesions [9] or lung nodules. Undiagnosed or untreated acute pulmonary blastomycosis can progress to acute respiratory distress syndrome (ARDS) or chronic pneumonia. Chronic pulmonary blastomycosis is non-specific and can mimic lung neoplasm [10], and presents as fever, persistent cough, hemoptysis, night sweats, weight loss and malaise. Chest radiography shows nodules, masses, pleural effusion and cavitary lesions [11]. Our patient's CT chest showed bilateral diffuse infiltrates mimicking CAP. Investigators from Indiana found diabetes to be a risk factor for ICU admission on multivariate analysis (OR 2.9, P = 0.04) [12]. This data suggests that persons with diabetes developing blastomycosis may be at increased risk of progression to respiratory failure and ARDS [13], In our patient, with a hemoglobin A1c of 10.3, reflective of poorly controlled diabetes, this is likely to have played a role in the severity of his disease. The definitive diagnosis is the culture of *Blastomyces* spp. For pulmonary blastomycosis, invasive bronchoscopy (92 %) or non-invasive sputum or tracheal secretions (86 %) [14] is recommended. Serial urine antigen concentration can be used both as diagnostic tool and to monitor response to treatment [15]. Treatment recommendations are based on the site and severity of infection, host immune status, and pregnancy. Antifungal treatment is recommended for all patients diagnosed with blastomycosis, including those with resolution of clinical symptoms before receiving therapy. Mild cases of pulmonary blastomycosis are treated with oral itraconazole 200mg TID for 3 days and then BID for 6–12 months. Severe cases are treated with amphotericin B 5mg/kg/day for 1–2 weeks, step down to oral itraconazole 200mg for 6–12 months [4]. Since our patient developed ARDS, he was started on liposomal amphotericin B. In ARDS patients, adjunctive steroids showed improved survival [16], however recent retrospective analysis of 43 patients with ARDS due to blastomycosis did not demonstrate reduced mortality in patients treated with steroids [17]. Our patient was therefore not treated with steroids. Take home point is to consider fungal co-infection when the patients presenting with CAP showed minimal response to bacterial pneumonia treatment and presence of underlying risk factors like poorly controlled diabetes.

Conflict of interest

We have no personal or financial disclosures.

Ethical Form

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report from the patient or legal guardian(s).

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr. **Please note that your manuscript will not be considered for publication until the signed Ethical Form has been received.**

CRediT authorship contribution statement

Dedeepya Gullapalli: Writing – original draft. **Ali Raza:** Resources. **Amna Khan:** Writing – review & editing. **Subramanya Shyam Ganti:** Visualization, Supervision. **Amina Pervaiz:** Writing – review & editing, Supervision.

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This case has been accepted and will be presented as a poster in ATS 2024, San-Diego.

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