Pulmonary Blastomycosis: Pediatric Cases Emphasizing Prompt Identification Using C-Reactive Protein and Procalcitonin to Distinguish Fungal vs Bacterial Origin

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ABSTRACT

Introduction: Pulmonary blastomycosis is a rare fungal disease with increased prevalence in states such as Wisconsin. Clinical manifestations of blastomycosis may vary from asymptomatic infection to multiorgan, disseminated disease.

Case Presentation: We present 2 pediatric patients with blastomycosis who were initially worked up secondary to cough and fever of suspected bacterial origin, though whose subsequent hospital course was notable for deterioration until antifungal treatment was initiated.

Discussion: In each case, the disease burden was monitored concurrently with serum procalcitonin and C-reactive protein levels, the former of which remained relatively normal throughout the hospital course signifying lack of bacterial involvement.

Conclusion: We emphasize the importance of obtaining an early C-reactive protein and procalcitonin, which may distinguish a bacterial from fungal pulmonary infection such as blastomycosis. This, in turn, may shorten hospital stay and reduce hospital inpatient cost, morbidity, and mortality by means of prompt antifungal intervention.

INTRODUCTION

Blastomycosis is a rare, geographically constrained, thermally dimorphic fungi of the genus and species *Blastomyces dermatitidis*. The disease is most prevalent near the Mississippi, Missouri, and Ohio River basins and notably infectious in states such as Wisconsin. The clinical symptomatology is diverse, and according to studies conducted before the development of successful antifungal therapy, more than 70% of a Veteran's Administration cohort with blastomycosis had multiorgan spread, with mortality rates as high as 90%.[1] Therefore, early antifungal therapy is paramount to an appropriate clinical recovery. However, the presenting signs and symptoms may be misattributed to a bacterial pneumonia. Nonspecific symptom, such as fever, cough, and chest pain, and physical exam findings, such as diminished breath sounds, are not reliable in distinguishing the 2 etiologies. When the clinical suspicion for pneumonia is high, results of simultaneous nonspecific inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT) may be used to guide empiric antifungal versus antibacterial therapy. While reports from Wisconsin describe a lower frequency of disseminated disease, the primary infection rates are high, and delay in recognition and treatment may significantly prolong hospital stay and increase total charges, morbidity, and mortality.[2]

CASE 1

A 16-year-old Somali male, born to immigrant parents who arrived in Wisconsin 5 years prior, was in his normal state of health until 11 days before admission to the pediatric intensive care unit (PICU), when he was seen at urgent care for a fever and cough. He was diagnosed with left lower lobe pneumonia following radiographic evidence of a consolidation and was prescribed a 5-day course of azithromycin 250 mg/5 ml by mouth and an albuterol inhaler. Two days later, he was brought to the emergency department (ED) with worsening generalized weakness and was sent home.

On return to the ED 1 week later, he had persistent decreased breath sounds in the lower left lung field, diffuse bilateral rhonchi, chest wall tenderness to palpation, and increased work

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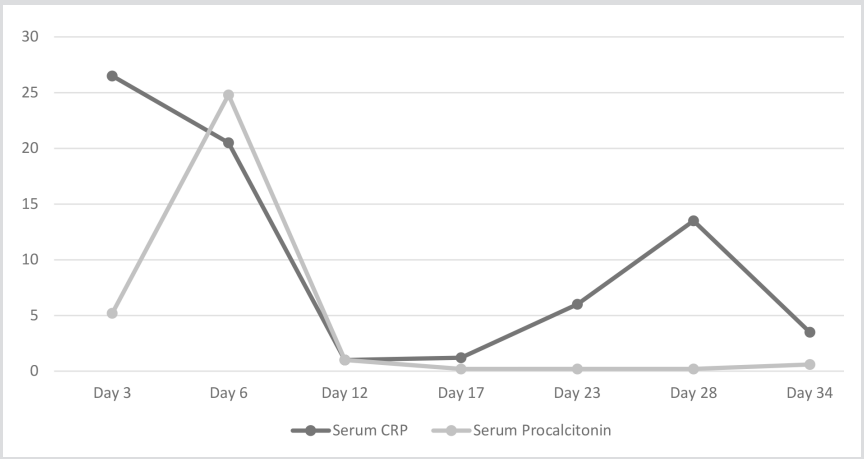
Figure 1. Serum Procalcitonin and C-reactive Protein (CRP) Levels (mg/dL) Recorded Throughout 35-day Hospital Stay of Patient 1



breathing. Vitals were normal at this time. Subsequent computed tomographic imaging revealed prominent bilateral infiltrates with complete opacification of the lower left lobe and a left-sided pleural effusion.

CRP level on admission was 29.60 mg/dL (normal: < 0.8 mg/dL) with a white blood cell (WBC) count of 13.1 x10^3 cells/uL (normal: < 11.0 x 10^3 cells/uL). Tuberculosis QuantiFERON and pneumococcal antigen panels were negative. Additionally, thoracentesis was performed, though pleural fluid bacterial and fungal cultures were negative at this time. On admission day 2 while intubated, the patient underwent bronchoalveolar lavage and bronchoscopy, which were significant for visible hemorrhagic lesions in the left main stem bronchus. Bacterial bronchial aspirate cultures showed no growth, though microscopy of fungal cultures demonstrated broad-based budding yeast. Additionally, *Legionella* urine antigen studies were negative, and *Blastomyces* urine antibodies were nonreactive at this time. He began therapy with intravenous (IV) ceftriaxone (Rocephin) (1000 mg/50 mL/24 hours) and, on admission day 3, therapy with liposomal amphotericin B IV (Ambisome) (300 mg/dextrose 5% 250 mL/24 hours) and piperacillin-tazobactam IV (Zosyn) (4500 mg/daily). The following day, admission day 4, his CRP and PCT were 26.7 mg/dL and 5.29 ng/mL (normal: < 0.25 ng/mL), respectively.

On admission day 6, the patient was deemed critically ill and therapy was initiated with veno-venous extracorporeal membrane oxygenation (ECMO) and mechanical intubation. On admission day 7, urine Histoplasma antigens came back positive, and on day 12, serum *Blastomyces* antigens returned positive, after which he was transitioned from strict ECMO oxygenation-ventilation to a combination of ECMO and mechanical ventilation. On day 23, pulmonary examination was normal on the right with residual decreased breath sounds on the left, and on day 35, he was transferred to a rehabilitation unit with normal vital signs and a benign clinical exam. Throughout the course of his hospital stay, the patient had simultaneously and regularly measured PCT and CRP levels (Figure 1). Upon transfer to the rehabilitation unit, he was weaned off liposomal amphotericin B IV (Ambisome) from a rate of 300 mg/dextrose 5% 250 mL/24 hours and started on oral itraconazole (10mg/kg/24 hours) for an anticipated 12 months duration. Prior to discharge, he underwent magnetic resonance imaging of the head, which was negative for evidence of cerebral blastomycosis. However, he did not receive a bone scan to evaluate for disseminated blastomycosis of the bone.

CASE 2

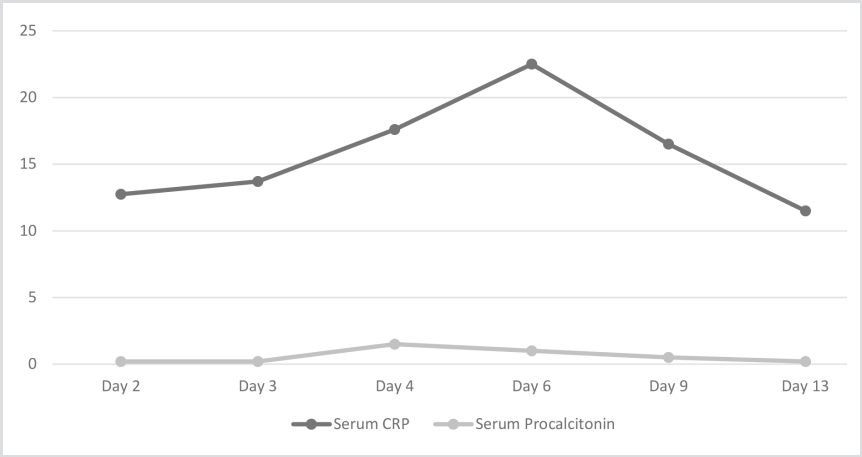
Two years following case 1, an 11-year-old Somali girl, accompanied by immigrant parents who arrived in Wisconsin 2 years prior, presented to the ED with a 3-day history of persistent cough and low-grade fever. Her parents reported a decreased appetite and markedly reduced activity level prior to presentation. Review of systems was negative for rhinorrhea, congestion, ear pain, throat pain, rashes, or dyspnea. She had no history of recent travel outside the Green Bay, Wisconsin area, and past medical history was negative. On admission, her temperature was 38.3°C, pulse 126 beats per minute, 24 respirations per minute, and an SpO_2 of 100% on ambient air. Physical examination was wholly unremarkable. Radiographs of her chest disclosed a dense consolidation in the left suprahilar region with no right-sided disease, and she was prescribed a 5-day course of azithromycin 200 mg/5 ml by mouth. Nine days later she returned to the ED afebrile, though with persistent cough and bilateral facial swelling. Her parents confirmed she completed her course of azithromycin and denied any significant interval history. On return to the ED, her temperature was 37°C, with a pulse of 117 beats per minute, respirations of 18 per minute, and an SpO_2 of 95% on ambient air.

At this time, the physical examination disclosed right periorbital ecchymosis, though was otherwise normal. Chest films demonstrated worsening left lobe opacification with a new right middle lobe consolidation. PCR nasal swab for viral antigens was negative, and she was started on ceftriaxone IV (Rocephin) (1620 mg/24 hours) and diphenhydramine IV (Benadryl) (12.5 mg as needed) and admitted to the PICU.

On admission day 2, the patient's CRP was 11 mg/dL (normal: < 0.8 mg/dL) and PCT was negligible (normal: < 0.25 ng/mL); she was started empirically on IV vancomycin (320 mg/6 hours) and liposomal amphotericin B IV (Ambisome) (160 mg/dextrose 5% 100 mL/24 hours). Serum antibody and urine antigen studies were nonreactive, and bronchial aspirate was negative for growth at that time. On admission day 5, serum *Blastomyces*

antibodies returned positive and ceftriaxone was discontinued. By day 7, her CRP began to fall (Figure 2), her vancomycin was discontinued, and she was thereafter started on levofloxacin (Levaquin) (319 mg/12 hours). On day 9, urine *Blastomyces* antigen test returned positive and by day 13, she was presumed to have been infected with blastomycosis and was discharged. During the course of her hospital stay, she neither exhibited signs nor symptoms of focal neurologic deficit, and imaging of the head, as well as a bone scan, were not performed. Prior to discharge, she was advised to return to the hospital for regularly scheduled liposomal amphotericin B IV therapy (160 mg/dextrose 5% 100 mL/24 hours) for 1 week, with an anticipated 6-months duration of oral itraconazole (10mg/kg/24 hours) thereafter, in addition to lactobacillus capsules by mouth twice daily. Chest radiography on discharge was negative and showed resolution of intrapulmonary disease.

Figure 2. Serum Procalcitonin and C-reactive Protein (CRP) Levels (mg/dL) Recorded Throughout 13-day Hospital Stay of Patient 2



DISCUSSION

Blastomycosis is an often-misdiagnosed fungal disease as its initial symptom profile may be nonspecific. Additionally, *Blastomyces*—as opposed to other fungal pathogens—has a proclivity of affecting healthy, immunocompetent patients.[3] While the usual presentation of blastomycosis involves pneumonitis in a patient within a certain geographical area that does not respond to typical antibacterial therapy, the subsequent course ranges from primary pulmonary disease, to fulminant hypoxic respiratory failure and acute respiratory distress syndrome, to extra pulmonary complications commonly involving the skin and bones.[4] As emphasized in the previous 2 cases, the initial presenting symptoms—here occurring in 2 immunocompetent patients—often mimic a routine bacterial infection. Without prompt recognition, the delay in diagnosis and treatment of blastomycosis leads to poor clinical outcomes, including increased morbidity and mortality, greater length of hospital stay, and increased inpatient costs.[5]

In the presence of nonspecific symptoms not relieved by antibiotics, the best initial test to identify blastomycosis is through microscopic examination of pulmonary (lower respiratory tract) secretions, obtained either by induced sputum production or pulmonary endoscopy. While some clinical data suggest fungal growth is insidious, often taking as long as 5 weeks to appear on microscopy, an induced sputum sample or one properly obtained from pulmonary endoscopy should show fungal growth within a few days.[6] Therefore, given the potentially broad time-course of growth, clinical suspicion is paramount to prompt recognition and treatment. We suggest that the early gathering and interpretation of nonspecific inflammatory markers that reveal a low PCT and elevated CRP may help promote subsequent distinguishing of a bacterial from fungal pneumonia by way of targeted diagnostic tests. This practice ultimately would permit a more expeditious antifungal treatment course and overall reduction in antibiotic exposure. The dissociation of PCT and CRP should stimulate the treating physician to rapidly obtain tests to confirm blastomycosis, such as microbiologic studies, urinary antigen testing, or cultures of pulmonary secretions. The benefit of early interpretation of these markers stems not only from antibiotic dismissal, but also from confirmation of the fungal pathogen via diagnostic testing before initiation of toxic antifungal therapy.

Serum CRP and PCT concentrations are of a relatively new clinical benefit used as an adjunct in the diagnosis and treatment of infections due to their accessibility and high specificity and sensitivity.[7,8] CRP is an acute phase reactant synthesized by the liver in response to inflammatory cytokines, and its rise is proportional to the severity of the inflammatory process, making CRP a reasonable proxy for identifying both a worsening or resolving bacterial or fungal infection.[9] PCT, another inflammatory marker, is a hormone secreted by parafollicular C-cells of the thyroid gland in response to hypercalcemia or systemic inflammation caused by infection. While the CRP has great sensitivity in identifying inflammatory conditions, it is often considered nonspecific for infectious disease as it may be elevated in response to various noninfectious stimuli, including trauma and inflammation.[10] Therefore, PCT is of great clinical significance for differentiating bacterial versus fungal infection, such as blastomycosis. Studies suggest that infections caused by a fungal pathogen do not elicit as great an increase in serum PCT (range, 0.69–1.23) compared to its conventional rise in patients who have an infection of confirmed bacterial origin (range, 4.18–12.9).[11]

In Case 1, we cannot explain the rapid increase in serum PCT

from admission day 3 (5.29 mg/dL) to admission day 6 (24.48 mg/dL), though in a previous study by Markova et al, the overall trend of elevated CRP concentrations with low PCT levels indicates invasive fungal infection, thereby warranting early initiation of antifungal therapy.[12] Due to ambiguities between invasive fungal and bacterial infections, however, blastomycosis is often treated initially as a bacterial infection until the course of the disease is markedly worse (inpatient stay, use of ECMO, etc) than were its presenting symptoms. *Blastomyces* can infect immunocompetent hosts and may occur as a cluster of outbreaks within a specifically populated area. For example, in the summer of 2015, individuals visiting the Little Wolf River were exposed to *Blastomyces*, with a subsequent infection rate of 59 confirmed and 39 probable cases.[13] Similarly, a large-scale outbreak in Marathon County, Wisconsin in 2009-2010 resulted in 55 confirmed cases.[14] Therefore, in states like Wisconsin where its prevalence is increased, or within which outbreaks are rare but not entirely uncommon, early use of serum PCT as a marker to promote further differentiation of bacterial from fungal infection may certainly decrease the prejudicial use of the antibiotics in patients with underlying fungal disease such as blastomycosis, as well as reduce cost, hospital stay, and inpatient morbidity and mortality.

CONCLUSION

Blastomycosis is a potentially fatal fungal disease that can be difficult to differentiate clinically from bacterial pneumonia. Prompt treatment and diagnosis, which can be persuaded by early dissociation of PCT and CRP, is undoubtedly associated with a better prognosis, less antibiotic resistance, and reduced costs.

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