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Pulmonary oxalosis in pulmonary aspergillosis syndrome

Abstract

The presence of pulmonary oxalosis in bronchoalveolar lavage (BAL) or biopsied tissue samples is considered pathognomonic for *Aspergillus* disease etiology. The finding of calcium oxalate crystals in the tissue samples infected with aspergillosis can serve as a vital diagnostic clue. Detection of calcium oxalate crystals is achievable within 24 hours by most hospital microbiology laboratories. It is much quicker than the time it takes to receive results of other tests like histopathology, sputum cultures, and aspergillus antigen assays. We present this case to emphasize the importance of pulmonary oxalosis as a crucial early diagnostic factor in pulmonary aspergillosis syndromes.

Key words: aspergillosis, *Aspergillus*, oxalosis, calcium oxalate

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Introduction

Aspergillus genus comprises hundreds of species that are ubiquitously found in soil, water, or decaying vegetation. A. *fumigatus* and A. *niger* comprise the majority of disease-causing agents in pulmonary aspergillosis syndromes. These include invasive pulmonary aspergillosis (IPA), chronic necrotizing aspergillosis (CNA), allergic bronchopulmonary aspergillosis (ABPA), and aspergilloma.

A frequently overlooked diagnostic clue for tissue infection by aspergillosis is the finding of calcium oxalate crystals. The presence of pulmonary oxalosis in BAL or biopsied tissue samples is pathognomonic for *Aspergillus* disease etiology. Oxalic acid is a byproduct of *Aspergillus* metabolism, which combines with calcium in the blood supply of invaded tissue to form calcium oxalate crystals. The presence of calcium oxalate crystals is detectable under polarized light within 24 hours by most hospital microbiology laboratories, which is earlier than the time to receive results of histopathology, sputum cultures, and sputum and blood aspergillus antigen assays. This article suggests that evaluation for pulmonary oxalosis may be included in the workup of cases suspicious for aspergillosis.

Case report

A 56-year-old African-American male presented with two months' history of weight loss, cough with yellowish expectorate. He also complained of pleuritic right-sided chest pain for one week, and hemoptysis for two days before admission. A review of systems was positive for fever and chills. He smoked one pack/day for 35 years, and had a long-standing history of alcoholism.

At admission, he was tachycardic at 118 bpm, and his respiratory rate was 20 bpm. His blood pressure was 137/88, his temperature was 98.6°F, and SaO_2 was 96% at room air. Other pertinent physical exam findings were cachexia, and inspiratory crackles and diminished breath sounds at right upper lung fields. He was admitted for further testing.

His complete blood count showed leukocytosis at 37.5 K/μL and normocytic anemia with a hemoglobin of 10 mg/dL. A chest X-ray (Figure 1A) revealed right upper lobe infiltrates. He was started on ceftriaxone and azithromycin for the treatment of community-acquired pneumonia.

On day three, his symptoms persisted, which prompted broadening of antibiotics coverage to imipenem/cilastin 500 mg Q6 hours and tri-

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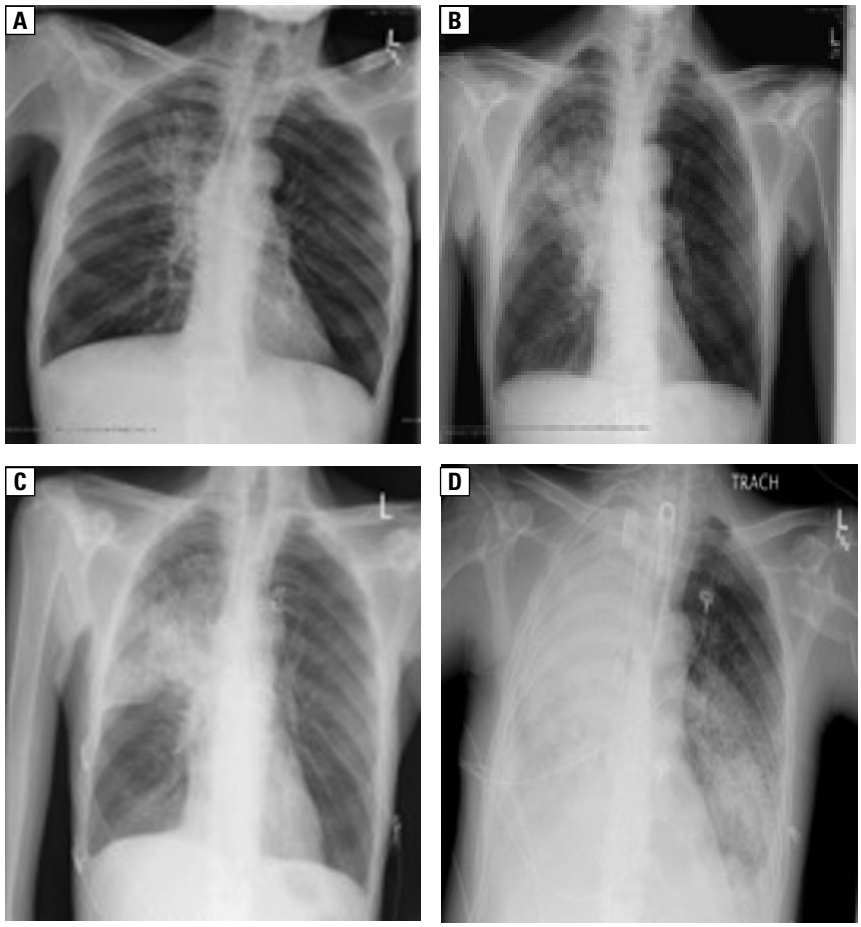

Figure 1. Chest X-ray results showing progression of RUL infiltrates to bilateral lungs from day 1 (**A**), 3 (**B**), 4 (**C**), and 8 (**D**) of admission respectively

methoprim/sulfamethoxazole 800 mg/160 mg 2 tablets BID. A repeat chest X-ray (Figure 1B) revealed worsening infiltrates of the right upper and middle lobes. His leukocytosis persisted at 37 K/μL. AFB of a sputum sample collected at admission returned negative. He continued to be normothermic and was saturating well on room air. On day 4, the patient continued to have leukocytosis at 32.5 K/μL. His chest X-ray (Figure 1C) showed worsening infiltrates. Linezolid 600 mg oral BID was also added to the aforementioned antibiotics. A CT of the chest with contrast (Figure 2) was obtained, which showed the right lung pulmonary consolidation with pleural effusion. His sputum culture results grew *Candida albicans* and *Aspergillus niger*. He was started on voriconazole loading dose of 6 mg/kg IV Q24 hours (which was subsequently followed by 4 mg/kg Q24 h).

On day 8, his leukocytosis worsened to 62 K/μL. Antibiotics were switched to meropenem 1000 mg Q12 hours, azithromycin 250 mg IV

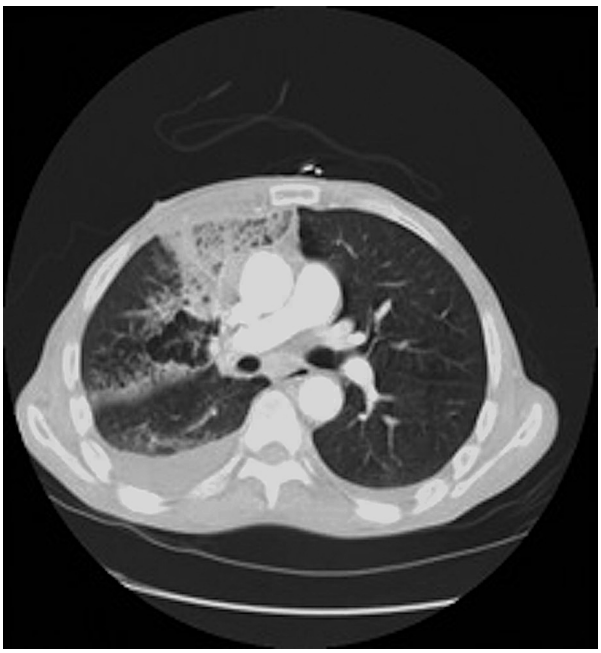

Figure 2. Computed tomography chest with contrast on day 4 of admission, showing right lung infiltrates, and right pleural effusion

Q12 hours, vancomycin 750 mg Q24 hours. He was also started on caspofungin 70 mg IV Q24 hours (followed by 50 mg daily on subsequent days). Based on the clinical course, broadened differential diagnoses were considered. These included pulmonary tuberculosis and nontuberculosis mycobacterial lung disease, pulmonary mycosis (chronic pulmonary aspergillosis or histoplasmosis), cryptogenic organizing pneumonia, pulmonary vasculitis (such as granulomatosis with polyangiitis, microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis), *Pneumocystis carinii* (PCP) pneumonia and lung cancer. He had also developed respiratory failure requiring BiPAP. He was subsequently intubated and underwent bronchoscopy with bronchoalveolar lavage (BAL). Within 24 hours of collection, his BAL sample showed calcium oxalate crystals under polarized light. Histopathology of biopsied tissue sample was negative for malignancy, fungal bodies, but also confirmed calcium oxalate crystals (Figure 3).

His sputum sample was also tested for AFB stain, TB culture, mycobacterium tuberculosis DNA by PCR, cytology, and PCP antigen, which were all negative. Urine histoplasma antigen and pANCA and cANCA blood titers were also negative. One week later, the patient's BAL sputum galactomannan antigen and Aspergillus DNA PCR returned positive. The serum galactomannan antigen was also positive. The patient's health continued to deteriorate; he developed multiorgan system failure and died one week later. Autopsy was not performed and necrotizing pneumonia was identified as the cause of death.

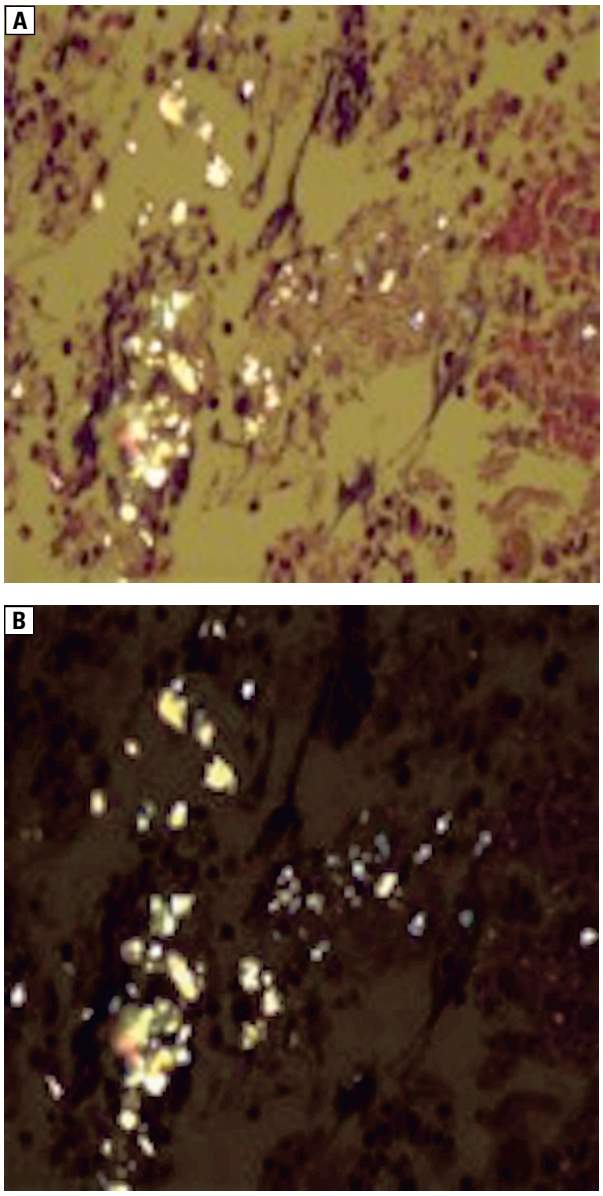

Figure 3. Showing calcium oxalate crystals in pulmonary tissue biopsy

Discussion

Pulmonary oxalosis is pathognomonic for *Aspergillus fumigatus* and *Aspergillus niger* tissue invasion. Oxalic acid is a byproduct of *Aspergillus* spp. metabolism which combines with calcium in the blood supply of invaded tissue to form calcium oxalate crystals. The deposition of calcium oxalate crystals and *Aspergillus* invasion both contribute to further inflammation and tissue destruction. Calcium oxalate crystals can occur in all spectrum of pulmonary aspergillosis such as aspergilloma, allergic bronchopulmonary aspergillosis, chronic necrotizing aspergillosis, and invasive pulmonary aspergillosis (IPA), but is more common in the latter two which are representatives of more invasive disease. Calcium oxalate crystals are readily identifiable under polarized light microscopy as birefringent granules in sputum and tissue samples of the infected host. This result is available at most standard hospital laboratories within 24 hours of sample collection, and in the appropriate clinical situation, it can facilitate early initiation of antifungal treatment, long before the results of other tests for pulmonary aspergillosis return.

Pulmonary aspergillosis is most frequently caused by A. *fumigatus*, and less commonly by A. *niger*. Invasive pulmonary aspergillosis (IPA) is an acute disease that manifests clinically in patients with risk factors which include neutropenia, prolonged use of high dose steroids, critical illness, and immunosuppression associated with organ transplant, chemotherapy or AIDS [1]. Typical symptoms reported are similar

to bronchopneumonia, i.e. cough with expectorating, dyspnea, fever, pleurisy, and hemoptysis. In contrast, CNA is a more indolent, sub-invasive disease in which full symptoms may take weeks to months from onset of *Aspergillus* exposure to become fully evident. CNA experience symptoms similar to IPA, with the addition of weight loss. Risk factors for CNA are centered around mild levels of immunosuppression, which include being elderly, underlying chronic lung diseases such as COPD, history of radiation therapy, diabetes mellitus, alcoholism, chronic liver disease, and low-dose corticosteroid therapy [1–3]. Patients with COPD are known to have pulmonary parenchymal modifications, which increases their risk of infections. Alcoholism is also known to affect innate and adaptive pulmonary immunity resulting in subclinical immunosuppression that becomes apparent with a heavy burden of infection [3, 4]. Our patient's indolent prehospital course was consistent with CNA secondary to chronic alcoholism and COPD, and his disease progressed rapidly to IPA and became critically ill after he was admitted.

The man was diagnosed with IPA based on positive respiratory cultures for *Aspergillus*, bronchial necrosis during bronchoscopy, imaging findings, and positive sputum culture, and galactomannan antigen assay which was positive in both sputum and blood (which returned two weeks later). Histopathology with Grocott's methenamine silver stain of the tissue sample from his right upper lobe biopsy was negative for fungal organisms; however, the diagnostic value of biopsy is highly correlative to the site sampled. The detection of calcium oxalate crystals in BAL within 24 hours of collection, coupled with tracheobronchial necrosis raised the clinical suspicion for IPA, and lead to early initiation of treatment.

The treatment for proven pulmonary aspergillosis is based on intravenous azoles, echinocandins, and amphotericin B [5–9]. Invasive forms of pulmonary aspergillosis require intravenous azoles (voriconazole as first-line), which can be deescalated to oral regimens with clinical improvement, and treatment lasts about 6–12 weeks at which time radiological and clinical symptoms are resolved. Frequently, parenchymal damages are irreversible [10–13].

According to the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG), pulmonary oxalosis is not currently considered a part of the standardized criteria for the diagnosis of aspergillosis. Checking for the presence of pulmonary oxalosis in the BAL sputum during the workup of patients suspected of invasive pulmonary disease is of high yield potential in early diagnosis. Eradication of pulmonary aspergillosis syndromes can be difficult to achieve with a heavy infectious burden and severe immunosuppression, and early initiation of treatment is recommended. We present this case to emphasize the importance of pulmonary oxalosis as an early diagnostic clue for *Aspergillus* tissue invasion prior to results from cultures, lab tests, and tissue biopsy, which can take longer to yield results.

Conflict of interest

None declared.

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