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INVASIVE PULMONARY ASPERGILLOSIS: DIAGNOSTIC CHALLENGES IN A RAPIDLY FATAL CASE

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Abstract: ***Introduction.*** Invasive pulmonary aspergillosis is a severe fungal infection with a rapidly progressive course and high mortality, particularly when early diagnosis is missed. In its atypical forms, aspergillosis may clinically and radiologically mimic lung cancer, leading to critical delays in both diagnosis and treatment.

Case Presentation. We report the case of a 47-year-old chronic smoker (25 pack-years), with no known occupational exposure, admitted for a 12 days history of acute respiratory symptoms including high-grade fever (up to 39.9°C), productive cough with muco-purulent sputum, chills, myalgia, and headache. Bronchial biopsies collected during bronchoscopy were initially interpreted as suggestive of poorly differentiated non-small cell lung carcinoma. The clinical evolution was rapidly unfavorable, with the patient dying three weeks after admission. The autopsy, performed at the family's request, ruled out malignancy and confirmed a diagnosis of invasive pulmonary aspergillosis with extensive parenchymal necrosis. Histopathological findings were suggestive of an infection caused by Aspergillus niger.

Conclusion. This case highlights the potential for misdiagnosis of invasive pulmonary aspergillosis in its forms that mimic lung tumors, and underscores the critical value of autopsy in establishing the etiological diagnosis in rapidly fatal cases.

Keywords: pulmonary consolidation, aspergillosis, Aspergillus niger, Calcium oxalate crystal deposition, brown deposits.

INTRODUCTION

The Aspergillus genus includes around 300 species, many of which are widespread in the environment. Aspergillus fumigatus is the most frequently encountered pathogenic species responsible for the majority of human infections, followed by A. niger, A. terreus, A. flavus (1). Aspergillus species can cause a wide spectrum of pulmonary disorders, varying from benign airway colonization to aggressive invasion of lung tissue and blood vessels, which may result in sepsis and death. Diagnosing the spectrum of pulmonary diseases caused by Aspergillus species can be difficult, as fungal elements are often scarce or entirely missing in biopsy samples. The identification of calcium oxalate crystals and dark-brown pigment deposits within the lung parenchyma is considered a histopathological evidence of Aspergillus niger infection (2, 3). This case report describes a 47-year-old male patient whose clinical presentation, along with paraclinical investigations, bronchoscopy, and biopsy findings suggested the presence of lung cancer. The autopsy was performed and histopathological analysis of the tissue samples established the presence of Aspergillus niger causing invasive pulmonary aspergillosis.

CASE REPORT

A 47-year-old male with a 25 pack-year history of chronic smoking and no occupational exposure to respiratory toxins, presented to the Emergency Department (ED) with a 12-day history of polymorphic symptoms. The clinical presentation included persistent high-grade fever (maximum 39.9°C), a dry cough that became productive with mucopurulent sputum, chills, generalized myalgia and headache. Prior to admission, the patient self-medicated with oral

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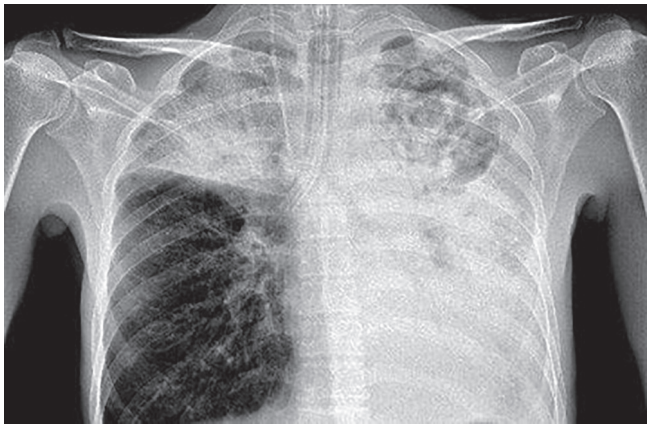

Figure 1. Chest radiography indicating a fibronodular lesion located in the left apical region.

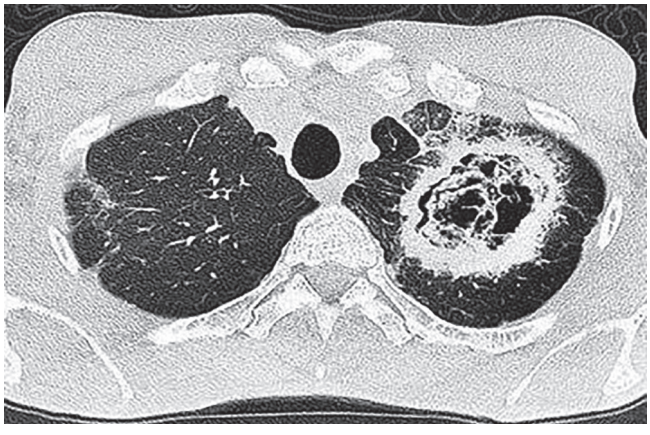

Figure 2. Thoracic CT indicating a cavitary lesion surrounded by adjacent consolidation in the left upper lobe.

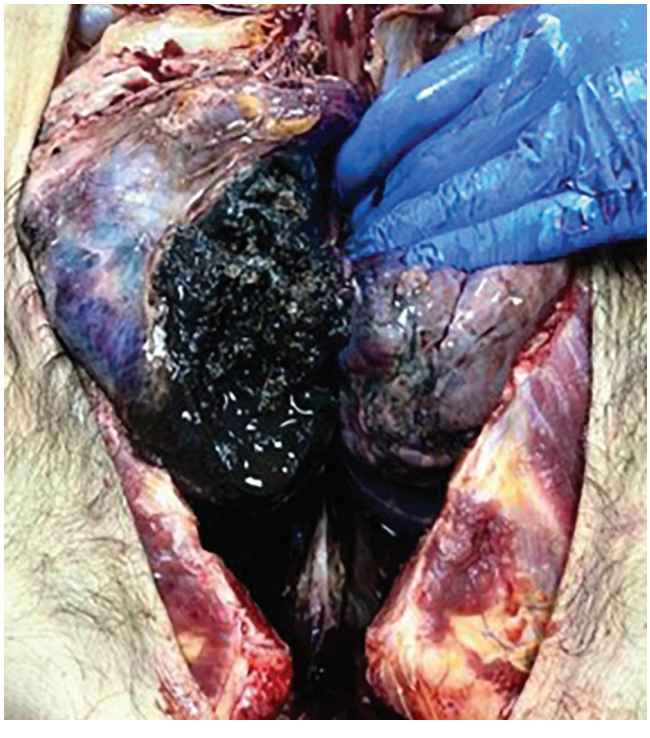

Figure 3. Gross appearance of left apical pulmonary parenchyma.

antibiotics: Amoxicillin-clavulanate (1g every 12 hours for 7 days), followed by Levofloxacin 500 mg every 12 hours for 3 days, without clinical improvement. At admission to ER, a chest radiograph was performed, revealing fibronodular, sequelae-like lesions in the left apico-supraclavicular region, raising the suspicion of reactivated pulmonary tuberculosis.

Laboratory results showed a marked inflammatory syndrome with leukocytosis (23,850/μL) accompanied by neutrophilia and monocytosis, elevated C-reactive protein (262,85 mg/L), elevated erythrocyte sedimentation rate (116 mm/h), fibrinogen 571 mg/dL, normochromic normocytic anemia (Hb 10,4 g/dL), thrombocytosis (607,000/μL), coagulopathy, mild hyponatremia and hypochloremia.

A non-contrast thoracic CT scan performed within 2 hours of admission revealed a cavitary lesion surrounded by adjacent consolidation in the left upper lobe.

Next day bronchoscopy was performed, which showed infiltrative-congestive mucosal lesions in the segmental and subsegmental bronchi of the left upper lobe. Serial biopsies (five large fragments) were taken. Histopathological analysis of the bronchial biopsy reported poorly differentiated bronchial carcinomatous infiltration, consistent with non-micronodular squamous cell carcinoma. Immunohistochemistry was recommended for further characterization.

Empiric broad-spectrum antibiotic therapy was initiated with piperacillin/tazobactam 4,5 g every 8 hours IV, moxifloxacin 400 mg daily IV, later combined with Metronidazole 1,5 g/day orally. Oral antifungal therapy was started with itraconazole 200

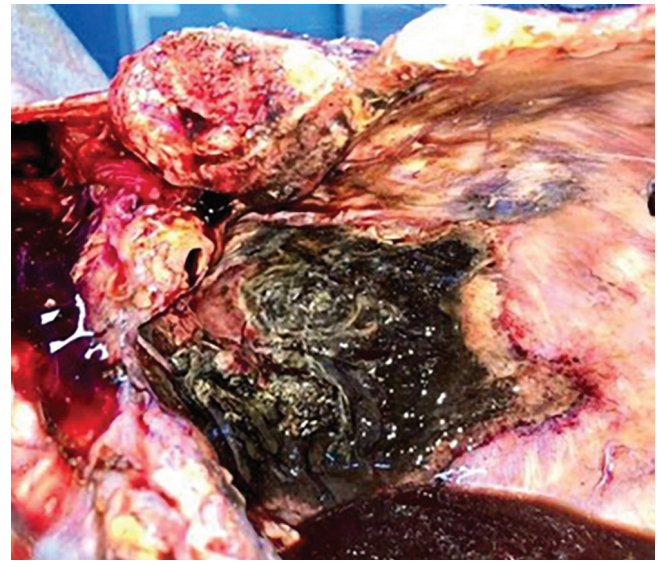

Figure 4. Gross appearance of diffuse gray-black infiltration of the left apical parietal pleura.

mg/day. After 4 days, piperacillin/tazobactam was discontinued and replaced with meropenem 1 g every 8 hours IV. Adjunctive treatments including mucolytics, hemostatics, antipyretics, hepatoprotective agents, probiotics, proton-pump inhibitors, and systemic corticosteroids (hydrocortisone hemisuccinate 100 mg/day IV) was also administered. Despite this regimen, the patient's condition deteriorated. Persistent fever and progressive inflammatory markers (including mildly elevated procalcitonin) persisted. Blood cultures collected during febrile episodes returned negative. As respiratory function continued to decline, the patient required endotracheal intubation and mechanical ventilation. The patient was pronounced dead after 15 days of hospitalization. Autopsy was performed on family's request.

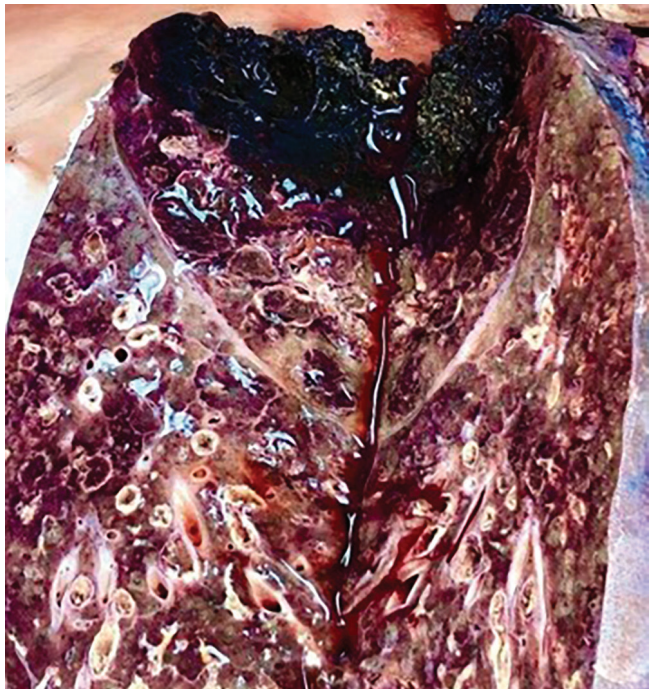

Figure 5. Gross appearance of well-circumscribed cavitary lesion filled with necrotic tissue, surrounded by consolidated lung tissue. The bronchial tree was markedly ectatic, with visible luminal debris, yellowish viscous secretions, and epithelial desquamation.

AUTOPSY AND HISTOPATHOLOGICAL FINDINGS

Gross examination at autopsy revealed diffuse gray-black infiltration of the left apical parietal pleura, with firm adhesion to the underlying lung. Upon removal, the left apical pulmonary parenchyma was torn, revealing a well-circumscribed cavitary lesion filled with necrotic, liquefied material. The surrounding lung tissue appeared consolidated. The bronchial tree was markedly ectatic, with visible luminal debris, yellowish viscous secretions, and epithelial desquamation.

Histological examination revealed numerous fungal spores and rare fungal hyphae within the alveolar spaces, interstitium, bronchi, and blood vessels. Polarized light microscopy showed birefringent crystalline structures (calcium oxalate crystals) located intra-alveolarly, interstitially, and intravascularly. Grocott's methenamine silver staining confirmed fungal invasion, demonstrating multiple septate hyphae, some at right angles, and abundant spores. These were

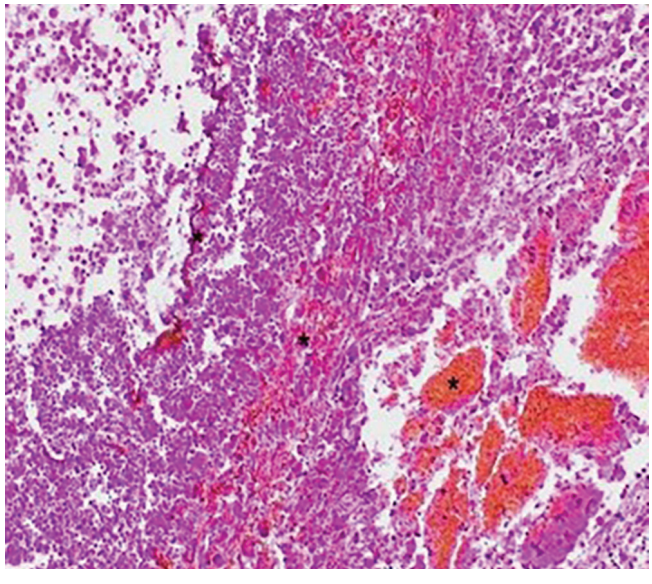

Figure 6. H-E stain, 4x, demonstrating pulmonary parenchyma with an extensive area of coagulative necrosis, with loss of nuclear detail, preservation of architectural structures, and prominent deposition of dark brown-black pigment throughout the tissue components (*).

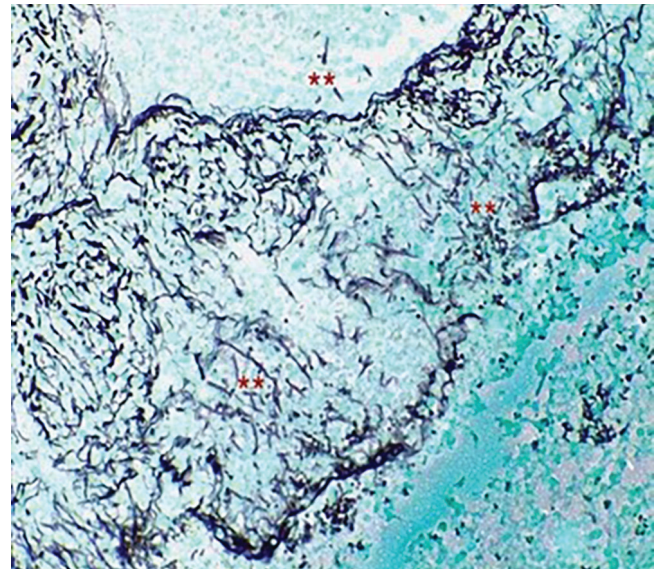

Figure 7. Grocott's methenamine silver stain, 20x, revealing numerous fungal spores and acute angles septate hyphae located within the lumen of a dilated bronchial structure, invading the bronchial wall and peribronchial vascular lumina (**).

present in the lumen and walls of dilated bronchi, with rare fungal structures also found in adjacent vascular lumina. The findings were compatible with invasive pulmonary aspergillosis caused by Aspergillus niger.

DISCUSSION

This case represents a severe form of invasive pulmonary aspergillosis (IPA), initially misidentified as non-micronodular squamous cell carcinoma. While

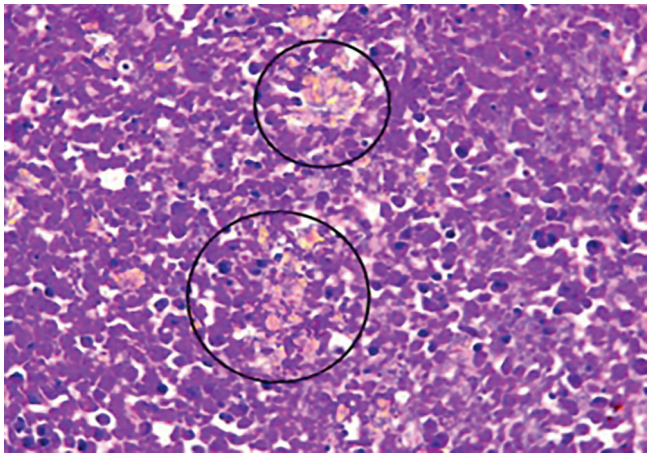

Figure 8. H-E stain, 40x, identifying frequent acellular, crystalline structures, consisting of calcium oxalate (black circles), within the bronchial lumen and wall, as well as in intra-alveolar, interstitial, and intravascular locations.

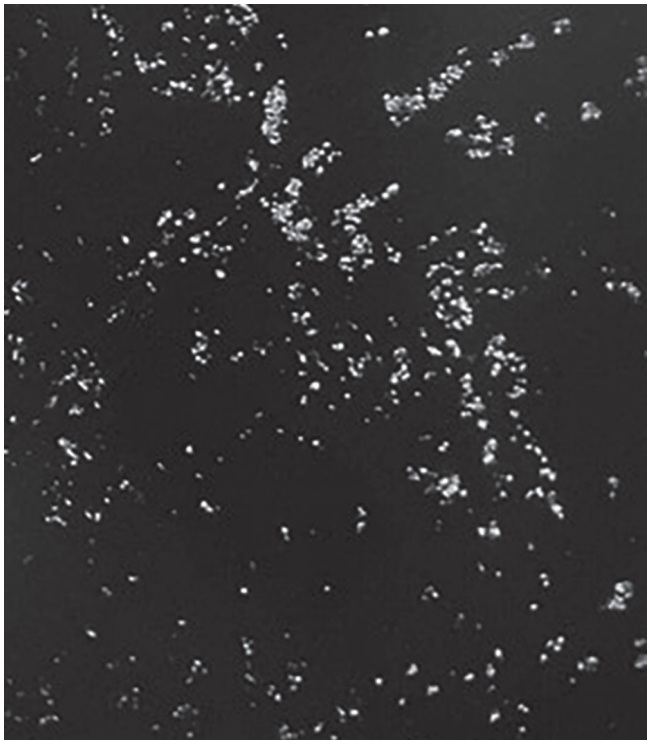

Figure 9. Birefringent calcium oxalate crystals on crossed polaroid light.

Aspergillus fumigatus is the predominant species in IPA, infections caused by Aspergillus niger are associated with aggressive pulmonary destruction, even in not classically immunosuppressed pacients.

The presence of a cavitary lesion, the infiltrative appearance on bronchoscopy, and even biopsies positive for neoplasm may obscure an active fungal infection. The diagnosis of IPA was established exclusively postmortem through histopathological examination of the lung, revealing parenchymal necrosis, vasculitis, early thrombosis, and fungal morphology consistent with Aspergillus niger. Autopsy was essential in this case to establish the definitive diagnosis. Both A. niger and A. fumigatus release oxalic acid as a mycotoxin, which precipitates as calcium oxalate by reacting with tissue fluids or blood (4), but the presence of calcium oxalate crystals and dark-brown pigment deposits is considered a characteristic of A. niger infection (5). The pathognomonic findings underscore the high degree of tissue invasion and vascular penetration, which likely contributed to systemic decompensation and death.

In conclusion, from a medico-legal perspective, this case highlights the value of autopsy as an essential tool in determining the true cause of death and in reassessing the therapeutic approach taken, particularly when the antemortem diagnosis may be incomplete or misleading. IPA may also occur in patients without significant immunosuppression, presenting in acute, aggressive forms with high mortality. The differential diagnosis between neoplasm and invasive fungal infection can be extremely challenging, even in the presence of biopsy findings.

Conflict of interest

The authors declare that they have no conflict of interest.

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