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Navigating Diagnostic Challenges in Pulmonary Aspergillosis: A Case Series Demonstrating the Synergy of Investigation Techniques

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ABSTRACT

Aspergillosis encompasses a spectrum of diseases caused by Aspergillus species, with pulmonary aspergillosis being a significant concern due to its increasing incidence and impact on both immunocompromised and immunocompetent individuals. The most prevalent chronic form, chronic cavitary pulmonary aspergillosis (CCPA), can progress to chronic fibrosing pulmonary aspergillosis if left untreated, highlighting the need for accurate and timely diagnosis. Diagnosis of pulmonary aspergillosis relies on a multi-faceted approach. While microscopy, especially with fluorescent dyes, allows for the rapid detection of fungal elements in samples like BAL, it lacks sensitivity and specificity for Aspergillus. Similarly, microscopy of sputum, although useful for initial assessment, has a sensitivity of only 50%. Culture, despite lower-than-expected sensitivity from sputum samples, remains essential for definitive diagnosis and management. It not only confirms the presence of Aspergillus but also critically enables antifungal susceptibility testing, guiding appropriate treatment. Culture, despite limitations, should be prioritized to ensure accurate species identification and susceptibility profiling, facilitating targeted and effective treatment strategies.

1. Introduction

Pulmonary aspergillosis refers to lung diseases caused by Aspergillus species, commonly Aspergillus fumigatus, which are ubiquitous fungi. Humans inhale fungal spores daily without complications unless underlying conditions exist. The manifestations depend on the host's immune status and the duration of the infection, ranging from non-invasive forms, such as aspergilloma and chronic cavitary pulmonary aspergillosis (CCPA), to life-threatening invasive pulmonary aspergillosis (IPA). IPA carries a high mortality rate, exceeding 50% in critically ill patients if not adequately treated early.[1, 2] Diagnosis is challenging due to non-specific symptoms and the difficulty of obtaining the 'gold standard' tissue biopsy or positive cultures from a sterile site.[1, 3] The ubiquitous nature of Aspergillus also means that isolating it from sputum may not be significant, and culture sensitivity from bronchoalveolar lavage (BAL) can be low.[1, 3] Clinicians may also lack awareness of the expanded patient populations at risk or fail to recognize the significance of positive respiratory cultures rapid,[4] accurate diagnosis using less invasive techniques is preferred. Combining multiple diagnostic modalities is crucial for achieving improved outcomes.[1] While histology and culture are definitive, timely diagnosis often relies on imaging like Chest CT (showing signs such as nodules, the halo sign, or cavities) and laboratory tests.[1, 3, 5] Other serological tests, such as Aspergillus IgG or precipitins, are highly reliable for CPA diagnosis, yielding positive results in over 90% of patients. For IPA, biomarkers such as galactomannan in serum or bronchoalveolar lavage (BAL) and beta-D-glucan (although less specific) are recommended. PCR assays detecting Aspergillus DNA in respiratory fluids are also valuable in conjunction with other tests and can help identify antifungal resistance.[6] Utilizing a combination of features, imaging, and mycological evidence significantly enhances diagnostic accuracy, enabling earlier initiation of treatment and potentially decreasing the high mortality associated with these infections. In this case series, we emphasize the importance of integrating clinical findings with radiological and microbiological data for accurate and timely diagnosis of pulmonary aspergillosis.

2. Case Presentation

Case 1

A 64-year-old male patient who has a known case of COPD and old PTB 35 years back. Known case of hypertension (HTN), coronary artery disease (CAD), and a history of COVID-19 infection. He came with h/o productive cough with purulent sputum, breathlessness, and hemoptysis for 1 week. No

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other cardiorespiratory symptoms. O/E vitals were stable. On respiratory system examination, bilateral crepitations were present. Other systemic examinations were normal. Chest x-ray was taken and showed hyperinflated lung fields with a right upper zone fibrocavitary lesion. The patient's sputum was sent for C/S and KOH, and the patient was started on antibiotics. HRCT thorax was taken, and it showed a 43 mm-sized aspergilloma in the right upper lobe fibrotic cavity. A bronchoscopy was done, and BAL was sent for investigation. KOH mount was negative in both sputum and BAL. Aspergillus flavus was grown in both BAL and sputum. The patient was started with antifungal Voriconazole, became symptomatically better, and was discharged with medication.

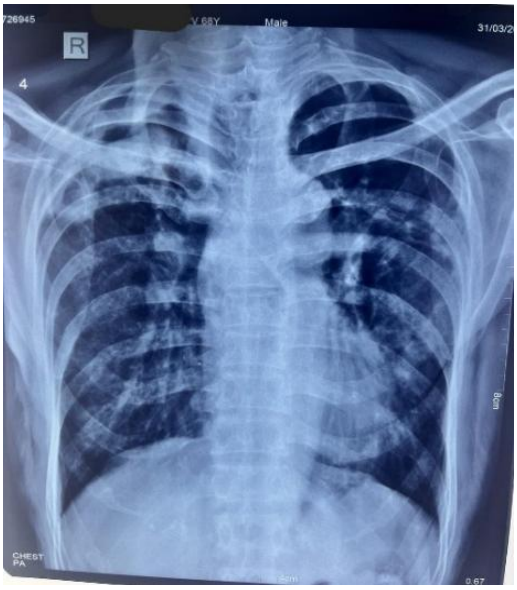

Fig. 1. Xray finding showing hyperinflated lung fields with right upper zone fibro cavitary lesion.

Case 2

A 72-year-old female who is a known case of bronchial asthma, diabetes, HTN, and chronic kidney disease presented with a gradual onset of breathlessness for 3 days. An associated cough was present. No h/o PND, orthopnea. O/E patient had tachypnoea and tachycardia. Respiratory system examination showed b/l rhonchi. Other systemic examinations were normal. A chest x-ray was taken, which showed b/l infiltrates. The patient was admitted and started on antibiotics and supportive measures. Sputum was sent for investigation. CT was taken, which showed multiple centrilobular and few random nodules in the right upper, middle, and lower lobe segments. Sputum KOH examination revealed fungal filaments and the culture yielded Aspergillus fumigatus. The patient was started with the antifungal Voriconazole. The patient became symptomatically better and was discharged with medication.

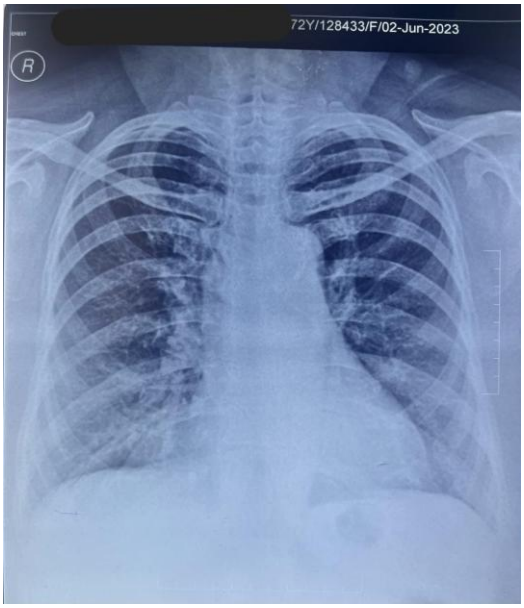

Fig. 2. Xray finding showing bilateral infiltrates.

Case 3

A 40-year-old male presented with abdominal pain, nausea and vomiting, and cola-colored urine. He was a known case of uncontrolled T2DM, diabetic bullosis, and hypothyroidism on medication. Upon examination, the patient presented with a fever and epigastric pain. The respiratory examination showed mild b/l crepitations and reduced breath sounds in the left interscapular region. Chest x-ray showed bilateral fluffy infiltrates in the lungs. USG showed gall bladder calculus. Bronchoscopy was done, and BAL culture grew Aspergillus flavus. Sputum was sent for KOH and culture, but the results were negative. NCCT thorax showed multiple scattered pulmonary nodules with a tree-bud pattern with areas of peribronchovascular thickening and consolidation, and the patient was diagnosed with fungal pneumonia. He was put on Itraconazole. Later on, the patient had an electrolyte imbalance, which was corrected, but there was a sudden drop in saturation levels, and despite intensive measures, he succumbed to death.

Fig. 3. Xray finding showing bilateral fluffy infiltrates in lungs.

Case 4

A 72-year-old male presented with increased breathlessness and cough. He had a known case of COPD and T2DM. On examination, b/l rhonchi was present, and chest x-ray showed bilateral infiltrates. Sputum was sent for culture, which isolated Aspergillus fumigatus, but in KOH mount, no fungal filaments were seen. He was started on Itraconazole. The patient got improved and was discharged.

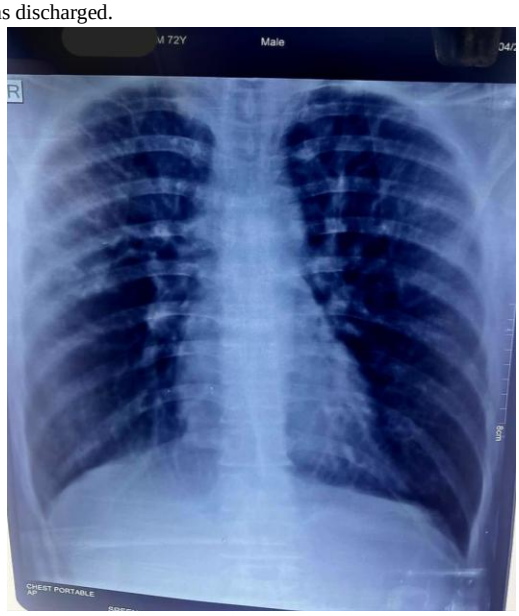

Fig. 4. Xray finding showing bilateral infiltrates.

Case 5

A 50 A 50-year-old male presented with fever and cough with left-sided chest pain. He reported a history of occupational exposure to dust. He was a known case of T2DM on ayurvedic medication. The chest x-ray showed a left upper zone nonhomogeneous opacity with a cavitary lesion. Sputum culture yielded Aspergillus niger. Sputum AFB was positive (3+), and he was started on ATT and antifungals and improved symptomatically.

Fig. 5. Xray finding showing non-homogenous opacity (Left upper zone) with cavitary lesion.

Case 6

A 68-year-old female presented with cough, breathlessness, and wheezing for 2 weeks with h/o fever. K/c/o T2DM not on medication. On examination, b/l crepitations and rhonchi were present in the left intrascapular region. Chest x-ray showed increased broncho vascular markings with right lower zone infiltrates. In sputum, KOH fungal filaments were seen, and the culture yielded Aspergillus flavus. The patient was started on Itraconazole, became symptomatically better, and was discharged.

Fig. 6. X-ray finding showing increased broncho vascular markings with right lower zone infiltrates.

Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger exhibit characteristic colony morphologies on culture. A.fumigatus produces blue-green, velvety colonies with a white periphery; A.flavus forms yellow-green, granular colonies; and A.niger displays black, powdery colonies with a pale reverse. These features aid in preliminary species identification in the laboratory. (Fig. 7).

Fig. 7. Culture growth of a) Aspergillus fumigatus, b) Aspergillus flavus, c) Aspergillus niger obtained from cases discussed above.

Table 1. Compilation of findings of different diagnostic modalities of all cases discussed.

No. Case	Chest Xray	Sputum KOH	Sputum C/S	CT Thorax	BAL Fluid	BAL C/S
Case 1	Hyperinflated lung fields with right upper zone fibro cavitary lesion	No fungal filaments were seen	Aspergillus flavus grown in culture	Aspergilloma in right upper lobe fibrotic cavity.	No fungal filaments were seen	Aspergillus flavus grown in culture
Case 2	Bilateral Infiltrates	Fungal filaments seen	Aspergillus Fumigatus grown in culture	Multiple centrilobular and few random nodules in the right upper, middle, and lower lobe segments.	-----	-----
Case 3	Bilateral fluffy infiltrates in the lungs	No fungal filaments were seen	-----	Multiple scattered pulmonary nodules (tree-in-bud pattern) with areas of peribronchial vascular thickening and consolidation.	No fungal filaments were seen	Aspergillus flavus grown in culture
Case 4	Bilateral infiltrates	No fungal filaments were seen	Aspergillus fumigatus grown in culture	Nil	Nil	Nil
Case 5	Non-homogenous opacity (Left upper zone) with cavitary lesion	No fungal filaments were seen	Aspergillus niger grown in culture	Nil	Nil	Nil
Case 6	Increased broncho vascular markings with right lower zone infiltrates.	Fungal filaments were seen	Aspergillus flavus grown in culture	Nil	Nil	Nil

3. Discussion

Aspergillus species are ubiquitous saprophytic fungi that inhabit soil, decaying vegetation, and organic debris. They can cause a wide range of pulmonary diseases, from allergic bronchopulmonary aspergillosis to invasive and chronic infections. Among these, Chronic Pulmonary Aspergillosis (CPA) is a progressive, destructive lung disease predominantly caused by Aspergillus fumigatus. Other commonly isolated species include Aspergillus flavus and Aspergillus niger.[6] The development of CPA is influenced more by the host's immune status, especially in individuals with underlying lung pathology or mild immunosuppression, than by the duration of fungal exposure. Accurate diagnosis of CPA poses a considerable challenge due to its non-specific symptoms and radiological overlap with other chronic pulmonary diseases, particularly pulmonary tuberculosis (TB). Both conditions can present with chronic cough, hemoptysis, weight loss, and cavitary lung lesions, often leading to misdiagnosis and delayed or inappropriate treatment in TB-endemic regions.[6, 7] Our findings highlight the importance of a comprehensive diagnostic approach that integrates clinical evaluation, radiological imaging, and microbiological investigations. While microscopy, including KOH mounts and special stains, provides rapid and cost-effective preliminary insight, it lacks the specificity required for a definitive diagnosis. Hyphae resembling Aspergillus seen in respiratory samples may indicate colonization rather than active disease due to the ubiquity of these fungi. Furthermore, microscopy cannot differentiate between Aspergillus species, which limits its utility in guiding antifungal therapy.[3, 4, 6] Culture-based diagnostic methods remain the gold standard for species-level identification and confirmation of active infection. The ability to reisolate the same Aspergillus species from serial specimens strengthens the evidence of pathogenicity and distinguishes colonization from invasive disease.[1, 6] Importantly, species identification is crucial for selecting appropriate antifungal treatment, as different species vary in antifungal susceptibility.[1] In our case series, we observed that sending only microscopy without concurrent culture often resulted in diagnostic ambiguity. This reflects a common clinical practice but can lead to missed opportunities for timely and accurate diagnosis. Our findings are consistent with studies by Patterson et al. and Denning et al., which emphasize the limitations of microscopy alone and recommend routine culture as part of the diagnostic workup.[4, 5] Although sputum cultures may exhibit low positivity rates, possibly due to a small sample volume, poor fungal viability in vitro, or overgrowth by bacterial flora, they still play a pivotal role in CPA diagnosis.[3] Bronchoscopic specimens, including bronchoalveolar lavage (BAL), offer improved yield for fungal cultures and are more indicative of infection than sputum samples alone.[5] Hence, obtaining the appropriate sample type is essential for maximizing diagnostic sensitivity. Furthermore, histopathological confirmation, when feasible, can provide valuable evidence of tissue invasion. Our findings align with international recommendations, particularly those from the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM), which advocate for a triad of direct microscopy, culture, and histopathology for diagnosing invasive and chronic aspergillosis.[1, 3] In resource-limited settings, optimizing available diagnostic tools and promoting awareness of CPA is crucial to avoid misdiagnosis as TB and to improve treatment outcomes. This case series highlights the importance of integrating clinical, radiological, and microbiological findings for the accurate diagnosis of CPA. While microscopy offers quick preliminary information, it lacks specificity and is not suitable for species-level identification. Our experience reinforces that culture should be routinely performed alongside microscopy to confirm active infection, identify the causative species, and guide appropriate antifungal therapy. Misdiagnosis of CPA as TB remains a significant concern, particularly in endemic regions, emphasizing the need for heightened clinical suspicion and robust diagnostic protocols. The implications of our findings support previous research and underscore the importance of culture-based methods in enhancing diagnostic accuracy and patient outcomes in CPA.

4. Conclusion

Opportunistic fungal infections, such as those caused by Aspergillus species and mucormycosis, are most commonly associated with immunocompromised patients, including those with diabetes, haematological malignancies, transplant recipients, and neutropenia. Microscopy can be used as an important initial step in evaluating suspected pulmonary aspergillosis; however, culture remains the cornerstone of diagnosis. Enhanced culture methods could improve the detection rates, which significantly affect treatment planning. Clinicians must be aware of the limitations of microscopic methods alone, which could lead to misdiagnosis, particularly in cases with overlapping clinical presentations. This requires a comprehensive approach that incorporates clinical, radiological, and microbiological findings for the accurate diagnosis and management of pulmonary aspergillosis.

Conflict of Interest

The authors declared that there is no conflict of interest.

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