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Persistent Fever and Urinary Hyphae as Diagnostic Clues to Aspergillosis: A Case Report

Dr. Manuel Rodriguez Navarro[1], Dr. Anthony Azael Lopez Rosas[2], Maria Del Rayo Mendez Palacios[3], Dil Gousha E Zainab[4], Aimen Zahra[5], Dr. Alejandra Merida Gonzalez[6], Yamil Fidel Caballero Bautista[7]

[1,2,6]Hospital Regional ISSSTE Puebla

[3,4,5]Universidad Popular Autónoma del Estado de Puebla

[7]Benemérita Universidad Autónoma de Puebla

ABSTRACT

Invasive aspergillosis is an opportunistic fungal infection that is frequently underdiagnosed, especially in critically ill or immunocompromised patients. This case involves a 45-year-old woman with no relevant medical history who developed persistent fever, respiratory symptoms, and hemodynamic instability. Despite receiving multiple antibiotic regimens, no clinical improvement was observed. The detection of hyphae and conidia in the urinalysis during hospitalization directed the diagnostic approach toward deep aspergillosis—a rare but significant finding. The patient exhibited septic shock with urinary and pulmonary foci, acute type 1 respiratory failure, severe thrombocytopenia, hypokalemia, and bilateral pleural effusion. Broad-spectrum antifungal treatment and intensive supportive care were administered. This case underscores the need to consider fungal etiologies in patients with fever of unknown origin, particularly when atypical clinical and laboratory findings suggest an invasive mycotic infection.

KEYWORDS: Invasive aspergillosis, fever of unknown origin, hyphae in urine, systemic fungal infection, septic shock.

ARTICLE DETAILS

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I. INTRODUCTION

Aspergillosis is an opportunistic fungal infection caused by species of the Aspergillus genus—hyaline, septate filamentous fungi commonly present in the environment. Aspergillus fumigatus is the most frequently implicated species in human infections, although others such as A. flavus, A. niger, and A. terreus may also cause disease. These spores are inhaled daily and typically pose no threat to immunocompetent individuals. However, in immunocompromised hosts, they can trigger severe infections, often resulting in high mortality.[1,2]

Aspergillosis encompasses a broad clinical spectrum, ranging from superficial colonization and allergic reactions to invasive and life-threatening infections. Allergic bronchopulmonary aspergillosis (ABPA) is commonly seen in patients with asthma or cystic fibrosis, while invasive pulmonary aspergillosis (IPA) occurs in individuals with prolonged neutropenia, hematologic malignancies, solid organ or stem cell transplants, and those receiving immunosuppressive therapy.[2,3] The invasive form may rapidly progress, causing pulmonary involvement and systemic dissemination to the brain, kidneys, gastrointestinal tract, or heart, with reported mortality rates exceeding 90%.[3, 4]

Diagnosing invasive aspergillosis remains a significant challenge. Despite the availability of advanced diagnostic tools such as imaging, galactomannan antigen detection, and PCR-based techniques, clinical diagnosis is often complicated by nonspecific symptoms, high colonization rates of the respiratory tract, and the possibility of false positives.[5] Definite diagnosis often requires histopathological evidence, which may not always be feasible in critically ill patients.[6] In this context, the detection of fungal elements in non-traditional specimens such as urine—though rare—can be crucial in guiding timely diagnosis and treatment.[7]

Moreover, the incidence of invasive aspergillosis has increased in non-classically immunocompromised populations, including those with chronic pulmonary diseases

(e.g., COPD, bronchiectasis, prior tuberculosis), diabetes, cirrhosis, or critically ill patients with prolonged hospital stays.[2,4] Chronic forms such as aspergilloma and chronic necrotizing pulmonary aspergillosis, though slower in progression, may also lead to severe complications and require early clinical suspicion, especially when complicated by hemoptysis or superimposed infections.[1,6]

This case report aims to emphasize the importance of detailed clinical evaluation in patients with persistent fever of unknown origin. It highlights how the identification of fungal hyphae in a routine urinalysis provided a pivotal diagnostic clue for deep aspergillosis, prompting the early initiation of antifungal therapy. Such rare findings can significantly alter outcomes in critically ill patients.

II. CASE REPORT

This case involves a 45-year-old female patient, with a background in education and no relevant chronic or surgical medical history, who presented to the emergency department with a month-long history of persistent fever of unknown origin. Initial symptoms included dry cough, mild dyspnea, and non-cyanotic episodes, later accompanied by intermittent fevers, fatigue, and general malaise. The patient reported an 8 kg weight loss over 45 days and had previously received various outpatient antibiotic regimens without improvement.

Upon admission, the patient showed signs of hemodynamic instability with hypotension (84/48 mmHg), tachycardia, fever (38.5°C), and somnolence. A focused physical examination revealed bilateral apical pulmonary crackles, mild pleural effusion, somnolence, altered mental status, and hypoventilation at pulmonary bases. A SOFA score of 10 was recorded, indicating severe multi-organ dysfunction.

Preliminary studies demonstrated normocytic normochromic anemia (Hb 10.2 g/dL), severe thrombocytopenia (33,000/mm³), leukocytosis, and hypokalemia (K+ 1.9 mmol/L). Urinalysis showed moderate proteinuria, leukocyturia, and microscopic hematuria, with presence of fungal elements (hyphae and conidia), raising suspicion of a systemic fungal infection. Imaging (CT) revealed bilateral pleural effusion, diffuse interstitial thickening, and left apical pulmonary condensation. A presumptive diagnosis of deep pulmonary aspergillosis was made.

III. METHODS

The Upon hospital admission, the patient was placed under continuous monitoring, including pulse oximetry and cardiac telemetry. Due to her unstable condition, she was admitted to the internal medicine service under absolute rest, receiving oxygen supplementation and strict hemodynamic surveillance. Initial management included broad-spectrum antibiotics (Meropenem 1g IV every 8 hours), antifungal therapy (Fluconazole 600mg IV every 24 hours), antipyretics (Metamizole), and correction of severe hypokalemia using IV potassium chloride.

A central venous catheter was placed for vasopressor infusion (norepinephrine) and fluid therapy. Daily laboratory evaluations were ordered, and diagnostic studies included blood cultures, urinalysis, procalcitonin, and chest CT imaging. Given the presence of fungal structures in the urine and pulmonary findings, systemic aspergillosis was suspected.

The patient remained in a semi-Fowler position, with hydration monitored closely through fluid balance charts. Naproxen was administered as part of a diagnostic test to assess fever response and rule out paraneoplastic or inflammatory fever. Additional tests, including tumor markers and autoimmune profiles, were requested. Internal medicine consultation was sought for comprehensive evaluation.

Since imaging findings already indicated a potential aspergillosis, it is essential to support the diagnosis with microbiological and histopathological tests. Sputum or bronchoalveolar lavage cultures and serum antigen detection such as galactomannan offer valuable diagnostic clues. Histopathological confirmation relies on specific stains like Grocott's methenamine silver stain and periodic acid–Schiff (PAS), which highlight the characteristic septate and branching hyphae of Aspergillus spp. These diagnostic tools are crucial for definitively establishing the infection and initiating appropriate treatment, especially in immunocompromised patients [7].

IV. RESULTS

In During the first hours of hospitalization, the patient remained clinically unstable. Despite fluid resuscitation with crystalloids and vasopressor support (norepinephrine), hypotension (SBP < 90 mmHg), tachycardia (HR > 110 bpm), and hyperthermia (38.5°C) persisted. She was somnolent and intermittently combative, with a fluctuating level of consciousness that hindered complete neurological evaluation. The presence of a positive Kernig sign raised concern for possible meningeal involvement.

Respiratory evaluation revealed apical bilateral crackles and hypoventilation at the lung bases. Oxygen saturation ranged between 92–94% with a FiO_2 of 36%. The abdomen was distended due to panniculus adiposus but soft and depressible, with discomfort on palpation in the colonic area, although without signs of peritoneal irritation. Her skin showed diaphoresis, and mucous membranes were dry.

Lab tests revealed persistent severe thrombocytopenia (33,000/mm³), normocytic normochromic anemia (Hb 10.2 g/dL), neutrophilic leukocytosis (WBC 16.4 x10⁹/L, NEU 15,800/µL), elevated CRP (192 mg/L), and ESR (36 mm/hr). Severe hypokalemia (K^+ 1.9 mmol/L) was corrected with IV potassium. Liver and kidney functions were preserved.

Urinalysis was notable for moderate proteinuria, leukocyturia, microscopic hematuria, and moderate presence of fungal elements (hyphae and conidia), suggestive of systemic mycosis. Chest CT imaging revealed bilateral pleural effusions, diffuse interstitial thickening, and apical consolidation in the left lung, compatible with probable invasive pulmonary aspergillosis.

Despite initiation of broad-spectrum antibiotics (Meropenem), antifungals (Fluconazole), and supportive therapy, the patient showed limited clinical improvement. The naproxen test for neoplastic fever was non-reactive. Given her neurological deterioration, persistent fever, and respiratory compromise, the prognosis was considered guarded.

After 48 hours of close observation in the internal medicine service and stabilization of hemodynamic parameters with minimal vasopressor support, the patient was referred to a regional hospital with an intensive care unit for specialized management, including mechanical ventilation support, targeted antifungal therapy, and advanced diagnostic studies.

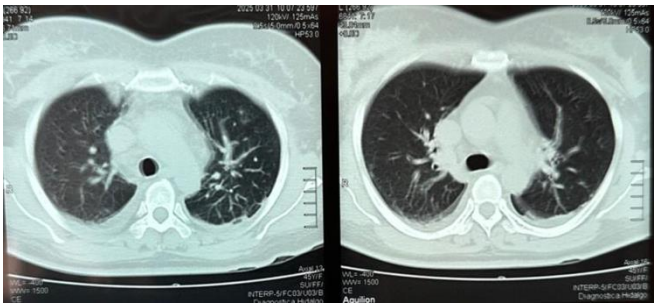

Figure 1. Axial chest CT scan reveals multiple bilateral pulmonary nodules with surrounding ground-glass opacities—commonly referred to as the "halo sign"—more prominent in the upper lobes. These findings are highly suggestive of invasive pulmonary aspergillosis in an immunocompromised host. No pleural effusion is noted.

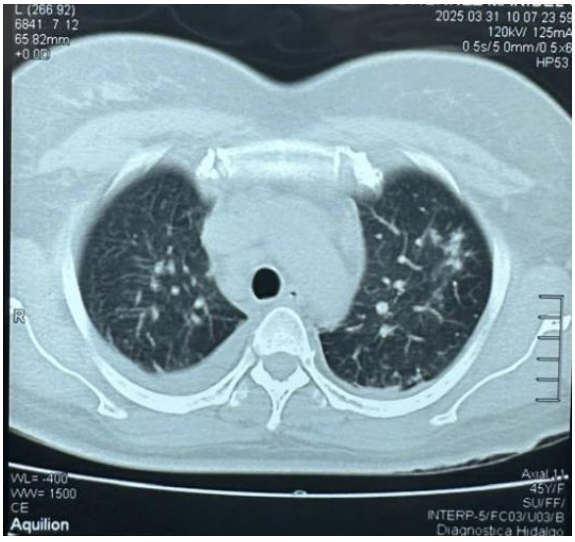

Figure 2. Additional axial CT views demonstrate areas of heterogeneous consolidation and thickening of the bronchovascular bundles, in the absence of cavitation. This bronchopneumonic pattern aligns with early angioinvasive aspergillosis.

V. DISCUSSION

Invasive pulmonary aspergillosis (IPA) is a life-threatening opportunistic infection that predominantly affects immunocompromised patients, especially those with prolonged neutropenia, hematologic malignancies, or who are undergoing immunosuppressive therapies. The respiratory tract is the main entry point, with the fungus exploiting weakened host defenses. Once the conidia are inhaled, and if macrophages and neutrophils fail to contain the infection, Aspergillus can invade tissue and disseminate hematogenously, often involving the brain, kidneys, or gastrointestinal tract [7].

The clinical presentation of IPA is often nonspecific and insidious, which complicates timely diagnosis. Symptoms like persistent fever, cough, and dyspnea are commonly observed, mimicking bacterial pneumonias or tuberculosis. In this case, the detection of fungal structures in urine, associated with bilateral pulmonary infiltrates and pleural effusion on CT imaging, strongly supported the diagnosis of invasive aspergillosis. Similar radiological patterns—such as nodules with halo signs, ground-glass opacities, and areas of consolidation—are well documented in early IPA, particularly in neutropenic patients [1,3,6].

Timely diagnosis remains a challenge. While fungal cultures and direct microscopic examination can be helpful, they are often nonspecific due to the frequent environmental contamination by Aspergillus species. The detection of galactomannan antigen in serum or bronchoalveolar lavage fluid has shown good sensitivity, especially in hematology patients, although histopathological confirmation with evidence of hyaline, septated hyphae remains the diagnostic gold standard [2,5].

Aspergillus species, particularly A. fumigatus, are ubiquitous environmental fungi that can colonize pulmonary cavities, especially in patients with structural lung disease. Chronic forms such as aspergilloma and necrotizing chronic aspergillosis may occur in individuals with COPD or a history of tuberculosis. These forms may remain stable or progress, occasionally leading to massive hemoptysis and respiratory compromise [4,6,7].

Given the patient’s deteriorating condition and the high suspicion of systemic fungal infection, timely referral to an intensive care unit was crucial. Early antifungal therapy, supportive care, and possibly adjunct diagnostic techniques (e.g., high-resolution CT, antigen assays) are essential to improve outcomes in patients with suspected IPA [3,6].

CONCLUSIONS

This case exemplifies the diagnostic and therapeutic challenges posed by invasive aspergillosis, a severe fungal infection with high mortality, especially in vulnerable

populations. Traditionally associated with profound immunosuppression—such as hematologic malignancies, neutropenia, and organ transplantation—recent evidence shows that invasive aspergillosis is increasingly affecting patients outside the classical risk groups. This includes individuals with chronic pulmonary conditions, malnutrition, diabetes, and those experiencing prolonged hospitalizations or critical illness, as was observed in the present case.

Although the patient did not present with neutropenia or known immunosuppressive conditions, her progressive clinical deterioration, persistent fever, and radiological evidence of pulmonary compromise raised suspicion for an underlying systemic infection. The presence of fungal hyphae and conidia in a routine urinalysis, although unusual, served as an important diagnostic clue that shifted the focus toward a systemic mycosis—likely invasive aspergillosis. While urine is not a standard specimen for diagnosing aspergillosis, in critically ill patients, such findings can be of high clinical relevance, particularly when traditional diagnostic tools such as bronchoscopy or biopsy are contraindicated due to instability.

Early initiation of empirical antifungal therapy with fluconazole, in conjunction with broad-spectrum antibiotics and hemodynamic support, likely contributed to the temporary stabilization of the patient's condition. Although definitive diagnosis was not established via histopathology or galactomannan antigen detection, the clinical, radiological, and microbiological context supported the diagnosis and justified early intervention. The patient's transfer to a regional hospital with intensive care capabilities was a crucial step in ensuring the continuity of advanced care, including respiratory support, further diagnostic evaluation, and tailored antifungal management.

This case also illustrates the pivotal role of interdisciplinary collaboration, timely decision-making, and flexible diagnostic reasoning. When faced with atypical presentations of common pathogens or rare presentations of severe infections, clinicians must consider a broad differential diagnosis and interpret non-traditional findings within the larger clinical picture. The utility of incidental findings—such as fungal elements in urine—should not be underestimated, particularly when they align with systemic manifestations and imaging results.

Furthermore, this report highlights the growing need for awareness of fungal infections in the context of global shifts in patient profiles. Factors such as antibiotic overuse, rising rates of diabetes, increased ICU admissions, and expanding populations with chronic respiratory diseases contribute to the changing epidemiology of aspergillosis. Enhancing early recognition of subtle or atypical signs, promoting access to rapid diagnostics, and ensuring timely antifungal treatment can significantly influence prognosis and reduce mortality in patients with suspected invasive fungal infections.

In conclusion, this case reinforces the importance of maintaining a high index of suspicion for invasive aspergillosis—even in non-traditional hosts—and demonstrates how timely diagnostic orientation and early treatment can alter clinical trajectories. It also underscores the need for continued education, diagnostic innovation, and integrated care strategies to confront the expanding burden of invasive fungal infections in both immunocompromised and critically ill patient populations.

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