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Diagnostic Mimicry: Invasive Aspergillosis Masquerading as Pulmonary Tuberculosis in a Patient with Chronic Granulomatous Disease

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Abstract

A 4.5-year-old boy was admitted to the hospital with a history of three weeks of fever, cough, and weight loss. He was initially started on empiric treatment for community-acquired pneumonia. Suspicion of tuberculosis led to the addition of anti-tuberculosis therapy. However, his condition further deteriorated, warranting persistent investigations. Chronic granulomatous disease (CGD) and pulmonary aspergillosis were confirmed in the patient by various laboratory tests. He responded quite well to a combination antifungal therapy including liposomal amphotericin B and voriconazole. This case emphasizes that CGD should be considered in patients with recurrent infections caused by opportunistic pathogens.

The current study shows that invasive aspergillosis in CGD can radiologically resemble tuberculosis, which may result in delayed diagnosis. It also demonstrates the effectiveness of rapid diagnostic methods, such as galactomannan and DHR flow cytometry, in resource-limited environments.

Key Words: Chronic Granulomatous Disease, Invasive aspergillosis, Pediatric Immunodeficiency, NADPH Oxidase.

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1- INTRODUCTION

Chronic Granulomatous Disease (CGD) is a rare, inherited immunodeficiency disorder that significantly compromises the ability of phagocytes (a type of white blood cell) to destroy pathogens (1). The underlying pathology of CGD involves mutations in the NADPH oxidase complex. A substance crucial for the generation of reactive oxygen species that phagocytes use to diminish ingested microbes (2). As a result, the susceptibility to bacteria and fungi increases, leading to recurrent and severe infections, often presenting early in childhood. CGD mostly passes through generations in an X-linked pattern. However, autosomal recessive forms of the disease are also reported (3).

Several infections are associated with CGD. However, some of these infections cause high mortality rates. Among these fatal pathogens are the Aspergillus species, especially Aspergillus fumigatus (4). This class of opportunistic pathogens can cause severe pulmonary symptoms in immunocompromised individuals, including those with CGD (5). In the absence of prompt and aggressive treatments, these infections rapidly progress and lead to a considerable number of fatalities. The mortality rate due to Aspergillus infection has declined over time. Reducing from 30 to below 20 (6, 7). Despite this reduction, pulmonary infection due to Aspergillus remains the leading cause of mortality among all infectious diseases in CGD patients (8).

Patients with CGD are especially susceptible to recurrent bacterial infections, including those caused by catalase-positive organisms such as Staphylococcus aureus and Serratia marcescens, in addition to fungal infections (7, 9). These infections commonly affect the lungs, skin, lymph nodes, and liver, with granuloma formation being a characteristic feature of the disease (9). Granuloma formation is the result of an extravagantly activated immune response. While they serve as a protective barrier against infection, their presence in certain organs (like the gastrointestinal or genitourinary tracts) can lead to complications such as obstruction (10, 11).

A high degree of suspicion, especially in children with recurrent or unusual infections, is required for CGD diagnosis. Two major diagnostic tools for CGD are the nitroblue tetrazolium (NBT) test and dihydrorhodamine (DHR) flow cytometry. Both tools are designed to assess the oxidative burst activity of neutrophils (12). Patients with CGD present with absent or significantly reduced respiratory burst activity (13). Genetic testing is also used to confirm the diagnosis and identify the specific mutations involved (3).

CGD management includes both prophylactic and therapeutic interventions. The use of long-term antibiotic prophylaxis, antifungals, and interferon-gamma is a major preventive strategy for infection prevention. In patients with severe CGD, hematopoietic stem cell transplantation (HSCT) could offer a solution to cure the disease by replacing the defective immune system with healthy donor cells (14). However, the success of HSCT depends on factors such as donor match, patient age, and disease severity at the time of transplantation (15, 16).

In this report, we aimed to highlight the challenges faced by physicians in the diagnosis and management of pediatric CGD patients. Here, we report the case of a toddler with CGD who presented with invasive aspergillosis, which was mistakenly diagnosed as tuberculosis. This case underscores the importance of early detection of immune-system disorders like CGD in patients with recurrent infections or unusual pathogens. It also emphasizes the importance of the need for aggressive treatment strategies to improve outcomes.

2- CASE PRESENTATION

A 4.5-year-old Iraqi boy was admitted to the hospital with complaints of fever, night sweats, cough, decreased oxygen saturation (SpO_2), dyspnea, persistent cough, chest pain and weight loss for three weeks' duration. The child had not been previously hospitalised or suffered from recurring infections. His younger brother also suffered from similar complaints and was receiving outpatient treatment. Family history revealed parental consanguinity. The patient had a documented drug sensitivity to penicillin. On presentation, the child had been treated for asthma with fluticasone, salbutamol, ketotifen, and acetaminophen. Physical examination showed a feverish, lethargic child with bilateral crackles on lung auscultation, and no lymphadenopathy or organomegaly was noted. Initial hematology tests showed leukocytosis (WBC: 23.4 x 10^9/L), anemia (Hb: 10 g/dL), thrombocytosis (PLT: 807 x 10^9/L), and elevated inflammatory markers (CRP: 174 mg/L, ESR: 64 mm/hr) blood culture negative, AST: 22.4 u/l, ALT:17.4 u/l, TB PCR negative, Acid fast stain negative, Urea:16 mg/dl, Creatinine: 0.4 mg/dl. A chest X-ray was done, which raised suspicion of pneumonia, and treatment for community-acquired pneumonia was initiated. Radiological findings were clarified as patchy consolidation and diffuse, scattered ground-glass opacities. The CT-Scan obtained from the lungs and mediastinum reported the presence of centrilobular nodules with a tree-in-bud pattern and random distribution in a confluent form in the lung field, suggestive of miliary tuberculosis, fungal infections, and bronchopneumonia. Brain CT-Scan and abdominopelvic sonogram showed no abnormal findings. Despite being asymptomatic, the patient underwent brain CT, abdominal and pelvic ultrasonography, skin examination, and echocardiography, all of which showed no significant abnormalities and revealed no evidence of extrapulmonary involvement.

Given the geographic origin and clinical presentation of the patient, suspicion for TB arose, and anti-TB therapy with four drugs was started. Gastric aspiration and PPD tests were also performed, but without evidence of TB. The condition of the patient continued to worsen despite treatment: there was persistent fever, and respiratory distress increased. Immunological investigations on the fourth day of hospitalization revealed an absence of NADPH oxidase activity, as evidenced by a 0% NBT test and 0.2 DHR test result, and chronic granulomatous disease was diagnosed. Given the potential for opportunistic infections, antifungal therapy with liposomal amphotericin B was administered, along with investigations for the diagnosis of aspergillosis. Aspergillus-PCR and smears were positive from blood and gastric aspirates; serum galactomannan was also raised to 39.1. This, however, is a serious infection; on improvement with a combination of amphotericin B and voriconazole, the patient was discharged after two weeks of therapy in a stable condition. The patient received 2 weeks of intravenous antifungal therapy followed by 6 months of oral voriconazole. His younger brother, who had similar complaints, was also diagnosed with CGD and started treatment for aspergillosis.

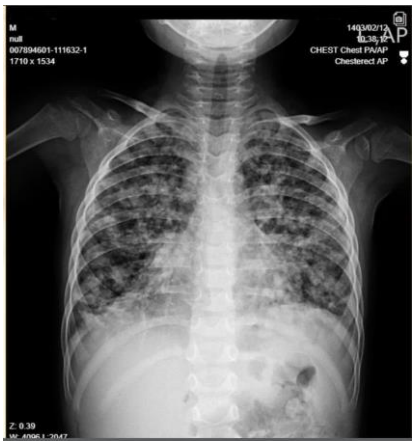

Figure-1: Patient's radiography image.

3- DISCUSSION

CGD is a rare inherited immunodeficiency caused by defects in the NADPH oxidase complex, resulting in impaired respiratory burst and increased susceptibility to recurrent bacterial and fungal infections, especially invasive aspergillosis (17). Among fungal pathogens, Aspergillus fumigatus is the most common cause of invasive disease in CGD, although other species such as A. nidulans and A. terreus have also been reported (17). CGD is often diagnosed in early childhood, but delayed recognition may occur, particularly in patients who present with atypical or recurrent pulmonary disease (17, 18).

The present case is notable because invasive pulmonary aspergillosis initially mimicked asthma and then pulmonary tuberculosis. This diagnostic overlap is clinically important in regions where tuberculosis is prevalent, since constitutional symptoms such as fever, weight loss, and chronic cough, together with nonspecific chest imaging, can strongly suggest TB. However, radiologic findings of invasive aspergillosis may also be nonspecific. Branching centrilobular nodules and tree-in-bud opacities are classically associated with infectious bronchiolitis and endobronchial spread, but they are not specific for tuberculosis and may also be seen in airway-centered invasive aspergillosis (17, 19, 20). Therefore, imaging alone may be insufficient to distinguish these entities.

This case also highlights the importance of considering an underlying immunodeficiency in any child with persistent or unusual pulmonary infection. In our patient, the family history, parental consanguinity, and severe recurrent respiratory symptoms raised suspicion for a primary immune disorder. Confirmation by abnormal NBT and DHR testing was crucial. DHR remains the most widely used screening test for CGD because it is a rapid flow-based assay that assesses oxidative burst function in neutrophils (21). When available, it is generally preferred over NBT because of greater sensitivity and practicality (21, 22).

Early fungal diagnostic testing was also essential in this case. Serum galactomannan and Aspergillus PCR supported the diagnosis of invasive aspergillosis and helped guide timely antifungal therapy. In immunocompromised hosts, galactomannan is an important adjunctive diagnostic marker, especially when interpreted together with clinical findings and compatible CT abnormalities (23, 24). In our patient, the combination of liposomal amphotericin B followed by voriconazole led to clinical improvement, which is consistent with current recommendations for invasive aspergillosis management (24).

Another important point is the need for family evaluation and genetic counseling. The diagnosis of CGD in the patient's brother suggests an inherited disorder and reinforces the value of screening siblings in families with a suggestive history. Early recognition of affected family members may reduce delay in diagnosis and improve outcomes (17, 18).

Overall, this case demonstrates that invasive aspergillosis in a child with CGD may closely resemble asthma or tuberculosis. In children with persistent pulmonary symptoms, poor response to standard therapy, or family history of immunodeficiency, clinicians should maintain a high index of suspicion for both CGD and invasive fungal infection. Early immunologic testing and fungal workup are essential to avoid diagnostic delay and initiate appropriate treatment.

4- CONCLUSION

This case highlights that invasive aspergillosis in children with chronic granulomatous disease may mimic asthma or tuberculosis and lead to delayed

diagnosis. In children with persistent pulmonary symptoms, poor response to standard therapy, or suggestive family history, clinicians should consider both underlying immunodeficiency and invasive fungal infection. Early immunologic testing and fungal diagnostic evaluation are essential for timely treatment and improved outcomes.

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