CASE REPORT

Invasive Pulmonary Aspergillosis and Nocardiosis in a Child with Possible Hyperimmunoglobulin E Syndrome

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ABSTRACT

Aim and objective: To highlight the importance of looking for rare opportunistic as well as coinfections in children with primary immunodeficiency.

Background: Opportunistic infections are often seen in children with primary immunodeficiency. Infections like nocardiosis and aspergillosis often mimic tuberculosis. So far, a single case of nocardiosis in hyperimmunoglobulin E syndrome (HIES) has been reported but none with coinfection with aspergillosis. Here we report a child with possible HIES presenting with nocardiosis and invasive pulmonary aspergillosis.

Case description: A 3-year-old boy with recurrent abscesses and pneumonia presented to us with persistent fever and cough for 5 months, unresponsive to antitubercular therapy. Considering the suggestive history, characteristic facies, and elevated immunoglobulin E levels, HIES was diagnosed based on the NIH (National Institute of Health)–HIES score. High-resolution CT chest revealed mediastinal lymphadenopathy with right-sided nodular infiltrates and bilateral bronchiectasis. A positive serum galactomannan assay and growth of Aspergillus in bronchoalveolar lavage confirmed invasive aspergillosis. Mediastinal lymph node aspirate showed acid fast bacilli on smear and culture grew Nocardia species.

Conclusion: It is important to look for rare opportunistic as well as coinfections in children with primary immunodeficiency. To the best of our knowledge, ours is the first report of pulmonary aspergillosis and nocardiosis in a child with HIES.

Clinical significance: Albeit much rarer, aspergillosis and pulmonary nocardiosis can be close mimics of tuberculosis. Nonresolving pulmonary symptoms in the immunocompromised host must raise a suspicion of opportunistic infections including nocardiosis as early diagnosis and treatment may alter outcomes.

Keywords: Hyperimmunoglobulin E syndrome, Invasive aspergillosis, Nocardia, Primary Immunodeficiency, Tuberculosis.

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BACKGROUND

Infection with uncommon organisms is the norm in children with primary and secondary immunodeficiencies. As tuberculosis (TB) is still the most common infection in an immunocompromised host, any pulmonary involvement is often treated with antitubercular therapy (ATT). However, infections with other opportunistic organisms like Nocardia and Aspergillus species go untreated as they closely mimic tuberculosis. Although colonization by Aspergillus is common in children with primary immunodeficiency, invasive aspergillosis with nocardiosis coinfection has rarely been reported in this population. So far, a single case of nocardiosis in hyperimmunoglobulin E syndrome (HIES) has been reported but none with coinfection with aspergillosis. Here we report a child with possible HIES presenting with nocardiosis and invasive aspergillosis.

CASE DESCRIPTION

A 3-year-old boy, second born of a third-degree consanguineous marriage, to an apparently healthy couple, presented to us with persisting fever and cough for 5 months, associated with poor weight gain and anorexia. He was already on ATT as his initial gastric aspirate done elsewhere was positive for acid fast bacilli (AFB), though culture did not show growth of Mycobacterium tuberculosis. Mycobacterial PCR by cartridge based nucleic acid amplification test (CBNAAT) was negative. In view of poor response to ATT, he had undergone a mediastinal lymph node aspirate before referral, which was positive for AFB. He had a history of recurrent pneumonia and skin abscesses since 6 months of age, including right testicular abscess requiring orchidectomy at 7.5 kg with multiple healed scars and clubbing. We also noticed a prominent forehead with a fleshy nasal tip. Respiratory examination, the child was pale, dyspneic, and wasted, weighing 7.5 kg with multiple healed scars and clubbing. We also noticed a prominent forehead with a fleshy nasal tip. Respiratory examination revealed bilateral coarse crepitations, more on the right.

Initial investigations showed Hb—8.8 g/dL, TC—32,890/mm³ (N—74.5%, L—22%, E—0.6%). Chest X-ray showed right upper and mid-zone opacity with bilateral infiltrates (Fig. 1). High-resolution CT chest revealed mediastinal lymphadenopathy with right-sided nodular infiltrates and bilateral bronchiectasis (Fig. 2).

The AFB stain and mycobacterial PCR by CBNAAT were repeated on gastric aspirate sample and found to be negative. The bronchoalveolar lavage (BAL) was again negative for TB but grew...
Aspergillus fumigatus. The positive serum galactomannan assay confirmed invasive aspergillosis. Meanwhile, the earlier mediastinal lymph node aspirate done elsewhere, cultured on the Lowenstein Jensen (LJ) medium grew Nocardia species (Fig. 3).

Immunodeficiency evaluation showed negative retrovirus status, normal neutrophil function, and normal lymphocyte subset assay. Serum immunoglobulin estimation revealed IgA—137 mg/dL (27–195 mg/dL), IgG—2107 mg/dL (504–1464 mg/dL), IgM—202 mg/dL (24–210 mg/dL), and IgE >2500 IU/mL (100–200 IU/mL).

Based on the National Institute of Health-Hyper Immunoglobulin E syndrome (NIH-HIES) scoring system, our child had a score of 45, which is 75% of the maximal score in the 3–6 year age group, suggesting a diagnosis of possible HIES.2 Also, our child had a score of 34 on a recent scoring system suggested by Woellner et al. to diagnose HIES with STAT 3 mutations3 (Table 1). Based on the clinical scenario, autosomal dominant HIES was likely. However, due to financial constraints, we could not test for Th17 deficiency and STAT 3 mutation and a diagnosis of possible HIES was made. Considering the respiratory distress and clinical, microbiological, as well as radiological features ascribable to either invasive aspergillosis or pulmonary nocardiosis, we decided to treat both with voriconazole and cotrimoxazole, respectively. The child improved symptomatically with resolution of fever and dyspnea, weight gain, and significant radiological improvement was noted at 3 months’ follow-up (Fig. 4). We had planned to continue treatment for a year. Parents were also counseled for stem cell transplantation.
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after genetic confirmation. Unfortunately, the child was lost to follow-up after 6 months of treatment.

**Discussion**

The HIESs comprise a group of primary immunodeficiency disorders that exhibit markedly elevated IgE levels, recurrent staphylococcal skin abscesses, eczema, and pulmonary infections. Similarly, our child presented with multiple skin abscesses and pulmonary infection. Both autosomal dominant and autosomal recessive forms of the disorder have been described. Most autosomal dominant HIESs (AD-HIESs) have been found to be due to mutations in STAT3. The skin and lung infections in AD-HIES might be a result of deficient Th17 differentiation. Internal abscesses like testicular abscess, seen in our child, have been reported in HIES with STAT3 mutations. Recurrent and severe pulmonary infections are the hallmark of HIES. Aberrant healing following these infections leads to pneumatoceles and bronchiectasis seen in 75% of the patients. These heterogeneous manifestations are often misdiagnosed as tuberculosis in endemic tropical countries. There are many case series from India for HIES wherein atypical features have been highlighted, however, this co-infection pattern is unique and not reported.

The most common causative organism is *Staphylococcus aureus*. However, once there is parenchymal lung disease, infections with fungi, nontuberculous mycobacteria, and Pseudomonas are known to occur. Growth of *Aspergillus fumigatus* from BAL fluid, along with positive serum galactomannan assay, suggested invasive aspergillosis in our child. Vinh et al. described invasive fungal infections, most commonly *Aspergillus* typically occurring in AD-HIES patients with concurrent anatomical lung defects from previous bacterial pneumonias. However, invasive fungal disease typically occurred in the fourth decade of life and only when there were concurrent anatomical lung defects from previous bacterial pneumonias. Invasive aspergillosis at such an early age has rarely been reported earlier.

Nocardiosis is a rare opportunistic disease caused by the actinomycete *Nocardia* spp., mainly affecting the immunocompromised. Pulmonary nocardiosis is the commonest manifestation seen more often in patients with structural pulmonary disease. Clinical presentations include acute, subacute, and chronic pneumonia with radiographic evidence of lobar infiltrates, abscesses, cavities, pleural effusion, or pulmonary nodules, making tuberculosis a close differential. The index child had radiological findings of pulmonary nodules. Direct smears from *Nocardia* show gram-positive, beaded, branching acid fast filaments. These acid-fast filaments can be easily confused with TB bacilli. Mycobacteria do not stain well with Gram stain and aspergillosis coinfections mostly in the immunocompromised and aspergillosis coinfections in them. To the best of our knowledge, ours is the first report of invasive pulmonary aspergillosis and nocardiosis in a child with HIES.

**Conclusion**

As we diagnose more and more children with primary immunodeficiencies, it is important to look for rare opportunistic as well as coinfections in them. To the best of our knowledge, ours is the first report of invasive pulmonary aspergillosis and nocardiosis in a child with HIES.

**Clinical Significance**

This emphasizes the importance of looking for opportunistic as well as coinfections in children with primary immunodeficiencies. Albeit much rarer, aspergillosis and pulmonary nocardiosis can be close mimics of tuberculosis. Nonresolving pulmonary symptoms in the immunocompromised host must raise a suspicion of opportunistic infections including nocardiosis as early diagnosis and treatment may alter outcomes.

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