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Pulmonary Nocardiosis in a Child with Hyperimmunoglobulin E Syndrome

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ABSTRACT

Hyperimmunoglobulin E syndrome (HIE) is a rare condition characterised by marked elevation of serum IgE level, chronic dermatitis, intense pruritus, and recurrent serious infection. The major organism is usually *S aureus*. We report a case of an infant with HIE, who had pulmonary nocardiosis. The clinical features, immunological abnormalities, and radiological features of the condition are described. The child finally succumbed to the complications of pulmonary nocardiosis.

Keywords: hyperimmunoglobulin E syndrome; nocardiosis, pulmonary

INTRODUCTION

In 1966, Davis, Schaller and Wedgwood described two red haired white girls with recurrent 'cold' staphylococcal abscesses, severe eczema, and recurrent sinopulmonary infection. The authors suggested the term Job's syndrome for these patients because of the remarkable absence of inflammation in the abscesses[1]. Subsequent work by others have shown that this condition is associated with high levels of immunoglobulin E[2], and are susceptible to recurrent bacterial, fungal, and viral infections[3,4]. Bacteria of the genus *nocardia* and related species of aerobic actinomycetes are infrequently encountered in clinical practice, but they are important potential causes of serious infection, particularly as opportunistic disease in immunocompromised hosts. Nocardiosis is usually a pulmonary disease with 75% of all cases having symptomatic pulmonary infections[5]. Pulmonary nocardiosis in patients with hyperimmunoglobulin E (HIE) syndrome has not been reported previously. We report a case of pulmonary nocardiosis in a child with HIE syndrome.

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Case report

LYY was delivered at full term, and her birth weight was 3.8 kg. Her parents are consanguinous; her father's grandmother and mother's father are siblings. Her two elder siblings in the family are well. When she was one month old, she started having extensive weepy, scaly seborrhoea of the scalp. Atopic eczema was also noted on the face and later it spread to the whole body. Treatment with emulsifying ointment and topical corticosteroids did not improve her condition. She began to have chronic diarrhoea and recurrent otitis externa when she was two months old. She was admitted to another hospital and was given several courses of antibiotics. *Pseudomonas aeroginosa* was isolated from the ear swab. The feed was changed to a protein-hydrolysate based formula (pregestemil). She was referred to this hospital at three months of age. On examination, there was extensive generalised exudative rash with both eczematoid and seborrhoeic elements. Her face looked normal. Her weight was on the third centile, body length and fronto-occipital circumference on the 50th centile for her age. There was no BCG scar. A generalised lymphadenopathy was noted. The liver and spleen were both enlarged, at 3 cm and 2 cm below the costal margin and furunculosis of the left axilla was noted. The following investigations were performed: haemoglobin 89 g/L total white count 16,000/μL (neutrophils 42%, lymphocytes 31%, eosinophils 23%); platelet count 727,000/μL. Culture from the pus swab from the left axilla grew *Staphylococcal aureus*. She was investigated for an underlying immunodeficiency (Tables I and II).

The results showed that at four months of age, she had normal immunoglobulins G and M but very high immunoglobulin E (3130 IU/mL). Her IgA level was reduced. She also had low B cells and markedly reduced CD8 cells. The lymphocyte proliferative responses to mitogens (phytohaemaglutinin and concanavalin A) were also deficient. Serology for HIV infection was negative. She was treated with topical steroids and emulsifying ointments for her eczema. Intravenous amikacin and ceftazidime were given for her ear infection. She made a complete recovery, and her diarrhoea subsided a few weeks later.

Since then she remained relatively well, with only oral candidiasis requiring oral nystatin suspension. At seven months of age, she was admitted for an episode of bronchiolitis and respiratory failure, requiring mechanical ventilation for one week. Full blood count showed: haemoglobin 135 g/L; white cells 15,400/μL (neutrophils 60%, eosinophils 18%, lymphocytes 21%, monocytes 1%); platelet 188,000/μL. Chest X-ray showed bilateral patchy consolidation and hyperinflation. Nasopharyngeal aspirate for respiratory syncytial virus using immunofluorescence technique was negative. In view of the underlying immunodeficiency, she was given intravenous vancomycin, high dose intravenous co-trimoxazole and fluconazole. She made a complete recovery. Oral co-trimoxazole was continued for a further two months.

Table I – Immunoglobulins levels of patient at 4 and 9 months of age.

Immunoglobulins	4 months	9 months	Reference values
Ig G	379	186	272 – 762 mg/l
Ig A	7	< 7	19 – 117 mg/l
Ig M	55	361	14 – 144 mg/l
Ig E	3130	1536	0 – 7 IU/mL

Table II – Immunoglobulins levels of patient at 4 and 9 months of age.

Investigations	Results	Reference values (%)
Total white cells	27,600	6400 – 1100/μl
Total lymphocytes (%)	5437 (19.7)	2700 – 5400/μl (39 – 59)
Total T cells (%)	4404 (81)	1700 – 3600/μl (58 – 67)
Total B cells (%)	217 (4)	500 – 1500/μl (19 – 31)
CD4 cells (%)	4350 (80)	1700 – 2800/μl (38 – 50)
CD8 cells (%)	54 (1)	800 – 1200/μl (18 – 25)
NK cells (%)	816 (15)	300 – 700/μl (8 – 17)
CD4 / CD8 ratio	80.0	1.5 – 2.9
C3	132	5090 mg/dL
C4	60	10 – 40 mg/dL

She remained well for the following two months, and was growing along the tenth centile for weight, 25th centile for length and head circumference of her age. She was again admitted at nine months of age for another episode of bronchopneumonia and relapse of eczema. At that time, her total white cells count was 15,400/μL, with lymphocytes 21% (3,234/μL) and eosinophils 18% (2,772/μL). A repeat serum immunoglobulin levels (Table I) showed low immunoglobulins IgG and IgA but normal IgM. The immunoglobulin IgE was still markedly increased (1536 IU/mL). Intravenous immunoglobulin, 2g/kg was given in view of low serum immunoglobulin IgG levels. This resulted in a remarkable improvement in her eczema. At ten months of age, she was readmitted for a relapse of exudative eczema around the perianal region, which was intensely pruritic. There were multiple abscesses noted on the abdominal wall and limbs, which were asymptomatic and painless. She was afebrile then and there was no sign of inflammation around the abscesses. The abscesses were drained surgically and the pus grew *Staphylococcus aureus*. She was treated with intravenous antibiotics, topical steroids for the eczema and oral zinc supplement. She was also given intravenous immunoglobulin infusion. The eczema responded to the above measures. A skeletal survey was carried out to exclude histiocytosis in view of the nature of the skin lesions resembling infiltration. No lytic bony lesions were seen. A few days later, the child became increasingly tachypnoeic and wheezy. Clinically there was reduced air entry in the left lung. Chest X-ray showed a hyperlucent left lung with reduced vascular markings. Despite intravenous ceftazidime, amikacin, amphotericin B and intensive chest physiotherapy, she failed to improve. A chest CT scan showed a soft tissue mass in the subcarinal region. A bronchoscopy was performed and it showed a small yellowish tissue mass blocking the entrance of the left main bronchus. Histology of the tissue showed fragments of fibrous stroma with acute inflammatory cells. The child subsequently underwent a thoracotomy and open lung biopsy. A mass was noted at the hilum of the left lung, encroaching on the arch of the aorta and infiltrating the parenchyma of the left lung. Histology showed epitheloid cells with plasma cells, lymphocytes and necrotic neutrophilic debris. Zeihl-Neelson stain of biopsied materials showed acid-fast organisms arranged in long beaded chain, consistent with nocardia infection. The child was started on intravenous co-trimoxazole. She became more unwell, and developed Stevens-Johnson syndrome five days later. She was taken off co-trimoxazole immediately and instead imipenem and amikacin were added. Despite this, she developed breathing difficulty and required mechanical ventilation and died four days later.

DISCUSSION

The hyperimmunoglobulin E syndrome (HIE) is a rare disorder characterised by a markedly elevated serum IgE level, chronic dermatitis, intense pruritus, and recurrent serious infection. It was first described by Davis, Schaller and Wedgwood in two red haired white girls with recurrent 'cold' staphylococcal abscesses in 1966[1]. The National Institute of Health (NIH) subsequently classified patients as having HIE if they had recurrent bacterial sinopulmonary and skin infections from birth or early childhood as well as IgE levels which were at least 10 times greater than the upper normal limit of > 2,000 IU/mL[3]. Patients with HIE have undue susceptibility to recurrent infections. Recurrent bacterial infections of the skin and sinopulmonary tract from birth or early childhood are common. The major organism is usually *S aureus*; however, other bacterial pathogens such as *pseudomonas, haemophilus,* and group A streptococcus are common as well[2,3]. Candidiasis and disseminated cryptococcal infection have also been documented[4,6]. The patient whom we described fulfilled the diagnostic criteria laid down by NIH. She presented in early childhood with recurrent infection of the sinopulmonary tract, ie. recurrent otitis externa and chest infections; multiple cold staphylococcal abscesses of the skin; severe, extensive and pruritic eczematoid lesions of the skin, and a markedly elevated serum IgE (3,130 IU/mL). Coarse facies is another clinical feature commonly found in patients with this condition though this was not seen in our patient.

Abnormalities of phagocytic, cellular, and humoral immunity have been described in HIE patients[7]. A selective deficiency of T3+ cells and T8+ cells have been demonstrated[8]. This patient had low T suppressor cells (CD8+), and a low number of B cells. Her IgA was noted to be low from the early course of the disease (at four months of age) and remained low five months later. The IgG was normal at four months of age, but became depressed at nine months of age. This is in contrast with other patients with HIE who usually have normal serum IgG, IgA and IgM[9]. The

other immunological abnormality that has been associated with this disorder, includes abnormal lymphoproliferative responses to phytohaemaglutinin and concanavalin A[10], which was demonstrated in this patient.

The undue susceptibility to recurrent severe infections seen in this patient made us consider some other forms of primary immunodeficiency state that have been associated with increased serum levels of immunoglobulin E. Conditions such as Wiskott-Aldrich syndrome, DiGeorge's syndrome, Nezelof syndrome, and selective IgA deficiency are some examples with elevated serum IgE levels[9]. However, none of the above conditions fits the clinical picture seen in this girl. Omenn syndrome, a form of severe combined immunodeficiency, was considered as a probable diagnosis. This autosomal recessive condition has the clinical features of exudative maculopapular erythema with alopecia and pachyderma, disseminated lymphadenopathy, liver and spleen enlargement, fever, and protracted diarrhoea with marked failure to thrive. The main immunological features are elevated blood and marrow eosinophils counts, high serum IgE concentrations, increased number of CD25+ lymphocytes, hypogamaglobulinaemia, and defective lymphocytic proliferative response to mitogens[11,12]. Many of these features were seen in our patient. However the abscence of alopecia, early cessation of chronic diarrhoea and the relative good physical growth that were seen in this child made the diagnosis of Omenn syndrome unlikely. Furthermore, majority of the cases with Omenn syndrome resulted in fatal outcomes before six months of age, unless they had undergone bone marrow transplantation[11,12].

Nocardiosis is an uncommon infection, usually of a chronic nature, and occurs infrequently in children[13,14]. It is usually seen in patients with immunodeficiency or who are immunosuppressed. The presenting symptoms in primary pulmonary nocardiosis are usually similar to those of other bacterial respiratory infections, such as bronchopneumonia, lobar pneumonia or necrotising pneumonia[15]. Occasionally, it can present as mediastinal mass[14]. The most common chest radiographs finding is consolidation, which usually involves large areas of lungs and not clearly confined to specific lobes or bronchopulmonary segments. Irregular masses, or large irregular solitary mass are less common[16]. In another series, more than half of the patients had pleural effusions[17]. Our patient presented with clinical features suggestive of obstruction to a major bronchus, which failed to respond to antibiotics and intensive chest physiotherapy. Her chest X-ray did not show any consolidation or pleural effusion. CT scan of the chest showed a large mediastinal mass. Differential diagnoses include tuberculous lymphadenitis or fungal mass. In order to diagnose the nature of the mediastinal mass, an open lung biopsy was necessary as bronchoscopy was not helpful.

Sulfonamide-based regimens presently appear to be the treatment of choice for nocardia infection[18]. Prolonged duration is often necessary. It is interesting to note that the child had previously received two months of co-trimoxazole therapy with no adverse effects. A few days after starting intravenous co-trimoxazole for pulmonary nocardiosis, she developed Stevens-Johnson syndrome which was eventually fatal.

In conclusion, patients with HIE are susceptible to various bacterial, viral, and fungal infections. However, pulmonary nocardiosis in HIE has not been reported previously. This child presented with typical features of HIE ie. recurrent bacterial infections of sinopulmonary tract; numerous cold *staphylococcal* abscesses; severe, extensive eczematoid rash; and markedly elevated serum IgE levels. She fulfilled the NIH diagnostic criteria for HIE. She finally succumbed to pulmonary nocardiosis and the complication of its management.

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