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CASE REPORT

Large mediastinal mass in a 15-year-old boy

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SUMMARY

Hyperimmunoglobulin E syndrome is a rare multisystem inherited disorder characterised by high serum IgE levels, skin disorder causing eczema, dermatitis, recurrent staphylococcal infections and pulmonary infections and various skeletal and connective tissue abnormalities. Common presentation is with recurrent skin and sinopulmonary infections. Several features unrelated to immune system such as characteristic facial features, hyperextensibility of joints, multiple bone fractures and craniosynostosis have been described in the literature. We describe a rare presentation of this disease with invasive aspergillosis presenting as mediastinal mass with extension to mediastinal structures and pulmonary vasculature.

BACKGROUND

Hyperimmunoglobulin E syndrome (HIES) is a rare immunodeficiency syndrome which was initially described as Job's syndrome by Davis *et al* in 1966.[1] Pneumonia in these patients is typically caused by infections with *Staphylococcus aureus*, *Haemophilus influenzae* or *Streptococcus pneumoniae* and leads to pneumatoceles, abscesses and behaves as a nadir for fatal infections with bacteria and fungi.[2]Lymphoma is a very important association of this disease[3 4] and commonly present as mediastinal mass or lymphadenopathy and should always be excluded with biopsy. Fungal infections presenting as a non-resolving pneumonia or mediastinal mass is an important differential in such cases.

CASE PRESENTATION

A 15-year-old boy presented with shortness of breath, cough, haemoptysis and fever. He was in good health until the age of 9 years, he then developed asthma-like symptoms (wheeze, dyspnoea and chest tightness) and recurrent upper respiratory tract infections. His medical history was significant for rashes at birth, recurrent eczema and staphylococcal skin infections and boil. He was treated initially as a presumed case of asthma/allergic bronchopulmonary aspergillosis with steroids by a family physician which he took for 3 weeks. He did not show much improvement and continued to have symptoms on and off so steroids were stopped.

On physical examination, he was a thin lean boy, of an average built. He had facial dysmorphic features of pinched nose, broad nasal bridge, large ears, new erupting teeth (figure 1) and delayed shedding of primary teeth. Chest examination revealed bilateral wheezes and decreased breath sounds in left lower chest.

Figure 1 New erupting teeth (arrow).

INVESTIGATIONS

Laboratory workup showed, IgE levels >7000 IU/mL, beta D glucan >523 pg/mL (cut-off < 60), serum galactomannan was 0.36 (cut-off < 0.5), CBC was normal and his serum electrolytes and liver function tests were normal. Chest X-ray showed left lung collapse and mediastinal widening (figure 2). Further evaluation with CT scan chest showed large anterior mediastinal mass (figure 3A,B). Bronchoscopy showed normal bronchial mucosa and mucoid secretions were aspirated and sent for microbiology which grew *S. aureus* (Methicilin sensitive *staphylococcus aureus* (MSSA)). CT guided biopsy was done which showed chronic granulomatous inflammation with multiple septate fungal hyphae

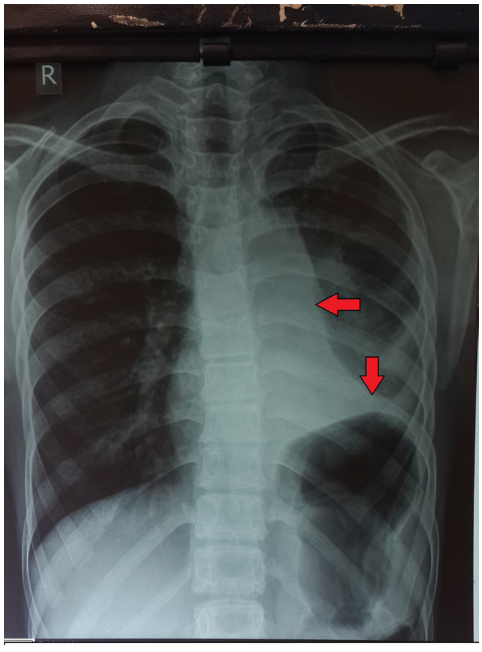

Figure 2 Chest X-ray showing mediastinal widening (arrow pointing left) and left lower lobe collapse (arrow pointing down).

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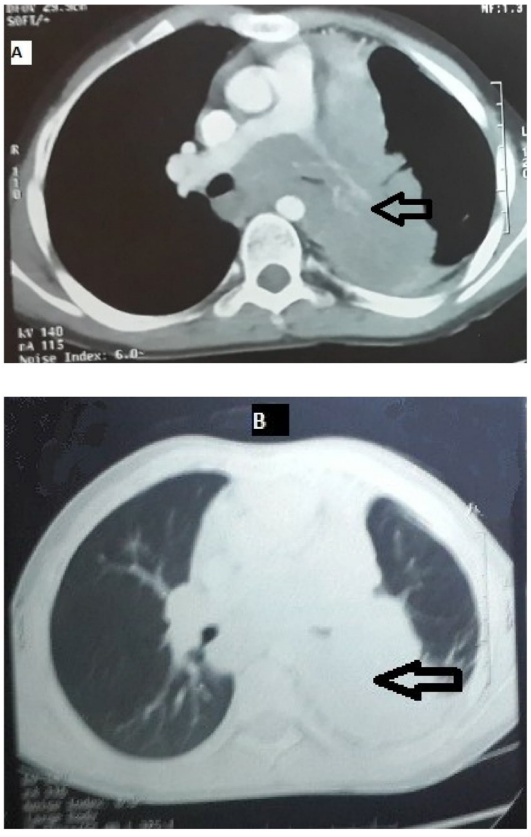

Figure 3 (A) CT scan chest mediastinal window showing left hilar mass involving mediastinal structures and causing left lower lobe collapse. (B) CT-scan chest lung window showing left hilar mass involving mediastinal structures and causing left lower lobe collapse. Arrow is showing left hilar mass together with lobar collapse.

(*Aspergillus*) stained with Periodic acid-Schiff-Diastase stain (PASD) (figure 4) and fungal culture performed on the tissue sample grew *Aspergillus flavus*. Cardiothoracic surgery and infectious disease consultation was taken and he was started on voriconazole.

Further workup revealed raised IgG level (sub class study not available) and normal IgA and IgM. Flow cytometry was done (CD3 +total T-lymphocytes, CD4 +T helper cells, absolute count CD8 +T regulatory cells, absolute count CD19 +total B-lymphocytes and absolute count CD56 +Natural killer cells) which showed reverse CD4+/CD8+ ratio and rest normal. STAT3 mutation is not available. Patient was diagnosed with HIES on the basis of his clinical features and NIH scoring system (59 score).[5]

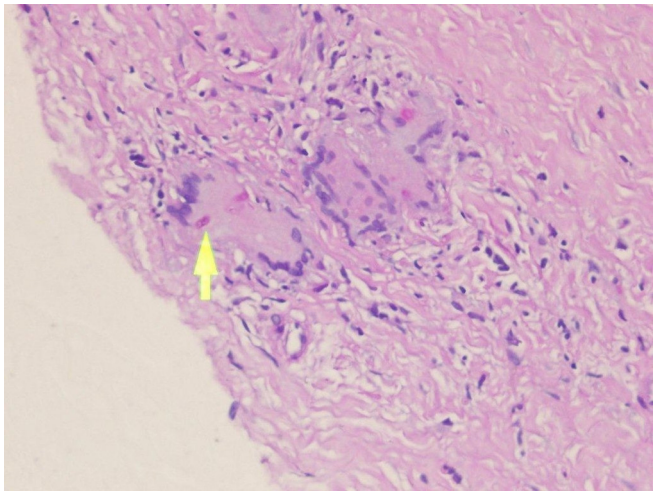

Figure 4 Multinucleated giant cell with fungus (arrow) against dense fibrous background periodic acid–Schiff stain.

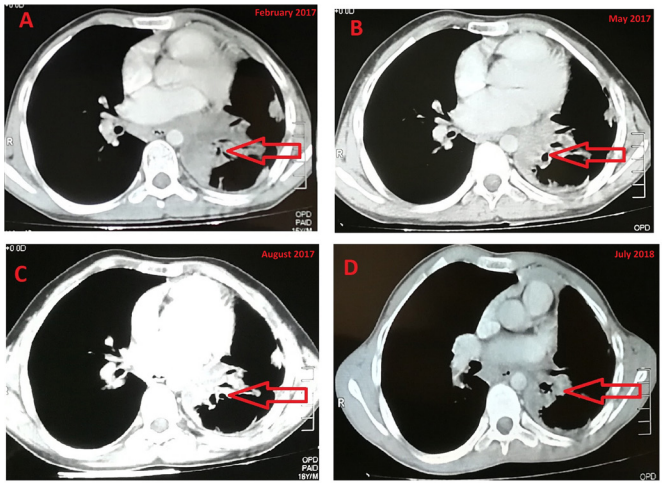

Figure 5 Serial follow-up CT chest images showing regression and almost complete resolution of the disease process. (A) February 2017 after 4 months of therapy sowing regression in the mass (arrow), (B and C) May and August 2017 showing further regression (arrows) and (D) almost complete resolution of the disease process (arrow).

DIFFERENTIAL DIAGNOSIS

- Malignancy, as the patient presented with mediastinal mass.
- HIES as the patient had characteristic facial abnormalities along with high IgE levels.
- Chronic infections like TB and fungal infection (aspergillosis).
- Paediatric chronic granulomatous disease.

TREATMENT

Patient was started on voriconazole 200 mg two times per day.

OUTCOME AND FOLLOW-UP

The patient showed dramatic improvement of symptoms and significant decrease in the size of mediastinal mass after 4 months of therapy (figure 5A-D). He was treated with antifungal therapy for 1 year due to the slower resolution of the disease process (mediastinal mass) as assessed by the serial CT chest images.

DISCUSSION

Autosomal-dominant hyper-IgE (Job) syndrome, is a result of negative mutations in signal transducer and activator of transcription 3 (STAT3)[6] and a link between STAT3 mutation and recurrent infection and connective tissue abnormality has been widely described in literature.[6 7] Recurrent bacterial pneumonias, attributed to dysfunctional STAT3, frequently lead to bronchiectasis and formation of pneumatoceles. Fungal pneumonias, typically aspergillosis have been described in literature as a cause of significant morbidity and mortality.[7]

Lung complications following respiratory infections are common in HIES. These pulmonary lesions facilitate secondary infections with opportunistic pathogens (eg, *Aspergillus fumigatus*, *Pseudomonas aeruginosa*), which are not among the initial

pathogen spectrum, but are a major contributing factor to overall mortality. Recent data comprising 32 patients undergoing thoracic surgery showed a high complication rate, in particular, bronchopleural fistulas.[8]

Invasive aspergillosis presenting as a mediastinal mass with extension to mediastinal structures and pulmonary vasculature is a rare presentation of Job's syndrome. To the best of our knowledge, no case has been reported in the literature so far with this unique presentation. Lymphoma is a known entity associated with this disease and should always be excluded. Recurrent infections and skin problems are the common clinical presentation of this disease and early treatment can prevent the serious complications like invasive aspergillosis, Methicilin resistant *staphylococcus aureus* (MRSA) and serious skin problems.

These patients have characteristic facial appearances which includes facial asymmetry, prominent forehead, deep-set eyes, a broad nasal bridge, prognathism and rough facial skin with prominent pores. Some individuals retain their primary teeth, because of the failure of those teeth to exfoliate. Other features are central depressions in the tongue and high arch of the palate.[1 2]

Recurrent pulmonary infections lead to premature death in patients with HIES; early diagnosis and treatment can be life-saving and can lead to a significant reduction in morbidity and mortality.[2] To best diagnose and treat, we should be familiarised with the clinical and laboratorial aspects of the disease. Besides the infections, we should not forget the risk of malignancy that is associated with HIES.

Learning points

- Hyperimmunoglobulin E syndrome (HIES), although a rare disease is well described in literature, should be kept in mind as a cause of recurrent or non-resolving pneumonia in children and adolescents.
- Lymphoma is a well-known entity associated with this disease and should be excluded.
- Sinopulmonary infections are a major cause of mortality and timely recognition and treatment is necessary.
- This case also highlights the importance of conservative approach of treating invasive aspergillosis with extensive mediastinal involvement and avoidance of unnecessary surgical intervention which can also increase the rate of morbidity and mortality in HIES.

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