CASE REPORT
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Histopathologic Findings of Pneumatocele in a Patient with Hyper-IgE Syndrome, Compatible with Cystic Adenomatoid Malformation

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ABSTRACT

Hyper-immunoglobulin E syndrome is a rare primary immunodeficiency disease characterized by recurrent abscess formation, respiratory tract infections and very high titers of serum IgE associated with peculiar face and skeletal features.

We report a seven-year old girl presenting with persistent productive cough and history of chronic eczematoid facial lesions since infancy and two episodes of hospitalizations due to pneumonia and perianal abscess. Additionally, in physical examination finger tip clubbing, laxity of joints and crackles in both lungs were detected. Immunologic work up revealed markedly raised IgE level and eosinophilia. The patient was diagnosed as hyper IgE syndrome based on his clinical and laboratory findings. Chest X-ray revealed multiple large cystic lesions in left lung which were confirmed by spiral CT-scan. Pneumonectomy specimen examination showed cystic adenomatoid malformation, characterized by the presence of various cysts lined by epithelium in different sizes.

There are few reports of cystic adenomatoid malformation in children. To our best known, this is the first report of cystic adenomatoid malformation in a child with hyper IgE syndrome. Early diagnosis and surgical therapy are helpful in prevention of repeated infections in these patients.

Key words: Cystic adenomatoid malformation; Hyper immunoglobulin E syndrome; Pneumatocele

INTRODUCTION

The hyper-immunoglobulin E (IgE) syndromes (HIES) are primary immunodeficiencies characterized by the clinical triad of recurrent staphylococcal abscesses, recurrent cyst-forming pneumonia and an elevated serum IgE level of >2000 IU/ml.[1] Most cases are sporadic; however, autosomal dominant and autosomal recessive inheritance have been described.[2] The usual lung histological feature of HIES is pneumatocele which is demonstrated as granulation tissue, necrosis and marked inflammation in the wall without epithelial lining.[3,4] Cystic adenomatoid malformation (CAM) is an uncommon anomaly of lung

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development, characterized by proliferation of dilated bronchiolar-like airspaces of varying sizes.[5] The absence of bronchiolar cartilage in the cystic wall suggests an embryological alteration before the sixteenth week of intrauterine life, when the cartilaginous bronchi are formed.[6] Several factors appear to influence lung development: 1) An interaction between endoderm and mesoderm 2) A careful orchestration between cell proliferation and cell death and 3) Correct vascular development. It has been hypothesized that CAM results from failure in any of the above named items.[5] We here report a case of HIES with unusual histologic findings in favor of CAM.

CASE PRESENTATION

A 7–year-old, Caucasian girl, was admitted to our hospital with productive cough and slow progressive dyspnea. Her dysnea was started since 2 years before admission which was aggravated in past two months. Reviewing her past medical history revealed facial eczema and furuncle at 4 months of age.

She had been hospitalized when she was 3 years of age due to perianal abscess and experienced two episodes of pneumonia later. There was no history of fever, weight loss, and allergic respiratory diseases. Family history of similar problems was denied. Physical examination revealed a well developed, but undernourished child. Facial eczematous dermatitis, prominent forehead, deep set eyes and broad nasal bridge were making a coarse face appearance(Figure 1). Eruption of teeth were normal. On chest examination bilateral crackles and rales especially in left lung were auscultated. She had significant clubbing and hyperextensible joints. Laboratory findings are summarized in table 1.

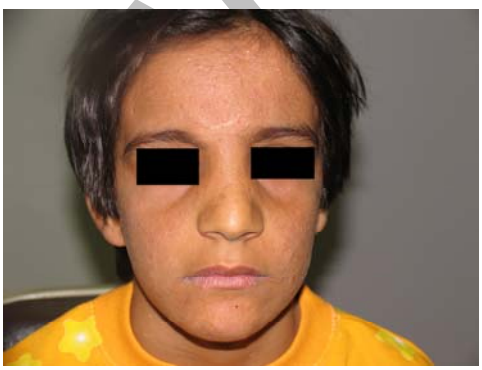

Figure 1. Characteristic coarse face with a prominent forehead, deep set eyes and broad nasal bridge

Table 1. Laboratory results on this patient

Variables & test	Results
White blood cell	13400/mm3
Neutrophil	30%
Lymphocyte	59%
Monocyte	2%
Eosinophil	9%
Hemoglobulin	12.2 gr/dl
ESR	34 mm/h
CRP	24 g/dl
CD3	70% (Normal)
CD4	42% (Normal)
CD8	31% (mildly increase)
CD19	26% (Normal)
NBT	95% (Normal)

Arterial blood gas analysis in room air showed: PH 7.39, O2 saturation 93.8% and PaCO2 32.2%. The serum immunoglobulin assay showed a markedly elevated IgE level with normal IgG, IgA and IgM levels.The clinical and laboratory data were applied to the scoring system of the National Institute of Health[(7)] and the patient received a score of 50 points (Table 2).

Chest x-ray and spiral CT-scan (Figure 2) revealed a normal cardiac size and patchy areas of consolidation bilaterally accompanied by multiple large cystic lesions in left lung. Left pneumonectomy was done and multiple cystic lesions in left lung were detected. Histological examination showed numerous cystic spaces lined by single layer of stratified columnar epithelium with ciliated bronchial lumen and collapsed alveolar spaces (Figure 3). This was compatible with the diagnosis cystic adenomatoid malformation.

Table 2. Scoring after clinical and laboratory findings for HIES diagnosis

Topics	Findings	Points
Highest IgE level	> 2,000IU/ml	10
Skin abscess	1	2
Paranchymal lung anomaly	CAM*	8
Pneumonia	2	4
Highest eosinophil count	> 800cells/ul	6
Characteristic face	Present	5
Eczema	Severe	4
Upper respiratory infections per year	> 6	4
Hyperextensibility	Present	4
Increased nasal width	>2 SD	3
Total scores		50

- CAM is assigned similar to pneumatocele.

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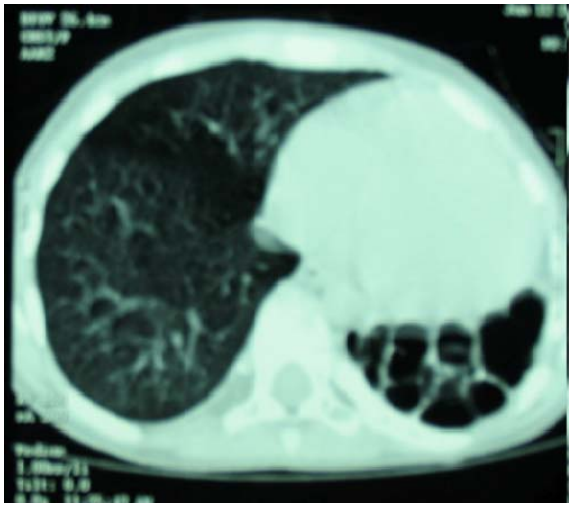
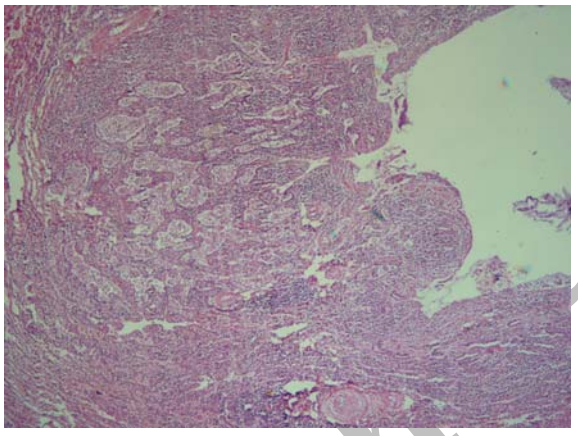


Figure 2. Spiral CT-scan showed multiple large cystic lesions in left lung



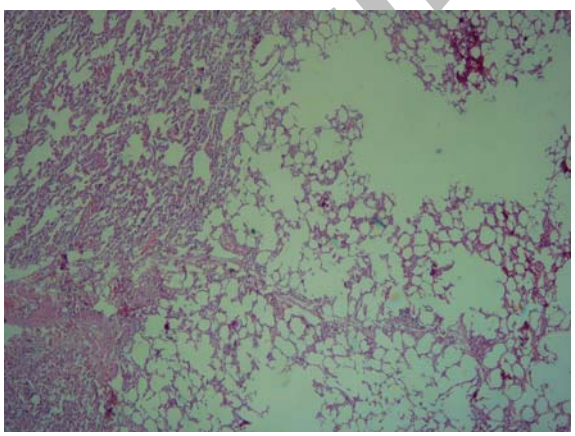


Figure 3. Large numbers of cystic spaces lined by single layer of stratified columnar epithelium with ciliated bronchial lumen and collapsed alveolar spaces

DISCUSSION

Most cases of hyper-immunoglobulin E syndrome are sporadic, and pathogenesis had remained mysterious for a long time. Minegishi et al showed that mutations in the human signal transducer and activator of transcription (*STAT3*) gene result in the classical multisystem HIES.[8] A patient with mild IgE elevation due to homozygous tyrosine kinase 2 deficiency has been also reported as an HIES case with recessive inheritance.[9]

STAT3 mutations clarify many disparate aspects of this syndrome that have puzzled investigators. Targeted mutations in mice show specific roles of STAT3 in organogenesis, organ preservation and organ inflammation.[9] Effect of STAT3 on apoptosis and proliferation of lung cancer cell line were seen.[10] The depletion of STAT3 in mouse cardiacmyocyte is associated with cardiac inflammation consistent with vessel involvement.[11] STAT3 deficiency specific to the pulmonary epithelium in mice exposed to hyperoxia caused excessive lung inflammation and airspace enlargement.[9]

STAT3 mutations are probably responsible for a defect in the switch from one stage to another in lung development by effect on organogenesis, apoptosis, cell proliferation and vascular development.

CAM is a congenital pulmonary disorder with associated anomalies and chromosome aberrations.[12] (Table 3)

The rare association between CAM and HIES as a genetic diseases can be considered. Although CAM sometimes occur as a sporadic non hereditary lesion [(14)], chronic lung infections of HIES may be the cause of CAM. However, further studies are needed to validate this speculation placing emphasis on the association

Table 3. Associated anomalies and chromosome aberrations in cases of CAM

Associated anomalies	Chromosomal abnormality
Hydrops fetalis	Trisomy 18
Agenesis of gall bladder	Trisomy 21
Complex heart disease	Trisomy 13
Bilateral renal agenesis	Klinefelter
Kyphoscoliosis	
Arteriovenous malformation[13]	

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