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CASE REPORT

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Hyper Ig E syndrome (Job syndrome, HIES) – radiological images of pulmonary complications on the basis of three cases

Katarzyna Jończyk-Potoczna[1], Aleksandra Szczawińska-Popłonyk[2], Małgorzata Warzywoda[1], Anna Bręborowicz[2], Bogdan Pawlak[1]

[1] Pediatric Radiology Department, Chair of Radiology, Poznań University of Medical Sciences, Poznań, Poland
[2] Clinic of Pulmonology, Pediatric Allergology and Clinical Immunology, Poznań University of Medical Sciences, Poznań, Poland

Author's address: Katarzyna Jończyk-Potoczna, Pediatric Radiology Department, Chair of Radiology, Poznań University of Medical Sciences, Szpitalna 27/33 St., 60-572 Poznań, Poland, e-mail: jonczyk@ump.edu.pl

Summary

Background: Hyperimmunoglobulinemia E syndrome (hyper-IgE syndrome, Job syndrome, HIES) is a complex immune deficiency with multiorgan clinical manifestations and diverse genetic background. The clinical triad of symptoms observed in approximately 75% of patients with HIES includes: recurrent abscesses of staphylococcal etiology, recurrent respiratory infections and elevated immunoglobulin E in serum.

Case Report: The paper discusses three cases of female patients presenting typical pulmonary complications of the hyper-Ig E syndrome. In the first case, the development of aspergilloma in a postinflamatory cyst was observed, in the other one, pneumonia with pleural effusion, and as a consequence of inflammatory infiltrations – fibrotic changes, giving rise to lobectomy, while in the last of these cases, the course of lung disease was complicated by formation of staphylococcal abscess. In one of the girls, bronchiectasis appeared at follow-up.

Conclusions: Complications of pulmonary infections are the most common causes of death in hyper-Ig E syndrome. Late diagnosis significantly worsens the respiratory function and reduces the chance for normal development of a child. Introduction of comprehensive treatment, including prophylaxis, decreases the recurrences. Therefore, the important role is attributed to the radiologist in the multidisciplinary care of patients with this syndrome.

Key words: hyper IgE syndrome • pulmonary complications • computed tomography

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Background

Hyperimmunoglobulin E syndrome (hyper-IgE syndrome, Job syndrome, HIES) is a complex immunodeficiency with multiorgan clinical manifestations and diverse genetic background. Classic form of hyper-IgE syndrome inherited in an autosomal dominant manner (AD-HIES) is caused by a mutation in a transcription factor gene STAT3 (signal transducer and activator of transcription 3). Mutation of STAT3 leads to impairment of signaling of many cytokines, including interleukin (IL)-6 and IL-22, as well as dysfunction of T-helper 17 lymphocytes, which play a crucial role in immune response to infections caused by pathogens such as extracellular bacteria and fungi [1,2]. The incidence of hyper-IgE syndrome is <1:1000 000 and it is diagnosed in both sexes equally often [3,4].

Clinical triad of symptoms observed in about 75% of patients with AD-HIES includes: recurrent abscesses of staphylococcal etiology, recurrent respiratory tract infections and elevated serum immunoglobulin E concentrations. This disorder displays abundance of symptoms such as dermatitis, furunculosis, dysmorphic facial features, skeletal and dental abnormalities as well as connective tissue defects [5,6].

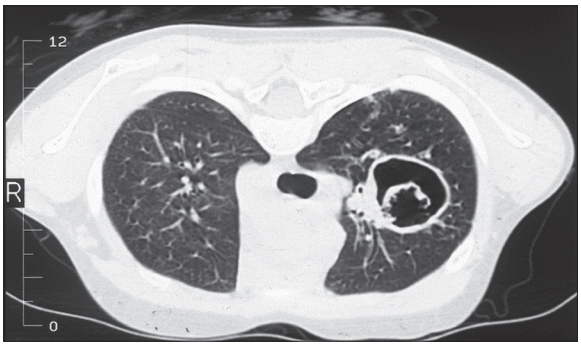

Figure 1A. Axial CT scan of the chest, pulmonary window. Inflammatory cyst in the upper lobe of the left lung complicated by fungal infection.

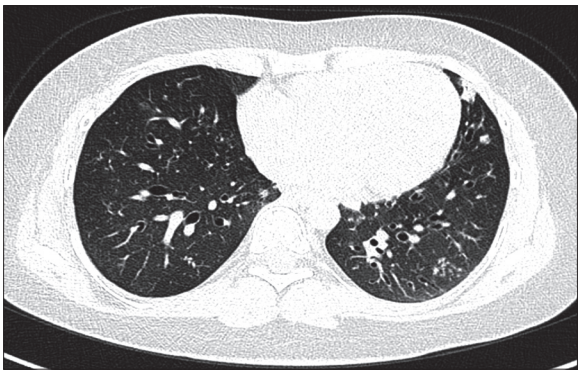

Figure 1B. Axial CT scan of the chest, pulmonary window. The same patient, follow-up examination. Bronchiectasis.

Chronic or recurrent respiratory tract infections and pneumonias are usually severe and associated with the risk of permanent damage to the lung tissue. Pneumonias are complicated with pneumatocoele or pneumothorax formation.

In this publication we present the radiological picture of pulmonary complications occurring in children diagnosed with hyper-IgE syndrome on the basis of three representative cases.

Case Reports

Case 1

The girl has been suffering from recurrent infections of the respiratory tract – otitis media, bronchitis or pneumonia, accompanied by lower airway obturation – since early infancy. Moreover, she became sick with pertussis at the age of four. Clinically severe pneumonia at the age of five was the reason for hospitalization at the Clinic of Pulmonology, Pediatric Allergology and Clinical Immunology at Poznań University of Medical Sciences. Her past medical history revealed symptoms such as: generalized pustular skin lesions and multiple furuncles since infancy, popleateal abscess requiring surgical intervention, recurrent peridental abscesses penetrating to maxillary sinuses and the orbit, delayed loss of deciduous teeth, pathological fractures and excessive joint mobility. Laboratory examinations showed eosynophilia, immunoglobulin E level of 51 820 IU/L and multidirectional neutrophil dysfunction involving migration, chemotaxis, phagocytosis and enzymatic activity. Considering the course of the disease to date and overall clinical picture, a diagnosis of hyper-IgE syndrome was stated, which was then verified with a genetic study and identification of STAT3 mutation. Clinical and radiological improvement was not achieved despite intensive treatment. Persistent areas of parenchymal consolidation visible on X-ray pictures, appearance of a radiolucent cystic lesion and presence of fluid in the pleural cavity prompted broadening of the diagnostic process by a CT examination (Figure 1A). CT imaging confirmed the diagnosis of postinflammatory cyst infection and aspergilloma. Lack of response to conservative treatment was an indication for a resection of the involved lobe. In long-term observation, the patient suffered from recurrent bronchopneumonias and recently performed CT examination revealed, apart from numerous nodular lesions, bronchiectasis (Figure 1B).

Case 2

Severe pneumonia complicated with pleuritis requiring drainage was the cause for hospitalization of the next patient. The girl did not suffer from any serious respiratory tract infections until the age of nine. Generalized pustular lesions with a tendency toward formation of multiple abscesses prevailed in the clinical picture. Diagnosis of hyper-IgE syndrome based on clinical signs such as skin lesions, dental anomalies, characteristic dysmorphic features – broad nasal bridge, prognathia – in conjunction with elevated serum IgE concentration (16 080 IU/l). Despite intensive treatment we achieved only little improvement in the radiological picture – regression of pleural lesions validated with ultrasound examination, with persistent parenchymal consolidation in the upper lobe of the left lung. A CT examination confirmed the presence of interstitial changes accompanied by atelectasis, cavities and apparent air bronchogram (Figure 2A). Pharmacotherapy was modified on suspicion of fungal infection. A follow-up CT after one month showed a thin-walled cavity with a linear band of fibrosis in the upper lobe of the left lung (Figure 2B). As the girl remained in poor clinical condition, lobectomy was performed.

Current improvement of the clinical state of the respiratory tract was obtained as a result of continuous antibiotic and antifungal treatment as well as intravenous administration of immunoglobulins. The patient remains under care of hospital outpatient clinic and does not present with chest X-ray abnormalities at this time.

Case 3

The next girl has suffered from generalized skin lesions such as eosinophilic folliculitis complicated by recurrent *Herpes simplex* infections since early infancy. Initially, the respiratory tract infections involved upper airways and manifested as chronic purulent rhinitis and paranasal sinusitis. At the age of six, she had to undergo a surgical procedure for laryngeal granuloma and acute respiratory distress, at the Pediatric Otolaryngology Clinic in Poznan. The first episode of pneumonia of documented *Mycoplasma pneumoniae* etiology complicated by a staphylococcal

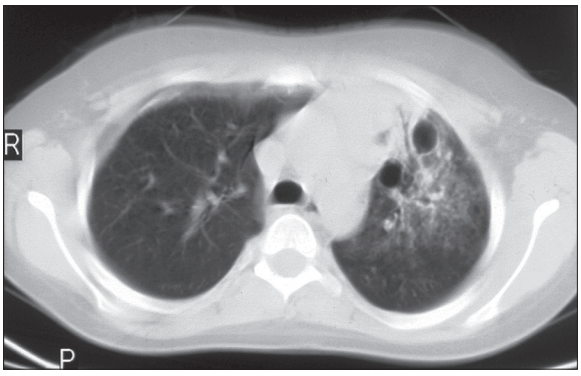

Figure 2A. Axial CT scan of the chest, pulmonary window. Parenchymal and atelectatic consolidations with air bronchogram, cavities in the upper lobe of left lung.

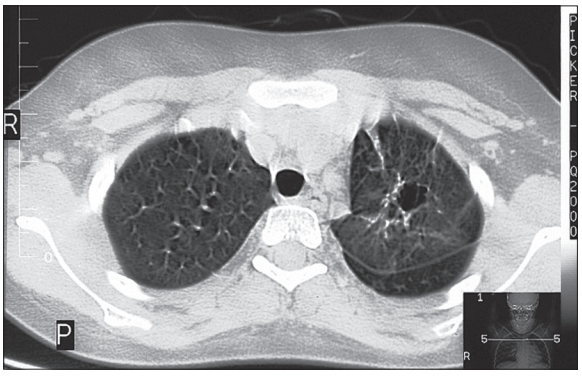

Figure 2B. Axial CT scan of the chest, pulmonary window. The same patient, follow-up examination. In the upper lobe of the left lung, linear densities and a thin-walled cavity.

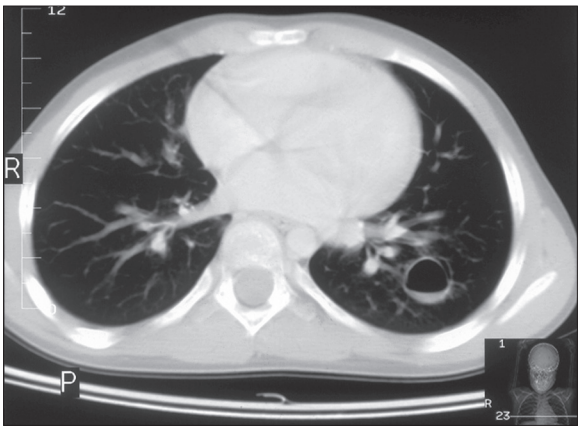

Figure 3. Axial CT scan of the chest, pulmonary window. Abscess of staphylococcal etiology in the lower lobe of the left lung.

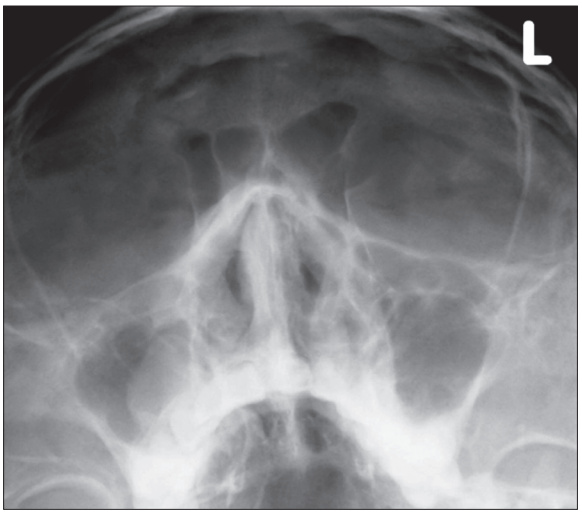

Figure 4. An X-ray of paranasal sinuses. The same patent, mucosal thickening in the right maxillary sinus.

abscess formation and sepsis requiring hospitalization at the Department of Pulmonology, Pediatric Allergology and Clinical Immunology also took place at the age of six (Figure 3). The hyper-IgE syndrome was suspected due to the presence of dysmorphic features – prognathia, gothic palate, broad nasal bridge, hypertelorism, a double set of deciduous and permanent teeth, extensive caries, hypermobile joints and scoliosis. We confirmed elevated serum IgE concentration (2000 IU/L) and a defect of neutrophil chemotaxis, and identified a mutation in the STAT3 gene. Alleviation of clinical symptoms from the respiratory tract that took a form of recurrent bronchopneumonias was attained by introducing chronic antibiotic and antifungal therapy as well as application of immunoglobulin preparations. Radiological changes underwent full regression. Control chest X-ray did not show inflammatory lesions in pulmonary parenchyma. The patient still complains of symptoms of paranasal sinusitis, confirmed with X-ray picture (Figure 4).

Discussion

Hyper-IgE syndrome is a rare disorder with multiorgan manifestations. Initial symptoms take a form of diffuse dermatitis and may be observed as early as during infancy. However, respiratory tract infections usually appear during the first two years of life. Immunological dysfunction accompanied by high immunoglobulin E (>2000 IU/mL) concentration prevail. Aside from skin lesions, the most commonly occurring complications include paranasal sinusitis, otitis media and respiratory tract infections [7]. Etiological factors of infection include *Staphylococcus aureus*, *Haemophilus influenza*e. Moreover, microorganisms such as *Pseudomonas aeruginosa* or *Aspiergillus fumigatus* are known for causing superinfections. In all discussed cases, microbiological studies confirmed the presence of the mentioned pathogens. The authors analyzing medical histories of patients with hyper-IgE syndrome emphasized that pneumonias as a typical picture of the disease, are often complicated by abscess formation [8]. Likewise, bronchiectasis and pneumatocoele are described in the literature as pathognomonic in this group of patients [9,10]. Abnormalities characteristic for the disorder presented here that were mentioned in the literature were also present in the described children. In the first case it was the development of an aspergilloma in a postinflammatory cyst, in the second case – pneumonia with pleural effusion and, as a consequence of the inflammatory process, cirrhosis that resulted in lobectomy. In the last discussed case the complication involved formation of a staphylococcal abscess. On follow-up, one of the girls presented with bronchiectasis. Moreover, in one of the patients we observed upper respiratory tract involvement, particularly paranasal

sinusitis accompanied by otitis media. Complications associated with pulmonary infections are one of the most common causes of death in the course of hyper-Ig E syndrome. Late diagnosis leads to significant impairment of patients' respiratory function and reduces the chances for normal development of a child. Introduction of comprehensive management, including prophylactic treatment, allows for a reduction in the frequency of recurrences. Therefore, the role of a radiologist who often analyzes patient's whole medical documentation is important for guiding further diagnostics including immunological evaluation. The risk of development of neoplastic diseases such as Hodgkin or non-Hodgkin lymphomas and acute myeloid leukemia should not be overlooked in hyper-IgE patients [11–14]. Diverse somatic picture and a variable clinical course depending on the variant of the disease makes the diagnosis difficult and requires an interdisciplinary approach for prevention of irreversible and life-threatening organ complications.

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