doi:10.1594/eaacinet2007/CR/4-270307 http://www.eaaci.net

SPECIFIC ANTIBODY DEFICIENCY PRESENTING WITH ASTHMATIC SYMPTOMS

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REASON FOR CONSULTING

A twelve year old girl, with a history of cough, wheezing, sneezing and dyspnea for a period of ten years, was consulted at our department for evaluation. She had her complains exacerbated 3-4 times per year. She had nocturnal cough, awakening her more than twice per month with seasonal runny nose/sneezing complaints. She had a history of recurrent sinusitis since 5 years old, 2-3 times annually. She had no history of admission.

She was a second child from first degree consanguineous parents. Her 18-year old brother was treated for hepatitis C. Her mother suffered from systemic lupus erythematosus (SLE). Her father had a history of acute rheumatic fever. The immunisations were done on time.

CLINICAL EXAMINATION

The anthropometric measurements were as follows: weight: 53 kg (75-90%), height: 160 cm (75-90%). On physical examination, mucopurulent nasal discharge and bilateral wheezing on auscultation was detected. Otherwise her systemic physical examination findings were normal.

DIFFERENTIAL DIAGNOSIS

Her pulmonary function test revealed a mild obstruction (FEV_1 = 78%, FVC = 76%, FEV_1/FVC = 89%) with a reversibility of forced expiratory volume in 1 second FEV_1 > 12%. Lung functions were assessed with a spirometer (Sensormedics, S3513, California, USA). Nasal smear cytology revealed normal epithelial cells, skin prick testing was performed with 20 common aeroallergens and positive (histamine) and negative (saline) controls (Stallergenes, France) demonstrating sensitization to house dust mites (*Dermatophagoides pteronyssinus:* 4x4mm, *D. farinae:* 4x4mm). Her complete blood count values were as follows; haemoglobin: 12.7 mg/dl, leukocyte: 7600 x 10^3 /ul, thrombocyte count: 323 x 10^3/ul, mean corpuscular volume (MCV): 79 fl, absolute neutrophil count: 4900/mm^3, absolute monocytes count: 500/mm^3 , absolute lymphocyte count: 2000/mm^3, and absolute eosinophil count: 200/mm^3. Blood biochemistry, urinary analysis, C-reactive protein and

erythrocyte sedimentation rate results were normal. Her chest X-ray was normal. As she had a family history of rheumatic diseases, ANA, anti-DNA, RF were determined and revealed negative results.

The patient was diagnosed as mild persistent asthma and was prescribed intranasal and inhaled corticosteroid therapy (Budesonide 800µg/day), whereby on follow up period of two years, she had 2-3 asthma exacerbations per year despite effective environmental control, good compliance of medication and appropriate usage of inhaler corticosteroid. Her recurrent upper respiratory tract infection, mostly sinusitis persisted. Since she was 12 years old she had no other complains with a regular menstruation cycle other than respiratory and sinusitis infections.

ADDITIONAL DIAGNOSTIC STUDIES

In this individual patient, a number of factors associated with recurrent asthmatic exacerbation and sinusitis were considered. Paranasal CT revealed normal anatomical structures. Quantitative sweat chloride test was 25 mmol/L (normal= <40 mmol/L), while serum immunoglobulin-A: 99 mg/dl (96-495), IgM: 92 mg/dL (70-322), IgG: 987 mg/dL (913-1884), IgE: 3.21 mg/dl and IgG subgroups were within normal range. Total serum IgG, A, and M levels were measured by nephelometry (BN ProSpec systems, Dade Behring Marburg GmbH, Marburg, Germany). Her lymphocyte subsets detected by flow-cytometry were within normal range for her age. Eventually, thorax HRCT was obtained, revealing an upper right lobe anterior segment minimal bronchiectatic pattern. PPD test was 5x5 mm.

CAUSE OF BRONCHIECTASIS

Before proceeding to invasive laboratory tests, specific antibody levels were measured before and 4 weeks after immunization with 23-valent pneumococcal vaccine, which revealed poor response to polysaccharides antigens (Pre-immunisation: 0.5 µg/ml, Post-immunisation: 0.7µg/ml). She was diagnosed as having Specific Antibody Deficiency (SAD) and started prophylactic antibiotic treatment (Trimethoprime / Sulfamethoxazole 4 mg/kg/day).

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FINAL DIAGNOSIS

Despite prophylaxis, her cough, phlegm and sinusitis complaints persisted. Monthly intravenous immunoglobulin (IVIG) treatment of 400 mg/kg was commenced in addition to prophylactic antibiotics and inhaler corticosteroids. Previously, she used to have an average of 3-4 episodes of infections (sinusitis) or asthma attacks. After IVIG treatment, she did not experience any. Immediately after commencing of IVIG treatment, the patients' respiratory symptoms such as cough and phlegm production resolved completely and symptoms like frequent headaches, nasal blockage and facial pain also resolved. Six months after IVIG treatment, inhaled corticosteroids were stopped; she continued taking TMT/SMZ prophylaxis treatment during winter and spring seasons only. Pulmonary function tests showed no deterioration of lung functions.

DISCUSSION AND CONCLUSION

Our patient had recurrent upper respiratory infections and a number of asthmatic attacks despite control of environmental measures and appropriate medications.

Specific antibody deficiency with normal immunoglobulin levels is a primary immunodeficiency of unknown origin (1). It is characterized by normal concentrations of IgG, IgA, IgM, and IgG subclasses and abnormal specific IgG antibody responses which is associated with variable clinical spectrum of recurrent and/or severe respiratory tract infections (2, 3). Inability to produce specific antibodies may occur in other primary immunodeficiency disease, including X linked agammaglobulinaemia, Wiskott-Aldrich syndrome and ataxia telangiectasia (Table 1). Treatment consists of daily

CAUSES OF SELECTIVE ANTIBODY UNRESPONSIVENESS
Primary Immunodeficiency
Specific antibody deficiency
X linked agammaglobulinaemia (btk mutation)
IgG subgroup deficiency
Common variable immunodeficiency
Wiskott-Aldrich syndrome
Ataxia telangiectasia
Secondary Immunodeficiency
Cytotoxic/myeloablative therapy
HIV infection
Chronic lymphotic leukemia
Multiple myeloma
After bone marrow transplantation

Table 1

antibiotic prophylaxis, immunoglobulin replacement and some patients may benefit from additional immunization with conjugated pneumococcal vaccines.

CONDITIONS ASSOCIATED WITH BRONCHIECTASIS
Congential Conditions
Primary ciliary dyskinesia
Alpha 1- antitrypsin deficiency
Cystic fibrosis
Cartilage deficiency (Williams-Campbell syndrome)
Tracheobronchomegaly (Mounier-Kuhn syndrome)
Marfan's syndrome
Immunodeficiency
Primary / Secondary hypogammaglobulinemia
Rheumatic Conditions
Rheumatoid arthritis
Systemic lupus erythematosus
Sjörgen's syndrome
Relapsing polychondritis
Postinfections Conditions
Bacteria (Pseudomonas, haemophilus)
Mycobacterium tuberculosis
Aspergillus species
Virus (HİV, adenovirus, measles virus, influenzavirus)
Others
Inflammatory bowels disease
Young's syndrome (secondary ciliary dyskinesia)
Yellow nail syndrome (yellow nails and lymphedema)

Table 2

The patient had a chronic sinusitis that was being followed-up since the age of 5 without any other severe infections. On follow up, bronchiectasis was detected and was evaluated accordingly (Table 2). Kainulainen et al (4) reported that silent progression of pulmonary changes may occur in patients with primary immunodeficiency. Recently, a study was conducted on adults with idiopathic bronchiectasis and found a fraction of patients associated with selective anti-polysaccharide response deficiency (5), while Schwartz et al reported remarkable clinical benefits of IVIG on severe asthmatic patients who were found to have specific antibody deficiency (6). Other primary immunodeficiencies were not considered due to the normal findings of IgG/IgA and B-lymphocytes (CVID/ Bruton).

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In conclusion, during the follow-up of children with asthma, when the symptoms persist despite a regular inhaler corticosteroid therapy, depending on characteristics of individual patients, quantitative and qualitative immunologic parameters as well as other confounding factors such as cystic fibrosis, ciliary dyskinesia, gastro-eosophageal reflux etc. should be evaluated before proceeding to a stepping-up mode of therapy.

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SUMMARY

Hereby we describe a case of asthma complicated by specific antibody deficiency progressing to bronchiectasis. Recommendations should be tailored appropriately according to the priorities of individual patients.

Keywords: Antibody response, Asthma, bronchiectasis, intravenouse immunoglobulins

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