

# Lung diseases in children with primary immunodeficiency

WIESŁAWA KARNAS-KALEMBA<sup>1</sup>, BARBARA BASIEWICZ-WORSZTYNOWICZ<sup>1</sup>, BOŻENA POLAŃSKA<sup>1</sup>, ALEKSANDRA LEWANDOWICZ-USZYŃSKA<sup>1</sup>, ADAM JANKOWSKI<sup>1,2</sup>

<sup>1</sup>Department of Pediatric Propedeutics and Division of Children Immunology and Rheumatology, Medical University of Wrocław, Poland;

<sup>2</sup>Institute of Genetic and Microbiology of Wrocław University, Department of Immunology, Poland

## Abstract

*Immunological disorders predispose to multiple changes in the pulmonary tissue. Frequent complications, such as bronchiectasis, interstitial lung damage, fibrosis, lymphoma are common. This study presents the findings in our 3 patients with severe primary immunodeficiency and lung disease. The first patient with both CVID and benign lymphoproliferative disorder, the second with both CVID and extrinsic allergic alveolitis recognised, the third – with undetectable IgA, low subclasses IgG1 i IgG3 had reticular pattern in chest HRCT scans. Prognosis is uncertain in both primary immunological disorder, as well as interstitial lung diseases. Early recognize of the dual presentation of primary immunological disorder and lung diseases and adequate treatment, will prevent irreversible structural lung damage.*

**Key words:** CVID, interstitial lung disease, children.

(Centr Eur J Immunol 2007; 32 (1): 1-4)

## Introduction

Immunological disorders predispose to multiple changes in the pulmonary tissue [1, 2]. Within developing organs of children with primary immunodeficiency, susceptible to a range of diseases, interstitial lung tissue disorder can develop [3].

Children with primary antibody deficiency suffer from recurrent rhinitis, sinusitis, tonsillitis, bronchitis and pneumonias. Frequent complications, such as bronchiectasis, interstitial lung damage, fibrosis, lymphoma are common. Most primary immunological deficiencies are detected during infancy. In severe untreatable cases a child undergo prolonged suffering followed by death. Of the total number of children with primary immunological disorder 3.1% have common variable immunodeficiency (CVID), where as 12.9% suffer with subclasses IgG deficiency and 12% with IgA deficiency [4, 5]. CVID is usually detected when a child is over 10 years old. Until recently the origin of CVID and cause of autoimmunological diseases within 20% of patients with CVID is uncertain [6].

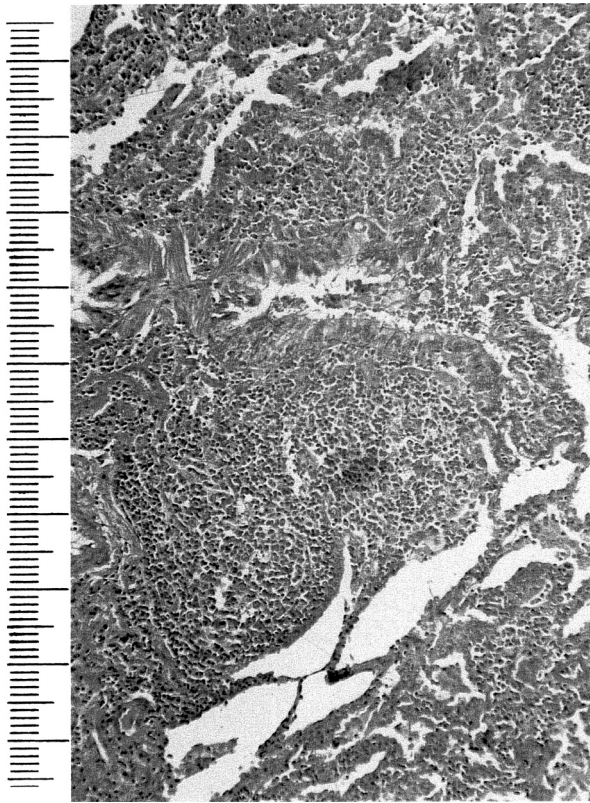
The clinical course of lung diseases and following symptoms are non-specific. Changes in pneumonia can

appear in dysfunctional lungs (restrictive changes of ventilation in pulmonary function tests, decrease in DL<sub>CO</sub> and low resting Pa<sub>O2</sub>) in some cases there are no clinical symptoms. X-ray of the chest may be clear when a disease is presently active or when a child is in good state of health, lung X-rays may revealed interstitial changes [1, 7]. Computed tomography (CT) is used for final diagnosis [8] but a lung biopsy may also be necessary. In this case specimens of lung tissue are removed for further histopathological and/or immunohistochemical tests. Inflammation of the pulmonary interstitium reveal histologic features, that may in worst cases lead to alveolar structures derangement with varying degrees of fibrosis [1, 9].

The report presents the findings in our 3 patients with severe primary immunodeficiency and lung disease.

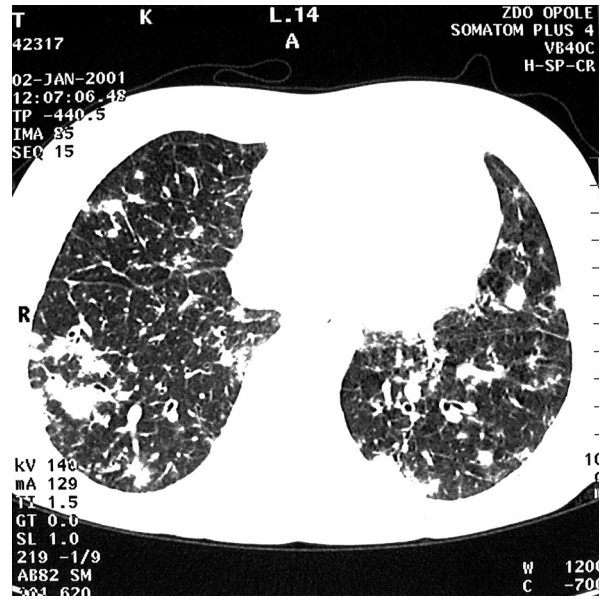
## Case reports

1. The first patient, NJ, a 15-year-old girl, was admitted to our hospital in 2003. Prior to this for a 2 year period she suffered from recurrent pneumonia, spending most of that time in hospital. From infancy she suffered from recurrent



**Fig. 1.** Microscopy of the lung biopsy. Infiltration of inflammatory cells including mostly lymphocytes (CD20+, CD3+, CD45RO+) and plasma cells, diagnosed as benign lymphoproliferative disorder

respiratory and urinary tract infections. She had two incidents of autoimmune haemolytic anaemia and idiopathic thrombocytopenia between 1995 and 1998. During her physical examination bilateral crackles in the lung bases and hepatosplenomegaly were detected. Initial investigations showed leukopenia ( $2.5 \times 10^9/l$ ), thrombocytopenia ( $68 \times 10^9/l$ ), hypogammaglobulinemia with IgG (1,81 g/l) and low subclasses (IgG1, IgG2, IgG4) serum levels, undetectable IgA, low  $CH_{50}$  also decreased T-cell proliferation to mitogens (PHA and ConA). Further to this she was diagnosed with CVID. The viral, bacterial and fungal infections were excluded. The chest X-ray and computed tomography examination showed extensive diffuse infiltrates along with enlarged lymph nodes of the mediastinum. The surgical lung biopsy was performed. Benign lymphoproliferative disorder was diagnosed using histopathology and immunohistochemistry (figure 1). The patient was given intravenous infusions of immunoglobulin (IVIg) (0,2 g/kg every three weeks) and prednisone beginning with a preliminary dose of 50 mg/day. Any side effects were observed. Abnormalities in the lungs disappeared and



**Fig. 2.** CT scan of the chest in patient 2 shows multifocal consolidation, ground glass abnormality, and reticular pattern

both in spleen and liver reduced in size. The IgG and IgA deficiencies remain. For now, she is stable continuing IVIG treatment.

2. The second patient, TK, a 14-year-old girl, had medical history of recurrent respiratory tract infections and idiopathic thrombocytopenia. Splenectomy was performed during the 9<sup>th</sup> year of her life. At the age of 14 while hospitalized for pneumonia, X-rays showed diffuse interstitial inflammation. A high-resolution computed tomography (HRCT) scan of the chest revealed the following: bilateral diffuse disseminated densities, centrilobular nodules, reticular pattern, bronchiectasies and hilar lymphadenopathy (figure 2). A surgical lung biopsy was performed and extrinsic allergic alveolitis was recognised. She was found to have hypogammaglobulinemia and was referred to our center in 2001 for evaluation of an immunological disorder. A physical examination showed lymphadenopathy. Her white blood cell count was  $23.1 \times 10^9/l$ , platelets of  $627 \times 10^9/l$ , CRP 12.3 mg/l. Serum immunoglobulin levels at the time were low (IgG of 2,04 g/l, undetectable IgA) and her T-helper cell count was 30%. From the course of the disease and laboratory tests she was diagnosed with CVID. The viral, bacterial and fungal infections were excluded. She received IVIG (0,2 g/kg every three weeks) along with prednisone until remission. Side effect including diabetes, osteoporosis and hypertension were observed during therapy. Two years later, in 2003, we observed a relapse of the disease. HRCT scans of the lungs revealed progression of bilateral nodular infiltrates and ground glass opacity. Pulmonary function tests also showed a restrictive pattern. She was treated with

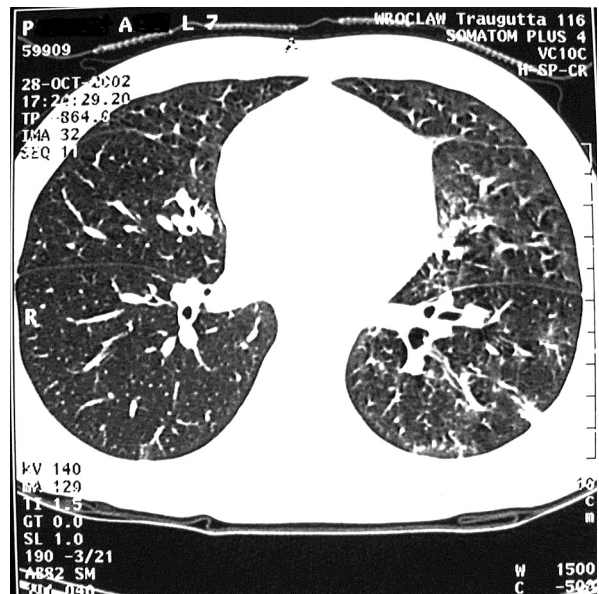
azathioprine (150 mg/day) along with prednisone (beginning with a dose of 40 mg/day) and also IVIG. Currently her pulmonary function tests are normal, she is receiving immunoglobulin replacement therapy, azathioprine (50 mg/day) and her health has improved.

- The third patient, PA, a 9-year-old boy, was suffering from recurrent respiratory tract infections. This onset occurred during the first 6 months of his life, during teething. At the age of 2 he was suffering with the following: severe suppurative, ulcerative gingivitis with inflammatory oedema, bleeding gums, sore oral cavity and weight loss. Initial laboratory investigations showed haemoglobin 9.3 g/dl, platelets of  $425 \times 10^9/l$ , white blood cells count was  $8.9 \times 10^9/l$  with neutrophenia ( $0,07 \times 10^9/l$ ). Laryngotracheoscopy and oesophagoscopy showed the oedema of laryngeal mucous and tracheal mucous. We collected *Actinomyces israeli* from the oral cavity [5]. Laboratory results indicated the following: undetectable IgA (in serum and saliva), low concentration of serum IgG levels (2,37 g/l with low subclasses IgG1 i IgG3), decreased numbers of CD4+ (29%), CD8+ (15%) subpopulations of lymphocytes. As for now he is receiving IVIG (0,2 g/kg every three weeks). At age 7, bibasilar rales and crackles appeared during lung auscultation. In spite of the treatment auscultatory changes remained for many weeks. The viral, bacterial and fungal infections were excluded. CT was required as the X-ray failed to reveal the ongoing problem. The HRCT detected the following: ground glass attenuation, bronchial dilatation, thickening of the walls along central and peripheral airways and enlargement of left hilar lymph node (figure 3). Currently the boy is awaiting a lung biopsy. During this period he receives immunoglobulin replacement therapy.

## Discussion

In a number of cases, who have primary immunodeficiency, inflammatory infiltrates in lung tissue can occur [10]. The disease is usually long-lasting, with periods of exacerbation [11]. Prognosis is uncertain in both primary immunological disorder, as well as interstitial lung diseases [11, 12]. Diagnosing pulmonary changes in children often requires surgery lung biopsy [13]. This can be a life threatening procedure in children who have immunological disorder. However, using histological examination specimens of lung tissue enable appropriate diagnosis and administration of treatment, until lung disease remission.

It is important that diagnosis is given early to minimize lung damage. Therapy is concentrated towards reducing inflammatory response to prevent possible fibrosis. Administering adequate treatment limits spread of the disease hence improving the patients' quality of life [14, 15]. In the case of first patient, treatment was administered enabling the patient to return to normal active life. Currently the girl attends school, meets her friends and takes part in social life of her



**Fig. 3.** CT scan of the patient 3 shows reticular abnormality and bronchiectasies

peers. Since IVIG therapy was administered, the second patient only suffers from sporadic respiratory infections. However, this treatment did not protect her from exacerbation. Although the third patient has been receiving immunoglobulin replacement therapy since the age of 2, changes in the lungs appeared at the age of 7. In both cases (patient 2 and 3) developed interstitial lung diseases, although immunoglobulin replacement had been administered throughout many years. Our findings are consistent with that of other authors about progression of pulmonary changes occurring in patients who received an adequate immunoglobulin replacement therapy [16]. Most studies indicate that prognosis improved under immunoglobulin replacement therapy, when coexists with COVID [17].

There was an inadequate reference material after thorough research into this disease. The mechanisms of pathogenesis, promote lung disorders, pathways of disease regulation, or molecular basis are all still unclear [9]. Thorough investigations and research still must be carried out. The long-term benefits of the treatment have not been revealed. It is possible, that patients who were diagnosed with lung disorders during childhood may develop further problems in later life. The effects of applied treatment on the evolution and spread of disease in adulthood are unknown.

It is essential to use critical monitoring to determine disease activity. Reliable non-invasive clinical markers allow to detecting any early symptoms of the disease further development or any relapse. There is no pathognomonic laboratory criteria for the diagnosis. It would be logical for the pediatricians and pulmonologists to cooperate, share data, files new methods and results. In summary, as more

patients are identified, it may be possible to understand the relationship between therapy and regression of these two uncommon diseases. Every effort to recognize the immunological defect responsible for the dual presentation of primary immunological disorder and lung diseases will prevent irreversible structural lung damage.

## References

1. American Thoracic Society, European Respiratory Society (2002): American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 165: 277-304.
2. Sneller MC (2001): Common variable immunodeficiency. *Am J Med Sci* 321: 42-48.
3. Cunningham-Rundles C (1989): Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. *J Clin Immunol* 9: 22-33.
4. Bernatowska E, Michalkiewicz J, Gregorek H, et al. (2000): Twenty years of investigations into primary immunodeficiency diseases in the Department of Immunology of the Children's Memorial Health Institute, Warsaw. *Centr Eur J Immunol* 25: 119-126.
5. Karnas-Kalemba W, Basiewicz-Worsztynowicz B, Polańska B, et al. (2004): Zapalenie jamy ustnej i dziąseł o etiologii promieniowcowej u 2-letniego chłopca z agammaglobulinemią IgA i niedoborem podklas IgG. *Ped Pol* 79: 742-744.
6. Primary immunodeficiency diseases. Report of WHO Scientific group (1997). *Clin Exp Immunol* 109 (Suppl 1): 1-28.
7. Thickett KM, Kumararatne DS, Banerjee AK, et al. (2000): Common variable immunodeficiency: A respiratory physicians perspective. *Thorax* 55 (Suppl 3): 41.
8. Manson D, Reid B, Dalal I, et al. (1997): Clinical utility of high-resolution pulmonary computed tomography in children with antibody deficiency disorders. *Pediatr Radiol* 27: 794-798.
9. Clement A, ERS Task Force (2004): Task force on chronic interstitial lung disease in immunocompetent children. *Eur Respir J* 24: 686-697.
10. Buckley RH (2004): Pulmonary complications of primary immunodeficiencies. *Paediatr Respir Rev* 5 (Suppl A): S225-S233.
11. Davies CW, Juniper MC, Gray W, et al. (2000): Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A. *Thorax* 55: 88-90.
12. Reichenberger F, Wyser C, Gonon M, et al. (2001): Pulmonary mucosa-associated lymphoid tissue lymphoma in a patient with common variable immunodeficiency syndrome. *Respiration* 68: 109-112.
13. Coren ME, Nicholson AG, Goldstraw P, et al. (1999): Open lung biopsy for diffuse interstitial lung disease in children. *Eur Respir J* 14: 817-821.
14. Busse PJ, Razvi S, Cunningham-Rundles C (2002): Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol* 109: 1001-1004.
15. Kohler PF, Cook RD, Brown WR, et al. (1982): Common variable hypogammaglobulinemia with T-cell nodular lymphoid interstitial pneumonitis and B-cell nodular lymphoid hyperplasia:

- different lymphocyte populations with a similar response to prednisone therapy. *J Allergy Clin Immunol* 70: 299-305.
16. Kainulainen L, Varpula M, Liippo K, et al. (1999): Pulmonary abnormalities in patients with primary hypogammaglobulinemia. *J Allergy Clin Immunol* 104: 911-913.
  17. Sweinberg SK, Wodell RA, Grodofsky MP, et al. (1991): Retrospective analysis of the incidence of pulmonary disease in hypogammaglobulinemia. *J Allergy Clin Immunol* 88: 96-104.