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Common variable immunodeficiency in a patient with suspected sarcoidosis

Abstract

Common variable immunodeficiency is a primary immunodeficiency disease, characterized by hypogammaglobulinemia, low serum immunoglobulin concentrations, and recurrent bacterial infections of the respiratory and gastrointestinal tracts. We report on a 33-year-old patient with suspected sarcoidosis, diagnosed on the basis of an open lung biopsy, who was admitted to the National Tuberculosis and Lung Diseases Research Institute because of severe pneumonia and streptococcal sepsis. During diagnostics based on typical, clinical and laboratory features, CVID was diagnosed. The antibiotic treatment was successfully administered and the patient was directed to supplementary treatment.

Key words: common variable immunodeficiency, granulomatous disease, hypogammaglobulinemia, pneumonia

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Introduction

Common variable immunodeficiency (CVID) is the second most frequent primary immunodeficiency syndrome. Its estimated prevalence among the European population is 1 in 50 000 to 1 in 200 000 [1]. This syndrome is characterized by hypogammaglobulinemia with a marked decrease in serum immunoglobulin concentration, particularly IgG and IgA, and a decrease in lymphocyte B and TCD4+ count [2, 3]. The underlying, still not fully explained heterogeneous genetic disorders, are probably related to MHC complex genes within chromosome 6 [4]. CVID clinical symptoms include recurrent infections of the nasopharynx, respiratory system, and gastrointestinal tract, due to the presence of encapsulated bacteria. Histological examination reveals noncaseating granulomas in specimens removed from the lungs, liver, spleen, and medulla in about 5–10% of CVID patients [5]. High-resolution computer tomography (HRCT) reveals intraparenchymal changes in the form of nodules, reticular and fascicular changes, enlarged lymph nodes, and bronchiectasis [6–8].

In CVID patients, basic treatment consists of systematic, parenteral immunoglobulin administration at monthly doses of 0.3–0.6 g/kg [9]. Many years of observation have shown that, apart from susceptibility to infections, such patients are also more prone to autoimmune diseases and the development of tumours, particularly lymphomas [10, 11].

The paper presents the case of a CVID patient observed for over a year and a half because of suspected sarcoidosis.

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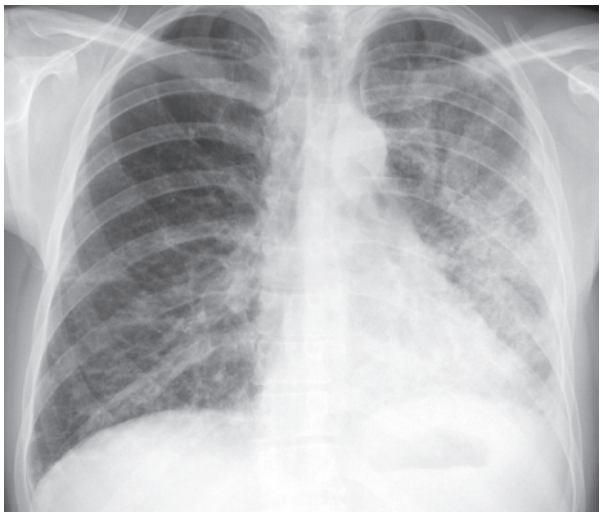

Figure 1. Chest X-ray: small nodules and linear structures disseminated bilaterally within medium and lower zones, obscured by area of confluent parenchymal consolidations with air bronchogram in the left lung

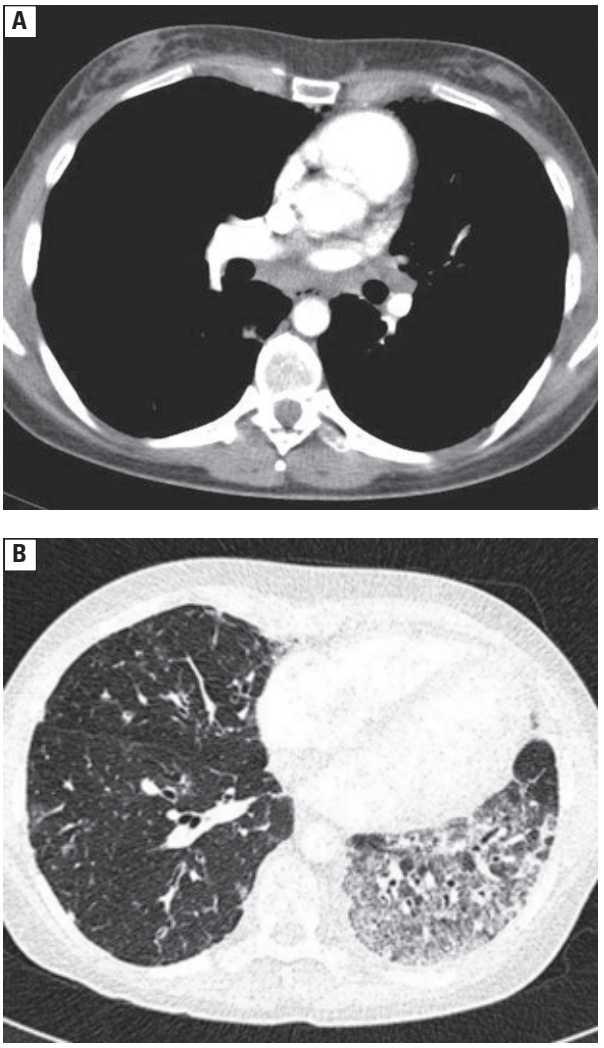

Figure 2. Chest CT scan. **A.** Moderately enlarged mediastinal and hilar lymph nodes. **B.** Loss of volume of the left lung with massive parenchymal consolidations; disseminated, ill-defined, small nodules within the right lung

Case report

A 33-year-old E.G. was admitted to the clinic on 5 November 2007 due to a fever as high as 40°C and a dry cough, which developed in mid October 2007, later accompanied by purulent rhinitis and headaches. Despite clarithromycin administration, only transient relief was obtained. Due to the worsening condition of the patient and relapse of fever up to 40°C with concomitant persistent dry cough, the patient was hospitalized on 5 November 2007 at the Institute of Tuberculosis and Lung Diseases.

On admission, the general condition of the patient was average. Physical examination showed elevated body temperature up to 40°C, tachypnoea, tachycardia, and increased respiratory activity of the nasal wings. Massive crepitation was audible over the entire field of the left lung. Blood morphology showed: WBC — 14×10^9/l, neutrophils — 84%, HGB — 10.8 g/dl, PLT — 496×10^9/l. Additional tests showed elevated CRP values, up to 325 mg/l, D-dimer up to 2200 μg/l and decreased total protein concentration to 5.2 g%. Blood gasometric parameters revealed a tendency toward hypoxaemia (PaO_2 — 67.8 mm Hg with $PaCO_2$ — 33.7 mm Hg). Chest radiogram (fig. 1) revealed micronodular and linear changes, obscured at the left side by a massive, cumulated parenchymal density, with air bronchogram corresponding to inflammatory changes. The patient was given amoxicillin with clavulanic acid and ciprofloxacin. Due to deterioration of the patient's condition, intensification of auscultatory changes over the lung fields, and respiratory insufficiency symptoms (PaO_2 — 52.6 mm Hg, $PaCO_2$ — 42.1 mm Hg), on the third day of hospitalization CT angiography (CTA) was performed (fig. 2 A, B), which did not show any pulmonary embolism. Instead, a decrease in the left lung volume was noted with massive, cumulated parenchymal densities of different degrees of saturation with a discrete pleural reaction and moderately enlarged lymph nodes of the mediastinum and hili.

In the meantime, blood culture results were obtained: *Streptococcus pneumoniae* was cultured from 4 blood samples. After obtaining results of the antibiogram, administration of amoxicillin with clavulanic acid was maintained and linezolid was additionally prescribed. Soon the patient's condition improved, the fever subsided, and a partial regression of radiological changes within the lungs was observed. Due to the severe course of extrahospital pneumonia in the young patient, the dia-

gnostics was additionally oriented towards immune disorders, notably because the patient added important facts to the history.

At the age of 6 she underwent an appendectomy, and at the age of 7 she had a Meckel's diverticulum removed due to inflammation. In addition, the history revealed atopic dermatitis the patient had suffered since early childhood. At the age of 29 and then at 33 she experienced miscarriages, twice, during the first trimester of pregnancy. Since the age of 30 she had suffered from recurrent paranasal sinusitis, throat inflammation and purulent inflammation of the periodontal tissue. In the same year, her brother developed AFB (+) tuberculosis. During family examination, the patient had a chest radiograph performed, which revealed disseminated changes. Thus, the patient was hospitalized at the Department of Lung Diseases in Otwock. The routine examination revealed normal test results: blood morphology, biochemical parameters, and general urine test. CT scan of the thorax revealed disseminated changes, prevailing in the lower fields in the form of micronodules, locally merged with the predilection toward peribronchial, perivascular, and subpleural structure formation, as well as enlarged lymph nodes of the hili and the mediastinum.

The whole clinical picture suggested second stage sarcoidosis; however, due to the atypical changes an open biopsy of the lung was performed in April 2006. Histological examination of the specimens revealed partial fibrosis of the lung parenchyma with tuberculoid-type granulomas. The results of specimen culturing and threefold examination of the sputum towards the presence of acid-resistant myobacteria proved negative. The patient was diagnosed with sarcoidosis. Two weeks after being discharged, the patient was readmitted to the surgical department due to postoperative wound abscess. She was given cefuroxime, amikacin, and amoxicillin with clavulanic acid. The treatment was continued for 3 weeks. During the hospitalization period, additional tests revealed a decreased concentration of total protein to 5.2 g%. The diagnostics, however, were not extended in this direction. The patient was directed to the Sarcoidosis Outpatient Clinic at the Institute of Tuberculosis and Lung Diseases in Warsaw, where the patient underwent functional examination of the respiratory system, which revealed decreased vital capacity (VC) of the lungs to 75% (–2.3 SR), decreased static compliance of the lungs to 59% of predictive values, and 52% carbon monooxide diffusion coefficient (–3.99 SR). The lung function tests repeated after 4 months did not show any dynamics, nor did a CT scan of the lungs. During the second half of 2007 the patient came to the ophthalmologist's due to dryness and pain of the conjunctives; subretinal changes were found with concomitant slight swelling of the retina, spread to the macular vascular fascicle. The changes raised the suspicion of sarcoidosis.

At this time the patient was admitted to the Institute of Tuberculosis and Lung Diseases where, after detecting *streptococcus*, a battery of tests was carried out because of suspected immune disorders.

Flow cytometry revealed lymphopenia with an extremely small leukocyte count CD8 (136 compared to the norm of 500–900) and NK cells (25 compared to the norm of 200–400) and a markedly decreased number of B lymphocytes. The number of CD 4 lymphocytes was also reduced. The CD4/CD8 ratio was 4 times elevated. Bone marrow biopsy with phenotype evaluation showed stimulation of the erythropoiesis with associated slight hypoplasia of the granulocyte system and a normal phenotype. Blood protein examination revealed a substantial decrease in gamma-globulin concentration, namely 0.21 g/dl (4.1%). Serum immunoglobulin concentration was exceptionally low: IgA — 14 mg%, IgG — 101 mg%, IgM — 19 mg%. The concentration of C3, C4 complement were within the lower limit of normal values. The degree of chemiluminescence was also decreased and amounted to 12 393 CPM (n > 26 600). No presence of HIV genetic material was demonstrated. At the same time, the specimens removed from the lungs one and a half years ago were verified (fig. 3). In-

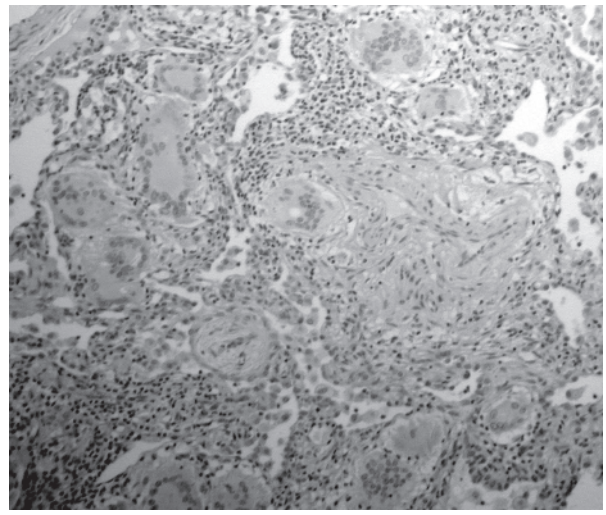

Figure 3. Microscopic picture of the lung: noncaseating giant cell granulomas and scattered multinucleated giant cells with active interstitial fibrosis. The granulomas are small, poorly formed and loosely arranged. Their borders are blurred by surrounding lymphocytes. Microphotograph, H + E stain, high magnification, × 20

terstitial inflammation with the areas of diffused infiltrations of the lymphoidal cells distorting the structure of lung parenchyma, with giant cells and small, poorly formed granulomas were found in histological examination. The granulomas were mainly composed of giant cells with no signs of necrosis or fibrosis. They did neither show any predilection to placement around broncho-vascular bundles, connective tissue partitions, nor intralobular location. The changes were accompanied by the accumulation of macrophages in the alveolar lumen and foci of organising pneumonia were revealed. The verification of the previous diagnosis revealed that the microscopic picture of changes was not characteristic for sarcoidosis. It required differential diagnosis with the consideration of other diseases with granulomatous reaction including immune disorders.

In the meantime the follow up chest radiogram (fig. 4 A, B), performed after 10 days of a modified antibiotic treatment, revealed a partial regression of parenchymal densities visible in the left lung but micronodular changes were still present.

Since sarcoidosis of the visual organ was suspected prior to patient hospitalization, an ophthalmologic examination was performed. It showed numerous foci in the left eye retina with slightly unclear borders. Sarcoidosis was questioned as the cause of this changes and birdshot chorioretinopathy was suspected. To confirm the diagnosis, fluorescence angiography was performed, which revealed the presence of isolated foci of growing hyperfluorescence with a slight pigment diffusion. The presence of healing inflammatory changes in the course of CVID was confirmed.

After 3 weeks of antibiotic treatment the patient's state was generally good and she was discharged from the hospital.

Two weeks later, the patient was given the first dose of immunoglobulin (15 g of Endobulin). The follow up examination, performed a month following hospitalization at the outpatient clinic, showed normalization of WBC parameters in blood morphology. The concentration of immunoglobulin G increased to 264 mg%. Chest radiograph showed further regression of parenchymal densities in the left lung and stabilization of the nodular changes within both lungs.

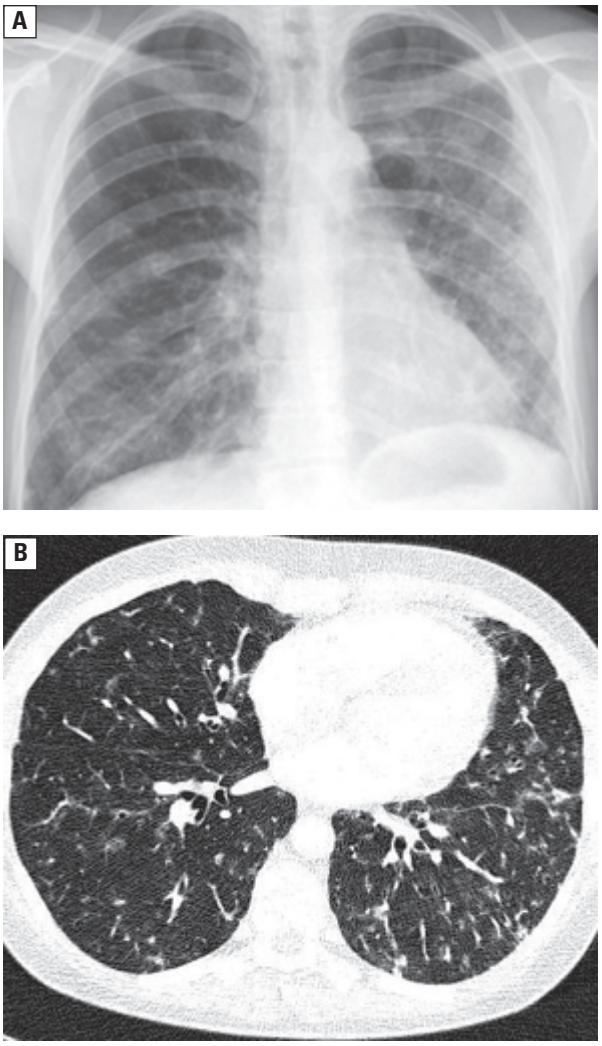

Figure 4A, B. Chest X-ray and lung HRCT scan: partial regression of parenchymal consolidations in the left lung; bilateral small nodules still visible

Discussion

Common variable immunodeficiency is a rare disease. In Great Britain there have been 1000 registered cases of it. The age in which the condition is usually diagnosed ranges from 3 to 72 years (29 on average), and in 95% of cases, the patients are above 6 years of age [1]. It is usually diagnosed late, after about 4–6 years [10] from the occurrence of the first symptoms. The reason for such a late diagnosis is mainly low specificity of the symptoms and slow exacerbation of immune disorders.

In this patient, the infections within the nasopharynx, upper airways, and periodontal tissue usually lasted about 3 years and occurred after the first spontaneous miscarriage. It is of note that miscarriages are one of the symptoms occurring in immunoglobulin deficient patients. The reason for this is still unclear, although the literature suggests no relation to the increased susceptibility to infections [12].

The basic criterion of CVID diagnosis is the recognition of severe hypogammaglobulinemia with associated extreme immunoglobulin G and A deficiency. IgM is variable and a substantial decrease in IgM concentration is reported in younger pa-

tients diagnosed with this condition [2, 10]. Peripheral blood flow cytometry revealed a substantial decrease in lymphocyte B count, a slightly decreased lymphocyte T count and decreased CD4/CD8 ratio < 4 [4, 10, 11]. All these changes, except the decreased CD4/CD8 ratio, were found in the patient. The disturbed humoral response results in a higher susceptibility to bacterial infections, particularly with encapsulated bacteria. The resistance to viral infections is, in turn, only slightly decreased, although there are described in the literature cases of increased incidence of *Herpes zoster* infections and aggressive course of hepatitis C [3, 4].

Radiography of the lungs in CVID patients is nonspecific. During the early stages of the disease the changes are discrete and poorly visible on a typical chest radiograph. High resolution CT is the preferred form of examination as it reveals mainly bronchiectasis, nodules and reticular changes, enlarged lymph nodes, and traits of fibrosis [6, 8]. The described changes occur more frequently in lower lung fields, something which was also visible in our patient. She also had enlarged lymph nodes in the mediastinum and hili, small, localy merged nodules with a predilection to peribronchial, perivascular, and subpleural structure formation, and discrete thickening of stromal septa resembling "ground glass". With no additional clinical information, the picture might suggest pulmonary sarcoidosis. It is extremely important to differentiate patients with CVID and those with sarcoidosis. CVID is characterized by micronodular changes, usually located in lower lung fields, a history of recurrent infections, and decreased values of gammaglobulin concentration. In patients with sarcoidosis, the nodular changes are located in the upper and middle lung fields and immunoglobulin concentration is usually increased. There are no literary data [11] suggesting that the extent of immunoglobulin deficit affects the prevalence of granulomatous lung disease.

It might seem that microscopic imaging of the lungs is decisive in the diagnosis. However, not only the radiological but also the histological picture of CVID is difficult to differentiate from that of sarcoidosis. Before the final diagnosis was made, the patient had been observed for sarcoidosis for almost 2 years. The diagnosis was based on histological examination of the specimens removed from the patient's lungs during open biopsy, which is the method of preference in case of interstitial diseases. Tuberculoid-type granulomas were present in the specimens, which might suggest sarcoidosis. In 5.4–10% of CVID patients, non-necrotic granulomas are found in the specimens taken from the lungs, liver, spleen, and salivary glands, lymph nodes, bone marrow, and meninges. Differentiation and diagnosing the above-mentioned underlying diseases is not possible based solely on the histological picture [5]. A complete evaluation of immune disorders is necessery. Both radiologists and the pathomorphologist, when evaluating the previous test results of the patient, confirmed that neither the radiological nor the microscopic image were typical for sarcoidosis, although they did not exclude it.

Basic treatment of CVID patients consists of a continuous, systematic parenteral substitution of immunoglobulin (IVIg) at a dose of 0.3–0.6 g/kg and antibiotic treatment in case of infection. Multiple studies on the efficacy of IVIg treatment showed a decreased risk of infection and normal course of pregnancy after IVIg administration, which is of particular importance as the diagnosis is usually established at the reproductive age and during childhood [3, 9, 12]. With a high serum IgG concentration maintained at > 800 mg%, a greater tendency towards regression of radiologic changes within the lungs (mainly bronchiectasis) was shown [9, 13]. No effect, however, was found on the decreased mortality rate among the studied patients, despite systematic supplementation [10].

The prognosis in CVID patients is similar for both genders, although in females the condition is usually diagnosed at an older age [1, 10]. The factors aggravating the disease course include: frequent severe infections leading to respiratory system insufficiency, too low serum IgG concentration and associated autoimmune diseases and neoplasms more frequent in CVID patients than in the remaining population. The studies also showed a statistically significant correlation between the percentage of peripheral lymphocyte B count and the baseline IgG concentration and a risk of death [10].

An additional negative prognostic factor should be considered in the studied patient, namely birdshot chorioretinopathy. This is a rare form of autoimmune inflammation of the choroidea, probably induced by infections, particularly with *Borrelia burgdorferi*, most frequently occurring in patients with a confirmed presence of HLA-A29 antigen [14]. In the reported case, no active inflammatory process was confirmed and the underlying factor was not detected. The patient, however, is undergoing regular ophthalmological follow ups.

Summing up, the presented case has shown that differential diagnostics of sarcoidosis and CVID is difficult even with good cooperation between the clinician, radiologist, and pathomorphologist.

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