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Autoimmune pulmonary alveolar proteinosis: a case report

Autoimmunologiczna proteinoza pęcherzyków płucnych
— opis przypadku

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Abstract

Autoimmune pulmonary alveolar proteinosis (APAP) is a rare interstitial lung disease characterised by abnormalities in surfactant metabolism. It is typically diagnosed in the 3rd or 4th decade of life with cough and dyspnoea being the most common manifestations. The condition is generally mild. The most advanced cases, in which the dyspnoea leads to limitation in daily activity, require treatment, and whole-lung lavage is the treatment of choice. We report a case of a 37-year-old female with incidental diffuse changes on a plain chest X-ray. The initial high-resolution computed tomography (HRCT) scan suggested allergic alveolitis, but due to the oligosymptomatic course of the disease and only mildly abnormal pulmonary function no further diagnostic tests were performed and the patient was left under observation. Due to the persistence of the radiographic abnormalities a decision was made to perform an open lung biopsy. Based on the histopathology results and the presence of antibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) the final diagnosis of APAP was made.

Key words: proteinosis, interstitial lung disease, GM-CSF

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare interstitial lung disease with a prevalence of 1 per 2 million. The condition is caused by abnormal metabolism of surfactant, the factor responsible for the appropriate surface tension in the pulmonary alveoli. PAP is characterised by intra-alveolar accumulation of large quantities of phospholipids and surfactant proteins, such as surfactant protein A, precursors of surfactant protein B, and sur-

factant proteins B, C, and D, which stain positive using the periodic acid Schiff (PAS) method [1]. PAP was first described in 1958 by Rosen et al. [2]. Three forms of PAP are recognised: autoimmune (formerly referred to as primary or idiopathic), secondary, and congenital. Autoimmune PAP (APAP) is the most common form, accounting for more than 90% of cases. Its development is associated with the presence of autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) [3]. GM-CSF deficiency leads to a defect of alve-

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olar macrophages and abnormal surfactant metabolism resulting in intra-alveolar accumulation of surfactant. Secondary PAP is associated with exposure to inorganic dusts and certain medications (busulfan, chlorambucil), haematological malignancies, or infections (tuberculosis, AIDS). The disorder is characterised by dysfunction or a reduced number of alveolar macrophages. Congenital PAP, an autosomal recessive disorder, is most commonly associated with a mutation in the genes that encode for surfactant B and C proteins [4], ABCA3 transporter, NKX2-1, and a mutation in the gene that encodes for GM-CSF. Congenital PAP is characterised by a variable, often acute clinical presentation.

In APAP, men are more commonly affected than women. The first clinical signs and symptoms typically present in the 3rd or 4th decade of life. Dry cough and gradually increasing, mainly exertional dyspnoea are the most common manifestations. The course of APAP is generally mild. Spontaneous remissions are seen in about 25% of the cases and progressions in a further 25% approximately. Cases in which the dyspnoea leads to limitations in daily activity and respiratory failure require treatment, with whole-lung lavage being the standard approach [5]. Replacement treatment with GM-CSF is also used in the management of APAP. GM-CSF is given via the subcutaneous or inhalation routes with the latter having recently been shown to be the more effective one [3, 4, 6, 7]. This approach offers the possibility of providing patients with less invasive treatment, although large studies are lacking and therefore make an objective assessment of this method impossible. There have been reports of successful management of APAP with methods that decrease the levels of antibodies to GM-CSF (anti-GM-CSF), such as plasmapheresis [8, 9] or treatment with rituximab, a monoclonal antibody to CD20, a B-cell antigen, which suppresses formation of anti-GM-CSF by decreasing the number of B cells [3].

We report a case of mild APAP diagnosed on the basis of a histopathological examination of lung biopsy material. The autoimmune nature of the disease has been confirmed by determination of anti-GM-CSF levels, which were significantly elevated. Cases of PAP have already been presented in the Polish literature but they are scarce, most likely due to the low prevalence of the disease [10–12].

Case presentation

A 37-year-old female with irritable bowel syndrome and multinodular goitre was admitted to the

Institute of Tuberculosis and Lung Diseases in Warsaw, Poland, for evaluation of disseminated lung changes on a plain chest X-ray. The patient complained about cough and shortness of breath associated with considerable exertion. She denied any chronic treatment but did admit she had often suffered from mild respiratory tract infections in the past. She worked in the kitchen and denied exposure to any dusts or toxic substances. She had never smoked. The disseminated lung changes were discovered in September 2006 while performing a plain chest X-ray before elective surgery for a benign breast cyst.

On admission the patient was in good general condition. Laboratory tests revealed no abnormal findings. White blood cell count, differential blood cell counts, and platelet count were low normal. Markers of inflammation: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were normal. A chest X-ray (Fig. 1) revealed disseminated fine reticulonodular opacities with predominant distribution in the middle and lower pulmonary fields. High-resolution computed tomography (HRCT) (Fig. 2) demonstrated interstitial changes in the form of extensive ground-glass opacities with predominant distribution in the upper pulmonary fields. The scan also revealed several segmentally thickened septal lines. The picture was suggestive of allergic alveolitis.

No precipitins to thermophilic actinomycetes or to avian excreta or serum proteins were detec-



Figure 1. Chest X-ray (PA view) (14.06.2007 r.) — disseminated, small reticulo-nodular opacities with predominant middle and basal distribution

ted. The six-minute walk test (6MWT) distance was 523 m with baseline and final oxygen saturations of 97% and 91%, respectively. As regards the mechanics of breathing, the ventilation parameters were normal and the diffusing capacity of the lungs for carbon monoxide (DL_{CO}) was mildly decreased (72% predicted). Bronchoscopy revealed a normal shape and course of the bronchial tree. Due to technical difficulties bronchoalveolar lavage (BAL) could not be performed. A transbronchial lung biopsy was performed but its results were inconclusive.

Due to the good general condition and only mildly abnormal pulmonary function the patient was discharged home with the recommendation to remain under medical observation.

The patient returned in September 2007 and February 2008 for follow-up evaluations. The previously reported symptoms had not worsened between the hospitalisations. The HRCT scan revealed regression of changes compared to the scan of June 2007. Arterial blood gas analysis and spirometry were all normal and the 6MWT distance was 570 m and was achieved without desaturation. Further observation was therefore recommended.

During another follow-up hospitalisation in June 2009 the HRCT scan revealed a partial regression of the disseminated changes in the left lower lobe with more ground-glass areas and poorly saturated fine nodular changes in the right upper and middle lobes; the linear and reticular changes were also clearly visible forming a cobblestone-like pattern (Fig. 3).

Pulmonary function tests revealed a mild decrease in DL_{CO} (65% predicted) and the patient walked the expected distance in the 6MWT of 553 m with an oxygen desaturation from 97% to 93%.

Due to the persistence of radiographic changes during the 2 years of follow-up a decision was made to perform an open lung biopsy. The biopsy was performed in August 2009 and the histopathological examination of the tissue material collected from the middle lobe revealed a preserved structure of the pulmonary parenchyma with no fibrosis but with areas of alveolar spaces filled with a finely granular, eosinophilic, PAS-positive substance. The areas of alveolar spaces filled with this material were separated by fragments of an intact parenchyma. Focally, light-coloured foamy macrophages were present in the alveolar lumen (Fig. 4 and 5). The microscopic picture was consistent with PAP.

In addition, Western blotting revealed a significantly elevated concentration of antibodies to GM-CSF, which confirmed the autoimmune nature of the disease.

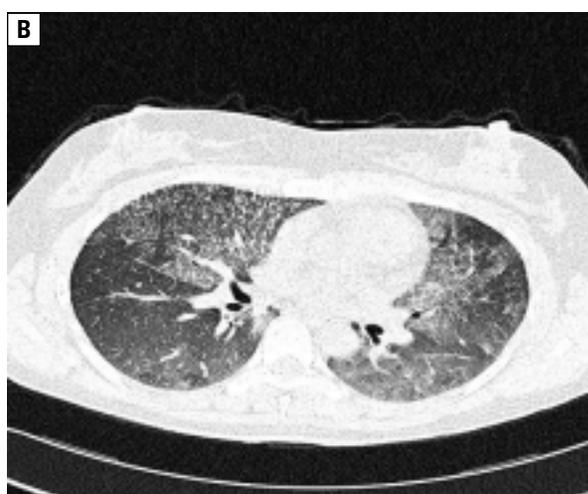


Figure 2. High resolution computed tomography (21.06.2007) **A** — ground-glass opacities with predominant upper distribution; **B** — thickened septal lines in the middle and lower lung fields

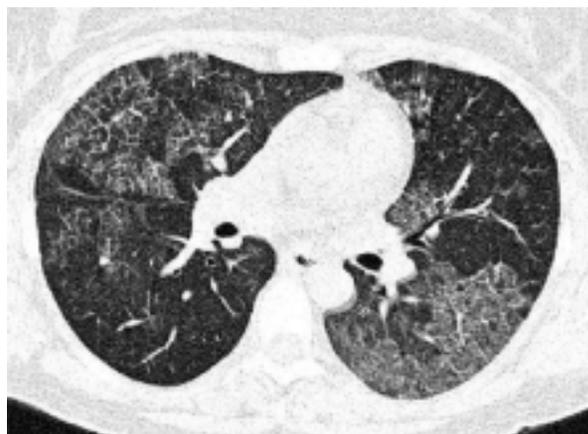


Figure 3. High resolution computed tomography (29.06.2009) — in comparison with previous examinations thickened septal lines superimposed on ground-glass opacities are forming cobblestones-like area

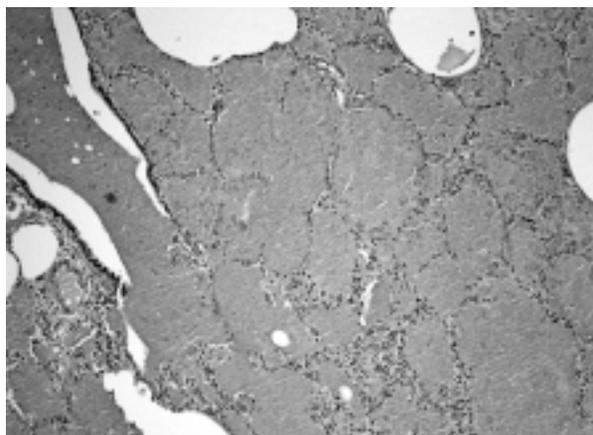


Figure 4. Autoimmunological pulmonary alveolar proteinosis. Alveolar spaces are filled with finely granular eosinophilic material. The alveolar septa are thin and preserved; microphotograph; H + E stain; high magnification.

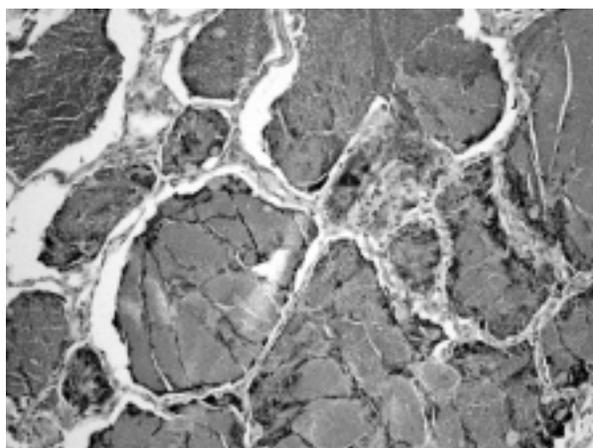


Figure 5. Autoimmunological pulmonary alveolar proteinosis. Finely granular material stain with periodic acid-schiff (PAS); microphotograph; PAS stain; high magnification

The patient remains under observation, and due to the oligosymptomatic course she has not required treatment so far.

Discussion

Pulmonary alveolar proteinosis is a rare condition, which typically poses no diagnostic problems due to the characteristic appearance of the lungs on HRCT. In the case of our patient, preliminary assessment of the radiological findings on lung HRCT suggested allergic alveolitis. An argument against this diagnosis was the clinical presentation that was uncharacteristic of allergic alveolitis as the patient had hardly any symptoms and only mildly abnormal pulmonary function compared to the significant abnormalities on HRCT. Furthermore, no antibodies to the most common anti-

gens triggering allergic alveolitis were detected. The baseline HRCT presentation was not typical of proteinosis, which is characterised by ground-glass opacities and reticular changes forming a cobblestone-like pattern. Areas of affected parenchyma are clearly delineated from the remaining portions of the parenchyma and form the so-called geographic pattern.

In our patient, due to technical reasons, BAL could not be performed. When performed in patients with alveolar proteinosis, BAL reveals extracellular eosinophilic deposits with a positive PAS stain. BAL is a very important tool in the evaluation of patients with suspected alveolar proteinosis and may be sufficient to establish this diagnosis in patients with a typical HRCT presentation [13].

The diagnosis was based on the results of an open lung biopsy, a procedure recommended to confirm the disease, particularly where BAL cannot be performed or is inconclusive. Microscopic examination of pulmonary parenchymal biopsies in patients with alveolar proteinosis reveals, as was the case with our patient, alveolar spaces filled with finely granular, eosinophilic material. The interalveolar septa are thin and intact. No remodelling of the pulmonary structure is observed. The PAS reaction is helpful in confirming the diagnosis of PAP; when applied, it causes the material that fills the alveoli to appear dark pink [14].

Currently, the diagnosis of APAP requires determination of antibodies to GM-CSF, which has been done in the case of our patient. An argument to support this diagnosis was also provided by the clinical data (no co-morbidities, no history of exposure to dusts).

Our patient was not offered any treatment due to the mild clinical presentation and only mildly abnormal pulmonary function.

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