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Pulmonary Alveolar Proteinosis: Case Report

Abstract

Pulmonary alveolar proteinosis is a rare disease caused by impaired surfactant clearance, and as a result, accumulation of protein-lipid substance in alveoli. The presented case study demonstrates the characteristics of this disease — a vague clinical pattern that does not correspond to the extensive changes in lung tissue detected via X-ray and computed tomography, which resulted in the late diagnosis of this disease. Pulmonary alveolar proteinosis was confirmed morphologically.

Key words: *pulmonary alveolar proteinosis; diagnosis*

BALF — bronchoalveolar lavage fluid, CT — computed tomography, DLCO — diffusing capacity of the lungs for carbon monoxide (II), ERF — external respiration function, GM-CSF — granulocyte-macrophage colony-stimulating factor, PaO_2 — oxygen partial pressure, PAP — pulmonary alveolar proteinosis, SaO_2 — oxygen saturation, TBAL — total bronchoalveolar lavage, TO — thoracic organs, VTS — videothoracoscopy

Pulmonary alveolar proteinosis (PAP) is a disease caused by impaired surfactant clearance, and as a result, the accumulation of protein-lipid substances in alveoli, which leads to impaired gas diffusion and progressive respiratory failure [1].

Rosen S.H. et al. (1958) first described this disease. The prevalence of PAP is 1–4 per 1 million population. The typical age at the onset of the disease is 30–50 years; the disease is less common in children and elderly patients; the men-to-women ratio is 2–3:1 [1].

There are three forms of PAP: congenital (genetic), autoimmune (idiopathic) and secondary. The genetic form results from mutations in genes that encode the structure of surfactant proteins B and C or β chain of granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor. The secondary form develops with underlying tumor processes of various localization, severe immunodeficiencies or due to inhalation damage to pulmonary parenchyma by inorganic dust or toxic gas. In most cases (90%), PAP is autoimmune and is characterized by the formation of antibodies against GM-CSF.

The pathogenesis of alveolar proteinosis is based on impaired surfactant metabolism, which is a key component in alveoli, which prevents their collapse at the end of exhalation by reducing surface tension. The process of surfactant inactivation by its transition to surface inactive substances is carried out by type II alveolocytes and alveolar macrophages, and is controlled by GM-CSF, which is a polypeptide cytokine. Antibodies against GM-CSF bind and block the biological potential of the surfactant, which impairs the interaction of GM-CSF with cell receptors. As a result, target cells receive no signal for surfactant cleavage, which leads to its excess production and accumulation in alveoli, which reduces the gas exchange surface [1].

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This disease develops slowly. Its course can be asymptomatic for a long time; X-ray of thoracic organs can accidentally reveal the disease. The principal clinical sign of PAP is slowly progressing dyspnea accompanied by low-productive cough, chest pain, rapid fatigue, sweating, and weight loss. Most patients with PAP (53–85%) smoke; many of them report occupational hazards [2].

During pulmonary function (PF) test, most cases showed ventilation disorders of the restrictive type; 30% of patients showed no PF disorder. All patients had impaired diffusion capacity of the lungs, decrease in DLCO (diffusion capacity of the lung for carbon monoxide) reached 40–50% [2].

X-ray scans of thoracic organs (TO) in patients with PAP show symmetrical bilateral shadowing primarily in perihilar and basal lung fields. There is no correlation between X-ray data and clinical signs — significant radiological changes may be accompanied by vague clinical symptoms [3].

Computed tomography (CT) is the main method for PAP diagnosis. It shows areas of GGO in both lungs with distinct boundaries from unchanged parenchyma; diffuse shadows are map-like, with alternation of healthy and abnormal areas. The thickening of interlobular septa in areas of GGO results in a "crazy paving" pattern, which is typical for PAP but does not have high specificity and sensitivity [4].

Bronchoalveolar swabs are milky-opaque; cytology results show amorphous masses with macrophages having multiple PAS-positive vacuoles in their cytoplasm [5].

Transbronchial and open lung biopsy reveal alveolar cavities filled with PAS-positive granular material; there were needle-shaped cholesterol structures, foamy macrophages, more intensely colored oval bodies; interalveolar septa are usually thin, of normal structure, and in some cases, their moderate fibrosis is described [5].

The following is a case study of pulmonary alveolar proteinosis.

Case Report

Patient M., 37 years old. In October 2019, he visited a local clinic with complaints of low-productive cough, feeling of chest congestion, tightness, shortness of breath with moderate physical exertion, and fatigue.

According to the patient, from 2016, he occasionally complained of cough with mucous sputum, chest congestion, weakness, and low-grade fever. He sought medical attention with these complaints in September 2016 for the first time; X-ray of TO revealed community-acquired bilateral lower lobe pneumonia. The patient was hospitalized; antibacterial therapy was carried out with a positive clinical and radiological effect (according to the patient and medical records).

In February–March 2017, complaints appeared again: cough, a feeling of chest congestion. According to X-ray of TO, bilateral infiltration in the lower parts of lungs was detected again. The patient was hospitalized in the therapeutic department; antibacterial therapy was performed. According to the patient, he was discharged with clinical and radiological improvement.

In 2017, the patient felt well; he noted an occasional cough with mucous expectoration.

In May 2018, the patient visited a pulmonologist at a private clinic with complaints of dyspnea when climbing to the 3th–4th floor and a feeling of chest congestion and tightness. The patient was provisionally diagnosed with asthma; combination inhalation drugs were prescribed, but the patient noticed no effect of their use and stopped treatment on his own accord.

In February 2019, cough with sputum, dyspnea and chest congestion increased, and weakness and malaise appeared. X-ray again revealed infiltrative-type bilateral changes in lung tissue. The patient was treated for community-acquired pneumonia at a private clinic. Due to the lack of significant clinical and radiological changes, the patient underwent CT of TO for the first time, which revealed the thickening of interlobular septa of both lungs, as well as multiple areas of lung tissue consolidation with ground-glass appearance. At discharge, the patient was recommended to consult a pulmonologist, but he did not follow these recommendations.

From anamnesis morbi: the patient smokes 15–18 cigarettes per day for 15 years, smoking index is 12 pack/years, he has been working at a bearing factory for 18 years, there are occupational hazards in the form of contact with hydrocarbons. No history of allergies.

Physical examination results: General condition is satisfactory. Skin is pale pink, no rash. Chest is hypersthenic, symmetrical, both halves equally participate in breathing. Respiratory rate — 18 breaths per minute. Chest is painless on palpation, resistant, vocal fremitus is equal in all lung fields. Percussion sound over lungs without changes, auscultatory decreased vesicular breath sounds, no rales. Heart rhythm is correct, tones are clear. Pulse 78 beats per min. Blood pressure 130/80 mm Hg. on both arms. Endocrine, digestive and urinary systems within normal. No pathological findings in CBC, common urinalysis, blood biochemistry. No data for HIV, tuberculosis, autoimmune diseases, neoplastic processes were obtained during examination.

X-ray scan of TO (Fig. 1) revealed areas of bilateral lung tissue infiltration with an underlying increased pulmonary vascularity. CT of TO performed in November 2019 (Fig. 2) revealed interstitial changes in the form of map-like diffuse GGO, thickened interlobular septa. Mediastinal and hilar lymph nodes were not enlarged; the negative trend was revealed compared to the images taken in March 2019.

Changes in PF, oxygen saturation (SaO_2) are shown in Table 1. Fibrobronchoscopy revealed no abnormality.

After examination together with a thoracic surgeon, it was decided to perform videothoracoscopy (VTS). In November 2019, VTS was performed with atypical resection of the upper lobe of the left lung and biopsy of the mediastinal lymph node. Histological results: "an area of the lung with focal collection of eosinophil granule substance in the lumen of alveoli"; cytological test result — "in scrape — masses of structureless substance, macrophages."

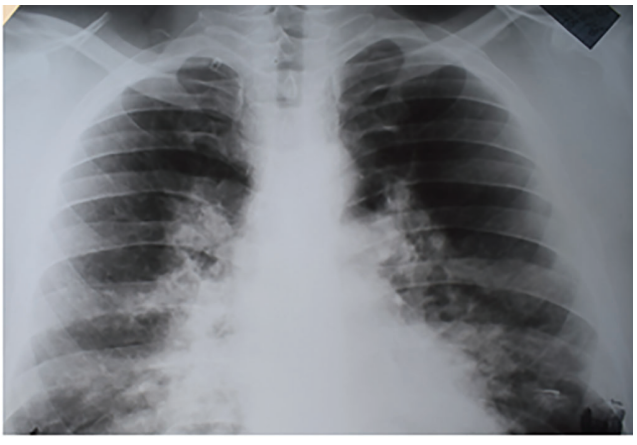


Fig. 1. X-ray scan of TO *reveals symmetrical bilateral shadowing primarily in perihilar and basal lung fields.*

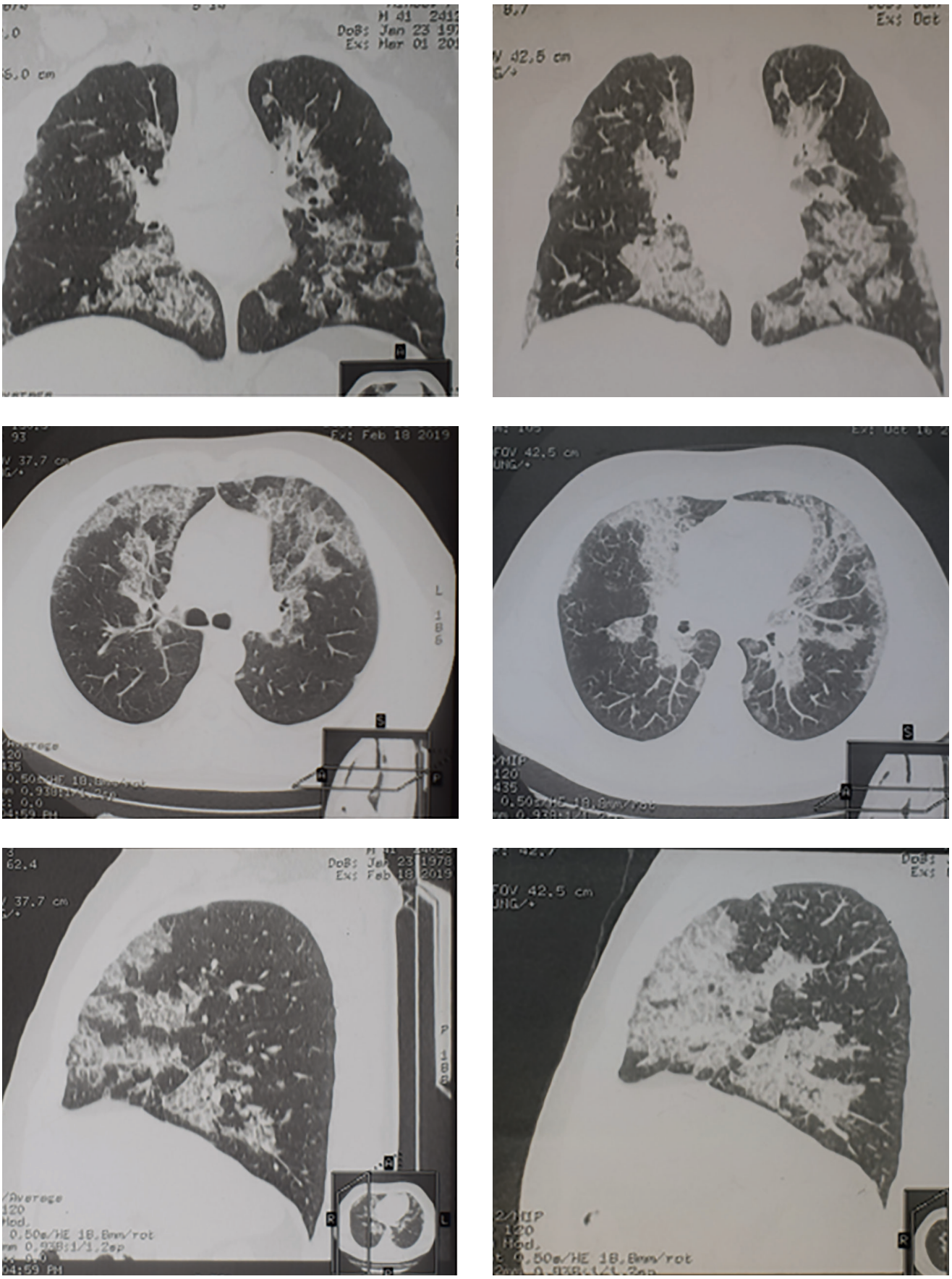
Samples were re-examined at the Federal State Budgetary Institution "Pulmonology Research Institute of the Federal Medical and Biological Agency" (FSBI "Pulmonology Research Institute", FMBA of Russia) by A.L. Chernyaev, Dr. Med. Sci., Prof. and M. V. Samsonova, Dr. Med. Sci. The description was as follows: granular, eosinophilic substance in the lumens of alveoli, interalveolar septa are thin, of normal structure, starch granules are found; conclusion: pulmonary alveolar proteinosis.

In January 2020, the patient was admitted to the Pulmonary Department for further examination: cardiac echocardiography revealed no pathology; PF parameters decreased (Table 1). A 6-minute walk test was performed: pulse before physical exertion was 72 beats per minute, SaO_2 95%; after physical exertion — 82 beats per minute, SaO_2 92%, distance covered was 356 meters. Taking into account significant dyspnea and limitation of physical activity, therapeutic total bronchoalveolar lavage (TBAL) was indicated; for this purpose the patient was referred to the FSBI "Pulmonology Research Institute", FMBA of Russia.

Discussion

Alveolar proteinosis is a rare interstitial lung disease. According to Ioachimescu O. C. et al. (2006), about 500 cases of this disease are described in literature. This disease is mainly found in men aged 30–50 years (this clinical case presents a man, aged 37 years). Clinical evidence varies greatly: from asymptomatic to a rapidly progressing course.

The disease is often described as a separate nosological form; in some cases, it is caused by a genetic mutation in surfactant proteins, which results in impaired surfactant production by type II alveolocytes. Secondary PAP results from exposure to several damaging factors that lead to dysfunction and decrease the number of alveolar macrophages. Etiological factors of secondary PAP include viral and bacterial infections (mycobacteria, fungi, pneumocysts), leukemia, lymphomas, immunosuppressive conditions, including drug-induced conditions, etc.



A *B*

***Fig. 2. Computed tomography of TO**, March, February 2019 (A), October 2019 (B). There are interstitial changes in the form of map-like ground-glass opacity across all lung fields.*

Table 1. *Changes in clinical signs and instrumental findings*

	September 2016	March 2017	May/ 2018	February/ 2019	October/ 2019	January/ 2020
Body temperature, °C	37.3	37.5	36.8	37.2	37.1	36.7
RR, min					18	20
SaO_2, %					95	93
PF, %	FVC 96% FEV_1 98%				FVC 89% FEV_1 88%	FVC 79% FEV_1, 83%
Diagnosis:	Community-acquired bilateral polysegmental pneumonia	Community-acquired bilateral polysegmental pneumonia	Asthma	Community-acquired bilateral polysegmental pneumonia	Interstitial lung disease	Pulmonary alveolar proteinosis

Note: RR — respiratory rate, SaO_2 — oxygen saturation, PF — pulmonary function, FVC — forced vital capacity, FEV_1 — forced expiratory volume per 1 sec.

According to the literature, 39–48% of patients with PAP face occupational hazards; there were reports of cases of secondary PAP in workers of plants for the extraction and processing of indium, coal dust, and harmful gases [4]. The patient in the clinical case also faced occupational hazards (contact with hydrocarbons). In 70% of cases, alveolar proteinosis is found in smokers (said patient is an active smoker).

This case study was characterized by a wave-like disease course with vague clinical signs in the form of cough, malaise, fatigue, shortness of breath, and a feeling of chest congestion. Bilateral infiltrations that were repeatedly found on X-ray of TO, together with the abovementioned complaints, were considered as bilateral pneumonia; therefore, the patient was hospitalized three times, and antibiotic treatment was performed. The first CT of TO was performed 3 years after the first respiratory symptoms in February 2019. The results described bilateral interstitial changes, but the patient was not examined further and was allowed to work with occupational hazards.

The CT of TO in November 2019 revealed changes that are typical for PAP: reticular changes, ground-glass opacity, map-like distribution of shadowed and healthy areas; however, given the vague clinical evidence and no possibility of bronchoalveolar lavage fluid (BALF) test, the patient underwent VTS with biopsy. According to the literature, histological results lead to a false conclusion in 20–30% of cases [4]. In our study, the pathologist suspected alveolar proteinosis, and this diagnosis was confirmed after re-examining samples at the FSBI "Pulmonology Research Institute", FMBA of Russia.

Currently, the conventional method of managing PAP is total bronchoalveolar lavage; this method is indicated for patients with dyspnea at rest, with partial oxygen pressure (PaO_2) less than 65 mm Hg, oxygen desaturation during a 6-minute walking test [1]. Symptoms improve in 85% of cases following TBAL. Results of retrospective data analysis show an improvement in patient prognosis: 5-year survival rate is 94% in the TBAL group compared to 85% in the group without TBAL [1]. Prognosis for PAP is unpredictable; spontaneous remission is reported in less than 10% of patients. According to the study, which included 39 asymptomatic patients with PAP, the condition remained stable in 64% of patients, while the disease progressed in 7% of cases [5]. Early diagnosis of the disease and timely referral for TBAL are important for the improvement of prognosis.

Conclusion

PAP is rare in medical practice and poses significant challenges in diagnosis due to the absence of pathognomonic clinical signs. In the course of differential diagnosis, many etiological factors and nonspecific symptoms with no significant pathognomonic signs of the disease should be considered. Under these circumstances, a detailed study of patient history, laboratory, instrumental, morphological, and X-ray methods of investigation is important, including timely computed

tomography of thoracic organs for the purpose of differential diagnosis with pneumocystic pneumonia, pulmonary tuberculosis, fibrosing alveolitis, malignant neoplasms, etc. In the present case study, about 3 years elapsed from the onset of the disease to the diagnosis; bilateral polysegmental pneumonia was repeatedly diagnosed, followed by antibiotic treatment. Clinical signs of this disease were nonspecific. However, the wave-like course of the disease and the mismatch between minimal clinical signs and the significant radiological changes in lung tissue caught the attention of clinicians and helped avoid diagnostic errors.-

Author Contribution:

N.A. Karoli (ORCID ID: https://orcid.org/0000-0002-7464-826X): article concept, analysis, data interpretation, manuscript writing, intellectual content verification, manuscript approval for publication.

E.E. Arhangelskaja: analysis, data interpretation, manuscript writing.

O.T. Zarmanbetova (ORCID ID: https://orcid.org/0000-0003-0201-7757): data collection, analysis, interpretation of results.

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