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PRACA ORYGINALNA

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# Pulmonary alveolar proteinosis during a 30-year observation. Diagnosis and treatment

## Proteinoza pęcherzyków płucnych w 30-letniej obserwacji. Diagnostyka i leczenie

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**Abstract**

**Introduction:** Pulmonary alveolar proteinosis (PAP) is a rare disease characterised by the abnormal accumulation of surfactant-like material in macrophages within the alveolar spaces and distal bronchioles. The course of the disease is variable and the prognosis is often good. However, progressive disease in some patients can cause respiratory dysfunction and can be life threatening. In this situation, the only effective treatment is whole lung lavage.

The objective of the study was to present the characteristics and the course of pulmonary alveolar proteinosis in our own material, the diagnostic methods used, the indications for treatment and the treatment efficacy.

**Material and methods:** Retrospective analysis included 17 patients: 6 women and 11 men, aged from 32 to 56 years, who were observed in the Third Lung Department of Pneumonology at the National Institute of Tuberculosis and Lung Diseases between 1984 and 2013. In all patients chest X-ray, pulmonary function test and blood gases were performed. In 15 patients, high-resolution computed tomography (HRCT) was obtained. Bronchoscopy was performed in all of the patients, and in 7/17, bronchoalveolar lavage (BAL) was carried out. Fourteen patients underwent open lung biopsy. The indications for whole lung lavage (WLL) were progression of dyspnoea with restriction of daily activity and/or hypoxaemia.

**Results:** In most of the patients (13/17) the diagnosis was established outside our institute. Patients were referred to our department to establish further procedures. The criteria of diagnosis of PAP in most patients (16/17) was the histological examination of lung tissue, obtained by open lung biopsy (14 cases) and transbronchial lung biopsy (TBLB) (2 cases). Only in one patient the diagnosis was established on the basis of BAL. HRCT imaging was characteristic of proteinosis in 11/15 patients, and BAL examination in 6/7 patients, in whom BAL was performed. In four patients, who had been exposed to injurious factors for many years, secondary proteinosis was recognised; in other patients, no exposure or no other disease was found, and primary alveolar proteinosis was diagnosed. In one patient granulocyte macrophage colony stimulating factor autoantibody was detected. The majority of patients (10/17) had clinical symptoms at the diagnosis. The most commonly reported was dyspnoea, followed by respiratory tract infections. The most common abnormality (12/17) in pulmonary lung test was a decrease of diffusing capacity of the lung for carbon monoxide (DLCO). Respiratory distress at rest was found in two patients. Patients were observed for the period of 6 months to 19 years. Spontaneous partial remission was observed in 10 out of 13 untreated patients, including one complete remission; in 3 cases stabilisation was found in radiological examinations; and in other 4 patients, whole lung lavage

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was used, resulting in clinical improvement with partial resolution of lesions in radiological examinations in 3 patients. In one patient, despite WLL being repeated three times, improvement was not achieved.

**Conclusions:** Pulmonary alveolar proteinosis is a rare interstitial disease with a mild course in most cases. In 13/17 patients diagnosis was based on histological examination of samples from open lung biopsy. The presented patients were observed in the years 1984–2004, and at that time histologic examination was the main diagnostic method. The most common abnormality in pulmonary function tests was decrease of DLCO. In most cases, spontaneous remission of the disease was observed. In four patients with severe course of PAP, WLL was performed with subjective, functional and radiological improvement in 3 of them.

**Key words:** pulmonary alveolar proteinosis, diagnosis, clinical course, whole lung lavage

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## Streszczenie

**Wstęp:** Proteinoza pęcherzyków płucnych (PPP) jest rzadką chorobą charakteryzującą się nieprawidłowym gromadzeniem substancji surfaktantopodobnej w makrofagach pęcherzyków płucnych i oskrzelikach końcowych. Przebieg choroby jest różnorodny, a rokowanie często jest dobre. U części chorych proces jednak postępuje oraz może być przyczyną dysfunkcji układu oddechowego i upośledzać jakość życia. W takiej sytuacji jedynym skutecznym leczeniem jest płukanie całych płuc.

Celem pracy jest przedstawienie charakterystyki i przebiegu PPP w materiale własnym z prześledzeniem metod rozpoznawania i okoliczności kierowania chorych do Instytutu Gruźlicy i Chorób Płuc z uwzględnieniem wskazań do leczenia i oceną jego efektywności.

**Materiał i metody:** Do retrospektywnej analizy włączono 17 chorych: 6 kobiet i 11 mężczyzn w wieku 32–56 lat obserwowanych w III Klinice Chorób Płuc Instytutu Gruźlicy w latach 1984–2013. Wszyscy chorzy mieli wykonane badania radiologiczne klatki piersiowej: badanie konwencjonalne (RTG) oraz 15 chorych — tomografię komputerową wysokiej rozdzielczości (HRCT), badania czynnościowe płuc i gazometrię. U wszystkich wykonano bronchoskopię, u 7/17 — płukanie oskrzelowo-pęcherzykowe (BAL), czternaścioro chorych było poddanych otwartej biopsji płuca (OBP).

Kryteriami kwalifikującymi do płukania całych płuc (WLL) była progresja choroby z dusznością ograniczającą dzienną aktywność i/lub hipoksemia.

**Wyniki:** U 13/17 chorych rozpoznanie ustalono poza Instytutem Gruźlicy. Chorych kierowano do Instytutu Gruźlicy (IG) w celu ustalenia dalszego postępowania. Podstawą rozpoznania PPP było badanie histologiczne wycinków z płuca pobranych podczas otwartej biopsji (w 14 przypadkach) i podczas biopsji przezoskrzelowej (w 2 przypadkach). Tylko u 1 chorego rozpoznanie ustalono w oparciu o badanie popłuczyn oskrzelowo-pęcherzykowych. Obraz płuc w HRCT był charakterystyczny dla proteinozy w 11/15 przypadkach, a obraz płynu z płukania oskrzelowo-pęcherzykowego w 6/7 przypadkach, w których wykonano BAL. U 4 chorych narażonych na czynniki szkodliwe, rozpoznano proteinozę wtórną, u pozostałych nie znaleziono narażenia na zanieczyszczenia środowiskowe ani choroby sprzyjającej zachorowaniu — rozpoznano zatem pierwotną proteinozę pęcherzykową. U jednej chorej wykryto przeciwciała przeciw czynnikowi stymulującemu dla monocytów/makrofagów (GM-CSF) w surowicy, co pozwoliło na rozpoznanie autoimmunologicznej postaci proteinozy (aPPP). Większość chorych (10/17) zgłaszała objawy w momencie rozpoznania: duszność lub objawy zakażenia dróg oddechowych. Najczęstszym zaburzeniem w badaniach czynnościowych płuc (12/17) było obniżenie wskaźnika dyfuzji dla tlenku węgla (DLCO). U 2 chorych stwierdzono niewydolność oddechową w spoczynku. Chorych obserwowano od 6 miesięcy do 19 lat. Samoistną częściową remisję zmian obserwowano u 10 spośród 13 chorych nieleczonych, w tym u jednego chorego remisję całkowitą, w 3 przypadkach stwierdzono stabilizację zmian w badaniach radiologicznych, a u kolejnych 4 chorych zastosowano leczenie w postaci płukania całych płuc, uzyskując u 3 z nich poprawę kliniczną oraz częściową remisję zmian w badaniach radiologicznych. U jednego chorego pomimo trzykrotnego płukania nie uzyskano poprawy.

**Wnioski:** Proteinoza pęcherzyków płucnych jest rzadką chorobą śródmiąższową, w większości przypadków o łagodnym przebiegu. U 13/17 chorych rozpoznanie ustalono poza Instytutem Gruźlicy na podsatawie badań histopatologicznych wycinków z płuca pobranych podczas otwartej biopsji płuca, co jest głównie związane z czasem, z jakiego pochodzi większość chorych (1984–2004), kiedy to otwarta biopsja płuca była wymaganym badaniem diagnostycznym. Po ustaleniu rozpoznania chorzy byli kierowani do Instytutu Gruźlicy w celu ustalenia dalszego postępowania. Najczęściej stwierdzanym zaburzeniem w badaniach czynnościowych płuc było obniżenie DLCO. W większości przypadków obserwowano spontaniczną remisję zmian. U czterech chorych z PAP o ciężkim przebiegu zastosowano płukanie całych płuc, uzyskując w 3 przypadkach poprawę.

**Słowa kluczowe:** proteinoza pęcherzyków płucnych, diagnostyka, przebieg kliniczny, płukanie całych płuc

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## Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterised by the accumulation of surfactant lipids and protein in the alveolar spaces. The incidence of PAP worldwide is estimated at approximately 0.2/1,000,000 people per year, and the morbidity rate at 3.7/1,000,000 [1]. According to the National Register of PAP in Japan, in 2008, the incidence and morbidity were

higher and amounted, respectively, to 0.49 and 6.2 per 1,000,000 people in the general population [2]. The mean age at the moment of diagnosis is 39 years for men and 35 for women. Among patients who smoke cigarettes, the prevalence of PAP is more frequent in men (M:W = 2.65:1), whereas among non-smokers, it is comparable for both sexes (M:W = 0.69:1) [3].

Pulmonary alveolar proteinosis was described for the first time in 1958 by Rosen, Castleman B and Liebow, who, in histological examinations of the material from 26 patients, paid attention to the presence of distinctive protein and lipid material that positively passed the examination using periodic acid-Schiff staining (PAS), accumulated in the alveoli and was without the features of fibrosis or inflammation [4]. Several years later, Gordinier and Larson named this substance surfactant [5]. The next 40 years of research showed that excessive accumulation of surfactant in the alveoli is caused by impaired catabolism of alveolar macrophages [6]. In 1994, a correlation was found between homeostasis of surfactant and granulocyte macrophage colony stimulating factor (GM-CSF), which plays a crucial role in the pathogenesis of the disorder [7].

As was mentioned previously, PAP is characterised by excessive accumulation of surfactant in the alveoli. Surfactant includes four proteins: apoproteins A, B, C and D, and lipids, such as: phospholipids, cholesterol, aminoglycerol and free fatty acids. In proteinosis, macrophages show many defects, such as impaired motility, adherence, chemotaxis, the power of phagocytosis and killing microorganisms, which increases the tendency to infections [6]. GM-CSF shortage causes macrophage dysfunction and excessive accumulation of surfactant in the alveoli [8, 9].

Detection of GM-CSF autoantibodies in serum and bronchial washings (BAL, bronchoalveolar lavage) of patients with PAP allowed PAP to be classified as an autoimmune disorder [10].

Autoimmune pulmonary alveolar proteinosis (aPAP) is the most frequent form of the disorder, comprising up to 90% of all cases. Apart from high-resolution computed tomography (HRCT), BAL and histologic examination, diagnosis is based on detection of GM-CSF autoantibodies in serum or bronchial washings [3]. Secondary PAP is a more rare form of the disorder. It develops in the course of other diseases or exposures that cause an increase in the count or dysfunction of alveolar macrophages (less than 10% of all cases). The most rare is the congenital form, caused by mutations of genes encoding for surfactant proteins or protein transporting ABCA3, and developing during the neonatal period [3, 11].

Clinical symptoms of PAP are uncharacteristic, and its course is usually mild and does not impair significantly the function of the lungs. A considerable proportion of patients do not notice symptoms of the disease despite distinct lesions in the lungs, which in some patients may regress spontaneously. In cases that require treatment, whole lung lavage (WLL) is used [11].

Cases of proteinosis have already been presented in Poland [12–15]; however, they are sparse, probably due to infrequent prevalence.

The objective of the study was to present the characteristics and the course of PAP in our own material, the investigation of diagnostic methods and reasons for referral of patients to the National Institute of Tuberculosis and Lung Diseases, indications for treatment and evaluation of efficacy thereof.

## Material and methods

Material included 17 patients with PAP (6 women and 11 men), 32–56 years of age, hospitalised at the Third Lung Department of the National Institute of Tuberculosis and Lung Diseases in the years 1984–2013. The patients had the following examinations performed: chest X-ray (Fig. 1), HRCT (15 patients) and lung function tests: blood

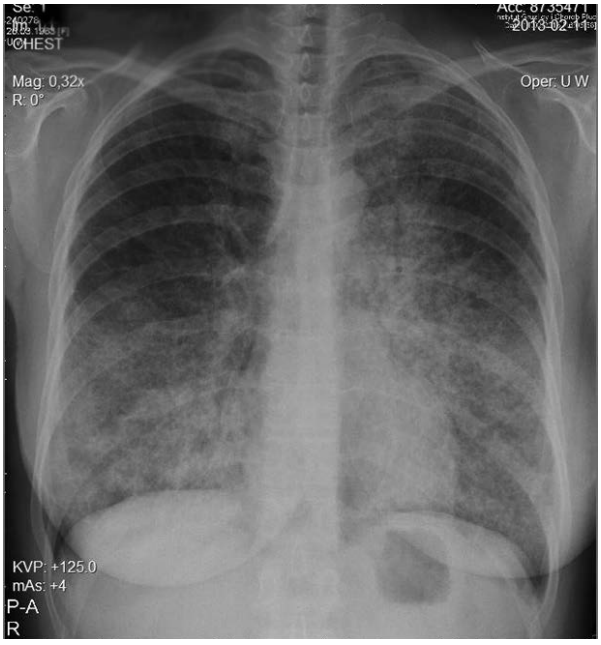


**Figure 1.** Chest X–ray showing diffuse bilateral alveolar infiltrates

**Rycina 1.** Badanie RTG klatki piersiowej przedstawiające rozsiane obustronne zagęszczenia pęcherzykowe

gases and plethysmography with determination of diffusing capacity of the lung for carbon monoxide (DLCO). In all of the patients bronchoscopy was performed, and BAL was done in 7/17.

In 14 patients open lung biopsy was obtained (OLB), and in a further two, some other type of lung biopsy. Additionally, one female patient, as well as OLB, had the level of serum GM-CSF autoantibodies determined.

Criteria used for WLL treatment were progression of the disease with dyspnoea that hindered everyday activities and/or hypoxaemia ($Pa0_2$ ≤ 60 mm Hg).

## Results

In the presented material, the majority constituted men (64.7%), M:W = 1.8:1. The mean age of patients was 42.5 years. Most patients (13/17) were diagnosed at other centres, beyond the National Institute of Tuberculosis. All of them underwent open lung biopsy, and 11 patients received definite histological diagnosis. In the remaining two patients, unspecified interstitial disease (case nº 9) or pneumocystis (case nº 17) were diagnosed. The patients were referred to the National Institute of Tuberculosis in order to establish further proceedings, including indication for WLL. One of these patients (case nº 9) was referred after 12 years of observation, due to interstitial disease, and the cause was pneumonia that had not regressed after treatment with antibiotics. 4 out of 17 patients were referred in order to establish causes of disseminated lesions in the lungs. In these cases, diagnosis was made at the National Institute of Tuberculosis, based on histological examination of lung specimens taken during OLB or transbronchial lung biopsy (TBLB) (two patients: cases nº 8 and 7). In one case (nº 10), diagnosis was established based on the result of BAL. Bronchoscopy was performed in all patients, but only 7/17 subjects underwent bronchoalveolar lavage; in 6 patients the fluid was characteristic and showed positive PAS staining.

The time that passed from the appearance of symptoms or detection of changes at chest X-ray to the moment of diagnosis was from 1 month to 12 years. In 7 patients, lesions in the lungs were found by accident, in 10/17 — due to ailments. The most frequent reason of performing chest X-ray was dyspnoea (6 patients), symptoms of infection of the respiratory system (3 patients) and pain in the chest (1 patient). In physical examination, only in one patient crepitations at the base of the lung and clubbed fingers were found. Most patients smoked cigarettes (13/17). 4 out of 17 patients reported exposure to harmful factors: cement dust, wood dust, sawdust and chemical compounds — these patients were diagnosed with secondary proteinosis (Table 1). The remaining patients were not exposed nor did they have a disease that favoured proteinosis, so the primary form of the disorder was diagnosed. In one patient who had the test performed, serum GM-CSF autoantibodies were found (case nº 1).

In all patients, chest X-ray showed a bilateral macular density located mainly in the perihilar area and in lower or upper lung lobes (Fig. 1), whereas in 15 patients, HRCT showed ground-glass opacities with the symptoms of the so-called "crazy paving" pattern, and separated areas of healthy parenchyma. In 13/17 patients, lesions found at X-ray were symmetrical, and in 4 patients (cases nº 5, 13, 14 and 17) they were asymmetrical. Based on HRCT, in 11 cases, radiologists suggested the diagnosis of PAP (Fig. 1A, B); in 4 patients, they considered another interstitial disease: in two subjects (cases nº 1 and 13) — allergic alveolitis, and in the successive two patients (cases nº 4 and 16) — idiopathic interstitial pneumonia. In cases nº 5 and 9, HRCT assays were not available and interstitial lung disease was diagnosed based on chest X-ray.

Pulmonary function tests showed ventilation disorders with restriction in three patients: in one patient — of mild degree, and the other two — of moderate degree. Reduced DLCO was found in 12 out of 17 patients; in 5 patients — of mild degree, in 4 — of moderate degree, and in 3 — of severe degree. Hypoxaemia (Pa02 < 70 mm Hg, but > 60 mm Hg) at rest was found in 8 patients, whereas respiratory insufficiency was diagnosed in 2 out of 17 patients (Table 2).

The observation time of patients lasted from 6 months to 19 years (median 4 years). Spontaneous partial remission of lesions was observed in 10 out of 13 untreated patients (69%) (Fig. 2A, B), including one patient with complete remission (case nº 6), and in 3 cases (30.7%) stabilisation of lesions was found at X-ray examination.

Four patients underwent whole lung lavage: in one patient it was performed once, in two patients — twice and in one patient — three times. Improvement in lung function was achieved (Table 3), and in three patients, partial remission of lesions at chest X-ray was observed (Fig. 2A, B). In one patient, despite whole lung lavage performed three times, improvement was not achieved. Comparison of the mean functional

**Table 1. Clinical characteristics of PAP patients in our own material**

**Tabela 1. Charakterystyka kliniczna chorych na proteinozę pęcherzyków płucnych w prezentowanym materiale własnym**

| Sex/ /age | Cigarette smoking | Exposure to injurious factors | Time to diagnosis | Symptoms at diagnosis | Diagnostic method | Date of diagnosis (year) | Time of follow up | Clinical course |
|---|---|---|---|---|---|---|---|---|
| 1.K/40 | – | – | 24 mth | – | OBP | 2009 | 4 years | SR |
| 2.K/56 . | + | – | 3 mth | chest pain | OBP | 2009 | 4 years | S |
| 3.K/49 | + | – | 2 mth | respiratory tract infection | OBP | 2005 | 8 years | SR |
| 4.K/47 | – | – | 3 mth | – | OBP | 2013 | 6 mth | SR |
| 5.K/44 | + | – | ND | dyspnoea | OBP | 1994 | 19 years | SR |
| 6.M/41 | – | cement dust | 2 mth | – | OBP, BAL | 2005 | 8 years | CSR |
| 7.M/53 | + | – | 5 mth | – | TBLB BAL | 2003 | 10 years | SR |
| 8.M/34 | + | sawdust | 12 mth | respiratory tract infection | TBLB BAL | 2005 | 8 years | S |
| 9.M/39 | + | – | 3 mth | dyspnoea | OBP | 1972 | 6 years | SR death during infection |
| 10.M/55 | + | – | 4 mth | – | BAL | 2012 | 7 mth | S |
| 11.M/38 | + | – | 1 mth | respiratory tract infection | OBP | 2012 | 1 year | SR |
| 12.M/55 | – | – | 2 mth | – | OBP | 2006 | 1 year | SR |
| 13.M/53 | + | wood dust | 2 mth | dyspnoea | OBP,BAL | 2012 | 1 year | SR |
| 14.M/38 | + | – | 3 mth | – | OBP | 2007 | 6 lat/years | WLL after 8 months since the diagnosis |
| 15.M/32 | + | – | 8 mth | dyspnoea | OBP | 2008 | 1 year | WLL at diagnosis |
| 16.M/42 | + | mercaptans, sulphur hydrogen chloride pit-coal dust | 12 mth | dyspnoea | OBP, BAL | 2001 | 11 years | WLL after 10 months since the diagnosis, death probably during infection |
| 17.K/49 | + | – | 4 mth | dyspnoea | OBP, BAL | 2012 | 6 mth | WLL after 3 months since the diagnosis |

OBP — open lung biopsy; BAL — bronchoalveolar lavage; TBLB — transbronchial lung biopsy; S — stabilizacjastabilisation; SR — spontaneous remission; CSR — complete idiopathic remission; WLL — whole lung lavage; ND — no data available

values of the respiratory system in the group that underwent lavage and in the group that was not classified to WLL, has shown distinct differences (Table 4).

Two patients died: one after 6 years of observation due to infectious complications (case n° 9), and the second one 11 years after diagnosis (case n° 16). Thirteen patients are under observation of the National Institute of Tuberculosis and Lung Diseases; these patients do not suffer from respiratory system troubles, and three of them occasionally have mild infections of the respiratory system (cases n° 1, 2, 3). There is no information about the remaining two patients (cases n° 12 and 15).

## Discussion

Pulmonary alveolar proteinosis is distinguished by excessive accumulation of phospholipids, surfactant lipids and protein in the alveolar spaces and distal bronchioles, which may lead to gas exchange disturbances and sometimes to respiratory insufficiency. The symptoms of the disorder are unspecific: cough, dyspnoea, lowered exercise tolerance and rarely pain of pleural nature in the chest. Approximately 20––30% of patients do not have clinical symptoms, and lesions in the lungs are found by accident. A disproportion between intensive radiological pathology and mild clinical symptoms is often

**Table 2. Pulmonary function test of PAP patients at the time of diagnosis**

**Tabela 2. Badania czynnościowe układu oddechowego chorych na PPP w chwili rozpoznania**

| Sex/age | VC L (%N) | TLC L (%N) | DLCO mmol/min/kPa (%N) | $PaO_2$ mm Hg |
|---|---|---|---|---|
| 1.K/40 | 3.9 (124%) | 5.41 (113.4%) | 5.78 (68.9%) | 80 |
| 2.K/56 | 3.18 (108%) | 4.87 (97%) | 6.76 (85%) | 80 |
| 3.K/49 | 2.62 (84.3%) | 4.15 (82.4%) | 5.39 (64.8%) | 62.2 |
| 4.K/47 | 3.00 (93.4%) | 4.51 (98.6%) | 5.26 (67.8%) | 64 |
| 5.K/44 | 3.0 (80%) | 3.75 (82%) | 4.9 (58%) | 66 |
| 6.M/41 | 4.55 (99.5%) | 6.15 (94.6%) | 9.20 (90.6%) | 87.5 |
| 7.M/53 | 4.48 (104%) | 7.15 (106%) | 7.97 (82%) | 61.5 |
| 8.M/34 | 5.18 (108.7%) | 6.55 (100.7%) | 6.06 (57.1%) | 75.4 |
| 9.M/39 | 2.95 (57%) | 4.53 (67%) | 8.45 (82.1%) | 68 |
| 10.M/55 | 5.11 (104.7%) | 6.92 (95.8%) | 7.45 (72.8%) | 74.2 |
| 11.M/38 | 6.35 (106.8%) | 8.35 (106.2%) | 11.05 (90.78%) | 75 |
| 12.M/55 | 3.79 (97.8%) | 5.45 (89.2%) | 6.24 (72%) | 76.9 |
| 13.M/53 | 3.61 (82.7%) | 5.54 (85.19) | 5.58 (60.05%) | 69 |
| 14.M/38 | 2.78 (67%) | 4.55 (77.6%) | 4.53 (47.9%) | 67 |
| 15.M/32 | 3.96 (81.6%) | 5.42 (83.4%) | 4.23 (39.1%) | 61 |
| 16.M/42 | 2.82 (59%) | 2.71 (58%) | 3.88 (39%) | 58 |
| 17.K/49 | 2.75 (86.6%) | 3.95 (85.2%) | 3.74 (38.8%) | 54 |

VC — vital capacity; TLC — total lung capacity; DLCO — diffusing capacity of the lung for carbon monoxide; $PaO_2$ — arterial oxygen tension

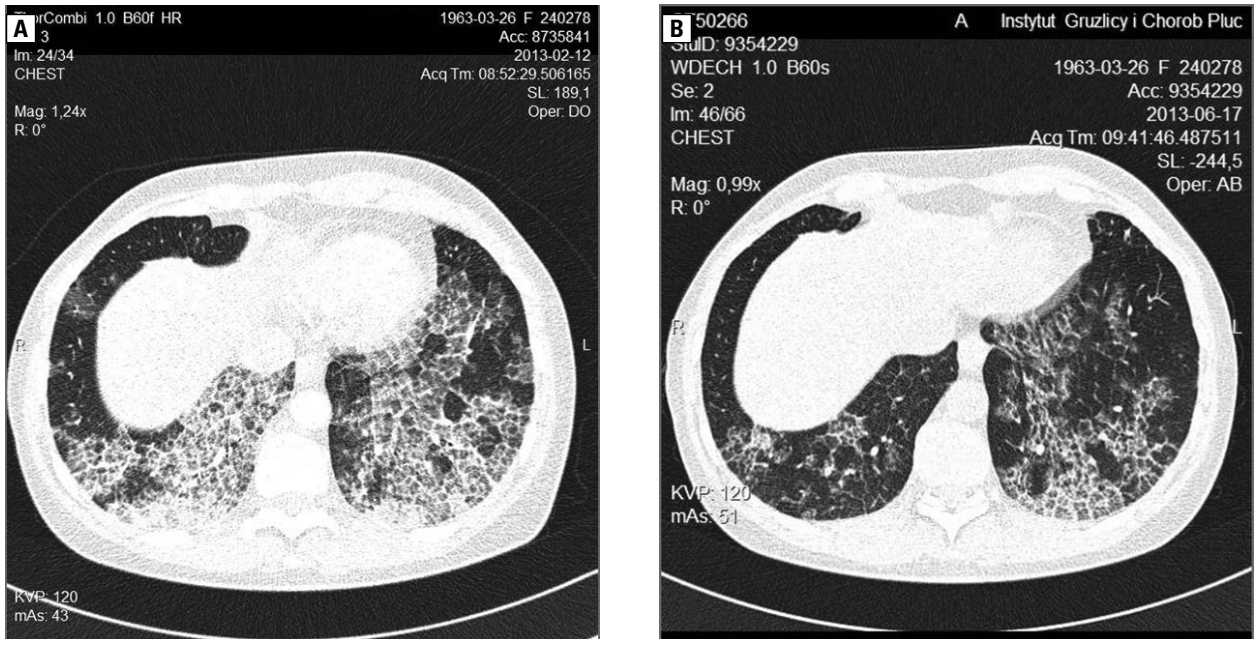


**Figure 2.** HRCT scan before (**A**) and after (**B**) whole lung lavage — visible partial regression of infiltrates

**Rycina 2.** Badanie tomografii komputerowej wysokiej rozdzielczości przed (**A**) i po (**B**) płukaniu płuc — widoczna częściowa regresja zmian

observed [3, 11]. In the study group, clinical symptoms occurred in 10 out of 17 patients (59%), and they were observed more rarely in comparison with other research. For example, in the retrospective analysis conducted on 241 patients with PAP, only 4 subjects (1.6%) did not report any ailments [16]. In another study, only 3 out of 70 patients (4.3%) were asymptomatic

**Table 3. The impact of whole lung lavage on respiratory parameters in four patients treated with WLL**

**Tabela 3. Wpływ płukania całych płuc na parametry oddechowe u 4 chorych leczonych płukaniem całych płuc**

| Case, sex/age | Parameter | Before WLL | After WLL |
|---|---|---|---|
| 14.M/38 | TLC | 4.16 L (70.9%N) | 4.40 L (72.2%N) |
| | VC | 2.56 L (64.1%N) | 3.18 L (76.2%N) |
| | DLCO | 2.96 L (31.5%N) | 4.48 L (46.2%N) |
| | $PaO_2$ [mm Hg] | 51 | 68 |
| 15.M/32 | TLC | 5.42 L (83.4%N) | 4.42 L (67%N) |
| | VC | 3.96 L (81.6%N) | 3.09 L (63%N) |
| | DLCO | 4.23 L (39.1%N) | 3.63 L (33%N) |
| | $PaO_2$ [mm Hg] | 61 | 46 |
| 16.M/42 | TLC | 2.56 L (55.3%N) | 3.9 L (66.2%N) |
| | VC | 2.5 L (57,2%N) | 3.5 L (67.4%N) |
| | DLCO | 3.69 L (38.1%N) | 5.4 L (53.2%N) |
| | $PaO_2$ [mm Hg] | 58 | 84 |
| 17.K/49 | TLC | 3.85 L (84.2%N) | 4.26 L (90%N) |
| | VC | 2.74 L (86.7%N) | 2.78 L (85%N) |
| | DLCO | 2.74 L (35.8%N) | 3.4 L (43%N) |
| | $PaO_2$ [mm Hg] | 49 | 60.7 |

TLC — total lung capacity; VC — vital capacity; DLCO — diffusing capacity of the lung for carbon monoxide; $PaO_2$ — arterial oxygen tension

**Table 4. The comparison between mean parameters of pulmonary function test in patients who underwent WLL, and in patients not classified to WLL**

**Tabela 4. Porównanie średnich wartości parametrów czynnościowych układu oddechowego u chorych, u których wykonano płukanie płuc, i u chorych nie kwalifikowanych do płukania**

| | Whole lung lavage | |
|---|---|---|
| **Parameter** | **Yes (N = 4)** | **No (N =13)** |
| $PaO_2$ (mm Hg) | 54.75 | 72.3 |
| $FEV_1$ (%N) | 82.3 | 93.0 |
| VC (%N) | 72.4 | 99.0 |
| TLC (%N) | 76.05 | 94.6 |
| DLCO (%N) | 36.12 | 71.7 |

$PaO_2$ — arterial oxygen tension; $FEV_1$ — forced expiratory volume in 1 second; VC — vital capacity; TLC — total lung capacity; DLCO — diffusing capacity of the lung for carbon monoxide

before diagnosis of PAP [17]. However, similar results were obtained by Sobiecka et al., who, in an analysis of 7 PAP patients, found symptomatic disease in 3 patients (42.8%) [12], and Inoue et al., who observed clinical symptoms in 68% of 223 patients [2]. The most frequent ailment reported by patients with PAP is dyspnoea [3]. In the study by Bonella et al., as many as 94% of patients complained about dyspnoea and poor exercise tolerance, 66% of patients had persistent cough, 49% had strength reduction and 43% had weight loss [17]. A comparison of the results of the chosen studies is presented in Table 5.

In PAP patients, areas of bilateral and symmetrical alveolar opacities are usually found at chest X-ray. The highest intensification of lesions is usually observed in perihilar areas, with omitted costophrenic angle, which is called butterfly wings, with the absence of radiological features of left ventricular insufficiency. One-sided or asymmetric distribution of lesions is rare, similarly to reticular and nodular image of disseminated lesions [1, 11]. An important examination for the diagnosis of the disorder is HRCT, which usually shows lesions in the form of ground-glass opacities with visible polygonal structures — the so-called "crazy paving" pattern (the result of accumulation of surfactant lipids and protein in peripheral parts of the lobules adhering to the interlobar septa, but not real thickening of the septa). The areas of filled alveoli are usually separated from the right lung parenchyma and located irrespective of anatomic borders, making a geographical pattern [18]. There is research that proves that it is possible to differentiate primary from secondary proteinosis, based on HRCT examination. Ishii et al. compared HRCT examination of 21 patients with aPAP and 21 patients with a secondary from of the disorder, and they found that the areas of geographical pattern were present significantly more frequently in the first group (71% vs. 24%). The "Crazy paving" pattern also occurred more often (71% vs. 14%), and subpleural location of lesions was more frequent, compared to the group of patients with secondary proteinosis (71% vs. 33%) [19]. All patients from the study group had chest X-ray

**Table 5. Pulmonary alveolar proteinosis — a comparison of selected published studies**

**Tabela 5. Proteinoza pęcherzyków płucnych — porównanie wyników wybranych opublikowanych badań**

| Parameter | Current series N = 17 | [12] N = 7 | [16] N = 241 | [20] N = 410 | [2] N = 223 | [17] N = 70 |
|---|---|---|---|---|---|---|
| Age at diagnosis | 42.5 | 40.7 | 42 | 39 | 51 | 43 |
| Ratio male to female | 1.8 | 0.4 | 2.2 | 2.6 | 2.0 | 1.3 |
| Primary PAP (%) | 76 | 86 | ND | ND | 90 | 91 |
| Secondary PAP (%) | 23 | 14 | ND | ND | 10 | 9 |
| Time to diagnosis (months) | 1–24 | 8–77 | ND | 3–19 | 4–36 | 1–36 |
| Spontaneous remission (%) | 69 | 57 | ND | 6 | 28 | 7 |
| Cigarette smoking (%) | 76.4 | 71.4 | ND | ND | 56 | 49 |
| Exposure to injurious factors (%) | 23.5 | 14 | ND | ND | 26 | 54 |
| $Pa0_2$ mm Hg (range) | 54–87 | 51–80 | ND | 46–70 | 58–85 | 36–96 |
| Whole lung lavage (%) | 23.5 | 0 | 28 | 54 | ND | 90 |
| Small volumes fluid lung lavage (%) | 0 | 43 | 31 | 0 | ND | 0 |
| Diagnostic method | | | | | | |
| Autopsy (%) | 0 | 0 | ND | 11 | 0 | 0 |
| Surgical biopsy (%) | 82 | 100 | ND | 71 | 7.2 | 20 |
| Transbronchial biopsy (%) | 11.7 | 0 | ND | 10 | 12 | 29 |
| Bal (%) | 6 | 0 | 72 | 4 | 70 | 76 |

ND — no data available

performed, and 15 patients had HRCT, but only in 11/15 cases radiologists implied diagnosis of PAP. In the remaining 4/15 patients they suspected another interstitial disease (allergic alveolitis and idiopathic interstitial pneumonia).

In PAP, ventilation disturbances of restrictive nature with lowered total lung capacity (TLC) may occur, but the most frequent disturbance that correlates with the disease severity is lowered DLCO [20]. Bonella et al., in their analysis of 70 patients with PAP, found lung dysfunction manifesting itself in lowered TLC and DLCO in 60% and 92% of patients, respectively [17], whereas in a Japanese study of 223 patients, the mean value of DLCO amounted to 68.6% [2]. In the present study, among 17 patients, in 3 (17.6%) — restrictive disorders were found, and in 12 (70.5%) — impaired DLCO, including 3 patients (17.6%) with severe DLCO decrease. Due to gas exchange disorders caused by the presence of surfactant in the alveoli, hypoxaemia often occurs, worsening during physical exertion [9, 10]. In the present study, in 10 out of 17 patients, hypoxaemia at rest was observed, including 2 patients who met criteria of respiratory insufficiency ($Pa0_2 < 60$ mm Hg).

Surgical lung biopsy was thought to be a gold standard of diagnosis of PAP [20]. However, current guidelines imply that an appropriate history, characteristic image at HRCT and typical results of the examination of bronchoalveolar lavage fluid are sufficient criteria for establishing diagnosis, without TBLB or OLB [21]. Detection of GM-CSF autoantibodies is an additional argument for PAP diagnosis, and it also confirms the autoimmune nature of the disease [22]. PAP is the only interstitial lung disease that can be diagnosed based on BAL examination. The BAL fluid is an opaque, iridescent substance, and a light microscope shows three characteristic features: the presence of acellular corpuscles staining pink during the examination using PAS staining, but not staining with alcian blue, which differs them from the mucus, the presence of foam macrophages filled with PAS-positive substance, and the presence of amorphous debris representing multistratified structures and lamellar corpuscles. In cases when the HRCT image indicates PAP, and BAL shows three of the above-mentioned features, it may be considered to be diagnostic [23]. Bonella et al., who analysed a group of 70 patients with PAP, used bronchoscopy and BAL as basic diagnostic methods, which resulted in the diagnosis of 83% of patients (in 49% of patients, BAL was a sufficient examination; in the remaining subjects, in addition, TBLB was performed). Open lung biopsy was necessary only in 20% of patients [17]. In

another analysis that included 223 PAP patients, in 58.7% of subjects, diagnosis was based on HRCT and BAL, and surgical biopsy was performed only in 7.2% of patients [2]. In the study by Sobiecka et al. conducted between 1989 and 1999, all patients underwent surgical lung biopsy [12]. In the present paper, in the majority of patients (14/17), diagnosis was also confirmed by histological examination of specimens taken during open lung biopsy performed in 13 cases, and in two cases — during TBLB. Only in one patient, diagnosis was made based on the result of the examination of BAL fluid (lung biopsy was not performed). Bronchoalveolar lavage was performed in 7 patients, and in 6 of them the fluid was typical and showed positive PAS staining. It should be emphasised that 13 out of 14 patients who were diagnosed after OLB, after the procedure were referred to the National Institute of Tuberculosis in order to establish further proceedings. The second factor that influenced the high proportion of diagnoses based on OLB is the period of time in which the patients were diagnosed — a great part of the patients were seen between 1984 and 2004, when OLB was required to establish diagnosis of the disease.

It is known that the most frequent form of PAP is autoimmune, the diagnosis is based on detection of serum GM-CSF autoantibodies. Test sensitivity for aPAP is 100% and specificity 98% [10]. However, such a test is not commonly available. Nowadays, efforts are being made so that the test could be used in everyday clinical practice. While waiting for the possibility to perform the test in Poland, blood samples were taken from 6/17 recently hospitalised patients to examine the presence of GM-CSF autoantibodies. One patient (case n° 1) had the test performed in Germany, and as a result, autoantibodies were detected, and consequently aPAP was diagnosed.

Recent examinations have also shown the presence of autoantibodies in some patients with secondary PAP, which is connected with inflammatory or neoplastic diseases, but these autoantibodies do not neutralise GM-CSF. In patients with secondary PAP connected with exposure to harmful factors, GM-CSF autoantibodies are rarely detected [3, 11].

In 4/17 (23.5%) patients (cases n° 6, 8, 13 and 16), evidence of long-term exposure to harmful factors was found, and this was recognised as one of the causes of secondary proteinosis. In these patients, at the present time, the secondary from of the disease was diagnosed. However, when analysing these cases it should be remembered that the development of aPAP is possibly caused by the influence of dust and external factors [22].

There are different opinions concerning the clinical significance of GM-CSF autoantibodies. Some researchers show a lack of correlation between serum concentration and disease severity, but show such correlation between concentration in BAL fluid and markers of the disease severity, such as blood oxygen partial pressure, DLCO or advanced lesions seen on HRCT [24]. Others confirm the relation between serum autoantibodies concentration and the course of the disease [17]. It is indisputable that the discovery of GM-CSF autoantibodies has opened up new possibilities for treatment of proteinosis in the form of subcutaneous or inhaled recombinant GM-CSF. In spite of tremendous interest in this form of therapy, to date there have not been any trials conducted concerning optimal drug doses, the length of treatment necessary for complete regression of changes, or the safety of applied treatment. In 2012, a meta-analysis including research published between 1996 and 2010 was made available. It showed that the proportion of responses to treatment with GM-CSF was 43%-92%, and that it was slightly higher in patients treated with inhaled drugs, compared to patients treated with subcutaneous injections. After finishing the treatment, the disease recurred in 29.7% of patients, and recurrences were more frequent among the patients treated subcutaneously (43.9% vs. 15.2%). No significant long-term toxicity was shown, the most frequent adverse effects were fever, erythema in the place of injection, and in patients treated with inhaled drugs — infections of the respiratory system [25].

The most effective and safe method of treatment of PAP is still whole lung lavage, which removes surfactant-like material from the alveoli [11, 26, 27]. The first procedure was performed in 1965 by Ramirez R. J. It is performed in the operating theatre under general anaesthesia. The lung that is going to be washed is excluded from respiration, and sterile, heated physiological saline is administered. The capacity of a single dose of liquid should correspond to preoperative functional residual capacity (FRC) — usually it is 500–1000 ml. To completely clean the lung of lipid material, approximately 20–40 L of physiological saline should be used at a single time. At the end of lavage, the residue of the liquid is sucked off and 100% oxygen is given. The procedure lasts for 3–5 hours and has to be performed by well trained staff in a properly equipped operating theatre [13]. There are no precise guidelines concerning the use of WLL, but according to the majority of authors, these are hypoxaemia ($Pa0_2$

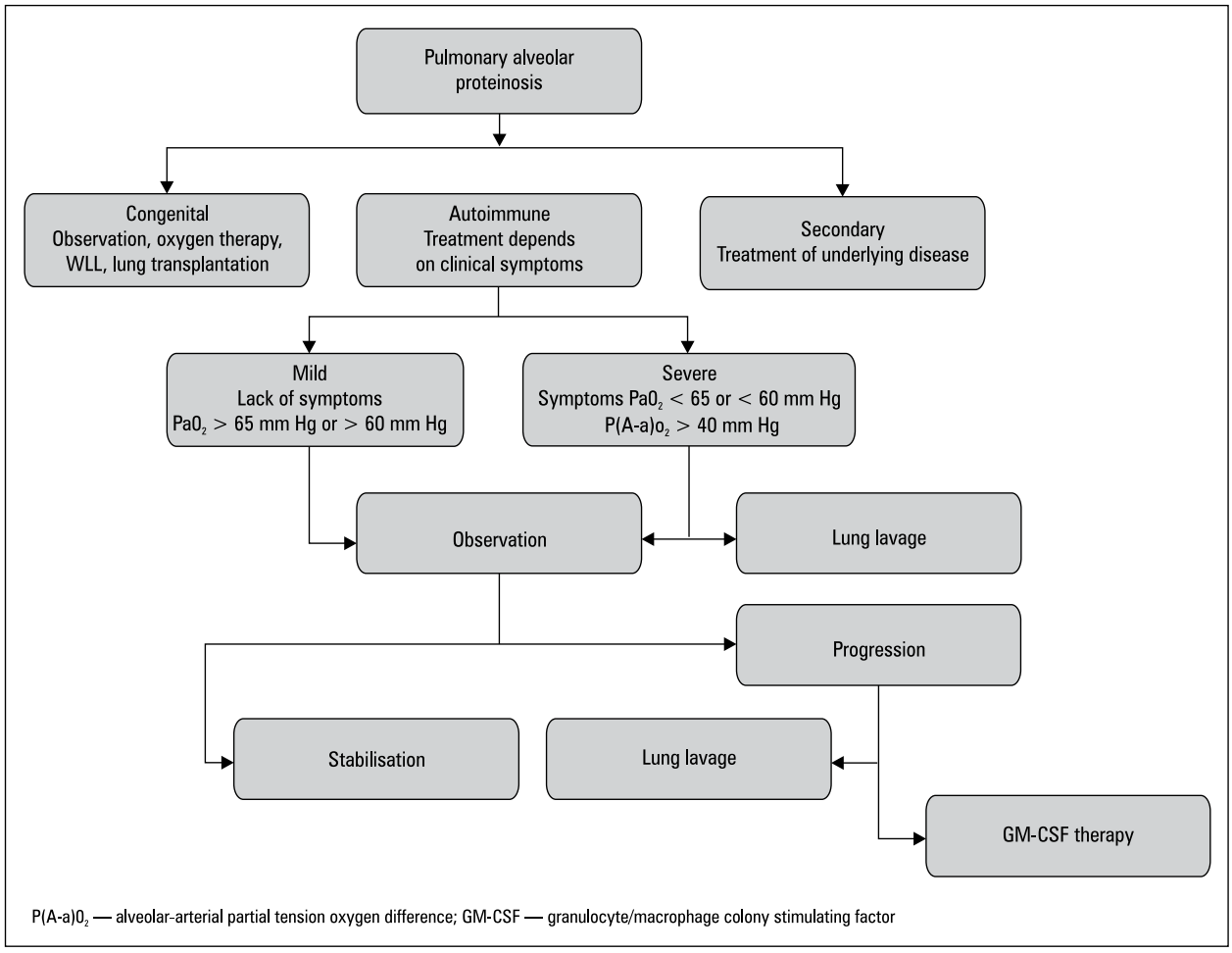


**Figure 3.** Management algorithm in PAP

**Rycina 3.** Algorytm postępowania w proteinozie pęcherzyków płucnych

< 65 mm Hg or < 60 mm Hg) or saturation below 90%, the growth of alveolo-capillary gradient of oxygen partial pressure above 40 mm Hg, pulmonary shunt exceeding 10–12% and/or dyspnoea limiting daily activities of the patient [26, 27]. Similar classification criteria were adopted in the study group ($PaO_2$ < 60 mm Hg, dyspnoea), where, among 17 patients, WLL was applied only in 4 (23.5%). In 3 patients (75%), clinical, radiological and gasometric improvement and improvement of functional parameters were achieved, whereas in one patient, despite WLL being performed three times, no improvement occurred. The frequency of indications for WLL in the study group was lower in comparison with other studies. In the analysis of 70 patients conducted by Bonella et al., lavage was performed in 63 patients (90%), and in 40 patients (63.5%) improvement was achieved after the first procedure [17]. In his study, classification criteria for treatment were more liberal; they classified to WLL patients with $PaO_2$ < 70 mm Hg and clinical symptoms in the form of dyspnoea. In another study, among 223 aPAP patients, 142 people (63.6%) underwent treatment with lavage [16]. The algorithm of treatment in PAP is presented in Figure 3.

The alternative method to WLL is the lavage of lung segments with small quantities of physiological saline during bronchofibroscopy. This method is less invasive and does not require access to an operating theatre. The procedure consists of lavage of separate lung segments with small quantities of saline (50–100 mL), with the total volume of solution up to 2 L during one session. The procedure should be repeated 2–5 times. Sobiecka et al. observed radiological improvement in 2 out of 3 PAP patients classified for treatment with lavage with small volumes of saline [12]. However, most authors conclude that this method is ineffective in patients with severe PAP, and contrary to WLL, its impact on opportunistic infections has not been proven [28]. In

2003, Wiatr et al. described a 42-year-old patient, in whom improvement was not achieved after the use of lavage with small quantities of liquid repeated for two successive days. Whereas, a twofold WLL resulted in distinct clinical and radiological improvement [13]. In a meta-analysis including 241 patients with PAP, 142 patients underwent treatment with small quantities of liquid or WLL with equal frequency, and the two methods showed comparable efficacy [16].

PAP patients have a good prognosis. A retrospective analysis showed that 5-year survival is more frequent in patients treated with lavage, compared to untreated patients (94% vs. 85%). The most frequent cause of death was respiratory insufficiency in the course of the disease (72%), followed by infections (18%) [20]. It was shown that the median time of remission after WLL is 15 months, and approximately 20% of patients need an additional lavage by the end of a 3-year period [20]. In a recently published study of 223 aPAP patients from Japan, no death occurred during a 5-year observation period, and severe infections were found only in 4% of patients [2]. In the study group, recurring infections of the respiratory system, usually with a mild course, were observed in 5/17 patients. Two patients died — one due to staphylococcaemia (6 years after diagnosis), the second one — presumably also due to infection — 11 years after diagnosis. The proportion of idiopathic remissions obtained in the study group was higher in comparison with other studies — it accounted for 77%, whereas, for example, in the analysis by Inoue it was 28% [2]. Stabilisation of the disease was observed in 23% of patients (3/13), compared to 64% in the study by Inoue [2]; in our study, the proportion of patients who needed whole lung lavage was also lower in comparison with other publications (23.5% vs. 54% or 90%) [17, 20].

## Conclusions

Pulmonary alveolar proteinosis is a rare interstitial disorder, usually with a mild course and mild clinical symptoms. Radiological image at HRCT is so typical that in the majority of cases, it is the deciding factor for diagnosis. According to recent guidelines concerning diagnostic and therapeutic management, the examination of bronchoalveolar lavage fluid showing the presence of PAS-positive substances is sufficient to establish a final diagnosis [21]. At that moment, the respiratory system function test, especially $Pa0_2$ and DLCO, and ailments of the patient are of crucial importance. Decreased lung function parameters or intensive dyspnoea, which were observed in a small number of patients, are an indication for evacuation of surfactant lipids and protein by the use of whole lung lavage. It is also vital to treat recurrent infections that may be a direct cause of death. However, in the majority of cases, prognosis is good.

## Conflict of interest

The authors declare no conflict of interest.

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