CASE STUDY

PULMONARY ALVEOLAR MICROLITHIASIS. DISCREPANCIES BETWEEN RADIOLOGICAL FINDINGS AND CLINICAL PATTERN- CASE STUDY

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Aleksandra Oraczewska[1], Marek Ochman[2], Mariola Ograbek-Król[1], Wiktoria Kowalska[3], Klaudia Glinka[1], Fryderyk Zawadzki[2], Adam Barczyk[1], Szymon Skoczyński[1]

[1]DEPARTMENT OF PNEUMONOLOGY, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, KATOWICE, POLAND

[2]DEPARTMENT OF CARDIAC, VASCULAR AND ENDOVASCULAR SURGERY AND TRANSPLANTOLOGY, SILESIAN CENTER FOR HEART DISEASES IN ZABRZE, MEDICAL UNIVERSITY OF SILESIA, KATOWICE, POLAND

[3]1ST DEPARTMENT OF CARDIOLOGY AND ANGIOLOGY, DOCTORAL SCHOOL OF MEDICAL UNIVERSITY OF SILESIA, SILESIAN CENTER FOR HEART DISEASES IN ZABRZE, MEDICAL UNIVERSITY OF SILESIA, KATOWICE, POLAND

ABSTRACT

Pulmonary alveolar microlithiasis is a rare genetic disorder, inherited autosomally recessively, which is characterized by intra-alveolar deposition of microliths built mostly of calcium salts and phosphorus. This case study describing management of patient with pulmonary alveolar microlithiasis. A 49-year-old woman, diagnosed with pulmonary microlithiasis in 1979 was admitted to Pneumology Department due to increased dyspnea. On admission there were no clinical signs of active infection. The chest computer tomography scan confirmed the presence of advanced microlithiasis. Pulmonary function test revealed mild restriction with moderate diffusion impairment, due to severe hypoxemia present on 6-minute walking test patient was sent for specific assessment to local lung transplant team in Zabrze for consideration for lung transplantation. According to International Society for Heart & Lung Transplantation guidelines the patient was observed in 6 months intervals to reveal whether further disease progression will be observed. Clinical condition of our patient does not correlate with radiological scans, severe respiratory symptoms and cardiological complications. Computer tomography scan should not be the only indication for lung transplant.

KEY WORDS: PAM, lung transplant, pulmonary alveolar microlithiasis

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INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is a rare genetic disorder, inherited autosomally recessively. The disease is characterized by intra-alveolar deposition of microliths of diameter from 0.5 to 5 mm, build mostly of calcium salts and phosphorus, with admixture of magnesium and aluminium. This disease was first described by Friedrich in 1856 [1]. Further description of microlithiasis was drawn by Harbitz in 1918, nevertheless Sosman et al. in 1957 described it thoroughly, giving it its present name [2].

The direct cause of this disorder is a mutation of SLC34A2 gene, mostly expressed in type II pneumocytes. This gene codes for a Sodium-dependent phosphate transport protein 2B, which actively transports phosphorus ions into cells. Mutation inhibits the SCL34A2 gene expression resulting in ineffective phosphorans removal [2,3]. The SLC34A2 gene is also expressed in other organs such as: kidneys, pancreas, ovaries, liver, mammary glands, small intestine. Familial occurrence of PAM is ranging between 32 to 61%. [4]

Until December 2014 only 1022 cases have been described in the world's literature, most of them in Turkey (139 cases; 13,6%), China (133 cases; 13%), Japan (119 cases; 11.6%). In Europe, the majority of cases were observed in Italy (65 cases; 6.3%). In Poland only 5 cases have been noted [4].

This rare illness was tried to be treated pharmacologically including corticosteroids, calcium-binding agents and mechanically as bronchoalveolar whole-lung lavage [5], however most of the trials were unsuccessful. Therefore, the only life-saving and improving patients' life quality treatment is a lung transplantation (LTx) [4, 5].

THE AIM

This case study describes a patient who was diagnosed with PAM considered to be scheduled for lung transplantation, but was not included into active recipient list due to her exceptionally good clinical status.

CASE STUDY

This case study concerns about 49-year-old woman, who was diagnosed with PAM. The beginning of the disease is difficult to determine due to the lack of medical records and inaccurate patient's history. According to our best

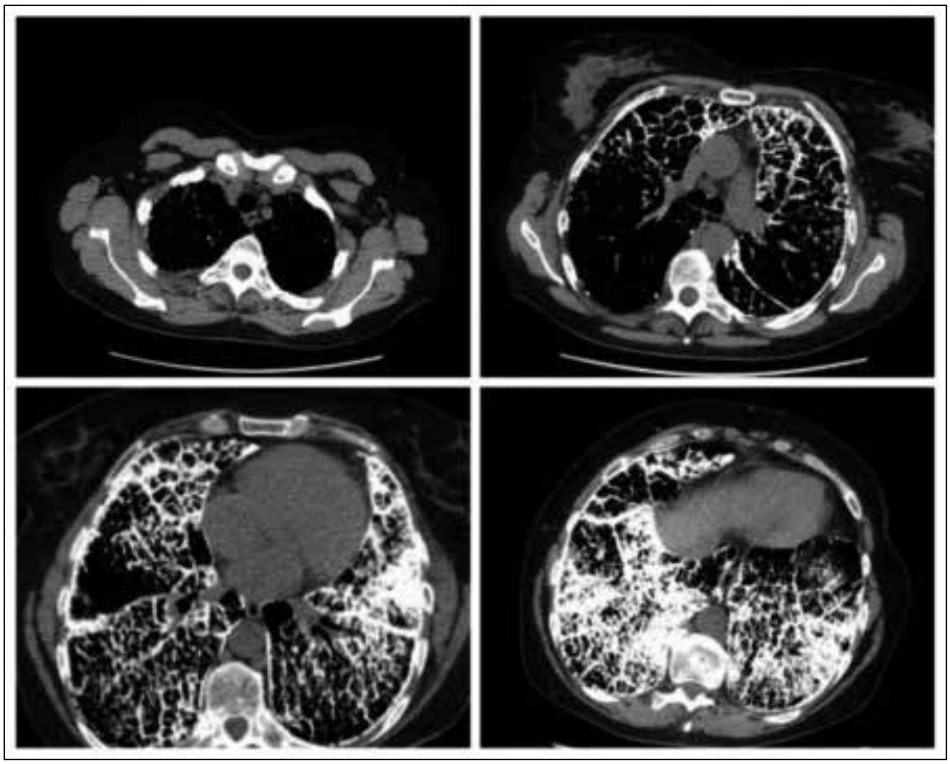

Fig. 1. Chest CT- the mediastinal window.

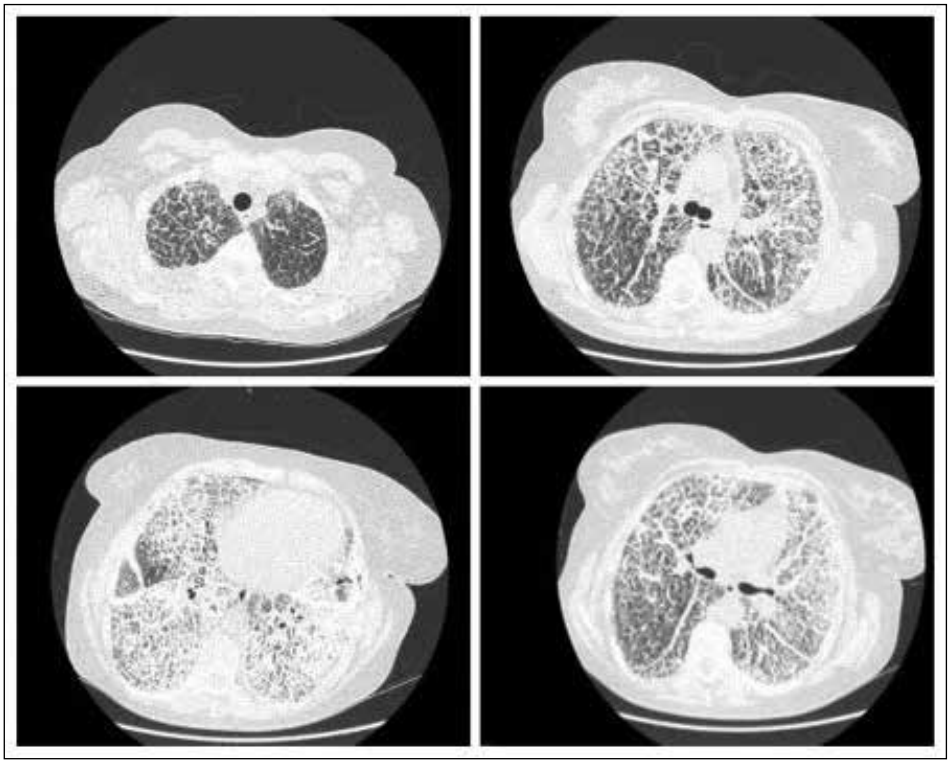

Fig. 2. Chest CT. Lung window.

knowledge, she was diagnosed at the age of seven. In 1993 the patient was temporary treated with systemic glucocorticosteroids, which were stopped due to lack of clinical improvement. After systemic treatment patient remained under pulmonological supervision.

After several years, during which she was asymptomatic, her clinical condition started to deteriorate and the patient came for medical consultation caused by exercise induced dyspnea (NYHA 2) which started to be clinically evident. The daily life limitations were more symptomatic on warm days, with temperature exciding 25 degrees Celsius. The dyspnea neither limited patient's daily functioning nor caused anxiety.

On environmental interview the patient reported temporary exposure to coal dust- she was working in coalmine as a supervisor. She was not an active smoker, with 5 pocket-years smoking history. Besides obesity (body mass index BMI 30.5kg/m^2), she was free of other chronic diseases.

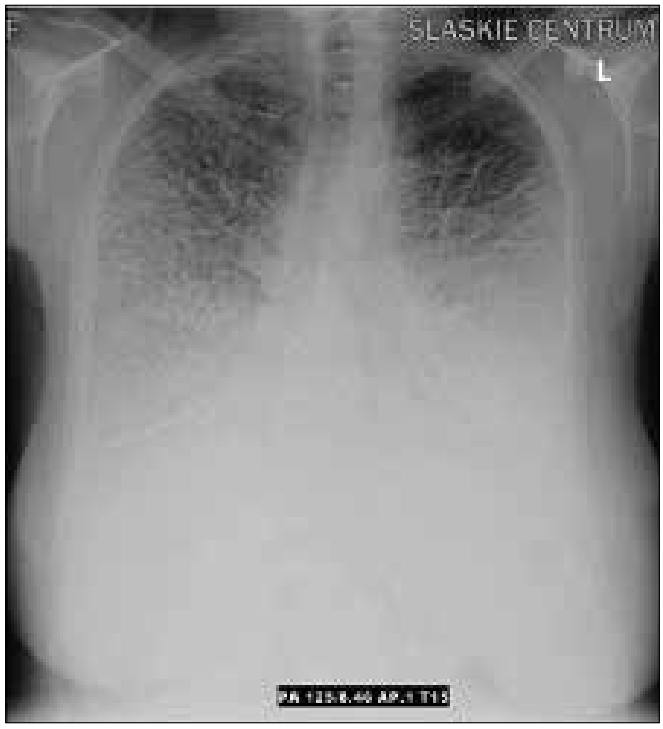

Fig. 3. Chest X-ray.

In gynecological history she reported two pregnancies terminated with two natural labors. Based on her medical family history it was found that her grandfather suffered from bronchial asthma.

In June 2017 the patient turned up at the Emergency Department complaining of progression of exercise-induced dyspnea.

The X-ray was typical for the advanced stadium of PAM. The arterial blood revealed mild hypoxemia: pO_2 61 mmHg, pCO_2 37 mmHg, pH 7.43. In order to control respiratory symptoms such as paroxysmal dyspnea superimposed on chronic disability with wheezing for patient was prescribed salmeterol with fluticasone at dose 25 ug + 50 ug twice a day.

In July 2017 patient was admitted to Pulmonology Department in University Hospital in Katowice-Ligota. Because of lack of past documentation all the basic tests were ordered at the admission. The chest computer tomography (CT), which was done before admission, confirmed the advanced stadium of microlithiasis.

CT performed on 30 June 2017 showed massive diffuse hyperdense changes in both lungs, especially dense in the bases of lower lobes with a sandstorm image characteristic for this disease. Additionally, there were pleural and pericardial calcifications and thickening of interlobular fissure (Fig. 1-2) There were no morphologic or biochemical abnormalities in kidneys, pancreas and liver. In bronchofiberoscopy the only pathology found was decreased respiratory mobility of sharp major carina. The bronchoalveolar fluid examination showed doubled total cell count (increased number of neutrophils and eosinophils, decreased number of lymphocytes) and presence of polynuclear giant cells. The bronchoalveolar lavage sediment contained no crystals. Moreover, the pulmonary function tests revealed restriction and impaired diffusion capacity. All results are shown in table I.

Due to restrictive respiratory abnormalities and no clinical improvement salmeterol with fluticasone was stopped. In July 2017 the patient was admitted to the Transplantology Department of Silesian Centre for Heart Diseases in Zabrze to carry all the test necessary for potential transplant qualification.

The blood tests showed increased NT pro-BNP levels (280,0 pg/ml) [nv<125 pg/ml]. On the X-ray sand-like calcification distributed throughout the lungs, bilateral distribution with reticular and linear opacifications, most intense in the middle and lower lobes were found; the heart shadow impossible to asses (Fig. 3). 6MWT and echocardiography results are summed up in table II.

The patient was assessed in modified BORG's scale and got a score of 0.5 (extremely light dyspnea). The echocardiographic evaluation showed no pathologies, sizes of atria and ventricles, ejection fraction of RV and LV (LVEF: 59%), diastolic function of LV were in norm, valvular apparatus efficient, features of pulmonary hypertension were absent. FVC/DLCO ratio was 0.97, which pointed on lower risk of pulmonary hypertension [6].

Basing on clinical picture and executed diagnostics the patient was enrolled to the observation group with the following recommendations: gynecological consultation, bone densitometry, dietitian consultation followed by body weight reduction (BMI 30.5).

In January 2018 the patient was admitted to Pulmonology Department in Katowice for a follow-up examination. The patient had lung function tests, 6MWT and she was assessed according to dedicated scales: mMRC, NYHA, BORG, her psychological state was assessed using HADS scale. The results from lung functions test are summed up in table I. During 6MWT in BORG scale she declared value 1 before exercise, and 1 after 6MWT (which means very light dyspnea, the level comparable to earlier assessments). In other dyspnea scale she was rated on: mMRC- 0 and in NYHA scale- 1.

On the HADS scale, the patient received 7/21 on the anxiety part, which means normal and 8/21 on the depression subscale, which means borderline abnormal. The patient was never under any psychological or psychiatric help. She was aware of her disease and knew the risks and prognosis of microlithiasis.

Based on teleconsultation conduced in September 2020 we found that the clinical condition of the patient is stable. Due to pandemic and high risk of infection and unsuccessful prognosis the patient did not show up to the proposed personal visit. Despite massive lung involvement currently the patient is still at acceptably good clinical condition (NYHA II) and has no complications such as pulmonary hypertension, therefore the qualification for lung transplantation program is not completed and the patient is not included into active waiting list. Based on remote observation the patient has been clinically stable for 2 years since last deterioration.

Table I. Parameters June 2017 and January 2018.

	Value	
Parameters	**JUNE 2017**	**JANUARY 2018**
DL_{CO} [mmol/min/Kp]	8.60	4.32
DL_{CO} [%pv]	61	61
KCO [mmol/min/Kpa]	1.35	1.35
KCO [%pv]	80	80
Spirometry TLC [l]	3.46	3.07
Spirometry TLC [%pv]	68	60
Spirometry FEV_1 [l]	1.90	1.69
Spirometry FEV_1 [%pv]	63	56
Spirometry FVC [l]	2.16	2.19
Spirometry FVC [%pv]	58	59
Spirometry FEV_1/FVC [%]	87.96	95
Plethysmography RV [l]	0.93	0.76
Plethysmography RV (%pv)	55	45
Plethysmography RV/TLC [%]	26.87	24.63
6MWT distance [m]	497	420
6MWT SpO_2 [%] (before and minimal value during 6MWT)	from 92 to 85	From 94 to 84
6MWT blood pressure [mmHg] (before and after 6MWT)	from 110/60 to 120/70	from 110/70 to 120/70
6MWT heart rate [bpm] (before and highest value during 6MWT)	from 86 to 155	from 75 to 112

Table II. Parameters July 2017.

Parameter	Value
LVEF [%]	59
RVFAC [%]	40
LV regional contractility	normal
MV, AV morphology	correct, efficient
TV: RVSP [mmHg]	30
TV: TAPSE [mm]	23
PV: PA [mm]	19
PV: AT [m/s]	108
PV: PR V max [m/s]	0.9
6MWT distance [m]	383
6MWT SpO_2 [%] (before and minimal value during 6MWT)	from 94 to 89
6MWT blood pressure [mmHg] (before and after 6MWT)	from 110/80 to 115/82
6MWT heart rate [bpm] (before and highest value during 6MWT)	from 78 to 90

DISCUSSION

This clinical case presents a detailed description of patient's condition with time related changes in lung functioning tests (DLCO, plethysmography), muscle of breathing strength and correlation with the degree of dyspnea. In current literature, the descriptions of similar clinical cases were focused on spirometry and arterial blood gases results, which our patient had values similar to predicted. Analysis of distribution of changes in the interstitial lung tissue indicates DLCO and 6MWT with the assessment of desaturation during exercise should be most important parameters and be monitored during consideration of lung transplantation.

The assessment of our and other clinical cases of patients showed a significant disproportion between massive lung involvement in radiological examinations and a relatively small intensity of restrictive changes with a slight reduction in DLCO compared to other interstitial diseases [7].

This observation of microlithiasis, accompanied by ventilation disorders, progressive exertional dyspnea without features of cor pulmonale and pulmonary hypertension can be observed. Due to lack of previous hospital documentation and incomplete information on the family history it is unclear whether the hereditary factors played an important role in etiology, even though the family incidence in literature is relatively high – 36% to 41% [4, 8]. According to the collected investigation, the diagnosis was stated when the patient was 7 years old, which places her in the group of the patients diagnosed before 20 years old (36.8% of patients).

The patient turned up at the hospital with the intensifying dyspnea at the age of 44 years of age, 37 years after the diagnosis. In numerous manuscripts, the authors point that microlithiasis has a long and mild clinical course despite massive changes in lung tissue [9, 10].

The asymptomatic many years' course and slowly increasing number of pulmonary microliths are characteristic for this disease. However, coughing with the content of microliths, which was also absent in this patient, is not pathognomonic for microlithiasis [2].

Abnormalities in lungs can be discovered accidentally in a chest's X-ray, in which a characteristic sand-like calcification distributed throughout the lungs can be observed. This is also an important part of disease differentiation. In the described case the clinical symptoms of respiratory failure were not in line with advanced changes in radiographic image. In other case presented by Hafiz W et al. a 17-year-old patient with family history of PAM, chest- CT showed massive lung changes: basal calcification, sand-like calcification, and black pleura sign. However, patient's clinical condition was satisfactory with oxygen saturation of 93% on room air. Clinical picture was similar to case study admitted to Department of Pneumonology [11].

Despite the high involvement of lung in CT, the patient presented only moderate restriction disorders in pulmonary function test and physical examination. She complained on slight exercise-induced dyspnea with no impact on her quality of life.

According to International Society of Heart and Lung Transplantation registry, 50% of patients live 7,8 years after double lung transplantation. For patients who underwent LTx due to interstitial lung disease median survival rate is 7,6 years with survival condition up to 3 months and 8,5 years with one-year conditional survival [12].

It is difficult to evaluate the prognosis for patients with microlithiasis. Multiple cases of severe clinical course of disease in children have been reported [13-15], but also three cases of people that survived above the age of 80 [16, 17]. Through the years many attempts were made to find the treatment, including usage of corticosteroids, bronchoalveolar lavage and calcium chelating agents, of which none proved to be efficient [1, 2, 4]. The trials of using disodium salt of etidronic acid had various effects. Some studies showed moderate improvement or lack of any effect [18, 19], while some of them suggested improvement of both pulmonary function and radiological image [20]. For hypoxemic patient's additional oxygen therapy is recommended. But the most effective therapy so far remains the lung transplantation. By the year 2019, 19 LTx have been performed, 14 were double lung transplantation, 5 were single lung and in 3 other cases details are not specified. In patients who received transplants, no relapses were observed [21].

CONCLUSIONS

Depressive and anxiety disorders often correlate with chronic diseases [22]. We did not find any obvious mood disorders in our patient. Nevertheless, we believe that the control of our patient's mental health should not be omitted during therapy, because of chronic and progressive nature of microlithiasis, which could be connected with mental strain.

Based on our case report and available scientific data it seems that in PAM massive lung involvement does not necessarily correlate with severe dyspnea and/or cardio-respiratory failure, therefore, CT pattern should not be the only prerequisite for lung transplant.

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ORCID and contributionship:
Alek*sandra Oraczewska: 0000-0002-9397-6963* [A, B, D-F]
Marek Ochman: 0000-0002-1410-5845 [A, D, E]
Mariola Ograbek-Król: 0000-0002-4649-5059 [A, B]
Wiktoria Kowalska: 0000-0001-5064-8217 [B, D, E]
Klaudia Glinka: 0000-0002-9610-4976 [A, B, D]
Fryderyk Zawadzki: 0000-0002-0356-2485 [D-F]
Adam Barczyk: 0000-0002-6567-9208 [D-F]
Szymon Skoczyński: 0000-0003-1796-7659 [A, B, D-F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Szymon Skoczyński
Department of Pneumonology,
Medical University of Silesia in Katowice, Poland
tel: +48 502519026
e-mail: simon.mds@poczta.fm

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