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Pulmonary Alveolar Microlithiasis with Atypical Radiologic Feature: A Rare Differential Diagnosis of Pulmonary Alveolar Proteinosis in a Patient with Hematologic Malignancy: Case Report

Atipik Radyolojik Görünümlü Pulmoner Alveoler Mikrolitiazis: Hematolojik Malignitesi Bulunan Bir Hastada Pulmoner Alveoler Proteinozisin Nadir Bir Ayırıcı Tanısı

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ABSTRACT Pulmonary alveolar microlithiasis (PAM) is a rare, diffuse lung disease characterized by intra-alveolar microliths. The disease is often diagnosed incidentally and it is usually seen as a primary disease. Turkey is one of the most prevalent countries of this entity. However, pulmonary alveolar proteinosis (PAP) which is characterized by deposition of intra-alveolar Periodic Acid-Schiff positive protein and lipid rich material may occurs primarily or secondarily to any malignancies (especially Hematologic Malignancies). Therefore, the lung lesions, especially in computerized tomography, with widespread significant ground-glass appearance of a patients with hematologic malignancy are mostly thought as PAP. In this article, we reported a case with PAM who had advanced Diffuse Large B cell lymphoma, no pulmonary symptoms and the changes observed in lung tomography were firstly interpreted in favor of PAP due to atypical radiologic feature for PAM. Additionally, we emphasized importance of lung biopsy in cases with PAM that they have with atypical radiologic feature.

Key Words: Lung diseases; pulmonary disease, chronic obstructive; pulmonary alveolar proteinosis; lymphoma

ÖZET Pulmoner Alveoler mikrolitiazis (PAM), intraalveoler mikroskobik boyutlu taşlarla karakterize, akciğerleri diffüz olarak tutan nadir görülen bir hastalıktır. Hastalık genellikle tesadüfi tanı alır ve primer hastalık olarak görülme eğilimindedir. Türkiye en çok görüldüğü ülkelerden biridir. Pulmoner Alveoler Proteinozis (PAP) ise intraalveoler protein ve lipitten zengin materyal birikimi ile karakterli bir hastalıktır ve primer olarak ya da herhangi bir maligniteye sekonder olarak (sıklıkla hematolojik malignitelere) ortaya çıkabilir. Bu sebeple hematolojik malignitesi olan bir hastanın özellikle Akciğer Tomografisinde insidental olarak tespit edilen önemli buzlu cam görünümü ve interalveoler septa kalınlaşmaları ilk önce PAP lehine yorumlanabilir. Biz bu makalede akciğer semptomları bulunmayan, ilerlemiş diffüz B hücreli lenfomasından dolayı ve akciğer tomografisinde gözlenen değişikliklerin PAM açısından atipik olması sebebiyle ilk olarak PAP düşünülen, ancak biopsi sonucunda pulmoner alveoler mikrolitiazis tanısı alan bir olgu sunduk. İlave olarak atipik radyolojik görünümlü benzeri olgularda biyopsi yapmanın önemini vurguladık.

Anahtar Kelimeler: Akciğer hastalıkları; pulmoner hastalık, kronik obstrüktif; pulmoner alveoler proteinoz; lenfoma

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Pulmonary alveolar microlithiasis (PAM) is a rare, diffuse lung disease characterized by intra-alveolar spherical calcium phosphate concretions (microliths) in the absence of any known calcium metabolism disorder.[1] The exact etiology and pathogenesis of PAM is unknown.[2] Most of patients are usually diagnosed during routine examinations. The diagnosis is usually based on the characteristic radiologic and histopathologic appearance.[1,3]

PAM is usually seen as a primary disease. To the best of our knowledge, PAM associated with any secondary disease or hematological malignancies (HMs) has not been reported in the literature whereas secondary Pulmonary Alveolar Proteinosis (PAP) which is characterized by deposition of intra-alveolar PAS (periodic Acid-Schiff) positive protein and lipid rich material occurs primarily or rarely secondary to HMs.[4]

In this article, we reported a patient whose lung lesion was thought as PAP due to lack of the characteristic radiologic findings of PAM and the presence of advanced stage Diffuse Large B Cell Lymphoma (DLBCL). In this case, lung biopsy revealed the histopathologic diagnosis of PAM.

CASE REPORT

A 45-year-old male was admitted to the emergency department with complaints of decreased urination, nausea, weight loss, and back and leg pain. He did not have not any pulmonary symptoms. The results of laboratory studies (blood, urine electrolits etc.) were within normal limits. The clinical examination revealed cervical, axillary, inguinal lymphadenopathy with the largest being 2 cm in diameter. Multiple intra-abdominal lymphadenopathy were detected in abdominal ultrasonography. Additionally both kidneys were larger than normal size and asymmetrical in dimension. Multiple lytic lesions in the thoracic, lumbar and sacral bones were detected on Magnetic Resonance imaging (MRI). Positron emission tomography (PET CT) showed multiple and bilateral cervical, axillary, inguinal, intra-abdominal lymphadenopathy showing increased FDG uptake, increase of the both kidneys size with diffuse FDG uptake (SUVmax: Right: 14.6 Left: 13.7) and increased FDG uptake in spleen and bone structures. Excisional biopsy of the cervical lymph nodes was reported as DLBCL and the patient was evaluated as Stage 4S due to the involvement of the bone marrow.

Thorax computerized tomography (CT) of the patient showed the presence of diffuse interlobular septal thickening and widespread significant ground-glass appearance in both of lungs parenchyma, mainly in the posterobasals of the lower lobes (Figure 1). Pulmonary function tests revealed FVC: 3.4 (86%), FEV1: 3.12 (93%), FEV1/FVC: 89 V., FEF25-75: 4.08 (102%), DLCO:14 (48%) and DLCO/ VA:2.7 (102%). In bronchoscopy, the endobronchial appearance was normal. Bronchoalveolar lavage and transbronchial lung biopsy were taken and the bronchoalveolar lavage fluid was evaluated as normal. Lung lesion was thought as PAP due to the presence of advanced stage DLBCL, thus lung biopsy was performed. Histopathological examination of the lung biopsy displayed numerous intra-alveolar rounded calcificated bodies with concentric lamels and was reported as PAM (Figure 2). There was no family history of the patient for PAM.

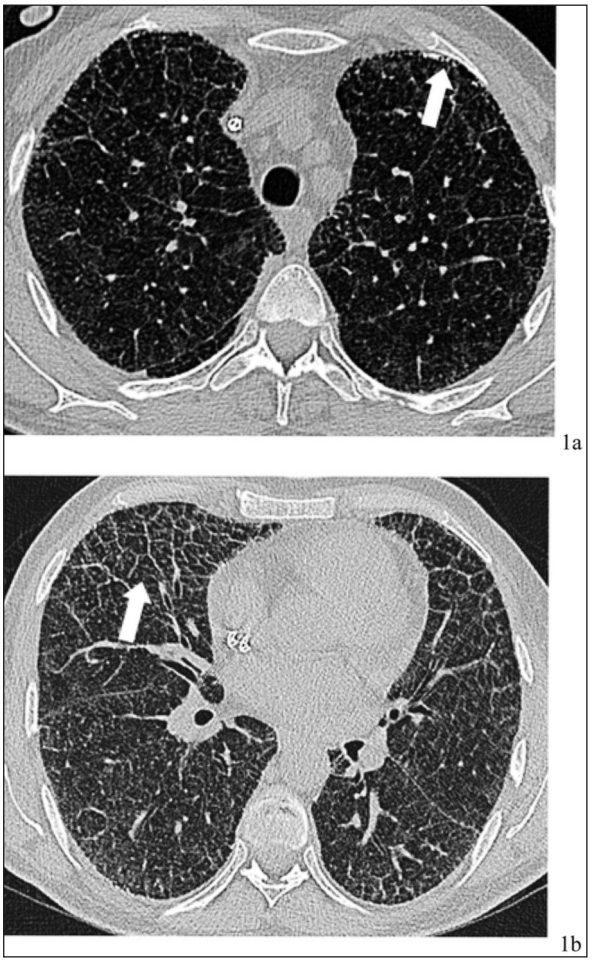

FIGURE 1: Axial High resonance Computerized Tomography of the patient with alveolar microlithiasis. Atypical radiologic appearances. **(a).** Interlobular septal thickening **(b)**.

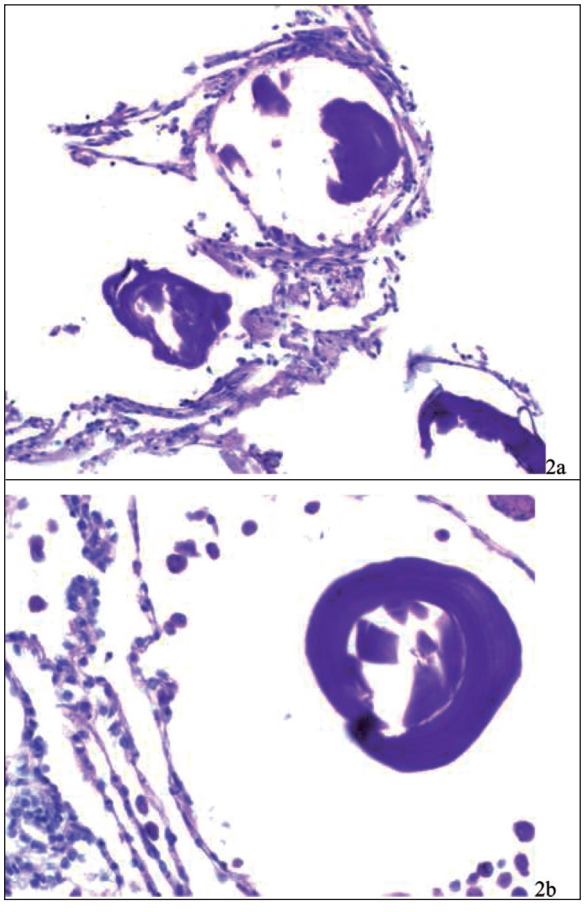

FIGURE 2: Bronchial biopsy section showing calcified microliths localised in the intra-alveolar spaces. Original magnification: **a)** X100, Periodic Acid-Schiff and **b)** X200, Periodic Acid-Schiff.

The R-CHOP treatment was started immediatelly as the patient had high International Prognostic Index (IPI) of lymphoma.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

DISCUSSION

PAM is a rare entity and it can be found almost anywhere in the world without a specific geographic or ethnic distribution. However, most cases of PAM have been reported from Turkey, Japan and Italy.[3]

PAM is generally diagnosed from birth to 40 years of age and does not have sex predilection. In a report analyzing 576 patients, 35,8% of patients were under twenty years of age and 88,2% were under fifty.[1] Many patients have no clinical symptoms and, generally, the diagnosis is incidental.[1,3] The clinical symptoms usually emerge between third and fourth decades. The most common symptoms are dyspnea, dry cough, chest pain, sporadic hemoptysis, and asthenia.[1,5,6,7]

The etiology and pathogenesis of PAM is unclear. Recently, some studies considered that homozygous mutations in the gene of solute carrier family 34 (SLC34A2) which encodes a type IIb sodium-dependent phosphate transporter are significantly related to PAM. The occurrence may be sporadic or familial.[1,7] In 1957, Sosman emphasized a high incidence of familarity.[2] Further analyses of familial cases indicate the characteristics of autosomal recessive disease.[1,5] Familial occurrence has been observed in 50 % of Japanese, 48% of Turkish, 43.7 % of Italian patients, whereas 35.6 % cases of PAM have familial presentation worldwide.[3,6]

Radiologically, the chest X-ray, CT, or high-resolution CT findings are often diagnostic. The chest radiography of PAM characteristically shows infiltrates as fine sand-like calcific micronodules also called ''sandstorm lung''. Commonly, both lungs are diffusely involved. Although the radiographic appearance is pathognomonic, in some cases, clinical and radiological findings may be misdiagnosed as miliary tuberculosis.[3,6] Therefore, diagnosis of the disease should be verified by histological examination of the lung biopsy.

Histologically, alveoli contain numerous microliths usually ranging from 50 to 1,000 μm in diameter. The microliths are PAS positive and consist of calcareous concentric lamellae around a central nucleus with an amorphous or granular aspect. This appearance is distinct from those of metastatic and dystrophic calcifications, which are located in the interstitial or vascular compartments.[8]

There is no specific treatment for PAM. Corticosteroids, chelating agents and bronchoalveolar lavage have been administered but were found to be ineffective. Patients with advanced lung disease may benefit from lung transplantation.[1,8]

PAP is a rare disorder characterized by deposition of intra-alveolar PAS positive protein and

lipid rich material. PAP occurs congenitally, secondarily (to usually malignancies) or primarily (idiopathic or autoimmune). Congenital PAP is rare. Primary PAP is the most common form. Secondary PAP usually occurs in association with malignancies (most commonly HMs). Optimal management of patients with PAP secondary to HMs is challenging. Apart from symptomatic and supportive respiratory care and therapy for HMs, there is no specific therapy in the treatment of PAP secondary to HMs.[4]

PAM usually occurs as a primary disease. To the best of our knowledge, PAM associated with any secondary disease has not been reported in the literature whereas PAP may occur in association with cancers, especially HMs.[4] Thus, the lung lesions with widespread significant ground-glass appearance on radiography of the patient with HM is thought mostly as PAP. Due to the different histopathologic findings of these two lesions, lung biopsy is cructial for definite diagnosis.

Our case was a 45-year-old male without any lung complaints. During the first examinations of the case with advanced DLBCL, the lung lesion was thought as PAP due to the widespread significant ground-glass appearance on CT. Additionally, he had no family history for PAM, although the high incidence of familarity is often reported in our country. Lung biopsy was performed for differantial diagnosis and the case was reported as PAM in the histopathological examination.

As a result; PAM usually occurs primarily and recently is shown to have a genetic background and familarity in some reports. In the literature, the association of PAM with any secondary disease could not be found. However, PAP may occur in association with malignancies (most commonly HMs). As in our case, if the radiological appearances are not clear in the lung lesions of patients with HM, it may be thought firstly as PAP. Making the differantial diagnosis of these two different entities is important because of different clinical approaches and this is only possible through lung biopsy and histopathological examination.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

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REFERENCES

1. Mariotta S, Ricci A, Papale M, De Clementi F, Sposato B, Guidi L, et al. Pulmonary alveolar microlithiasis: report on 576 cases published in the literature. Sarcoidosis Vasc Diffuse Lung Dis 2004;21(3):173-81.
2. Sosman MC, Dodd GD, Jones WD, Pillmore GU. The familial occurrence of pulmonary alveolar microlithiasis. Am J Roentgenol Radium Ther Nucl Med 1957;77(6):947-1012.
3. Günay E, Ozcan A, Günay S, Tatci E, Keyf AI, Simsek C. Pulmonary alveolar microlithiasis with low fluorodeoxyglucose accumulation in PET/computed tomography. Ann Thorac Med 2011;6(4):237-40.
4. Chaulagain CP, Pilichowska M, Brinckerhoff L, Tabba M, Erban JK. Secondary pulmonary alveolar proteinosis in hematologic malignancies. Hematol Oncol Stem Cell Ther 2014; 7(4):127-35.
5. Lauta VM. Pulmonary alveolar microlithiasis: an overview of clinical and pathological features together with possible therapies. Respir Med 2003;97(10):1081-5.
6. Castellana G, Lamorgese V. Pulmonary alveolar microlithiasis. World cases and review of the literature. Respiration 2003;70(5):549-55.
7. Tachibana T, Hagiwara K, Johkoh T. Pulmonary alveolar microlithiasis: review and management. Curr Opin Pulm Med 2009; 15(5):486-90.
8. Ortaköylü G, Ketenci A, Bahadır A, Çağlar E, Ürer N. Pulmonary alveolar microlithiasis. Turkish Respir J 2006;7(1):34-7.