

Pulmonary Alveolar Microlithiasis: Radiologic Findings of Eight Cases in Turkey

Pulmoner Alveoler Mikrolitiazis: Türkiye'de Sekiz Olgunun Radyolojik Bulguları

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ABSTRACT Objective: Pulmonary alveolar microlithiasis (PAM) is a rare idiopathic disease characterized by presence of diffuse innumerable minute calculi called microliths. The aim of this report was to describe the radiographic findings of PAM with particular attention to features provided by chest X-ray and high resolution computerized tomography (HRCT). **Material and Methods:** We diagnosed three index cases of PAM who came from the same village in 1996. In 2005 we performed a study including 279 residents of that village by using microfilm screening to determine undiagnosed cases. Five additional cases of PAM were detected and underwent HRCT. HRCT and chest X-ray images of eight cases were assessed specifically for patterns, distribution, and profusion of pulmonary abnormalities. **Results:** Of eight cases, four were adults and four were children. Diffuse typical microcalcifications were detected in chest X-ray in three cases while reticulonodular pattern was seen in three cases and reticular pattern in two cases. Fine microcalcification, parenchymal band and fissural prominence were the most common findings on HRCT. Small subpleural cysts were detected in five cases but only case 1 showed black pleural line in chest X-ray. One case had small subpleural bullae and bronchiectatic changes in both lower lobes predominantly in the left lung in HRCT. **Conclusion:** Relatives of a patient with PAM having reticular or reticulonodular pattern in chest X-ray must be investigated in detail for PAM because it can be the early stage of the disease. HRCT has a major importance for the detection of the rapid progression.

Key Words: Lung diseases; mass chest X-ray; thorax

ÖZET Amaç: Pulmoner alveoler mikrolitiazis (PAM), mikrolit olarak adlandırılan diffüz sayılamayan küçük kalkulusların varlığı ile karakterize nadir görülen idiyopatik bir hastalıktır. Bu çalışmanın amacı PAM hastalığının radyolojik bulgularını düz akciğer grafisi ve yüksek rezolüsyonlu akciğer tomografisi (YRBT) aracılığı ile beraber ortaya koymaktır. **Gereç ve Yöntemler:** 1996 yılında aynı köyden başvuran üç hastaya PAM tanısı koyduk. 2005 yılında bilinmeyen olguları araştırmak amacıyla aynı köyde yaşayan 279 kişiyi mikrofilm tarama tekniği kullanarak araştırdık. İlaveten beş kişiye PAM tanısı konuldu ve YRBT çekildi. Toplam sekiz hastanın YRBT ve düz grafileri özellikle pulmoner anormalliklerin paterni, dağılımı ve tutulumu açısından değerlendirildi. **Bulgular:** Sekiz olgunun dördü erişkin dördü ise çocuktu. Düz grafide difüz tipik mikrokalsifikasyonlar üç olguda görülürken retikülodüler pattern üç olguda ve retiküler pattern iki olguda tespit edildi. En sık görülen YRBT bulguları hafif mikrokalsifikasyon, parankimal bant ve fissür belirginleşmesi idi. Beş olguda küçük subplevral kistler tespit edilirken sadece bir vakada düz akciğer grafisinde siyah plevral çizgi görüldü. Bir olgunu YRBT'sinde solda daha belirgin olmak üzere her iki alt lobda küçük subplevral büller ve bronşektazik değişiklikler görüldü. **Sonuç:** Akciğer grafisinde retiküler ve retikülodüler patern saptanan olguların aile bireyleri, bu bulgular PAM için hastalığın erken safhasının göstergesi olabileceği için taranmalıdır. YRBT hızlı progresyonu göstermek açısından çok önemlidir.

Anahtar Kelimeler: Akciğer hastalıkları; akciğer grafisi; toraks

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Pulmonary alveolar microlithiasis (PAM) is a rare idiopathic disease characterized by the diffuse presence of innumerable minute calculi called microliths.^{1,2} A familial occurrence is frequently found.³⁻⁶ The disease develops slowly and the symptoms can remain unchanged for more than 13 years.⁷

Patients with PAM usually show sand-like micronodular infiltration particularly marked in the lower zones predominantly at paracardiac areas in their chest X-rays. On chest radiographs of adults, abnormal findings are described as ground-glass or sand-like opacities in addition to a nodular pattern obscuring the heart and diaphragm depending on the amount of calcium.⁸ Even though pulmonary parenchyma can be examined in much more detail with high resolution computed tomography (HRCT) when compared to chest X-ray, CT findings of PAM are not fully described in the current literature. There are several studies indicating CT findings of PAM as thickening of interlobular septa, thickening of peribronchovascular interstitium, ground glass opacity and paraseptal emphysema.⁹

The aim of this report was to describe the radiographic findings of PAM with particular attention to features provided by HRCT.

MATERIAL AND METHODS

Three cases diagnosed as PAM in 1996 were considered as the index cases and since the disease is autosomal recessive, microfilm screening was performed in 2005 to determine the undiagnosed cases. Microfilm screening was performed to all of 279 residents (101 females, 178 males; with an age range: four months- 86 years old) in a village of Diyarbakır where the relatives of our index cases lived. Five additional cases of PAM were detected and underwent HRCT. HRCT and chest X-ray images of all eight cases were assessed specifically for patterns, distribution, and profusion of pulmonary abnormalities. HRCT scannig (Toshiba, X-Vision GX CT scanner) was performed in supine position. Bone (high resolution) program was used as protocol. All slices were taken in deep inspiration with 15 mm intervals and 2 mm slice thickness.

HRCT scans were evaluated independently and in random order by two observers and the final assessment was achieved by consensus if there were disagreements in interpretation. HRCT and chest X-ray images were assessed specifically for patterns, distribution, and profusion of the following pulmonary abnormalities.^{10,11}

Micronodule: Discrete, small, round focal opacities smaller than 3 mm in diameter.

Confluent micronodule: Opacities greater than 3 mm in diameter.

Interlobular septal thickening: Abnormal widening of interlobular septum.

Peribronchial septal thickening (Peribronchovascular interstitial thickening): Thickness of bronchial wall is greater than one-sixth of the diameter of the lumen.

Paraseptal (subpleural) emphysema: Emphysema characterized by subpleural regions of low attenuation or subpleural small cysts.

Centrilobular emphysema: Centrilobular areas of decreased attenuation usually without visible wall; of nonuniform distribution.

Panacinar emphysema: Emphysema that tends to show uniformly distributed parenchymal attenuation and a paucity of vessels.

Parenchymal band: Elongated opacity, usually several millimeters wide and up to about 5 cm long often extending to the pleura.

Bronchiectasis: Dilatation and an abnormal depiction of the airways in the peripheral portion of the lung (bronchiectasis was present if the bronchial diameter was greater than that of the accompanying artery or there was a lack of tapering of the bronchi and the signet ring sign was seen).

Ground glass opacity: Hazy increased attenuation of lung parenchyma but preservation of bronchial and vascular margins.

Bullae: A sharply demarcated region of emphysema 1 cm or more in diameter.

Air bronchogram: The radiographic shadow of an air-filled bronchus peripheral to the hilum and surrounded by airless lung (whether by virtue of

absorption of air, replacement of air, or both).

Prominence of the fissure: Fissure becoming evident by calcification or another reason.

Pleural calcification (PC): Marked calcification of pleura.

Black pleural line: A linear radiolucency in the area of the lateral pleura on chest radiographs.

Reticular pattern: A collection of innumerable small linear opacities that together produce an appearance resembling a net.

Reticulonodular pattern: A collection of innumerable small, linear, and micronodular opacities that together produce a composite appearance resembling a net, with small, superimposed nodules.

RESULTS

Three cases were diagnosed as PAM in 1996. These male patients (35, 13 and 17 years of age) (cases 1, 2 and 3 respectively) with PAM were the index cases for our study. We detected additional five cases during microfilm screening in the village of the relatives of the index cases in 2005. These five cases included three asymptomatic male children aged as 11, 15 and 17 years (cases 4, 5 and 6, respectively), a girl aged 12 years (case 7) and a relative of case 7 aged 7 years (case 8).

Five of the cases were asymptomatic. The most common symptoms were dyspnea and cough. Other symptoms were sputum production, malaise, chest pain, weight loss, wheezing and headache. Three patients did not have any complaints at presentation. Pulmonary function tests showed a restrictive pattern with reduced diffusing capacity for CO in one patient while were normal in others. Results of spirometry parameters of other patients were in normal limits. None of our patients had any disorders in the metabolism of calcium or phosphorus elements.

Case 1 was diagnosed as having active pulmonary tuberculosis (TB) in 1994. Furthermore, six of our cases were initially misdiagnosed as having miliary TB and were given antituberculous therapy. Flexible bronchoscopy (FOB) and bronchoalveolar

lavage (BAL) were performed in case 1 and 7 and calcium microliths were seen in the BAL fluid smear. Diagnosis was based on biopsy taken by video assisted thoracoscopy in case 8.

CHEST X-RAY

The most common finding in chest-X ray was microcalcification and prominence of fissure while intraparenchymal cyst or bronchiectasis were detected in none of the cases. Large bullae were detected in case 1 having tuberculosis history. Typical confluent microcalcifications were detected in only three cases whereas reticular pattern was found in two cases. The picture was more obvious in the cases 4, 7 and 8 with micronodules superimposed over fine reticular pattern in the both lungs. Both of two cases having reticular pattern were not index cases, but asymptomatic cases detected during the family screening. Table 1 shows chest-X ray findings of eight cases.

HRCT FINDINGS

Micronodular infiltrations with variable density were the most common finding. This characteristic finding of PAM was present in all cases. There was a fine dense rim in the parenchyma along the visceral, mediastinal, and fissural pleura in cases 1, 2, 3, 4, and 6. Right middle lobe and lingula were found to be more frequently involved with microcalcifications than the upper lobes. Microliths were predominantly located in upper lobes of only one case while right lung was markedly involved in two cases.

Subpleural cysts were detected in 5 cases in HRCT and of these cases, case 1 having 5-6 mm cysts was found to have black pleural line (Figure 1).

The cysts resulting from parenchymal destruction were determined on the radiography of the case 1. These cysts were localized exclusively in the left lower lobe. Highly dense microliths and the other findings on HRCT were observed for case 1 (Figure 2).

Subpleural bullae which are 5-6 mm in diameter were found were localized in all areas from apices to the basis and were arranged in string of beads style in case 1 whereas they were 1-2 mm in

TABLE 1: HRCT findings in the eight patients with PAM.

HRCT FINDINGS	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8	
	35	17	13	17	11	15	11	15	17	12	17	12	17	12	17	7
Age	35	17	13	17	11	15	11	15	17	12	17	12	17	12	17	7
Localisation	Diffuse	Predominantly right lung	Predominantly right middle lobe and lingula	Predominantly right lung	Predominantly lower lobes	Predominantly lung and more prominent in upper lobes.	Predominantly lower lobes	Predominantly right lung and more prominent in upper lobes.	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Predominantly middle lobe, lingula and lower lobes
Fine microcalcification	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confluent microcalcification	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Interlobular septal thickening	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Peribronchial septal thickening	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes
Paraseptal emphysema (Subpleural cyst)	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	Yes	Yes
Centrilobar emphysema	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Panasinar emphysema	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Parenchymal band	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bronchiectasis	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Ground-glass opacifications	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes
Bullae	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Air bronchogram	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Prominence of the fissure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pleural calcification	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

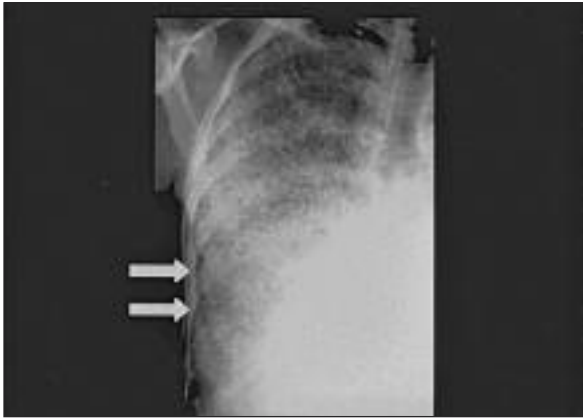


FIGURE 1: Chest radiograph of right hemithorax shows “sandstorm” lung and obscured cardiac silhouette with black pleural line (arrowheads) between ribs and lung parenchyma.

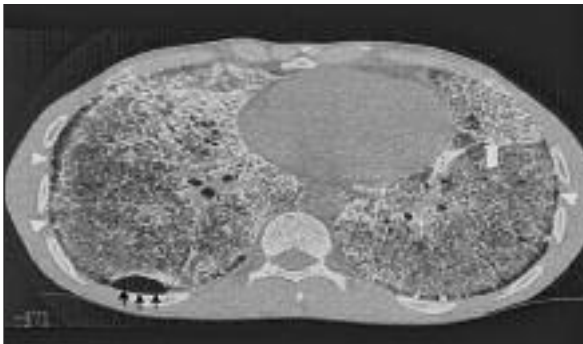


FIGURE 2: High-resolution CT scan of case 1 showing extensive small subpleural cysts surrounding the entire lung. Some of them (black arrows) coalesce to form a larger cyst. In addition this figure shows the prominence of the fissure (white arrow) and calcific densities predominantly located in the right middle lobe and lingula.

diameter and localized to posterior areas in cases 2, 5 and 6. The density of regions with small subpleural cysts was measured between -920 and -940 Hounsfield units.

Case 3 showed bronchial wall thickening and mild luminal enlargement in left lower lobe, and progression of lesions in HRCT although a HRCT that was performed four years earlier showed only sand-like appearance (Figure 3, 4). Table 2 shows HRCT findings of all cases.

DISCUSSION

A study divided the radiographic images of PAM into four stages. In this study, it was reported that interstitial infiltrates could be seen due to the small number and poor calcification of the microliths in

stage 1 and intense calcifications in stage 4.¹² Reticulonodular pattern was detected in chest X-ray of three cases whereas only reticular pattern was detected in two cases. These five cases are asymptomatic cases detected during the family screening, therefore PAM must be considered whenever these images are seen in microfilm screening. Case 8, being 7 years old, having diffuse micronodular pattern and case 5 being 15 years old and having just reticular pattern show that different radiologic images of the disease may be seen in different ages.

On chest radiographs of adults, abnormal findings are described as ground-glass or sand-like opacities in addition to a nodular pattern obscuring the heart and diaphragm depending on the amount of calcium. In contrast to the findings of PAM in adults, the major finding on chest radiographs of



FIGURE 3: HRCT of case 3 performed four years ago shows extensive micronodular infiltrations in both lower lobes.



FIGURE 4: Recent HRCT scan of case 3 showing bronchiectatic changes in both lungs being prominent in the left one and subpleural cysts (black arrows). This case did not show black pleural line on chest x-ray.

TABLE 2: Chest x-ray findings in the eight patients with PAM.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
CHESTX-RAY FINDINGS	Diffuse	Diffuse reticular pattern, especially involvement of paracardiac and diaphragmatic sides.	Diffuse micro-calcifications. Especially involvement of paracardiac and diaphragmatic sides.	Diffuse reticulonodular pattern	Diffuse reticular pattern, especially in the right lung	Diffuse micronodular infiltrations	Diffuse reticulonodular pattern.	Diffuse reticulonodular pattern
Localisation	micro-calcifications except in the apices; bullae in the apices. Silhouette sign (+)	paracardiac and diaphragmatic sides	paracardiac and diaphragmatic sides. Silhouette sign (+)	reticulonodular pattern	especially in the right lung	micronodular infiltrations	Silhouette sign (+)	reticulonodular pattern
Pleural black line	Yes	No	No	No	No	No	No	No
Microcalcifications	Yes	No	Yes	Yes	No	Yes	No	Yes
Confluent microcalcifications	Yes	No	Yes	Yes	No	No	No	No
Bronchiectasis	No	No	No	No	No	No	No	No
Bullae	Yes	No	No	No	No	No	No	No
Air bronchogram	No	No	No	No	No	No	No	No
Intraparenchymal cysts	No	No	No	No	No	No	No	No
Kerley-B lines	No	No	No	No	No	No	No	No
Prominence of fissures	No	No	Yes	Yes	No	No	Yes	Yes
Reticular pattern	No	Yes	No	No	Yes	No	No	No
Reticulonodular pattern	No	No	No	Yes	No	No	Yes	Yes

children is ground glass opacifications. Ground glass opacifications represent an initial finding related to microscopic calcifications that are later followed by macroscopic calcific depositions. This finding is corroborated in the pediatric literature where cases with a clear silhouette of the diaphragm and heart without overlying opacifications are reported unlike the findings in adults.⁸ This feature was present in only two of our pediatric cases on HRCT. The finding that calcifications are so prominent that they can form conglomerations in some areas and that the absence of ground-glass appearance suggest that ground-glass appearance is a feature which can be detected early in the course of the disease. Since three of our pediatric cases did not show this feature, we supposed that it should be considered as an early finding in all decades rather than being specific in pediatric ages.

Felson described a black pleural line as a zone of increased translucency between the lung parenchyma and the ribs.¹³ Later reports using HRCT scan suggested that this line was caused by subpleural cysts.^{14,15} These cysts were representative of early lung fibrosis. In addition, they are often an early radiological finding in patients with PAM. In pediatric cases, only Helbich et al. has reported this feature.⁸ We detected scattered subpleural cysts in five cases as was reported by Helbich et al. When compared to previously reported adult cases and also to our adult cases, these cysts were of lesser extent and severity in children and may represent an early manifestation of a peculiar variant of fibrotic disease. Hoshino et al. demonstrated that the black pleural line on the chest radiograph corresponded to the fat dense layer between the ribs and calcified parenchyma.¹⁶ However, we think this suggestion is not valid for all PAM cases. We detected black pleural line in chest X-ray of case 1 having 5-6 mm subpleural cysts. Measurement of air density values in regions of subpleural cysts in HRCT sections also indicates that black pleural line appearance results from small subpleural cysts. Hideaki et al reported that translucent zones caused by subpleural cysts should be called by another name and should be distinguished from the line that Felson originally mentioned.¹⁷

The advantages of high-resolution CT in detecting minimal structural changes in the lung parenchyma have been reported previously.^{18,19} High-resolution CT scans show that there is a gradient of distribution of the calcifications in which lung bases, especially posterior are more involved more than the middle and upper lung zones.²⁰ As well, high attenuation of lung parenchyma caused by calcispherites smaller than 1 mm (up to 5 mm) is visible on high-resolution CT scans.²¹ Some authors believe that the HRCT findings are pathognomonic for PAM and the open biopsy may be avoided in the presence of these characteristic findings.²²

In PAM, the distribution of calcific densities in the middle and lower lung zones can be explained by relatively more blood supply of this area of the lungs but a symmetric appearance may not be expected in all cases. In most cases, patients have mild clinical symptoms in contrast to the severe radiographic appearance which is a typical feature that should raise the suspicion of PAM. In recent years, HRCT has made it possible to define the extent and severity of the disease more precisely and has demonstrated calcifications in anatomical sites that could not be shown by conventional radiology.¹² We found that right lung was predominantly involved in two cases while one patient had upper lobes predominantly involved. We think that factors other than blood supply may be encountered in deposition of microliths since these two patients did not have oligemia in their left lungs.

The extent and severity of calcific densities increase from the lung bases to the apices depending on the age and the clinical course.⁸ We think that this concept may not be valid for all cases since we detected diffuse involvement in three cases who were at the age of 35, 17 and 12 years. Although the disease has a very slow progression, case 3 showed bronchiectatic changes in the left lower lobe and progression of lesions in HRCT. His previous HRCT which was performed four years earlier showed only calcified densities. However, chronic cor pulmonale was developed in case 1 after a period of four years. The rarity of PAM in addition to the fact that most of these patients die from respiratory failure

renders the coincidence of severe pulmonary hypertension with PAM, a rather rare phenomenon.²⁴ Reasons of this rapid progression need to be investigated. In Turkey a similar case was reported.²⁵

The differential diagnosis of this disease includes a variety of pulmonary conditions such as tuberculosis, sarcoidosis, pneumoconiosis (desert lung syndrome), ornithosis or pulmonary adenomatosis.^{12,21} The major reason of misdiagnosis is reticulonodular pattern mainly seen in miliary pulmonary tuberculosis. Consequently, PAM must be considered in differential diagnosis in Turkish population having radiological diffuse micronodu-

lar infiltrations not well-adjusted with the clinical features of tuberculosis, because our six cases were misdiagnosed as tuberculosis before.

In conclusion, our report showed that;

1- Small subpleural cysts may lead to black pleural line formation, but they must enlarge to at least 5-6 mm in diameter for this formation to be observed.

2- While screening the family members, all members having reticular or reticulonodular pattern in chest X-ray must be investigated for PAM because it can be the early stage of the disease.

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