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Pulmonary alveolar microlithiasis: quantitative approach by bone scintigraphy

Pulmoner alveolar mikrolitiyazis: kemik sintigrafisi ile kantitatif yaklaşım

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Abstract

Pulmonary alveolar microlithiasis (PAM) is a rare idiopathic disease of unknown etiology and pathogenesis. PAM is characterized histopathologically by extensive intra-alveolar calcium and phosphate deposition throughout both lung parenchymas. None-invasive diagnosis of pulmonary calcification and ossification requires various imaging techniques, including chest radiography and computed tomography, while bone scintigraphy may play a role in the disease staging by quantitative analysis. In this report, we presented a quantitative assessment technique for calcified foci in lungs by means of relative density analysis in successive bone scintigraphies of a patient with PAM.

Keywords: Pulmonary alveolar microlithiasis, bone scintigraphy, density, computed tomography.

Özet

Pulmoner alveolar mikrolitiyazis (PAM) etiyoloji ve patogenezi bilinmeyen nadir idiopatik bir hastalıktır. Histopatolojik olarak her iki akciğer parankiminde yaygın intra-alveolar kalsiyum ve fosfat çökmesi ile karakterizedir. Pulmoner kalsifikasyon ve ossifkasyonun non-invaziv tanısı direkt akciğer grafisi, bilgisayarlı tomografi gibi görüntüleme tekniklerini gerektirirken, kemik sintigrafisi de kantitatif analiz ile hastalığın düzeyi hakkında bilgi vererek rol alabilir. Bu raporda, bir PAM hastasının bir birini takip eden kemik sintigrafilerinde rölatif dansite analizi ile akciğerlerdeki kalsifiye odakların kantitatif olarak değerlendirildiği bir yöntem sunuldu.

Anahtar sözcükler: Pulmoner alveolar mikrolitiyasis, kemik sintigrafisi, dansite, bilgisayarlı tomografi

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Introduction

Pulmonary alveolar microlithiasis (PAM) is a rare idiopathic disease of unknown etiology and pathogenesis. PAM is characterized histopathologically by extensive intra-alveolar calcium and phosphate deposition throughout both lung parenchymas [1]. None-invasive diagnosis of pulmonary calcification and ossification requires various imaging techniques, including chest radiography and computed tomography (CT).

Bone scintigraphy is a valuable tool in the diagnosis and follow-up of various bone diseases in routine practice. The tracer used in bone scintigraphy today is mostly diphosphonate compounds, labeled usually with 99m-technetium, which has also natural

affinity for calcification foci at the soft tissue level. Thus, bone scintigraphy may serve in detection of early pulmonary calcifications, not only in PAM but, also some other diseases [2]. In this report we presented a quantitative technique for calcified foci in the lungs by means of density analysis on bone scintigraphy which was carried out in a patient with PAM.

Case

A 37 years old male patient, who had PAM since 12 years, had been referred to our department for a bone scintigraphy. He suffered from effort dyspnea for 10 years. The physical examination; pulse rate: 80/min., blood pressure: 140/80mmHg. Auscultation of lungs demonstrated diminished respiratory sounds on the left basal hemithorax and fine rales in bilateral postero-basal segments. No abnormality was found in hematologic examination and also in biochemical blood tests, including the serum levels of calcium and phosphorus. Findings of urine analysis were pH: 5, density: 1015, and protein (Esbach): 0.3 g/L. Erythrocyte sedimentation rate (ESR) was 8 mm/hr. A recent spirometric test (15/09/2008) showed diminished respiratory functions as FEV1: 2.40 L (64% of a normal values obtained as age and sex matched), FVC: 3.16 L (71%), FEV1/FVC: %76 (Normal >%81). Results of diffusion capacity tests were DLCO: 5.2 mmol/k.Pa.min^{-1} (%50), DLAdj: 5.2 mmol/k.Pa.min^{-1} (%50), DLCO/VA: 1.16 DLCO/L (%57). Arterial blood gas values were normal. No endobronchial pathology was found in fiberoptic bronchoscopy and microscopy of bronchoalveolar lavage findings was compatible with chronic bronchitis. Posteroanterior chest roentgenogram showed multiple, fine micronodulations at the middle and lower lung zones (Figure 1).

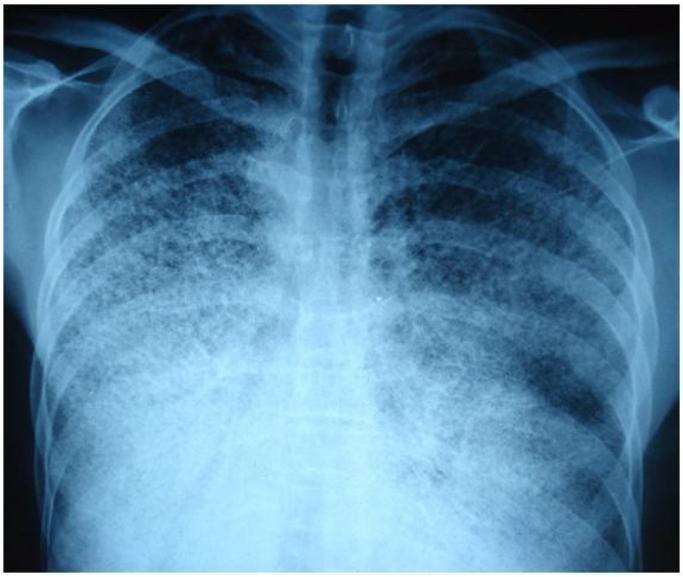

Figure 1. Posteroanterior chest roentgenogram showed multiple, fine micronodulations at the middle and lower lung zones.

CT examination revealed calcified millimetric-sized nodules in accordance with alveolar microlithiasis in the basal lobes of lungs (Figure 2).

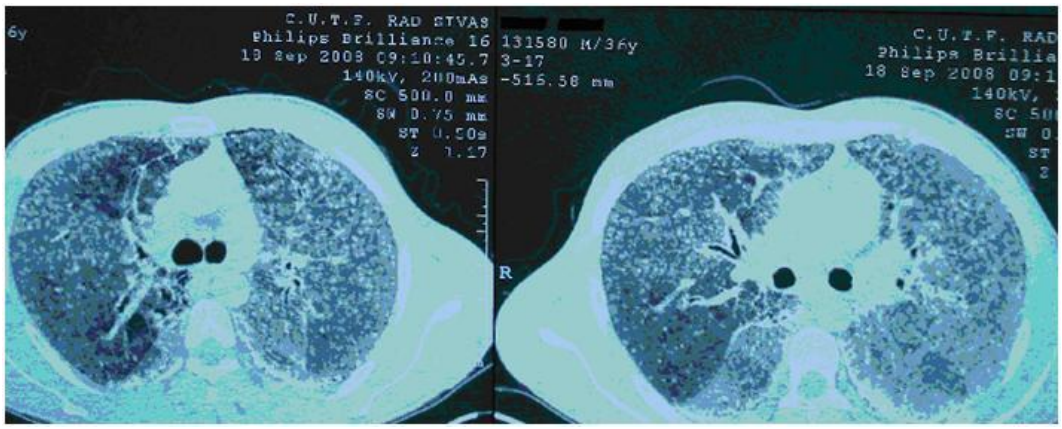

Figure 2. Bilateral micronodular calcified densities (microliths) are apparent on CT examination.

Bone scintigraphy

Whole body bone scintigraphy (WBS) was performed 3 hours following i.v. injection of 880 MBq (24 mCi) of technetium-99m methylene diphosphonate (Tc-99m MDP) using a gamma camera with a low energy high resolution collimator (Toshiba-ECAM.). The photo peak was centered at a 20% window. WBS was performed two times; at 20/04/2007 (Figure 3) and at 26/09/2008 (not shown). In both instance whole-body bone scintigraphy showed diffusely increased radiotracer uptake in bilateral lungs, especially at the basal lobes, slightly more prominent at the left lung than the right.

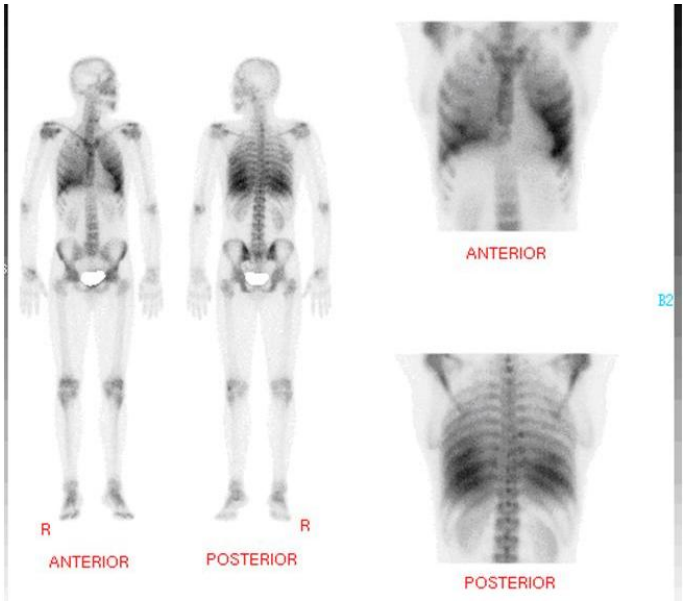

Figure 3. First whole body bone scintigraphy of the case showing diffuse Tc-99m MDP uptake, especially at the basal level of both lungs.

The density analysis performed on bone scintigraphy images. Analysis was carried out dedicated software, which is in routine use in the department for scintigraphic image processing. First, density values of both lungs and L2 vertebra were obtained by placing region of interests (ROI) on each lung fields and on the L2 vertebra in scintigraphic images. The same ROIs were used thorough out the image processing. Then, relative lung density (RLD) was determined with the help of following formula; RDL= Lung count /

[(area lung/area L2 vertebra) x L2 vertebral count]. Thus, lung density was indexed to L2 vertebra of patient and expressed as relative to vertebral density (Figure 4).

Moreover, the analysis was repeated on bone scintigraphies of 10 male patients (mean age; 48±13) with no known of lung pathology (control group). Mean RDL values in the control group were; 0.41±0.09 (range; 0.30-0.59) on the right and 0.39+0.09 (range; 0.28-0.58) on the left side.

RLD values obtained from successive bone scintigraphies of the patient with a one year apart and in the control group were given in Table 1. RDL values of left lung of the patient were higher than the right ones, in both occasions. On the other hand, if normal values are considered to be within 95% CI level, as approximately 0.40 ± 0.18, RDL values of patient seem quite higher than those obtained in the control group. We may also speculate with that reasoning that there were no significant differences between RDL values of two scintigraphies of the patient, since the differences seem within 2SD.

Table 1. Calcified soft tissue density analysis (RDL) of both lung fields in the case and in PAM free patients.

	Relative Lung Density	
	Right lung	Left lung
First scan (20/04/2007)	0.9	1.1
Follow-up scan (26/09/2008)	1.0	1.2
PAM-free patients (mean±SD)	0.4±0.1	0.4±0.1

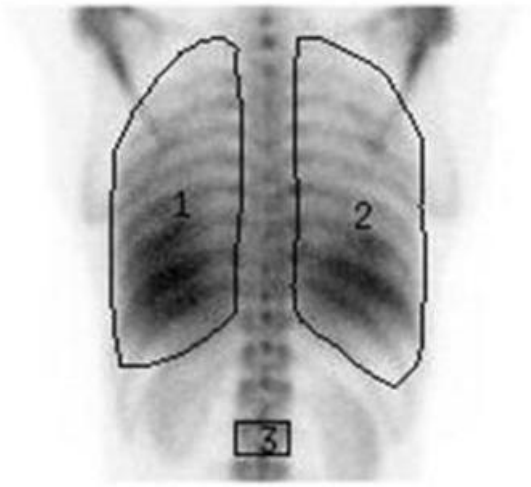

Figure 4. Calcified soft tissue density analysis of both lung fields.

Discussion

PAM is a rare disease characterized by intra-alveolar calcium deposits. The incidence is similar in both sexes and it is higher in age brackets between 20 and 50 years [3]. The etiology of the disease is still unknown and about 580 cases have been reported to date worldwide, most of them from Asia (40.6%) and Europe (42.7%), mainly from Turkey [4]. PAM is believed to be a heritable disease occurring as a result of deficient phosphate excretion from alveolar type II cells [5]. The microliths develop within alveolar spaces because of calcium salt sedimentation and in relation with increased endoalveolar pH, or after alveolar cell damage [6-8]. Patients may remain asymptomatic for many years and do usually become symptomatic between the third and fourth decades [9]. The disease follows a long-term, progressive course, resulting in a slow deterioration of lung

functions. In a meta-analysis, respiratory function tests had showed a restrictive pattern in 70% of cases (8/25) with PAM [10].

There is no known therapy and patients develop cor pulmonale in advanced-stage. The radiological findings are useful in the diagnosis of PAM. The typical radiological finding is the widespread calcified micronodules in mid and basal pulmonary lobes [11]. In addition, apical bulbs and blebs can be seen [12]. On the other hand, Gasparetto et al. and Deniz et al. [13]have reported "crazy-paving pattern" in patients with PAM, which is usually seen by high resolution CT in pulmonary alveolar proteinosis [9, 11]. Diffuse pulmonary infiltration, appreciated in direct roentgenogram is not a specific finding and crazy-paving pattern at thin-section computed tomography has a variety of causes, including infectious, neoplastic, idiopathic, inhalational, and sanguineous disorders [14].

Bone scintigraphy can be useful in the detection of early pulmonary calcifications [12, 15]. PAM is one of these clinical pathologies that associated with characteristic appearance on bone scintigraphy with diffuse bilateral basal uptake of radiopharmaceutical in the lungs. This aspect was mentioned almost in all of the case reports, in which a bone scintigraphy had been obtained. Cases with no scintigraphic pulmonary uptake were also notified in the literature, mostly in children [16, 17].

First and only report that we met in the literature was published in 1982, relating the correlation between pulmonary uptake of labeled biphosphonate compounds in bone scintigraphy and the quantity of pulmonary microcalculi [18]. Deniz et al. [13] also reported significant correlation between the pulmonary perturbations and the microcalculi score, obtained in the high resolution computed tomography. In the light of these reports, we intended to quantitatively evaluate calcified lung tissue by the help a bone scintigraphy, which might be helpful in the assessment of the disease stage. Our data, although limited, have shown that there were significant differences in density of the both lung fields of the patient as compare to the control group. Density analysis results were also in line with the spirometric tests that a moderate functional restriction pattern was present. However, functional spirometric tests do not permit to discriminate the degree of affection between two sides.

The relating quantitative analysis technique is simple, non-invasive and permits global and separate quantitative assessment of lung fields, using a vertebral density as an index. It is costless and easy to apply once a bone scintigraphy image is present. We speculated that Tc-99m MDP bone scintigraphy may add helpful information, in conjunction with other radiological and laboratory findings not only for the diagnosis of PAM, but also for follow up of the disease. The first density analysis result of the patient was close to the second analysis. These results show that there is no significant progression in terms of calcified foci. However, this observation merits clinical validation with a series of cases together with the precision analysis of the technique.

In conclusion, the presented report suggested that a quantitative analysis of calcified foci in the lung fields of patients with PAM by bone scintigraphy seems feasible and warrants further investigations.

References

1. Senyigit A, Yaramis A, Gürkan F, Kirbas G, Buyukbayram H, Nazaroglu H, Alp M.N, Topcu F. Pulmonary alveolar microlithiasis: A rare familial inheritance with report of six cases in a family. Respiration 2001; 68:204-9.
2. Chan E.D, Morales D.V, Welsh C.H, McDermott M.T, Schwarz M.I. Calcium Deposition with or without Bone Formation in the Lung. Am J Respir Crit Care Med 2002; 165: 1654-69.
3. Lauta VM. Pulmonary alveolar microlithiasis: an overview of clinical and pathological features together with possible therapies. Respir Med 2003; 97: 1081-5.
4. Mariotta S, Ricci A, Papale M, De Clementi F, Sposato B, Guidi F, et al. Pulmonary

alveolar microlithiasis: report on 576 cases published in the literature. Sarcoidosis Vasc Diffuse Lung Dis 2004; 21: 73–181.

5. Corut A, Senyigit A, Ugur SA, Altin S, Ozcelik U, Calisir H, et al. Mutations SLC34A2 cause pulmonary alveolar microlithiasis and are possibly associated with testicular microlithiasis. Am J Hum Genet 2006; 79: 650–6.
6. Mariotta S, Guidi L, Papale M, Ricci A, Bisetti A, Pulmonary alveolar microlithiasis: Review of Italian reports. Eur J Epidemiol 1997; 13: 587-90.
7. Castellana G, Gentile M, Castellana R, Fiorente P, Lamorgese V. Pulmonary Alveolar Microlithiasis: Clinical Features, Evolution of the Phenotype, and Review of the Literature. Am J Med Genet 2002; 111: 220-4.
8. Castellana G, Lamorgese V. Pulmonary Alveolar Microlithiasis. World Cases and Review of the Literature. Respiration 2003; 70: 549-55.
9. Gasparetto E.L, Tazoniero P, Escuissato D.L, Marchiori E, Frare E Silva R.L, Sakamoto D. Pulmonary alveolar microlithiasis presenting with crazy-paving pattern on high resolution CT. Brit J Radiol 2004; 77; 974-6.
10. Ucan ES, Keyf AI, Aydilek R, Yalcin Z, Sebit S, Kudu M, Ok U. Pulmonary alveolar microlithiasis: review of Turkish reports. Thorax 1993; 48; 171-3.
11. Chung MJ, Lee KS, Franquet T, Müller NL, Han J, Kwon OJ. Metabolic lung disease; imaging and histopathologic findings. Eur J Radiol 2005; 54: 233-45.
12. Coolens JL, Devos P, De Roo M. Diffuse pulmonary uptake of 99mTc bone-imaging agents: case report and survey. Eur J Nucl Med. 1985; 11: 36-42.
13. Deniz O, Ors F, Tozkoparan E, Ozcan A, Gumus S, Bozlar U, Bilgic H, Ekiz K, Demirci N. High resolution computed tomographic features of pulmonary alveolar microlithiasis. Eur J Radiol 2005; 55: 452-60.
14. Rossi SE, Erasmus JJ, Volpacchio M, Franquet T, Castiglioni T, McAdams HP. "Crazy-paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics. 2003; 23: 1509-19.
15. Shah TC, Talwar A, Shah RD, Margouleff D. Pulmonary alveolar microlithiasis: radiographic and scintigraphic correlation. Clin Nucl Med. 2007; 32:249-251.
16. Sahin U, Yildiz M, Bircan H.A, Akaya A, Candir O. Absence of pulmonary uptake of Tc-99m methylendiphosphonate in alveolar microlithiasis. Ann Nucl Med 2004; 18: 695-8.
17. Turktas H, Ozturk C, Guven M, Ugur P, Erzen C. Pulmonary alveolar microlithiasis with the absence of technethium-99m MDP uptake of lungs. Clin Nucl Med 1988; 13: 883-5.
18. Shigeno C, Fukunaga M, Morita R, Maeda H, Hino M, Torizuka K. Bone scintigraphy in pulmonary alveolar microlithiasis: a comparative study of radioactivity and density distribution. Clin Nucl Med 1982; 7: 103-7.