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Noninfectious causes of diffuse pulmonary infiltrations in chronic renal failure: metastatic pulmonary calcification

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Abstract

Metastatic pulmonary calcification (MPC) is a metabolic lung disease characterized by the deposition of calcium in pulmonary parenchyma. It may occur due to many benign or malignant pathologies. Especially it is most commonly seen in patients with end stage chronic renal failure received renal replacement treatment. The case we report here involved a history of renal transplantation about 22 months ago. His thorax computed tomography had demonstrated bilateral disseminated infiltrations with ground-glass densities predominantly in the upper lobes and it was seen partially preserved subpleural areas and basal zones. The histopathological results in transbronchial lung biopsy indicated metastatic pulmonary calcification. We wanted to discuss patient with the accompaniment of literature.

Key words: diffuse pulmonary infiltration, immunosuppressed patient, renal transplantation, chronic renal failure, metastatic pulmonary calcification

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Introduction

Metastatic pulmonary calcification (MPC) is a metabolic lung disease characterized by the deposition of calcium in pulmonary parenchyma. It may develop with many diseases causing hypercalcemia. The causes related to benign conditions include chronic renal failure, primary or secondary hyperparathyroidism, excessive exogenous administration of calcium and vitamin D, sarcoidosis, milk-alkali syndrome, osteoporosis and Paget's diseases. And the etiologies of malignant nature are multiple myeloma, parathyroid carcinoma, leukemia, lymphoma, breast carcinoma, synovial carcinoma, choriocarcinoma, malignant melanoma, hypopharyngeal squamous carcinoma. MPC is defined as the deposition of calcium in normal lung tissue without tissue damage and due to chronically elevated calcium-phosphorus products.

On the contrary, in dystrophic calcification serum calcium levels are normal. Calcium phosphate crystals come into existence on necrotic or inflamed cells. Uncommonly, MPC is seen in patients with normal renal functions, normal calcium and phosphate levels and without underlying lung disease [1–10]. Chest radiographs of MPC reveal multiple diffuse calcified nodules and confluent or patchy airspace opacities simulating diffuse interstitial process, pulmonary edema, pneumonia, alveolar hemorrhage, hypersensitivity pneumonitis, vasculitis, sarcoidosis, chronic eosinophilic pneumonia, occupational lung disease and pulmonary alveolar microlithiasis [11, 12].

Case report

A 43-year-old male patient was referred to emergency department with complaints of dysp-

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Figure 1. Initial chest radiograph

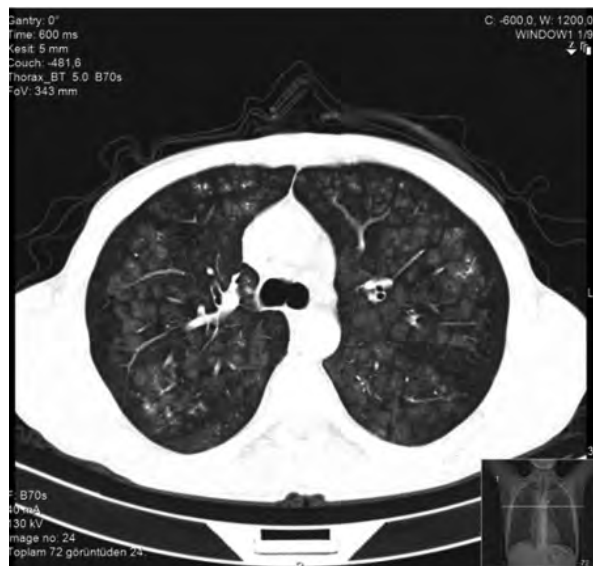


Figure 2. Initial thorax computed tomography

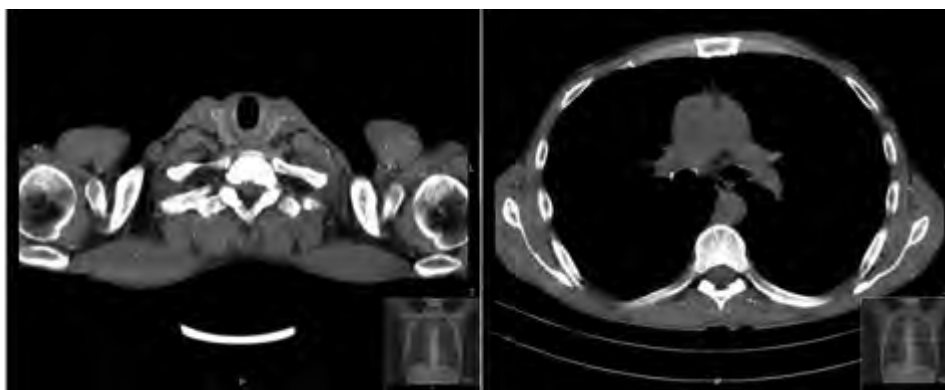


Figure 3. Calcifications are seen on skin and muscle structure out of bronchial mucosa

nea and fever. His symptoms had persisted for two months and he observed a progression of dyspnea especially the previous week. There was a history of renal transplantation due to chronic renal failure about 22 months ago. His maintenance of immunosuppressive therapy consisted of prednisolone, tacrolimus and mycophenolate mofetil. There were no characteristics in his family history. The physical examination revealed bilateral decreased breathing sounds. Oxygen saturation was 98% in room air and his temperature was 36.7°C. Laboratory tests showed hemoglobin 11 g/dL, platelet $135 \times 10^9/L$, CRP 4.18 mg/dL, creatinine 1.34 mg/dL, albumin 3.3 g/dL, alkaline phosphatase (ALP) 32 U/L, serum sodium level 124 mmol/L, serum potassium level 4.29 mmol/L, serum calcium level 8 mmol/L, serum phosphate level 2.8 mmol/L. Chest X-ray disclosed bilateral nonhomogeneous densities, predominantly in the

upper and mid zones (Fig. 1). Thorax computed tomography demonstrated diffuse bilateral ground-glass opacities, predominantly in the upper lobes, while subpleural and basal areas were semi-conserved. Also, on mediastinal sections, calcifications are seen on skin and muscle structure out of bronchial mucosa (Figs 2, 3). The patient was hospitalized with a pre-diagnosis of pneumonia, tuberculosis, drug-induced pneumonitis, noninfectious complications of renal transplantation. According to the subject's medical history and bilateral diffuse involvement on radiological imagings, viral infections, especially pneumocystis jiroveci, citomegalovirus (CMV), gram-negative bacterial infections, staphylococcus aureus infection, tuberculosis were initially considered. Piperacillin/tazobactam, linezolid, trimethoprim sulfamethoxazole therapy was introduced even though clinically no pneumocystis jiroveci was

considered but could not be ruled out radiologically with normal oxygen saturation patient. Blood, sputum and urine cultures were taken. Respiratory tract panel (microarray), blood IgM of CMV, EBV, HSV and PCR for BK virus (BKV) were studied. On the second day of the hospitalization bronchoscopy, bronchoalveolar lavage (BAL) and transbronchial lung biopsy were performed. There was no growth in cultures of the patient who was receiving antibiotherapy for fourteen days. Rhinovirus growth in respiratory tract panel (microarray), Herpes simplex virus (HSV), Epstein-Barr virus (EBV), CMV, BKV PCR were detected negative. With the negative results of bronchoalveolar lavage culture, following a transbronchial lung biopsy, pulmonary metastatic calcification was finally diagnosed in the patient. The reported case reminds of the possibility of metastatic pulmonary calcification in differential diagnosis of noninfectious causes of diffuse pulmonary infiltrations in patients with chronic renal failure and renal transplantation.

Discussion

Metastatic calcification means deposition of calcium in normal tissue. The lung is the one of the main area of metastatic calcification [1]. Metastatic calcification of pulmonary parenchyma correlate with chronically elevated calcium-phosphorus products as chronic renal failure, primary hyperparathyroidism, hypervitaminosis D, milk-alkali syndrome, multiple myeloma [2]. Calcium salts accumulate predominantly in the alveolar epithelial basement membranes, and to a lesser extent, the bronchial walls, pulmonary arteries and vascular structures [3]. Calcium accumulation occurs denser in alkaline environments. Metastatic pulmonary calcification usually occurs in the upper zones of the lung due to a more alkaline environment in the upper zones than basal areas [2]. The degree of respiratory distress is often uncorrelated with the degree of calcification in radiological findings. Patients with extensive parenchymal calcification may be asymptomatic, whereas those with subtle calcification or normal chest radiographs may have severe respiratory compromise [4]. Metastatic pulmonary calcification is a well established complication of end-stage renal failure and its treatment [5]. This interstitial process is characterized by the deposition of calcium salts, predominantly in the alveolar epithelial basement membranes. MPC is seen at autopsy in 60–75% of patients with renal failure. It is often asymptomatic but

can potentially progress to respiratory failure [11].

Our patient with renal failure and renal transplantation had no severe symptoms limiting his daily activity even though bilateral diffuse lesions were seen in his lung radiogram. Standard chest radiographs have poor sensitivity for the identification of metastatic pulmonary calcification in the parenchyma. Metastatic pulmonary calcifications have been described as airspace opacities simulating pulmonary edema or pneumonia on chest radiographs. Metastatic pulmonary calcifications can also appear as an interstitial pattern or diffuse calcific nodules on chest X-ray [2, 6]. High-resolution computed tomography (HRCT) has high sensitivity for the detection and characterization of parenchymal calcification. HRCT shows frequently three radiological patterns for malignant pulmonary calcification. These are bilateral calcific nodular lesions predominantly in the upper lobes, patchy areas of groundglass opacity or consolidation, and finally, a parenchymal consolidation with a predominantly lobar distribution. The differential diagnosis of MPC include pulmonary edema, pneumonia, atypical infections, recurrent alveolar hemorrhage, hypersensitivity pneumonitis, vasculitis, sarcoidosis, chronic eosinophilic pneumonia, pulmonary metastasis (osteogenic sarcoma, chondrosarcoma, thyroid malignancies), miliary tuberculosis, histoplasmosis, fungal infections, varicella pneumonia, occupational lung disease (silicosis, coal workers' pneumoconiosis, siderosis, stannosis, and baritosis), chronic hemorrhagic conditions, rheumatic mitral stenosis, and pulmonary alveolar microlithiasis [11–13]. As these patients are highly immunosuppressed, infection should always be excluded. In our case, HRCT revealed diffuse ground-glass opacities. Blood, sputum and urine cultures, respiratory tract panel (microarray), blood IgM of CMV, EBV, HSV and PCR for BK virus were evaluated to investigate infectious agents due to immunodeficiency in the patient. Also, bronchoalveolar lavage cultures were negative. Following a bronchoscopic parenchymal biopsy, pulmonary metastatic calcification was finally diagnosed in the man.

Dual-energy digital chest radiography has been reported to be more sensitive and accurate than standard chest radiography for the detection of MPC. However, this technique is not widely used, most likely due to the availability and advantages of computed tomography (CT) for the assessment of patients suspected of other respiratory problems [12]. In our case, dual-e-

nergy digital chest radiography was not used, we had observed calcifications on skin and muscle structure computed tomography [11].

Nuclear medicine studies are used for early detection of metastatic pulmonary calcification. Technetium-99m bone scanning is one of the sensitive techniques to detect pulmonary calcification. In addition, this technique with SPECT (single-photon emission computed tomography) may allow detection and localization of the lesion [4]. In our patient, bone scintigraphy or SPECT were not performed.

The findings of pulmonary function tests are usually normal in patients with MPC [9]. Alveolar septa are diffusely involved in MPC, diffusing capacity is decreased. Restrictive and diffusion defects may appear, even when chest radiography appears normal. Vital capacity has been inversely correlated with severity of calcification [10].

Although the optimal treatment of metastatic pulmonary calcification is not known, attempts to normalize calcium and phosphate biochemistry have been the mainstays of the therapy [14]. An increase in the dialysis dose is indicated for patients with end-stage renal disease [15]. There is no certain data about the course of MPC after renal transplantation. Some studies have shown regression of the lesions, whereas others have revealed progression after transplant [16]. In conclusion, MPC is frequently associated with end-stage renal failure and is rarely diagnosed because of being asymptomatic. It may progress to irreversible lung injury and respiratory failure. MPC should be kept in mind when unexplained radiographic changes or pulmonary symptoms develop in dialysis patients. HRCT or Tc99m-MDP bone scanning can be helpful for diagnosis and may obviate the need for open lung biopsy.

Noninfectious causes and metastatic pulmonary calcifications in the differential diagnosis of diffuse pulmonary infiltrates were discussed with the accompaniment of the literature.

Conflict of interest

The authors declare no conflict of interest.

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