Metastatic Pulmonary Calcification in a Patient With End-Stage Renal Disease on Hemodialysis: A Common Complication But a Rare Clinical Diagnosis

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ABSTRACT

Metastatic pulmonary calcification (PC) is the deposition of calcium salts in normal lung tissue, usually as a result of abnormalities of calcium or phosphorus metabolism. Most commonly PC is seen in patients with chronic renal failure who are on hemodialysis. However, PC is diagnosed rarely—not only because of its often benign clinical course, but also as a result of the low sensitivity of standard chest radiographs to detect the calcification. Calcifications therefore are most often found on autopsy. Presented is a case of metastatic PC leading to hypoxemia in a patient with end-stage renal disease on hemodialysis. The diagnosis was initially not considered and the patient underwent a thoracotomy and biopsy. A higher index of suspicion followed by a less invasive technetium-99m-labeled bone scan would have aided in making the diagnosis, thus avoiding the need for lung biopsy.

A 37-year-old African-American man presented with a complaint of shortness of breath that worsened upon exertion and that had been present for several years. He had a history of intermittent chest tightness associated with the shortness of breath, cough that sometimes produced blood-tinged sputum, orthopnea, and paroxysmal nocturnal dyspnea—all of which were chronic. The patient denied a decrease in appetite; weight loss; fever and chills; chest pain; palpitations; diaphoresis; nausea; vomiting; abdominal pain; change in bowel habits; urinary complaints; or swelling of the feet.

The patient's past medical history was significant for systemic hypertension (14 years); end-stage renal disease (ESRD) resulting from hypertension on hemodialysis (12 years); newly diagnosed pulmonary hypertension; chronic hepatitis C infection; iatrogenic hypothyroidism; and chronic anemia. Past surgical history was significant for a parathyroidectomy for secondary hyperparathyroidism and multiple surgeries for arteriovenous grafts for hemodialysis access. His social history was remarkable for a past 10 pack-years smoking pattern and past alcohol abuse. Medications included metoprolol, clonidine, minoxidil, enalapril, nortriptyline, nephroviite, sevalamer, folic acid, and calcium carbonate.

On admission the patient was in mild respiratory distress. He was afebrile, with a blood pressure of 146/86, pulse 84 beats per minute, and regular respiratory rate of 24 breaths per minute. His oxygen saturation was 84% on room air and 94% on 2 L of oxygen by nasal canula. The physical examination was significant for a loud pulmonic component of second heart sound; a 4/6 holosystolic murmur best heard at the left lower sternal border without radiations; intermittent bibasilar crackles on lung examination; and trace bilateral lower-extremity edema.

Arterial blood gas (ABG) showed a pH of 7.45, pCO2 of 38 mm Hg, pO2 of 51 mm Hg, and bicarbonate of 24 mEq/L. Chest radiograph was significant for bilateral pulmonary infiltrates suggestive of pulmonary edema (Figure 1). The patient was admitted for further evaluation and treatment. A review of the records showed that on a previous admission, the patient also had been hypoxic and was diagnosed with pulmonary edema secondary to fluid overload, for which he underwent ultrafiltration with hemodialysis.

Figure 1. Chest X-ray

Posterior-anterior view shows enlarged pulmonary arteries and bilateral infiltrates, more prevalent centrally and consistent with pulmonary edema.
Previous chest radiographs, computed tomography (CT), pulmonary angiogram, and transthoracic echocardiogram had shown findings suggestive of this diagnosis.

A working diagnosis of pulmonary edema was made and the patient underwent ultrafiltration with hemodialysis. Interestingly, there was no significant change in the ABG readings. At this point alternative diagnoses of hypoxemia were considered. A repeat high-resolution CT (HRCT) scan again only showed diffuse ground glass opacification suggestive of pulmonary edema (Figure 2). Another trial of ultrafiltration with a total of 2-L fluid removal failed to show improvement in the ABG and the patient continued to be symptomatic. A diagnosis of interstitial lung disease (ILD) now appeared more likely, however, there were no apparent drugs or environmental or occupational causes for the patient’s suspected ILD. Levels of angiotensin-converting enzyme, rheumatoid factor, antinuclear antibody, and complement also returned as normal.

A video-assisted thoracoscopic lung biopsy showed metastatic pulmonary calcification with diffuse calcium deposits in the interstitium of the alveolar septa, with diffuse thickening and fibrosis of the septa, bronchial walls, and pulmonary blood vessels (Figures 3 through 5). Von Kossa stain confirmed the presence of the calcium deposits (Figure 6). A bone scan performed showed a diffuse uptake in bilateral lung fields (Figure 7). A diagnosis of metastatic pulmonary calcification was made. As there is no definitive treatment for this condition, the patient was discharged on phosphate binders and supplemental oxygen.

**DISCUSSION**

Metastatic PC is the deposition of calcium salts in normal lung tissue. The mechanism of lung calcification is not precisely known; however, it is likely that no single factor is responsible. It can be influenced by serum calcium and phosphate concentration, alkaline phosphatase activity, parathyroid, vitamin D, and local physiochemical conditions such as pH. Calcification can occur in any tissue of the body, but commonly deposits in the lungs, kidney, and stomach (tissues with alkaline pH). The cavity of the stomach is acidic secondary to secretion of H+ ions, thus making the stomach tissue alkaline and predisposing it for calcium deposition.

Metastatic PC is associated with a variety of benign and malignant disorders (Table). It is most commonly found in patients with ESRD who are on chronic hemodialysis therapy. The prevalence of PC in an unselected population is relatively low. By contrast, it was found on autopsy in 60% to 75% of patients who had been on hemodialysis. In patients undergoing hemodialysis for ESRD, 4 factors predispose them to metastatic calcification. First, acidosis can leach calcium and phosphate from bone. Second, hypercalcemia from secondary hyperparathyroidism as a result of deranged vitamin D metabolism is commonly associated with chronic renal failure. Although patients with this form of hyperparathyroidism are already at risk for metastatic calcification, occasionally the stimulated parathyroid gland becomes autonomous, resulting in tertiary hyperparathyroidism and severe hypercalcemia. Third intermittent alkalosis, which often accompanies bicarbonate hemodialysis, can predispose to soft-tissue precipitation of calcium salts. Finally, the decreased glomerular filtration of phosphate may contribute

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**Figure 2. High-Resolution Computed Tomography Scan of the Thorax**

Diffuse ground glass opacities are present that are most consistent with a diffuse pulmonary process such as pulmonary edema.

**Figures 3-5. Lung Parenchyma, Showing Significant Fibrous Alveolar Wall Thickening**

The calcium deposit appears as a layer of hematoxyphilic material in the alveolar wall (Figure 3), blood vessel (Figure 4), and bronchiolar wall (Figure 5).
to an elevated serum calcium phosphate product. Elevated serum phosphate levels have been shown to correlate highly with vascular calcification in uremic patients. Elevated serum phosphate levels have been shown to correlate highly with vascular calcification in uremic patients. The extent of calcification, however, correlates poorly with the serum calcium and phosphorus levels, the etiology of renal disease, the length of dialysis, and the degree of parathyroid hyperplasia.

In the lungs, calcium deposits are found in the interstitium of the alveolar septum, bronchiole walls, in the large airways, and even in the walls of the pulmonary vessels. The extent of lung calcification can vary from mild and patchy to severe and widespread. A study of 56 hemodialysis patients showed that in general, vascular and parenchymal calcification are parallel. However, this may not be true given emerging clinical data that show pulmonary vascular calcification not to be the cause for pulmonary hypertension in this patient population, suggesting nonsignificant vascular calcification.

Contrary to pathologic studies, PC seldom is recognized clinically. The clinical manifestations of PC usually are minimal but occasionally may cause dysnea, as in this patient. Rarely, progressive respiratory insufficiency and death may ensue. Metastatic calcification can cause acute respiratory failure and death due to destruction of the alveolar capillary barrier secondary to progressive calcification of the alveolar walls. The typically benign course of PC is explained by the relatively minor tissue reaction evoked by the small size of calcium deposits on most occasions. No correlation is found between the extent of macroscopic calcification and clinical symptomatology; some patients with extensive calcification may be asymptomatic, whereas others with more subtle calcification in the face of normal chest radiographs may have significant physiologic impairment. However, there is a direct correlation between the extent of alveolar septal thickness and fibrosis in response to calcium deposits and the magnitude of restrictive and diffusional defects.

The etiology of pulmonary hypertension in patients with ESRD who are on hemodialysis is unclear. Data from earlier studies by Akmal et al suggested secondary hyperparathyroidism and subsequent PC as the cause of pulmonary hypertension in this patient population. Recent clinical trials that studied the association between pulmonary hypertension and PC in patients on chronic hemodialysis do not support the role of PC as the etiology of pulmonary hypertension in these patients. Both ESRD and long-term hemodialysis via arteriovenous access may be involved in the pathogenesis of pulmonary hypertension by affecting pulmonary vascular resistance and cardiac output. Further studies are needed to establish the exact pathophysiology of pulmonary hypertension in these patients.

**DIAGNOSTIC STRATEGIES**

The standard chest radiograph is relatively insensitive for detection of PC. Conger reported an abnormal chest x-ray in only 1 out of 15 patients on hemodialysis who had microscopic PC. Even when seen on chest radiograph, diffuse calcification often is mistaken for another process such as pulmonary edema (as in this patient), because it appears as nondiscrete infiltrates. Similarly, localized pulmonary calcification often is confused with infarction, pneumonia, or malignancy. HRCT scan and 99m technetium-methylene-diphosphonate (99mTc-MDP) bone scintigraphy are relatively specific for PC. On HRCT scan PC may be seen as multiple calcified and or noncalcified nodules, diffuse or patchy areas of ground glass opacification (as in this patient), ill-defined patchy infiltrate, or as a relatively dense area of calcification that mimics lobar pneumonia.

However, false negatives may result from the microscopic size of calcium salt crystals or from signal averaging from a relatively large soft-tissue component. The bone scintigraphy appears to be more sensitive than HRCT scans for detecting PC. This observation is based on case reports without prospective comparison studies, and is supported by this case. However, some studies have questioned the specificity of the scan. One
study demonstrated markedly increased 99mTc-MDP lung uptake confirmed by histology in only 1 of 30 patients. Because histologic studies are not always available, there is a need to elucidate the sensitivity and specificity of available tests as well as any new tests to detect presence and extent of PC.

**Therapeutic Options**

The progression of disease and management of patients with metastatic PC remains poorly understood. Specific treatment aims at correction of isolated hyperphosphatemia or elevated calcium phosphate product, if present. Oral phosphate binders are the first line of treatment in such cases. In case of severe refractory hyperphosphatemia associated with secondary hyperparathyroidism, parathyroidectomy (PTX) may help. This patient had a PTX several years earlier and his PC had progressively worsened. Renal transplantation may ameliorate PC, or conversely, PC may inexplicably progress despite a normally functioning renal allograft and normal or near-normal calcium and phosphate levels. In hypoxic patients supplemental oxygen provides symptomatic relief.

**Conclusion**

Metastatic PC is a common subclinical complication in patients with ESRD who are on hemodialysis, however it is a rare clinical diagnosis given its typically indolent course. PC findings on chest radiograph and CT scan may be difficult to distinguish from other parenchymal processes. The relative stability of these infiltrates, in contrast to infectious processes or fluid accumulation, is of diagnostic value. Given the high incidence of misinterpretation of PC as pneumonia or pulmonary edema on chest x-ray and CT scan, 99mTc-MDP bone scintigraphy may be useful for evaluation of hypoxemia in patients with chronic renal failure when there is an index of suspicion for metastatic calcification, possibly avoiding the need for lung biopsy.

**References**