The goal of the present case report is to enhance recognition of the incidence of tissue calcifications, which are quite common in patients with end-stage renal disease. We focus on pulmonary metastatic calcifications and the potential progression of this condition to tissue necrosis and lung cavitations in the setting of severe electrolyte imbalance. This case highlights the importance of early identification of the causes and potential risk factors leading to visceral calciphylaxis.

Key words
Pulmonary calciphylaxis, metastatic pulmonary calcification, high-resolution computed tomography, HRCT, end-stage renal disease, ESRD, hemodialysis

Introduction
Ectopic pulmonary calcification is divided into two types based on pathophysiologic and underlying histologic characteristics. Dystrophic calcifications occur when calcium salts are deposited into pathologically abnormal tissues. For instance, in granulomatous diseases, calcium salts precipitate in necrotic tissue. On the other hand, metastatic calcification is considered a metabolic disorder that occurs in the setting of electrolyte imbalance and involves calcium deposition into otherwise normal tissues. The metastatic calcification process predominantly affects blood vessels, periarticular soft tissues, lungs, stomach, kidneys, and myocardium.

Visceral calcification may develop silently over many years and is often detected incidentally. Most cases of metastatic pulmonary calcification occur in patients with hypercalcemia, particularly those with hyperparathyroidism secondary to chronic kidney disease. Less common causes include primary hyperparathyroidism, extensive bone metastasis, hypervitaminosis D, milk–alkali syndrome, and multiple myeloma (1–3).

Multifocal patterns of pulmonary parenchymal calcification may also be associated with infection (especially histoplasmosis and tuberculosis), silicosis, diffuse parenchymal amyloidosis, alveolar proteinosis, idiopathic pulmonary hemosiderosis, and alveolar microlithiasis. It may also occur in metastatic malignancies such as osteogenic sarcoma, chondrosarcoma, and mucin-producing adenocarcinomas (3,4).

Histologically, metastatic pulmonary calcification is an interstitial process characterized by deposition of calcium in the elastic tissue of alveolar septa, arteries, veins, bronchioles, and bronchi (3,5). As deposition continues, the areas of involvement become more fibrotic, and calcium deposition becomes more plate-like (1).

Chest radiography is a relatively insensitive diagnostic tool. The most common radiologic manifestation consists of poorly defined nodular opacities (6,7). More severe interstitial calcification can result in dense areas of consolidation (2). Recently, high-resolution computed tomography (HRCT), dual-energy digital chest radiography, and isotope imaging using hydroxymethylene diphosphonate (Tc-99m MDP) have been used as effective tools to detect the presence of pulmonary calcifications (8,9). The most common parenchymal finding on HRCT is the presence
of centrilobular “ground glass” nodular opacities, with numerous fluffy and poorly defined nodules measuring 3 – 10 mm in diameter (2,7). Calcification, when evident on CT, can be punctate within the nodular opacities or ring-like, or they can involve the entire nodule (2,3,6,7). Additionally, calcification in the vessels of the chest wall is often seen on the CT scan as well. The combination of pulmonary and vascular calcification is characteristic of metastatic pulmonary calcification (7). When the calcification pattern becomes confluent, it may mimic a consolidative process and may be misdiagnosed as pulmonary edema or pneumonia (2).

Most patients with metastatic pulmonary calcification are asymptomatic. Pulmonary function tests are usually normal in the early stages of the disease. With disease progression, restrictive lung changes may develop, with decrease in vital capacity and diffusion capacity leading to hypoxemia (6).

Several types of tissue calcification have been described from radiographic evaluation of patients with end-stage renal disease (ESRD). Abnormal pulmonary and cardiac calcifications have been reported at autopsy in 40% – 80% of these patients (7,10). Patients who have high Ca×P product have a higher incidence of such findings. An ion product in excess of 60 (mg/dL)² has been associated with tissue calcifications. Local and systemic changes in pH are both responsible for inducing calcification in soft tissues. Because of their relative alkaline environments, the lungs, kidneys, and stomach wall are predisposed (11).

In lung, metastatic calcification tends to involve mainly the upper zones. This distribution is related to the lower partial pressure of CO₂ in the upper zones as a result of a higher ventilation–perfusion ratio and thus a higher pH. A locally elevated pH favors the deposition of calcium salts (6).

Calciphylaxis is a rare and life-threatening disorder characterized by small-vessel mural calcification with intimal proliferation, fibrosis, and thrombosis, resulting in ischemic necrosis of the tissue (8). It has been viewed largely as a systemic disease involving dermohypoderminic arterioles, subcutaneous fat, or muscles of the extremities. However calciphylaxis of other organs has been reported occasionally in the literature. It occurs mostly in chronic kidney disease patients with elevated Ca×P product in the setting of secondary hyperparathyroidism (12).

The prevalence of calciphylaxis in dialysis patients may be as high as 20% (13). Several risk factors contributing to the syndrome have been identified, including severe hyperparathyroidism, total or subtotal parathyroidectomy, adynamic bone disease, and diabetes mellitus (13,14). Furthermore, local trauma, steroid or warfarin use, protein C and S deficiencies, and vitamin D excess have all been documented to contribute to the development of calciphylaxis (8).

Case report
Our patient is a 22-year-old Hispanic male with ESRD secondary to congenital dysplastic kidneys. When he was 3 years old, an attempted kidney transplant failed when complicated by immediate rejection. Subsequently, continuous ambulatory peritoneal dialysis (CAPD) was initiated.

The patient’s medical history is also significant for hypertension, anemia, asthma, obstructive sleep apnea, and severe secondary hyperparathyroidism. He underwent parathyroidectomy in 2003. After multiple admissions for bacterial peritonitis, he was converted to hemodialysis in December 2004. He also has diffuse peritoneal calcifications with thickened calvarium, causing pseudotumor cerebri.

Since 2005, the patient has been suffering with nausea and vomiting of unclear origin. An extensive gastrointestinal workup—including a gastric emptying scan and multiple esophagogastroduodenoscopies—failed to identify a cause of the persistent vomiting.

In 2004, patient was noted to have a normal chest X-ray (CXR). In April 2005, the patient was admitted to hospital with persistent fevers. Based on an abnormal CXR, he underwent a chest HRCT, which was significant for diffuse pulmonary calcifications and renal osteodystrophy (Figure 1). At that point, the patient’s calcium and vitamin D supplements were discontinued. The fevers resolved, and he was discharged home.

In August 2005, the patient was readmitted to hospital with a primary diagnosis of pneumonia [CXR showing right upper lobe (RUL) infiltrate]. He was treated with a course of intravenous vancomycin and piperacillin–tazobactam.

In January 2006, patient was readmitted with a chief complaint of shortness of breath and worsening of nausea and vomiting. Medications on admission included sevelamer hydrochloride 800 mg 3 times daily as a phosphate binder and metoclopramide 5 mg
daily. Physical exam revealed a blood pressure of 82/50 mmHg, a heart rate of 86 bpm, and a temperature of 98.2°F. A lung exam showed decreased breath sounds with no evidence of wheezing. Heart was regular with no murmurs, rubs, or gallops. Livedo reticularis and other signs of calciphylaxis were not seen. Hematologic tests showed a white blood cell count of 12,200/µL with a differential of 73% neutrophils and 20% lymphocytes, a hemoglobin of 15.8 g/dL, a hematocrit of 49%, and a platelet count of 159,000/µL. Blood chemistry screening showed sodium, 152 mmol/L; potassium, 3.8 mmol/L; chloride, 69 mmol/L; serum bicarbonate, >50 mmol/L; calcium, 10.5 mg/dL; albumin, 5.0 g/dL; phosphorus, 9.2 mg/dL; Ca×P product, 96.6; and magnesium, 3.6 mg/dL. Renal function tests showed a blood urea nitrogen of 38 mg/dL and a serum creatinine of 10.1 mg/dL. Intact parathyroid hormone measured during the course of that admission was 122 pg/mL (normal range: 10 – 65 pg/mL). Liver function tests were unremarkable. Arterial blood gas showed a pH of 7.39, a $P_{O_2}$ of 85 mmHg, and a $P_{CO_2}$ of 59 mmHg. The CXR was significant for a cavitary process in the RUL. Chest CT showed a large, complexly septated cavity in the RUL, and some destruction of lung parenchyma in the left upper lobe (LUL), although not as severe as that in the RUL (Figure 2).

The patient was started on broad spectrum antibiotics with intravenous vancomycin and piperacillin–tazobactam for presumed necrotizing pneumonia.

FIGURE 1 Diffuse pulmonary calcifications were initially noted on this high-resolution computed tomography chest scan from April 2005.
He improved clinically and was discharged in stable condition. In March 2006, a repeat chest CT scan showed a septated cavitary right apical lesion and LUL structural distortion relatively unchanged as compared with the chest CT scan from January 2006. Subsequently, the patient was started on 4 weeks of intravenous levofloxacin for a presumed RUL infectious process.
A follow-up chest CT scan in May 2006 showed a large RUL cavitary lesion similar in appearance to that uncovered in previous studies. In addition, he had progressive structural distortion and fibrotic changes of the LUL. Bronchoscopy with bronchoalveolar lavage was performed in July 2006, and cultures of the washing fluid for bacteria, mycobacteria, and fungi were negative. Staining for *Pneumocystis carinii* pneumonia was also negative. Bronchoscopic examination showed a diffuse pattern of shiny, whitish, linear images in the bronchial tree of both lungs, suggestive of submucosal pulmonary calcification.

**Discussion**

Metastatic pulmonary calcification is a relatively common complication in patients with ESRD. It manifests as tissue calcification without ischemic and necrotic changes. Calciphylaxis, on the other hand, is associated with medial and intimal calcification of small- and medium-sized arteries, with ischemic necrosis of involved tissue (8,15).

Pulmonary calciphylaxis is a rare disorder that has been associated with lung necrosis. The diagnosis of pulmonary calciphylaxis requires high suspicion, and a definite diagnosis requires pathology examination of tissues. Although no tissue biopsy has been done in the present case, the setting of electrolyte imbalance, negative culture results, and the progressive nature of the lung lesions on serial imaging studies are highly suggestive of lung tissue necrosis secondary to pulmonary calciphylaxis.

We speculate that high calcium and phosphate levels and an alkaline environment exacerbated by chronic vomiting are the main culprits in accelerating the development of diffuse metastatic calcifications and ultimately fulminant pulmonary calciphylaxis. Predilection for calcification in the lung, especially the upper lobes, and ultimate necrosis in those areas is consistent with the relative alkaline environment in those areas as a result of higher ventilation-to-perfusion ratios and hence lower partial pressures of CO₂.

**Conclusions**

Although patients with metastatic pulmonary calcifications are usually asymptomatic, calcium, phosphate, and parathyroid hormone levels should be monitored, and abnormalities should be treated to avoid progression to calciphylaxis. Few options exist for treating calciphylaxis, and the outcome is generally poor.

Several causes have been proposed to explain the development of calciphylaxis at the molecular level. Uremia is a proinflammatory state in which levels of interleukin-6 and tumor necrosis factor α are reported to be elevated in most patients with ESRD. These proinflammatory cytokines are known to contribute to endothelial dysfunction and vascular calcification, which may lead to the development of calciphylaxis (8,16). In addition, a decrease in calcification inhibitors such as osteoprotegerin has also been reported in patients on hemodialysis, possibly contributing further to development of calciphylaxis (8,17).

**References**


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