Localized Pulmonary Calcinosis: A Unique Presentation of a Rare Disease

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Metastatic pulmonary calcinosis (MPC) is characterized by deposits of calcium in normal pulmonary parenchyma. Diffuse pulmonary calcinosis commonly occurs in hypercalcemia and/or hyperphosphatemia and is more commonly related to renal failure than primary hyperparathyroidism, skeletal metastases, or multiple myeloma [1]. Calcium depositions favor alkaline tissue and are thus more common in the upper lobes of the lung, which have a higher ventilation to perfusion ratio and a low capillary pCO_2, resulting in an alkaline pH [2]. Therefore, the most common radiographic manifestation consists of poorly defined nodular opacities bilaterally in the upper lung zones [3].

Dystrophic calcifications occur in damaged lungs, typically following an inflammatory process such as a localized organized collection of hydroxyapatite calcium salts [2]. Cecchini and colleagues [2] described a rare case of a patient with localized pulmonary calcifications following Pseudomonas pneumonia. Kang et al. [3] described a patient with bilateral lower lobes calcifications who presented with MRSA pneumonia and a parathyroid nodule with hypercalcemia, a case that might represent a combined situation of metastatic and dystrophic pulmonary calcification or an atypical manifestation of MPC.

MPC is present in 60–75% of patients with chronic renal failure on autopsy. However, it is under-diagnosed because chest radiography is not sensitive enough to detect it and most patients are asymptomatic. Depositions of calcium in the pulmonary interstitium are commonly seen in high resolution computed tomography (CT) but are rarely seen in radiographic images [4].

Among those who have symptoms, the manifestations can include progressive dyspnea, hypoxemia, hemoptysis, and rarely alveolar hemorrhage and respiratory insufficiency [3].

PATIENT DESCRIPTION

We present a case of a 53-year-old male with a history of resistant Crohn's disease and chronic renal failure who was undergoing hemodialysis. In the past, the patient received immunosuppression, including methotrexate and a long course of high dose of prednisone.

The patient approached his primary care physician with complaints of worsening dyspnea lasting a month, especially at night, without fever or other complaints. A chest X-Ray showed a new right-sided pulmonary effusion, and the patient was referred to the emergency department (ED). In the ED the patient had hypotension of 70/43 mmHg and had tachycardia with a heart rate of 107 bpm. The oxygen saturation was 93–94% in room air. On his physical pulmonary examination, there were decreased breathing sounds over his lower right lung field, diffused wheezing, and crackles.

Blood samples showed an increased white blood cell count of 21,400 cells/µl of blood (normal range 4–11.0 cells/µl) with a neutrophilic predominance. The patient was hyperkalemic (6.6 mmol/L, normal range 3.5–5.1 mmol/L) and had an increased C-reactive protein (CRP) (228 mg/L, normal range 0–5 mg/L). Calcium levels were 8.9 mg/dl (corrected to 9.7 mg/dl, normal range 8.6–10.3 mg/dl) and phosphate levels were 9.4 mg/dl (normal range 2.6–4.5 mg/dl). Because of hyperkalemia, an emergent hemodialysis was performed in the ED.

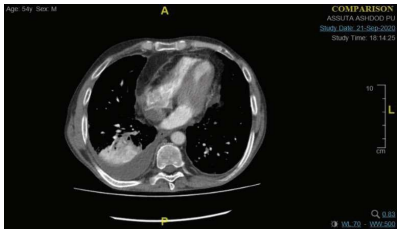
A chest X-ray showed an increased interstitial pattern over the right lung, with consolidations on the right lower lung field. Due to a recent event of an acute deep vein thrombosis in his right jugular vein involving the dialysis catheter and a differential diagnosis of pulmonary emboli, the patient was sent for a chest CT. The exam showed asymmetric bilateral pleural effusions with an adjacent pulmonary consolidation in the right lower lobe and mediastinal lymphadenopathy. No pulmonary emboli were detected.

The patient was admitted to the internal medicine ward with an initial diagnosis of pneumonia because of marked leukocytosis, increased CRP, and consolidation on the chest X-ray and CT scan. A broad-spectrum antibiotic therapy was started. A diagnostic pleurocentesis was performed with an exudative fluid. No signs of empyema were detected in the pleural fluid.

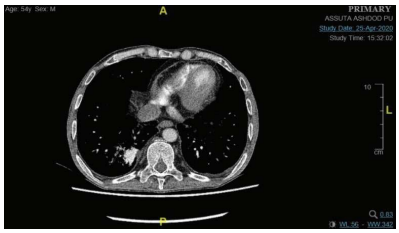
Blood cultures obtained at admission and cultures from the pleural fluid were negative. The dialysis line was removed, and its tip sent to microbiology. A total body CT scan did not reveal any findings suggesting localized infection. A diagnostic bronchoscopy with bronchoalveolar

Figure 1. Localized pulmonary calcinosis in a patient with chronic renal failure
CT = computed tomography

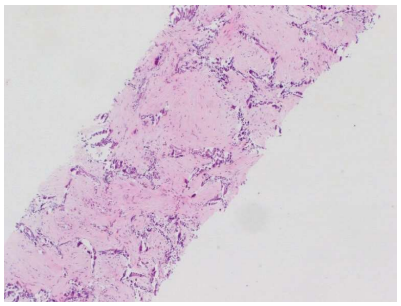
[A] CT scan at admission, asymmetric bilateral pleural effusion with pulmonary consolidation and increased mediastinal lymph nodes (September 2020)



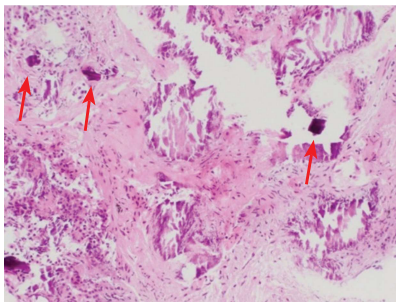
[B] CT showing a hyperdense consolidation in the right lower lobe (April 2020)



[C] CT-guided true cut biopsy of lung, showing extensive lung fibrosis with calcium deposits (H&E), ×100



[D] CT-guided biopsy of lung, showing thickened, fibrotic alveolar walls with calcified material (red arrows) (H&E), ×400



lavage (BAL) from the right lower lobe was performed. The cultures and cytology of BAL were negative. The patient's state gradually improved with empiric antibiotics and intensified hemodialysis sessions.

A pulmonologist council mentioned that the lung consolidation in the right lower lobe showed obvious partially radiopaque finding [Figure 1A]. This finding had been smaller in a previous chest CT scan 5 months prior to current hospitalization [Figure 1B]. The differential diagnoses included amyloidosis, bleeding into a consolidation, aspiration of contrast such as barium, sarcoma, amiodarone, or hyper calcinosis. Therefore, a CT-guided lung biopsy was performed, which showed extensive calcified material in lung parenchyma with accompanying fibrosis. These features are consistent with MPC [Figures 1C and 1D).

COMMENT

MPC is a known complication of end-stage renal disease (ESRD) caused by calcium deposition in the lung parenchyma. Usually, it is diffuse; however, it can be localized in cases of localized lung injury, such as pneumonia. The primary pathogenic mechanism of MPC is unexplained but can be related to factors such as hypercalcemia, hyperphosphatemia, dialysis-associated intermittent acid-base imbalance, and local secretion of free hydrogen ions in the lungs. In general, such calcifications occur after a long period of dialysis, but there are case descriptions of calcifications appearing within months of starting dialysis.

Significant progress has been made during the last 20 years in all fields of respiratory medicine [5]. However, the optimal treatment for metastatic pulmonary calcinosis remains unknown [3]. In chronic renal failure patients, metastatic pulmonary calcinosis is associated most frequently with a calcium-phosphate product due to hypercalcemia and/or hyperphosphatemia [1]. The mainstay of therapy is the normalization of calcium and phosphate biochemistry. Bisphosphonate has been suggested to normalize calcium in hypercalcemic patients and to halt the progression of calcinosis. Hyperphosphatemia can be treated with phosphate binders. An increase in dialysis frequency is generally indicated for patients with ESRD. Some authors have suggested that nocturnal hemodialysis promotes superior control of serum phosphate level and uremia compared with conventional treatment (3 times weekly). Renal transplantation may be considered for eligible patients [1,3].

Our case describes a unique presentation of an uncommon clinical phenomenon. We described a localized, unilateral pathology in a dialysis patient, in which we expected to find diffuse, rather than localized, pulmonary calcinosis. Although our patient was admitted with an initial working diagnosis of acute infection, bacteriological evidence of pneumonia was not found. A right lower lobe radiopaque consolidation was present in a prior CT scan when there was no clinical suspicion of pneumonia. The infiltrate probably increased in size secondary to the pleural effusion. Our patient had a normal calcium level and markedly increased phosphate levels, which can be attributed to the development of pulmonary calcinosis. The gradual enlargement of the calcified part of the pulmonary lesion during that period suggests chronic activity, as in MPC. No documented evidence of recurrent pneumonia, either related or unrelated to aspiration, was known. Bronchiectasis was not detected in any of the patient's chest CT scans. Interestingly, the calcification in the right lower lobe was not identified in a serial chest X-ray and was visible only in chest CT scans.

CONCLUSIONS

We present an unusual case of a radiopaque lung consolidation that was diagnosed as

pulmonary calcinosis following a CT-guided true cut lung biopsy. Due to the presence of a calcified lesion in a series of chest CT scans in an interval, we concluded that it was a long-standing and gradually worsening process without an acute cause. A localized MPC in ESRD patients without evidence of active processes such as pneumonia or malignancy have not been described in the past. This case shows that localized MPC might appear in ESRD patients on hemodialysis, which should be considered for differential diagnoses in similar circumstances with radiopaque pulmonary consolidations or masses.

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The happiest is the person who suffers the least pain; the most miserable who enjoys the least pleasure.
Jean-Jacques Rousseau (1712–1778), Genevan philosopher, writer, and composer

A great deal of intelligence can be invested in ignorance when the need for illusion is deep.
Saul Bellow (1915–2005), writer, Nobel laureate

Capsule

Effect of donor sex on recipient mortality in transfusion

Conflicting observational evidence exists regarding the association between the sex of red-cell donors and mortality among transfusion recipients. Evidence to inform transfusion practice and policy is limited. The authors assigned 5190 patients to the male donor group and 3529 to the female donor group. At baseline, the mean age of the enrolled patients was 66.8 ± 16.4 years. The setting of the first transfusion was as an inpatient in 6969 patients (79.9%), of whom 2942 (42.2%) had been admitted under a surgical service. The baseline hemoglobin level before transfusion was 79.5 ± 19.7 grams per liter, and patients received a mean of 5.4 ± 10.5 units of red cells in the female donor group and 5.1 ± 8.9 units in the male donor group (difference 0.3 units; 95% confidence interval [95%CI] −0.1 to 0.7). Over the duration of the trial, 1141 patients in the female donor group and 1712 patients in the male donor group died. In the primary analysis of overall survival, the adjusted hazard ratio for death was 0.98 (95%CI 0.91–1.06). This trial by **Chasse** et al. showed no significant difference in survival between a transfusion strategy involving red-cell units from female donors and a strategy involving red-cell units from male donors.

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Capsule

Dispensable dural lymphatics

Lymphatic vessels in the dura, the outermost layer of the meninges, provide a vascular path for immune cells connecting the meninges with the systemic circulation. Dural lymphatics have been proposed as a gateway that T cells targeting CNS autoantigens use to access the brain and spinal cord. The formation and maintenance of dural lymphatics can be abrogated by genetic or pharmacologic interference with vascular endothelial growth factor C (VEGF-C) or its receptor, VEGFR3. **Li** et al. found that atrophy of dural lymphatics by VEGFR3 blockade in mice was insufficient to block autoimmune neuroinflammation initiated by immunization with myelin autoantigens or transfer of encephalitogenic T cells. These findings suggest that therapies aimed at disrupting dural lymphatics are unlikely to attenuate human autoimmune neuroinflammatory diseases such as multiple sclerosis.

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