**CASE REPORT**

**Diffuse Pulmonary Ossification Associated With Idiopathic Pulmonary Fibrosis**

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**Abstract**

Diffuse pulmonary ossification is a rare entity that presents with the formation of mature bone in the pulmonary parenchyma and is associated with diffuse and chronic lung disease, heart disease, or other system disorders. Diffuse pulmonary ossification is usually a postmortem finding by the pathologist. In the case we report, the diagnosis was established by open lung biopsy. The patient was a 79-year-old man with dyspnea, dry cough, and weight loss. He had been a smoker. A chest x-ray revealed reticulonodular bilateral pulmonary infiltrates. Computed tomography revealed interstitial disease predominantly in the septum with multiple cavitations that tended to form honeycomb patterns. Pleural thickening, retraction of the parenchyma, and bilateral fibrosis were also visible. A clinical diagnosis of interstitial fibrosis was established and the patient’s course was unfavorable. An open lung biopsy was performed. The lung tissue specimens revealed zones with collapsed alveoli and others with emphysema, some of which produced secretion and erythrocytic extravasation. Interstitial vascular congestion was apparent; bronchioles presented mononuclear and some polymorphonuclear inflammatory infiltrates. Noteworthy was the presence of predominantly interstitial, multicentric foci of osseous trabeculae—some of which included adipose bone marrow. Diffuse pulmonary ossification is usually an incidental finding in autopsies of patients with a history of diffuse chronic pulmonary disease, but it is an unusual diagnosis in living patients. Diffuse pulmonary ossification is of no prognostic significance in pulmonary fibrosis. It is a marker of the chronicity and/or severity of the fibrosis.

**Key words:** Dendriform pulmonary ossification. Idiopathic pulmonary fibrosis. Lung biopsy.

**Introduction**

Diffuse pulmonary ossification (DPO) is a rare, asymptomatic entity that is usually diagnosed postmortem as an incidental finding by the pathologist. DPO can be idiopathic or associated with a variety of
pulmonary, cardiac, and other disorders. DPO, characterized by the formation of mature bone in the pulmonary parenchyma, may be either granular or dendriform. The granular type, also known as nodular, usually occurs in the context of chronic congestion. Dendriform DPO is interstitial, occurring in a setting of chronic fibrosis.

We report a case of DPO associated with idiopathic interstitial pulmonary fibrosis that was an incidental histopathological finding after open lung biopsy.

Case Description

The patient was a 79-year-old man with progressive dyspnea on exertion, dry cough, asthenia starting 6 months before admission, and weight loss (15 kg in 3 months). He had been a smoker of 20 cigarettes per day until 10 years before onset of symptoms. He had no history of working in high-risk occupations. Physical examination revealed bilateral basal crackles. Analysis of peripheral blood showed a white cell count of 10,800 µL (83% neutrophils, 14% lymphocytes); red cells: 3,340,000 µL; hemoglobin, 10.5 g/dL; hematocrit: 30%; platelets: 161,000 µL; and erythrocyte sedimentation rate: 70 mm in the first hour. Arterial blood gas analysis showed pH to be 7.54; PaCO₂: 27.7 mm Hg; PaO₂: 85.8 mm Hg; arterial oxygen saturation: 97.7%; bicarbonate: 23.2 mEq/L; and base excess: 2 mmol/L. A chest x-ray revealed basal, reticulonodular pulmonary infiltrates on both sides, with right basal predominance (Figure 1). A walking test revealed exercise-induced hypoxic insufficiency and 93% oxygen saturation. Spirometry showed moderate restriction and reduced forced vital capacity. Pulmonary fibrosis, tuberculosis, and neoplasia were considered as possible diagnoses. No acid-fast, alcohol-resistant bacilli were detected in specimens of mouth washings, direct sputum, or sputum culture. Purified protein derivative (tuberculin) testing was negative and tests of bronchial brushings and washings were negative for malignancy.

A computed tomography (CT) scan of the chest revealed bilateral basal interstitial images that were reticular and predominantly peripheral. Subpleural septal thickening and multiple cavities tending to form a honeycomb pattern were evident. Pleural thickening with irregular infiltration and retraction of the parenchyma was visible at both lung apexes, but there was no lymph node enlargement (Figure 2). An open lung biopsy was performed through a right anterior minithoracotomy; numerous nodules 1 mm in diameter were apparent to the touch. A small lung biopsy sample was taken and a drainage tube was placed and removed the next day. Macroscopic observation of a section of lung tissue (4×2.3×1.1 cm) from the sample revealed a rough, grayish-black external surface with whitish nodular areas 1 mm in diameter and elastic in consistency. Microscopic examination of hematoxylin-eosin stained paraffin-embedded tissue samples revealed atelectatic alveolar zones with interstitial fibrosis and lymphocytic infiltrates. Some parts had collapsed alveoli and others were emphysematous, some showing signs of secretion and erythrocytic extravasation. Intersitial vascular congestion was apparent; bronchioles with acidophilic secretion and mononuclear (and some polymorphonuclear) inflammatory infiltrates were visible. Noteworthy was the presence of predominantly interstitial, multicentric foci of osseous trabeculae—some of which included adipose bone marrow (Figure 3).

Discussion

Pulmonary ossification is defined as the histologic presence of mature bone, with or without bone marrow islets, in interstitial or alveolar spaces. It is a rare entity: the literature describes 141 cases of DPO written since Luschka’s first report in 1856. Most of the cases were
isolated, postmortem findings. Jaderborg and Dunton described a case in which the diagnosis was established by endoscopic biopsy. Duarte et al. found that 17% of histological findings were DPO cases in a study of 65 patients undergoing lung volume reduction surgery as an alternative treatment for pulmonary emphysema.

DPO can be idiopathic or associated with a variety of pulmonary, cardiac, and other disorders (Table). Many of the diseases associated with DPO frequently present with metastatic or dystrophic calcification; thus ossification may be a continuation of either of these 2 processes in the lungs.

The pathogenesis of DPO is unknown. Most studies suggest that any fibrosis, regardless of the cause, is a precursor of DPO, and a genetic predisposition for DPO may play a role. Concentrations of calcium and phosphorous in serum are usually normal, as are alkaline phosphatase levels, although they should be assessed. Ossification is the result of a series of benign events that cause arterial deterioration and are followed by inflammation and hyalinization of the perivascular tissue. DPO may in fact be a peculiar way of repairing, or scarring, the parenchyma in certain patients in and certain environmental conditions. Various theories have been postulated to explain the development of DPO—

for example, that an acid, anoxic environment stimulates fibroblast metaplasia into osteoclasts, as it is well known that such an environment favors that transformation in other tissues. Metaplasia of this type may occur in patients with multiple episodes of pneumonia or other lung diseases that lead to scarring. It has also been suggested that stress forces may favor metaplastic bone formation and lead to dendriform distribution. Another theory—the dystrophic theory—suggests that senile alterations of the perivascular, connective, and interstitial tissue may lead to ossification. Chan et al. mention in their review of calcium deposition in the lungs that in patients with chronic pulmonary venous congestion, intraalveolar bleeding has been named as a factor that predisposes an individual to fibrosis and ossification. Furthermore, they note, it may be that cell growth factors involved in the extracellular matrix formation and resolution of inflammation are involved in ossification as well. An example they give is that the transforming growth factor-β, a product of inflammatory macrophages and damaged epithelial cells, affects the growth of collagen and the extracellular matrix and plays an important role in idiopathic pulmonary fibrosis and other fibrotic diseases of the lungs. Transforming growth factor-β also stimulates the formation of osteoblasts and chondrocytes. Yet another growth factor that may be important in DPO is bone morphogenetic protein (BMP), which is a member of the transforming growth factor-β superfamily and seems to play a certain role in the development of familial primary pulmonary hypertension according to literature reviewed by Chan et al. They note that an increase in the expression of BMP in tumor cells with increased collagen type III has been reported in colorectal adenocarcinoma; likewise, interleukin 1 increases BMP-induced heterotopic ossification in laboratory animals, and interleukin 4 together with monococyte-colony stimulating factor may also transform human alveolar macrophages into osteoclasts, cells essential to bone remodeling. Fibrogenesis, angiogenesis, osteogenic growth factors, and cytokine may turn out to induce ossification in lungs with fibroproliferative disorders, such as idiopathic pulmonary fibrosis, although the involvement of these factors in idiopathic and secondary ossification have yet to be researched, Chan et al point out. Local ion alterations, inflammation, and chronic tissue anoxia promote the transformation of fibroblasts into osteoblasts. The fibrotic transition in bone tissue has been observed microscopically. In a series of isolated cases pulmonary fibrosis was visible neither in ossified areas nor in the parenchyma adjacent to the DPO. Overall, a definitive theory to explain the development of DPO is lacking.

Interstitial bone deposits may be local or extensively distributed throughout the pulmonary parenchyma.

Two histologic types of pulmonary ossification have been described: the circumscribed nodular type and the...
Dendriform type. The nodular type—characterized by layered deposits of calcified osteoid material within the alveolar spaces, frequently without bone marrow—is the most common manifestation of DPO and is usually associated with pre-existing heart diseases leading to chronic pulmonary venous congestion—such as mitral stenosis, chronic left ventricular failure, and idiopathic hypertrophic subaortic stenosis. Dendriform ossification, in contrast, refers to the interstitial ramified osseous spicules that are found mainly in alveolar spaces and that contain occasional bone marrow islets with osteoblastic and osteoclastic activity. This type of DPO is found in idiopathic pulmonary ossification, which can be caused by undetected pulmonary lesions, and it presents with interstitial fibrosis.

DPO is most commonly found in men between 70 and 80 years of age, but cases have been reported in young men and women. Friedrich et al. point out that the male-to-female ratio in patients more than 80 years of age is 7:1 and in patients less than 80 years of age it is 1:1.

DPO is slowly progressive and may be detected as an unexplained radiographic finding in patients who are asymptomatic or complain of only mild symptoms. Most cases of DPO are diagnosed during autopsy. When the disease is extensive, lung function shows a restrictive pattern and diffusing capacity is low. The signs, symptoms, and physiological abnormalities pointing to DPO may be secondary to another process. Pulmonary ossification is not usually visible in chest x-rays. When visible, it appears in the inferior lobes as an unspecified reticulonodular density and is usually bilateral. In most cases it is difficult to determine whether the very fine lines in the x-ray image indicate calcified areas or pulmonary fibrosis. Consequently, the disease is usually discovered by chance during autopsy. However, differential diagnoses for pulmonary calcification should be kept in mind, such as alveolar microlithiasis. High resolution CT scans of the thorax reveal lines of 1 to 4 mm in the form of either branching calcifications of bronchovascular distribution in the dendriform type or multiple areas of tiny calcified subpleural nodules in the nodular type. DPO can also be detected by bone scintigraphy using a contrast agent (technetium-99m methylenediphosphonate).

Establishing a prognosis is difficult as few living cases are diagnosed. Some case reports describe no changes of interest over time; others describe a slow evolution. The literature contains no cases of spontaneous regression.

Corticosteroids, which lead to decreased absorption of calcium from the intestine and increased loss of calcium from the kidneys and which are often prescribed along with low-calcium diets, have offered no clear benefits although such use of corticosteroids still remains to be systematically evaluated. The role of bisphosphonates also needs to be determined. Any treatment of DPO should be considered experimental and reserved for only symptomatic cases.

Improvements in intensive care units, mechanical ventilation, and treatment of critical patients will surely lead to improved survival rates for patients with chronic pulmonary diseases, and the prevalence of DPO may rise in the near future.

REFERENCES