Diffuse Pulmonary Ossification Associated With Idiopathic Pulmonary Fibrosis

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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, multilocular 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.

Osificación pulmonar difusa asociada a fibrosis pulmonar idiopática

La osificación pulmonar difusa es una rara entidad que consiste en la formación de hueso maduro en el parénquima pulmonar, asociada a patología pulmonar difusa y crónica, cardíaca o extracardiopulmonar. Esta entidad constituye habitualmente un hallazgo anatomopatológico post mortem. En este caso se realiza el diagnóstico mediante biopsia pulmonar a cielo abierto.

Presentamos el caso de un varón de 79 años, con disnea, tos seca y pérdida de peso. Había sido fumador. En la radiografía de tórax se apreciaba un infiltrado pulmonar bilateral reticulonodular. La tomografía computarizada evidenció afectación intersticial con predominio septal y múltiples cavidades con tendencia a la panalización; engrosamiento pleural, retracción del parénquima y fibrosis bilateral. Se estableció el diagnóstico clínico de fibrosis intersticial idiopática, y el paciente evolucionó desfavorablemente. Se realizó una biopsia a cielo abierto. La biopsia pulmonar evidenció zonas de colapso alveolar y otras enfisematosas, algunas con secreción y extravasación eritrocitaria. Había vasoscongestión intersticial; los bronquiolos presentaban infiltrado inflamatorio mononuclear y algunos polimorfonucleares. Llamaba la atención la presencia de trabéculas óseas, algunas que incluían la médula ósea, de tipo adiposo, en focos multicéntricos, predominantemente intersticiales.

La osificación pulmonar difusa constituye habitualmente un hallazgo incidental en autopsias de pacientes con antecedentes de enfermedad pulmonar crónica difusa, siendo inusual el diagnóstico en un paciente vivo. La osificación pulmonar difusa no posee significación pronóstica en la fibrosis pulmonar. Constituye un signo de cronicidad y gravedad de la enfermedad.

Palabras clave: Osificación pulmonar dendriforme. Fibrosis pulmonar idiopática. Biopsia pulmonar.

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 lung 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 morphogenic 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 monocyte-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

REFERENCES