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Case report

Diffuse pulmonary ossification associated with fibrosing interstitial lung disease

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ABSTRACT

Diffuse pulmonary ossification (DPO) is a rare condition that presents with metaplastic mature bone formation in the pulmonary parenchyma. DPO is usually associated with cardiovascular or respiratory disease. We report a case of 75-year-old man with chronic dyspnea, cough, asthenia and low sputum production. A chest x-ray revealed reticular pulmonary infiltrates on both sides. Computed tomography (CT) revealed peripheral, basilar predominant reticular opacities with areas of subpleural cystic change, compatible with fibrosis, fine branching calcifications within areas of linear reticulations were also visible in both mid and lower zones. Based on the clinical presentation and CT results, the patient was diagnosed with diffuse pulmonary ossification associated with idiopathic pulmonary fibrosis.

Despite its rarity, the radiologist must know suggest the diagnosis of DPO especially in the presence of idiopathic pulmonary fibrosis associated with linear branched calcified densities in areas of fibrosis, avoiding a surgical biopsy that is not stripped of risk.

1. Introduction

Diffuse pulmonary ossification (DPO) is a rare entity characterized by ectopic bone formation within lung parenchyma. The diagnosis was most often made by histological study after post mortem autopsy. DPO can be idiopathic or associated with a variety of cardiovascular, respiratory diseases or other disorders. There are mainly two forms of DPO: nodular and dendriform. The nodular type occurs mainly in the context of chronic pulmonary congestion, whereas the dendriformed DPO occurs in patients with diffuse interstitial lung disease (ILD), as a non-specific sign of an advanced stage of the disease.

We herein report a case of DPO associated with idiopathic interstitial pulmonary fibrosis that was diagnosed based on the results of the CT scan which showed a typical pattern of usual interstitial lung disease associated with the presence of diffuse calcifications in the areas of fibrosis .

2. Case report

A 75-year-old man was admitted to the pneumology department for acute worsening of chronic dyspnea with, cough, asthenia and low sputum production. Our patient was followed by his family doctor for chronic obstructive pulmonary disease which was treated by combination of inhaled steroids and long-acting beta2-agonists. He was an exsmoker of 20 cigarettes per day until 40 years before onset of symptoms. He had no history of professional or environmental allergen exposure or tuberculous contact. No symptoms or signs of connective tissue disease were identified. Serology for autoantibodies was negative. Physical examination revealed bilateral basal crackles.

The respiratory rate was 28c/min, the temperature at 38° c, and arterial oxygen saturation (Sa02) was evaluated at 88%. Analysis of peripheral blood showed a white cell count of 12 300 μL (80% neutrophils); hemoglobin: 14 g/dL; hematocrit: 30%; platelets: 250 000 μL; C-reactive protein level: 157mg/L, concentrations of calcium, phosphorous and alkaline phosphatase in serum were normal. Spirometry showed moderate restriction.

A chest x-ray revealed, bilateral reticular pulmonary infiltrates, predominant in the middle and lower zones. A computed tomography scan of the chest (CT) was performed and showed peripheral, linear reticulations with subpleural cystic lesions, compatible with fibrosis, it is associated with fine calcifications (Fig. 1) in both mid and lower regions. The pleura was normal especially without calcifications which

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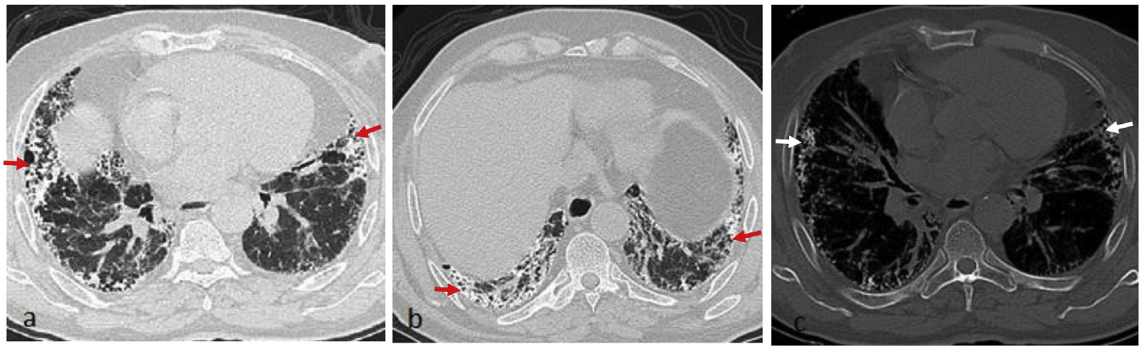

Fig. 1. (a,b) Axial CT images at a lung window, show bibasal subpleural reticulations with areas of subpleural cystic change, compatible with honeycomb lesions (red arrows). **(c)** Axial CT image at a bone window, shows diffuse branching calcifications within areas of fibrosis (white arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

allowed to eliminate a pulmonary asbestosis.

Based on the clinical presentation and CT results, the patient was diagnosed with diffuse pulmonary ossification associated with idiopathic pulmonary fibrosis. A lung biopsy was not believed to be helpful in the case.

3. Discussion

Diffuse pulmonary ossification (DPO) is a rare condition that consists of mature bone formed in the interstitial or alveolar spaces. The first description was made by Luschka in 1856, since then several cases have been reported in the literature, most of them were isolated after the autopsy [1].

DPO is classified as a nodular or a dendriform type. The nodular form is known to be associated with pre-existing heart disease particularly pulmonary congestion secondary to mitral stenosis leading to calcified or ossified mass formation within the alveolar spaces. The dendriform ossification type, which originates within the alveolar septa and spreads into the alveolar spaces, is known to be idiopathic or associated with diffuse and chronic lung disease or other system disorders (Table 1) [2–5].

According to the autopsy examinations, the incidence of DPO in patients with respiratory diseases was estimated between 0.6% and 1.63%. Mainly found in men between 70 and 80 years of age at advanced stages of chronic obstructive pulmonary disease and some interstitial lung diseases, however cases have been reported in young men and women [1,5].

In fact, the main risk factors for DPO identified by Egashira and all [3] in a study comprising 892 patients with fibrosing ILD included age, male sex, a history of positive smoking, and an idiopathic pulmonary fibrosis. Our patient was at risk the notion of chronic smoking, male sex and pulmonary fibrosis.

The pathogenesis of DPO is uncertain, but most studies suggest that inflammation is a precursor to DPO. Indeed the inflammation is responsible for anoxia, producing an acidic environment, this can induce fibroblastic proliferation and transformation into osteoblasts, followed by metaplastic bone formation in the lung interstitium, this can be considered as a way of repairing, or scarring the parenchyma [1,6]. Transforming growth factor-b, which is produced by damaged epithelial cells, bone morphogenic protein (BMP) genes [1,3,5], and the recently described Glast-expressing progenitor MSCs [7], have been shown to plays an important role in idiopathic pulmonary fibrosis as well as in the formation of chondrocytes and osteocytes this is the basis of the theory of a genetic linkage(5). Another theory (dystrophic theory) suggests that senile alterations of the perivascular, connective, and interstitial tissue may lead to DPO [1].

A possible family predisposition was also described in two case reports [5,8] with DPO in a father and son, however, additional study is needed to prove this theory.

DPO is slowly evolving and patients may be asymptomatic or complain of only mild symptoms, however when DPO is secondary to another cause, especially idiopathic pulmonary fibrosis as in our case, the lung function may shows a restrictive pattern and diffusing capacity is low [1].

Pulmonary ossification is not usually visible in chest x-rays. When visible, it consist of mature bone in the periphery portions of the inferior lobes as an unspecified reticulonodular density is usually bilateral.

With technology advances in high-resolution computerized tomography (CT) and the widespread use of CT in lung disease, DPO is becoming a more frequent imaging diagnosis [3,9]. With use of bone window settings (width, 2500 HU; level, 500 HU), DPO can be identified as multiple tiny calcifications in the bibasilar lung periphery superimposed on predominantly subpleural pulmonary fibrosis of usual interstitial pneumonia (UIP) or interstitial pulmonary fibrosis (IPF), and this was in accordance with the pathologic distribution of ossifications

Table 1
Etiologies of pulmonary ossifications.

Primary injury	Pre-existing lung injury	Pre-existing heart diseas	Pre-existing noncardiopulmonary conditions
Idiopathic pulmonary ossification	- Idiopathic pulmonary fibrosis - Asbestosis - Interstitial lung fibrosis following busulfan therapy - Respiratory distress syndrome - Sarcoidosis - Silicosis - Histoplasmosis - Tuberculosis - Amyloidosis - Metastasis(melanoma, breast cancer, osteogenic sarcoma colorectal, adenocarcinoma	- Mitral stenosis - Chronic left ventricular stenosis - Idiopatic hypertrophic subartic stenosis	- Chronic kidney failure - Hemodialysis - Hyperparathyroidism - Diabetes mellitus - Rheumatism arthritis - Congenital protein C deficiency disorders - Hypervitaminosis - Calcitonin producing tumors - Myeloblastic leukemia - Hypercalcemia Acromegaly

[3,4].

On the other hand, CT finding of multiple tiny pulmonary calcifications could be of some help in the differential diagnosis between (UIP) and non-specific interstitial pneumonia (NSIP). Indeed, Kim et al. retrospectively reviewed thin-section CT and pathologic specimens of biopsy-proven UIP (75 patients) and NSIP (44 patients), in this study DPO was present in 5 patients in association with UIP, which corresponds to an incidence of 6.7%. However, it was not seen in any patient with NSIP.

There is no consensual treatment, and neither low-calcium diets or systemic corticosteroids therapy which helps in calcium depletion have proven a clear benefit, therefore their use remains to be evaluated systematically [10]. Warfarin and bisphosphonates have been proposed as future potential therapies but there is no study proving their benefit in improving symptoms and prognosis [11].

The evaluation of the DPO prognosis remains difficult as there is no large published series that has been interested in the evolutionary profile of this entity. However, according to the case report published we can deduce that the evolution of DPO is slow and when combined with UIP the prognosis is rather related to interstitial disease [1]. Moreover, the literature does not contain any case of spontaneous regression of the disease [12].

4. Conclusion

Diffuse pulmonary ossification is a rare disorder that is characterized by the heterotopic bone formation in the pulmonary parenchyma. In cases associated with idiopathic pulmonary fibrosis, the role of CT is crucial in the diagnosis by showing linear branched calcified densities in the setting of pulmonary fibrosis. Further studies including therapeutic modalities and long-term follow-up are needed to plan the management of this entity.

Conflicts of interest

There are no conflicts of interest.

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