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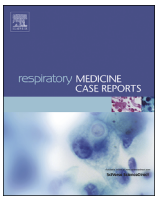

Case Report

Diffuse pulmonary ossification: A case report unveiling clinical and histopathological challenges

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ABSTRACT

Diffuse pulmonary ossification (DPO) is a rare pulmonary condition characterized by the diffuse formation of mature bone in the lungs. Pulmonary ossification, in general, can be subdivided into diffuse pulmonary ossification (DPO) and nodular pulmonary ossification (NPO). DPO occurs most commonly in the settings of chronic pulmonary conditions; however, idiopathic cases have been reported. We present a case of DPO in a 36-year-old man with progressive exertional dyspnea, productive cough, and occasional hemoptysis. Imaging studies showed innumerable pulmonary nodules scattered throughout both lungs. Initially, the diagnoses of pulmonary alveolar microlithiasis (PAM) or, less likely miliary tuberculosis (TB) were considered. However, Quantiferon TB test was negative and genetic testing was negative for *SLC34A2*, lowering the probability of PAM. The patient underwent a segmentectomy. Microscopic examination showed ramifying spicules of mature woven bone and fatty marrow consistent with DPO. There were no significant underlying pathologic findings, such as interstitial fibrosis, granulomas, organizing pneumonia, or significant inflammation in the background lung parenchyma. In conclusion, clinicians and radiologists need to be aware of DPO in the differential diagnosis of miliary tuberculosis and pulmonary alveolar microlithiasis. The absence of an underlying chronic pulmonary condition does not exclude the possibility of DPO.

1. Introduction

Diffuse pulmonary ossification (DPO) is a rare lung disease characterized by the formation of bone within the lungs, along the interstitium, or within alveolar spaces [1]. It was first described by German anatomist and pathologist Hubert von Luschka as a post-mortem discovery in 1856 [2,3]. DPO is usually associated with chronic pulmonary diseases such as idiopathic interstitial pneumonitis, chronic obstructive pulmonary disease, acute respiratory distress syndrome, and inhalation-related conditions.

Pulmonary ossification can be subdivided into DPO (i.e., dendriform pulmonary ossification) and nodular pulmonary ossification (NPO) [4–6]. DPO is characterized by ramifying spicules of mature woven bone arranged in a serpentine fashion along the alveolar

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septa and is associated with fat or bone marrow elements in most cases [7]; conversely, NPO has round, and well-circumscribed outlines and is generally devoid of fat and marrow elements [6]. While inter-alveolar septa are preferentially affected in DPO, the involvement of alveolar spaces is characteristic of NPO [8–10]. NPO occurs most commonly in the settings of passive pulmonary congestion, especially mitral stenosis [8,9]. DPO, on the other hand, occurs most commonly in the background of chronic lung diseases, including pulmonary fibrosis, especially usual interstitial pneumonia (UIP) and chronic obstructive pulmonary disease (COPD) [11]. However, a nationwide 2-year survey in Japan [5] reported twenty-two cases of idiopathic diffuse pulmonary ossification (IDPO) and identified no underlying chronic pulmonary conditions. 80% of patients were asymptomatic with DPO found incidentally during medical check-ups. The patient population was markedly younger, with an average age of 38 years at the time of diagnosis, compared to an average of 69 years in an autopsy-based retrospective study [11]. In a retrospective study by Enomoto et al. [12] patients classified as idiopathic DPO were screened for other comorbidities, among which they found obstructive sleep apnea, GERD, or a chronic neurological disorder; however, our case does not exhibit any of these.

We present a case of DPO in a 36-year-old man. This case will shed some light on the possibility of DPO in absence of underlying chronic pulmonary conditions and will highlight other entities that could be considered in the list of differential diagnosis when evaluating potential DPO cases.

2. Case presentation

A 36-year-old lifetime non-smoker obese man with no history of smoking was referred to our office due to a 9-year history of progressive exertional dyspnea and yellow productive cough accompanied by occasional hemoptysis. He reported being able to climb two flights of stairs before becoming dyspneic. His medical history was significant for childhood asthma, hypertension, and impaired glucose tolerance. Outpatient medications included Lisinopril 10 mg daily orally. He works as a security guard in a hospital five days per week and is relatively high functioning. He denied any workplace exposure or alcohol consumption. He migrated from Cuba at the age of seven. And there was no relevant family history.

Vital signs and physical exam were unremarkable. Initial chest radiograph (Fig. 1) showed innumerable pulmonary nodules in both lungs, up to 4 mm in greatest dimension, predominantly involving the middle to lower lung fields. Findings were concerning for miliary tuberculosis (TB) given a history of positive purified protein derivative (PPD) skin test, which might also be attributed to Bacille Calmette-Guérin (BCG) vaccination during childhood. High-Resolution Computed Tomography (HRCT) (Figs. 2 and 3) showed innumerable pulmonary nodules scattered throughout the lungs and along the broncho-vascular bundles measuring 2–5 mm. Differential diagnosis included miliary TB, granulomatous diseases, pneumoconiosis, certain deposition diseases (such as amyloidosis), or alveolar microlithiasis in the appropriate clinical setting. The findings also were suggestive of dystrophic calcifications in the setting of scarring from prior infection/inflammation. A presumptive diagnosis of pulmonary alveolar microlithiasis (PAM) was at this time presumed, given radiographic progression and clinically indolent presentation. Pulmonary function tests (PFT) revealed a total lung capacity (TLC) of 5.37 L (89% predicted), forced vital capacity (FVC) 3.57 L (87% predicted [normal ≥80%]), forced expiratory volume in 1 second (FEV1) 3.19 L (94% predicted [normal ≥80%]), FEV1/FVC 90% (normal ≥70%), diffusing capacity for carbon monoxide (DL_{CO}) 69% (normal ≥70%). In summary, normal lung volumes and a mild isolated decrease in DL_{CO} was found.

Bronchoscopy, bronchoalveolar lavage, and transbronchial lung biopsy revealed no abnormalities. The Quantiferon TB test was negative, ruling our active or miliary TB. Histoplasma antibody test was also negative. Genetic testing for *SLC34A2* mutation was neg-

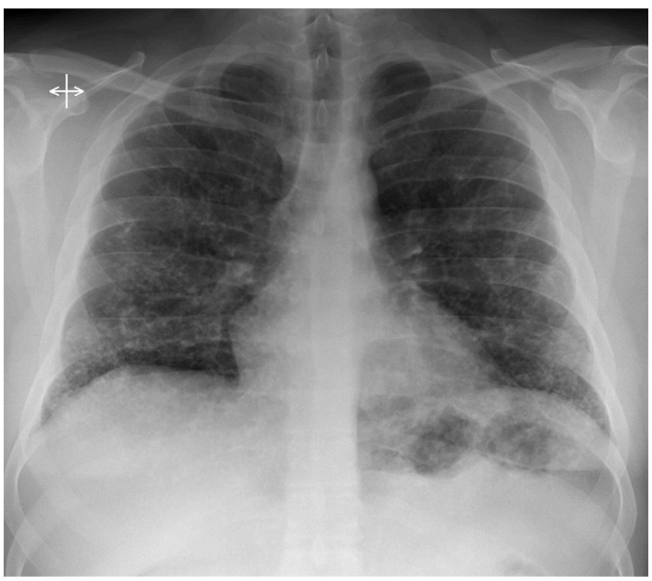

Fig. 1. Antero-Posterior (AP) chest radiograph showing innumerable pulmonary nodules up to 4 mm in greatest dimension in both lungs, predominantly involving the mid to lower lung fields.

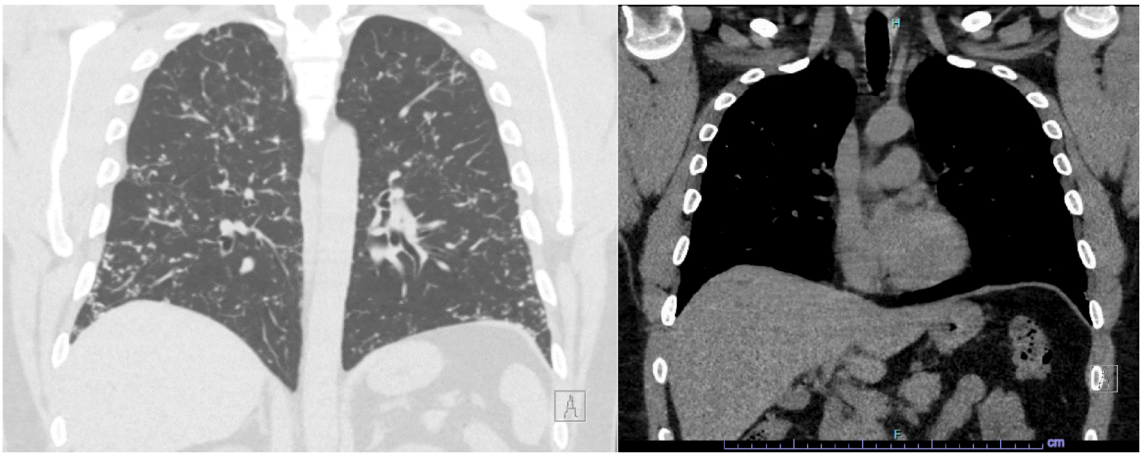

Fig. 2. Computed Tomography (CT) chest showing innumerable pulmonary nodules scattered throughout the lungs measuring 2–5 mm in greatest dimension.

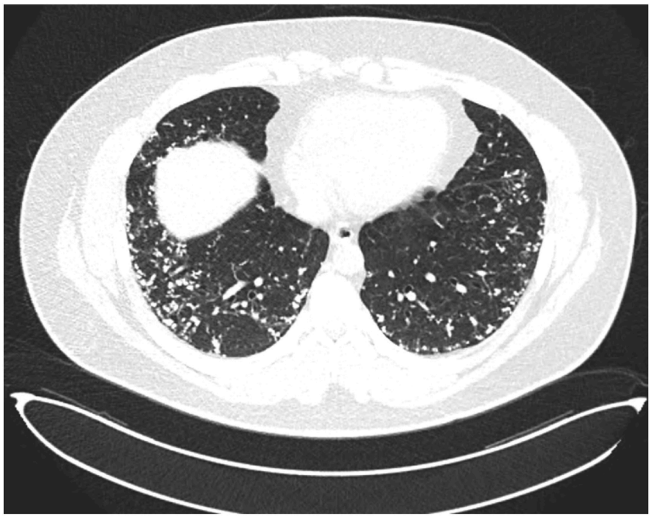

Fig. 3. Computed Tomography (CT) chest showing innumerable pulmonary nodules scattered throughout the lungs measuring 2–5 mm in greatest dimension.

ative, lowering suspicion for PAM. The patient subsequently underwent a right video assisted thoracoscopic surgery (VATS) (Fig. 4) and segmentectomy of the basilar segment of the right lower lobe, the medial segment of the right middle lobe, and the anterior segment of the right upper lobe without any complications.

Upon gross examination, palpation of the specimen revealed multiple firm sub-pleural nodules. Sectioning through the specimen revealed innumerable calcified nodules. Microscopically (Figs. 5 and 6), diffuse ramifying spicules of mature woven bone arranged in a serpentine fashion along the alveolar septa associated with fatty bone marrow were identified, confirming the diagnosis of DPO. Although bone marrow was present, extensive sampling failed to reveal hematopoiesis. Of note, there was no evidence of significant underlying pathologic findings, such as interstitial fibrosis, granulomas, organizing pneumonia, or significant inflammation in the background lung parenchyma.

3. Discussion

Diffuse pulmonary ossification (DPO) is a rare pulmonary condition characterized by diffuse formation of mature bone in the lungs [5]. Based on two retrospective autopsy-based studies, the incidence of DPO ranges from 0.16% to 0.4% [6,11] with 80%–88% of cases occurring in men [5,6,11]. It is believed that DPO is a clinically under-recognized entity [7,13,14].

Several theories have been suggested to explain the histogenesis of pulmonary ossification. Ossification is the deposition of calcium in a collagen matrix in the presence of osteoblastic cells. Given the association of NPO with chronic heart failure and valvular disorders, especially mitral stenosis [9]. It was suggested that NPO arises as a consequence of autolysis of extravasated red blood cells resulting in hemosiderin deposition which in turn triggers fibrosis and hyalinization and attracts calcium salts and osteoclasts [15]. It was postulated that DPO, on the other hand, arises in low PH and low-oxygen tension conditions where lung fibroblasts and macrophages undergo metaplasia into osteoblasts and osteoclasts, under the effect of various growth factors [16]. This is supported

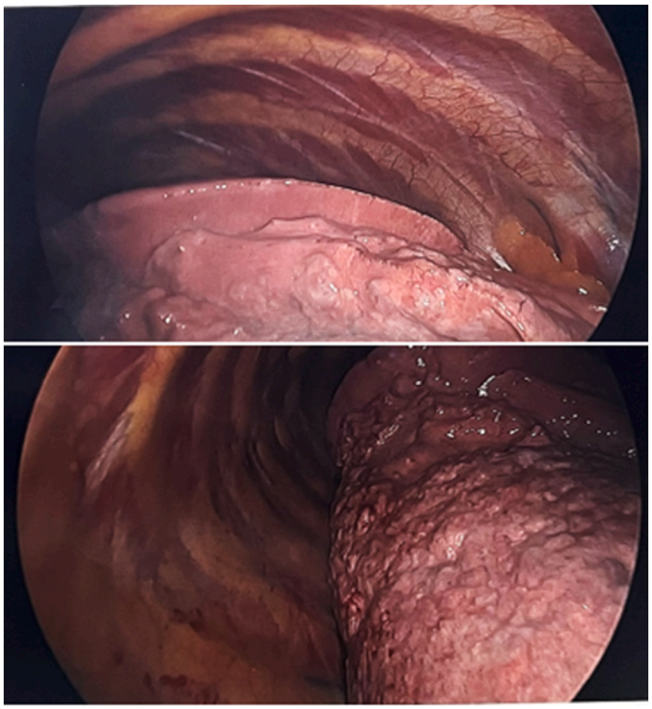

Fig. 4. Right robotic video assisted thoracoscopic surgery (VATS). Notice the granular appearance of the surface of the lung.

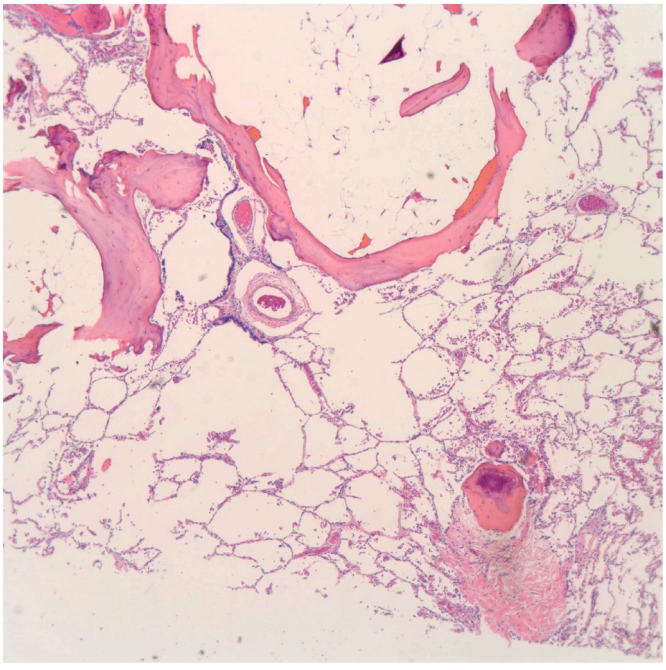

Fig. 5. Microscopic image showing ramifying spicules of woven bone along the inter-alveolar septa (Hematoxylin and Eosin staining; 100× objective).

by the fact that DPO occurs in the chronically injured lung and lower lobes, an area with a lower ventilation-perfusion ratio that results in lower oxygen tension and lower pH [16]. However, later in the disease, the upper lobes and central parts of the lunges are commonly affected [6].

Interestingly, there is an association between diabetes mellitus (DM) and DPO [3,17]. It is well known that DM results in medial vascular calcification by inducing osteogenesis and subsequent mineralization under oxidative stress, inflammation and glycation

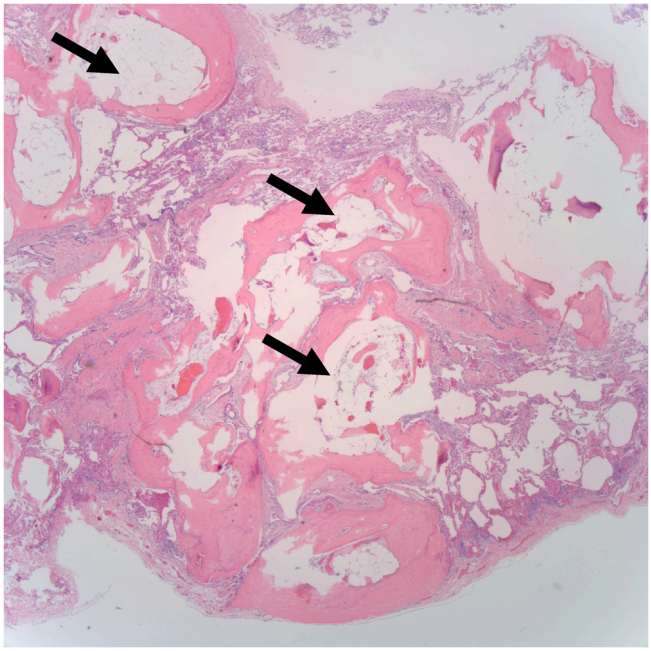

Fig. 6. Microscopic image showing ramifying spicules of woven bone arranged in a serpentine fashion. Notice the presence of a fatty bone marrow element (black arrows; Hematoxylin and Eosin staining; 100× objective).

end-products [18]. Hence, it was suggested that DPO results from the extension of medial vascular calcifications involving alveolar blood vessels into inter-alveolar septa [15]. Our patient had impaired glucose tolerance; however, he was not diabetic.

Gruden et al. showed in their study of 52 patients who had DPO without chronic interstitial lung disease, an association with gastro-esophageal reflux disease (GERD), obstructive sleep apnea or chronic debilitating neurological conditions in 75% of cases [19]. Given the increased predilection of gastric acid aspiration in all of these conditions, it was suggested that DPO is linked to acid aspiration [19]. Our case did not exhibit any of these conditions; thus, it represents an idiopathic diffuse pulmonary ossification.

In our case, the differential diagnosis included PAM. PAM is a rare progressive pulmonary condition characterized by the accumulation of hydroxyapatite microliths within the lumen of the alveolar spaces due to deficiency of the sodium-phosphate cotransporter NPT2B [20]. While PAM may resemble DPO clinically and radiologically, it is genetically characterized by homozygous loss of function mutation involving *SLC34A2* in most cases [21]. Histologically, PAM is characterized by concentrically laminated calcifications of variable sizes scattered in alveolar spaces and the interstitium [22].

Granulomas of various etiologies particularly those secondary to tuberculosis, Histoplasma capsulatum, Coccidiosis immitis or less commonly sarcoidosis can undergo dystrophic calcification over time; thus, mimicking DPO radiologically [23–26]. Additionally, Hypercalcemia secondary to increased 1,25 vitamin D in various granulomatous conditions provide an element of metastatic calcification further contributing to the possibility of calcification in these intrathoracic granulomas [26,27]. However, diffuse, central or laminated calculations are the typical calcification patterns seen radiologically in calcified granulomas; while DPO typically display dendriform calcification pattern [28]. Moreover, involvement of mediastinal lymph nodes is commonly seen in granulomatous conditions [28]. Histologically, the distinction is easy given the presence of bone in DPO.

Finally, a potential mimicker of DPO is metastatic calcification that can arise in normal lung parenchyma secondary to increased calcium levels in conditions that predispose to hypercalcemia including hyperparathyroidism, chronic kidney disease, sarcoidosis, multiple myeloma, and osteolytic metastatic carcinomas [28]. Radiologically, poorly demarcated nodular opacities predominantly involving the upper zones of lungs are characteristic [28,29]. When present, involvement of chest wall blood vessels in a helpful clue to the diagnosis [29].

4. Conclusion

We suggest that, as with many diseases, a constellation of factors may contribute to DPO, including genetics, intrinsic risk factors, and environmental changes. Clinicians and radiologists need to be aware of DPO in the differential diagnosis of miliary tuberculosis and pulmonary alveolar microlithiasis. The absence of an underlying chronic pulmonary condition does not exclude the diagnosis of DPO. Due to the progressive nature of DPO in most cases, it is essential to maintain a high index of suspicion in the proper clinical and radiological context.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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