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Case Report Open Access

A Rare Case of Alive Dendriform Pulmonary Ossification

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Abstract

Diffuse pulmonary ossification is a rare entity of characterized by diffuse small bone fragments in lung tissue. Two types are described: 'nodular' and 'dendriform'. Living cases are rarely encountered; most are diagnosed at autopsy.

A 29-year-old man had a moderate chest pain ongoing for two weeks was referred to our hospital with bilateral, multifocal, diffuse calcified nodular densities on chest radiography and computed tomography (CT). Use of risperidone and valproic acid due to bipolar personality disorder for three years, working as a car repairer for one year were present in his history. On positron emission tomography (PET-CT) was taken for suspected metastatic disease, increased metabolic activity was detected in multiple nodules with low density. Video-assisted thoracic surgery (VATS) lung biopsy was performed for diagnose. Even though macroscopic appearance of specimens suggestive of malignancy, histopathology was consistent with DPO. Drugs used by the patient were found not to be the direct cause of pathology in lung however previous studies have reported valproic acid effects osteogenesis *in vitro* and *in vivo* through by mesenchymal pluripotent cell proliferation and differentiation in extracellular matrices. Although the exact pathogenesis of diffuse pulmonary ossification is unknown, underlying fibrosis is the precursor of DPO has been shown. Also pulmonary fibrosis can be triggered with deposition of heavy metals (eg., serium oxid/phosphate). Based on this, sodium valproate and heavy metals may play a role in inflammation-mediated heterotopic ossification was considered in our case.

In conclusion, we herein presented a case of living DPO accompanied by an inflammation-mediated heterotopic ossification related to sodium valproate and/or heavy metals with high probability.

Keywords: Dendriform pulmonary ossification; Sodium valproate; Heavy metals; Calcified nodules

Introduction

Pulmonary ossification may be diffuse or localized resulting from a variety of underlying pulmonary, cardiac and extra cardiopulmonary disorders [1,2]. Localized type defined as focal deposition of bone within or adjacent to lung tissue injured by any kind of disease process, mainly including lung abscess, tuberculosis and other infectious diseases, trauma, primary and metastatic tumors. The diffuse pulmonary ossification is a rare entity characterized by diffuse small bone fragments in the interalveolar, interlobular, and subpleural connective tissue of the entire lung and in the alveolar spaces [2,3]. It is also an asymptomatic disease which mostly diagnosed at autopsy. The number of diagnosed cases with diffuse pulmonary ossification in living is quite low [4].

Case Report

A 29-year-old, non-smoker, male patient was referred to our hospital for further investigation with abnormal findings on chest radiography and computed tomography (CT). He was admitted to the hospital for a moderate chest pain ongoing for two weeks. The use of risperidone and valproic acid due to bipolar personality disorder for three years, working as a car repairer for one year were present in his personal history. His physical examination was normal. Laboratory values were no abnormal findings except increased erythrocyte sedimentation rate (30 mm/h) (Figure 1).

His pulmonary function tests were showed mild restriction (FVC: 65%, FEV_1: 61%, FVC/FEV_1: 78%) and decreased diffusion capacity (DLCO: 71%, DLCO/VA: 101%). Bilateral, multifocal, diffuse calcified nodular densities were observed on both his chest radigraphy and CT.

Fiberoptic bronchoscopy along with transbronchial biopsy was showed no spesific pathology. On positron emission tomography (PET-CT) was taken for suspected metastatic disease; 10 mm in sizes ranging from 3 mm nodule in low density along with increased metabolic uptake in a fusiform area with diameter of 13 mm × 11 mm in the left gluteus maximus muscle in bilateral testicular involvement were detected. Magnetic resonance to the left gluteal maximus imaging showed no pathology in the area. Testicular tumors were excluded through scrotal ultrasonography and specific tumor markers. Lung biopsy through video-assisted thoracic surgery (VATS) was performed for diagnosis. Macroscopic appearance of specimens taken by biopsy suggestive of malignancy, but histopathology was consistent with dendriform pulmonary ossification (Figure 2).

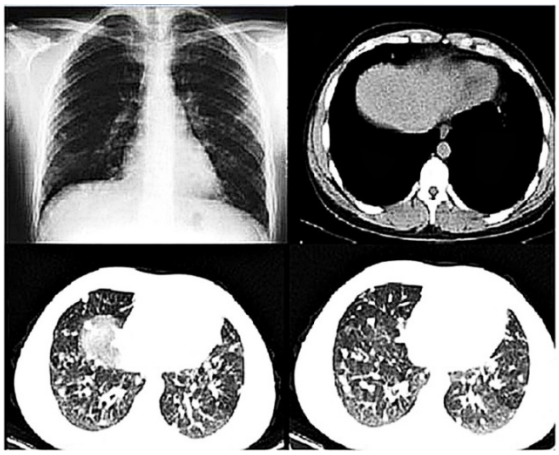

Figure 1: Bilateral, multifocal, diffuse calsified nodular densities were observed on both chest radiography and CT.

Discussion

Two types of diffuse pulmonary ossification are defined, nodular and dendriform. Of the two entities, DPO is less common. Nodular form of pulmonary ossification is characterized by rounded intra-alveolar bone fragments and occurs with heart diseases especially mitral valve stenosis and other conditions leading to chronic congestion such as chronic left ventricular failure [2,3,5]. The dendriform pulmonary ossification (DPO) (named because of the dendritic appearance) is usually intra-parenchymal with branching osseous structures of mature lamellar bone often containing marrow and occurs in the setting of chronic inflammation, including interstitial fibrosis; however, sometimes it is idiopathic [1,2]. It was first described by Luschka in 1856 [6].

DPO is rarely which was histologically found only in 11 cases out of 10,426 postmortems in Australia (incidence of 0.95 cases/1000 autopsies) [4]. Approximately 160 cases of DPO have been published in the world since the first description and only <40 cases were diagnosed with lung biopsies through open surgery or a thoracoscopic approach [7].

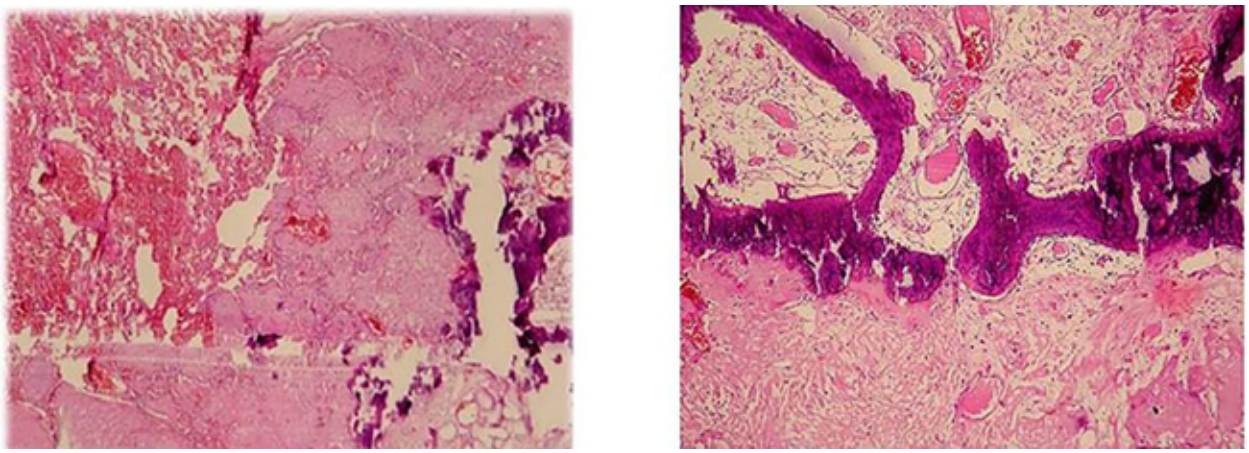

Figure 2: a) Dendriform pulmonary ossification. Ossification is observed between fibrosis and hyalinization areas in the bleeding and congestion of lung parenchyma (H&E, × 100), b) In this larger magnification, ossification contains bone marrow is seen (H&E, × 200).

Although our patient is 29-year-old and has a moderate chest pain, DPO most commonly occurs in men in their fifth and sixth decades of life and it is frequently asymptomatic. DPO represents as branching linear interstitial opacities on chest radiography. This radiologic view is similar to many diseases such as fibrosis, bronchiectasis, or lymphangitic spread of tumor and CT is better for demonstrating the presence of calcium in affected lung parenchyma.

Because of dendriform pulmonary ossification is usually diagnosed by autopsy, pathophysiology has not been elucidated. DPO can be idiopathic or can result from a variety of pulmonary, cardiac, or extracardiopulmonary disorders but in our case these diseases were not mentioned. Hypercalcemia, a local alkaline environment and previous lung injury are predisposing to pulmonary calcification and ossification. Scar tissue injury is also the responsible factor for an alkaline environment. Increased alkaline phosphatase activity, active angiogenesis and mitogenic effects of growth factors have also a role in pathogenesis [1]. Transforming growth factor-β (TGF-β) released by inflammatory cells plays a role in inflammation-mediated heterotopic ossification *via* induction of endothelial-mesenchymal and epithelial-mesenchymal transition. TGF-β also stimulates strongly the biosynthesis of type 1 collagen, fibronectin, proteoglycans and protease inhibitors while inhibiting the expression of proteases [8] and the proliferation of osteoblasts in a similar manner with bone morphogenic protein (BMP) [9]. Type I collagen and fibronectin, two extracellular matrix components that play a critical role in osteogenic cell proliferation and differentiation [10]. Drugs used by the patient (risperidone and valproic acid) were found not to be the direct cause of pathology in the lung; but previous studies have reported that valproic acid effects osteogenesis *in vitro* and *in vivo* through mesenchymal pluripotent cell proliferation and differentiation in extracelluar matrices. This may be a priority factor for DPO but there is no information about the duration of exposure for osteogenesis [11]. Although the exact pathogenesis of diffuse pulmonary ossification is unknown, it has been shown that underlying fibrosis is the precursor of DPO and also pulmonary fibrosis can be triggered with deposition of heavy metals (eg., serium oxid, serium phosphate) [12]. He worked

as an auto repairer and may have been exposed to heavy metals. Based on this, heavy metals through inflammation *via* especially TGF-β and sodium valproate through cell reparation *via* type 1 collagen and fibronectin, may play a role in inflammation-mediated heterotopic ossification in our case. Treatment of the disease is not described yet. There are a few reports with efficacy of biophosphonates and warfarin in the management of DPO [13] and further investigations are needed.

In conclusion, we herein presented a case of living DPO accompanied by an inflammation-mediated heterotopic ossification possible related to sodium valproate and/or heavy metals. The patient is still being followed up using chest radiography and pulmonary functional test.

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