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CASE REPORT

Dendriform Pulmonary Ossification in a Young Man: A Case Report

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INTRODUCTION

Diffuse pulmonary ossification is characterised by metaplastic mature bone formation in the lungs. There are two distinct morphologies, namely, nodular and dendriform. The more common nodular pulmonary ossification occurs within alveolar spaces due to organisation of intra-alveolar exudates. The underlying culprits include chronic pulmonary congestion, such as in mitral valve stenosis, as well as previous insults causing haemosiderin accumulation.[1] On the contrary, dendriform pulmonary ossification (DPO) describes bony depositions in the alveolar interstitium that produce a branching 'dendriform' pattern.[2] It is sparsely reported with <100 cases recorded in the literature. In addition, DPO is often diagnosed only during autopsy. It is generally seen in older individuals aged >60 years.[3]

CASE PRESENTATION

A 23-year-old Chinese man with good past health presented to the accident and emergency department (AED) in June 2017 with acute abdominal pain, vomiting and diarrhoea for 1 day. Apart from obesity (body mass index 32.5 kg/m^2), his physical examination and vital signs were normal. Chest radiograph incidentally revealed reticulonodular shadows over both lungs with basal predominance (Figure 1a). He was discharged 4 days later after recovering from acute gastroenteritis. Computed tomography (CT) of the thorax and medical specialist outpatient clinic consultation were arranged but the patient defaulted from follow-up.

Four years later, at the age of 27 years, the patient again presented to the AED with a 5-day history of mild right ankle pain. His physical examination was normal other than mild right ankle tenderness that quickly resolved with analgesics. Nonetheless chest radiograph revealed mild interval progression of bilateral pulmonary reticulonodular shadows (Figure 1b). The patient agreed to further workup of his abnormal radiographic findings.

Early CT of the thorax was performed 4 days later (Figure 2). There were numerous small (<3 mm)

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hyperdense nodules in the bronchovascular, interlobular septal, perifissural and subpleural spaces of both lungs with basal and peripheral predominance. These interstitial nodules appeared to form contiguous branching lines producing a 'dendriform' pattern. Lung volumes were preserved with no honeycombing or traction bronchiectasis. There were no focal consolidations, ground-glass opacities, pleural effusion or pleural plaque. Mediastinal and hilar lymph nodes were not enlarged or calcified. Trachea and main bronchi

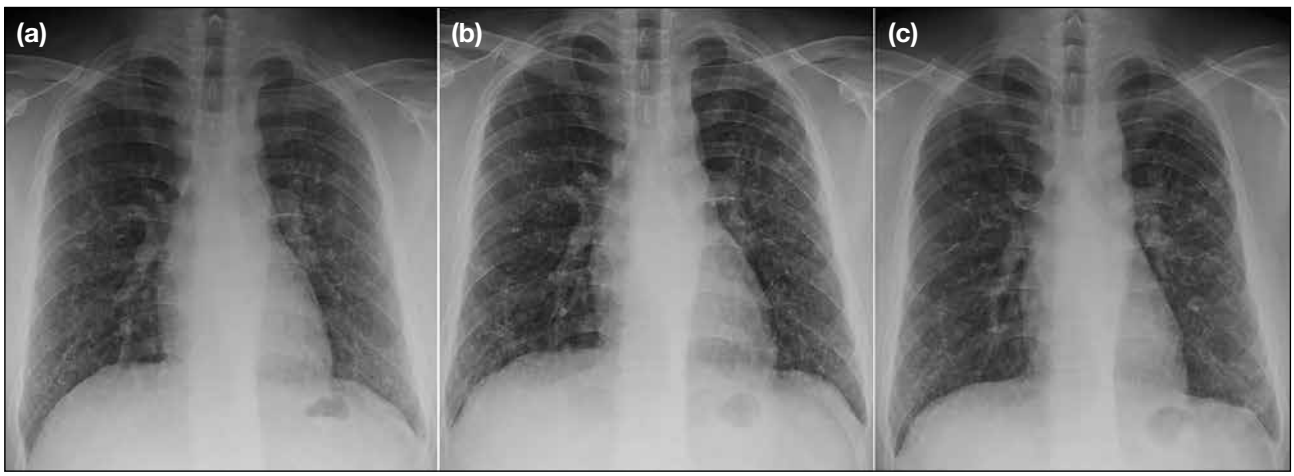

Figure 1. Chest radiographs in frontal projection. (a) Scan performed when the patient first presented to the Accident and Emergency department (AED) at the age of 23 years showing reticulonodular shadows over both lungs with basal predominance. (b) Scan performed when the patient presented to the AED at the age of 27 years showing mild interval progression of bilateral pulmonary reticulonodular shadows. (c) Scan performed at the age of 28 years, 1 year after pathological confirmation of dendriform pulmonary ossification, showing no significant interval progression.

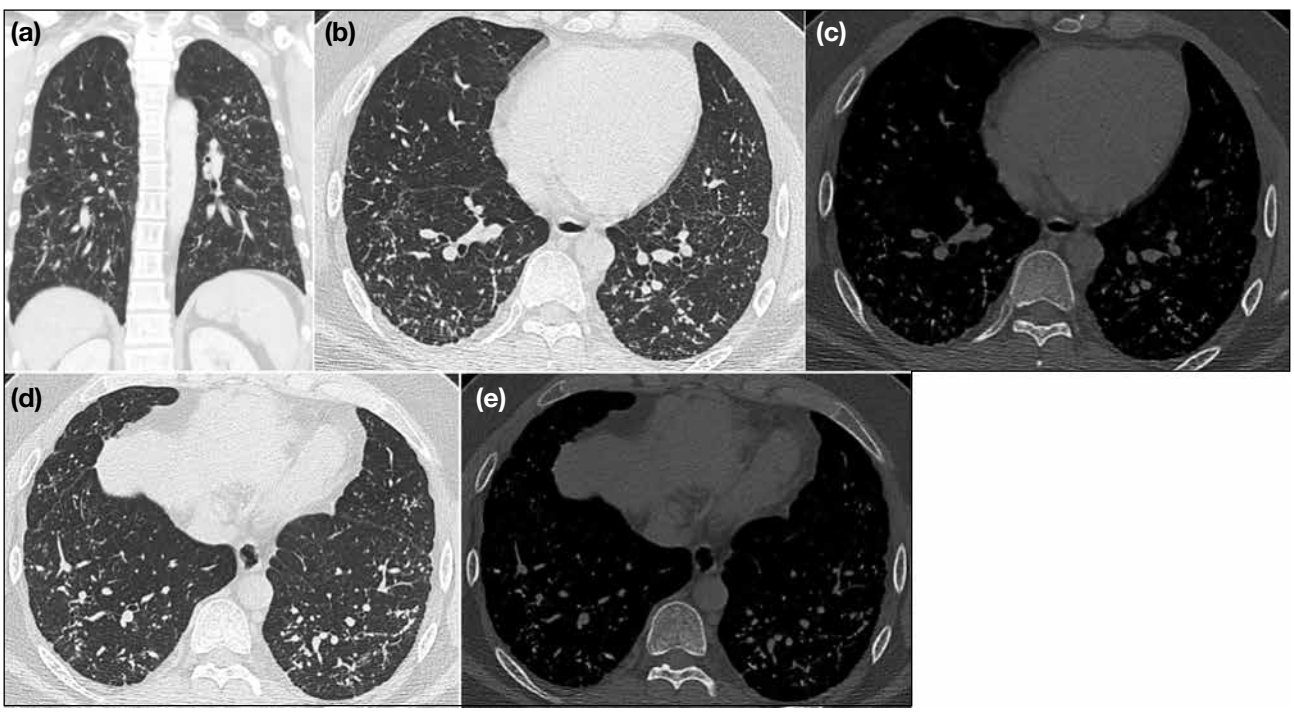

Figure 2. Computed tomography of the thorax with coronal reformatted image in the lung window (a). Axial images at T8 level in the lung (b) and bone windows (c), respectively. Axial images at T9 level in the lung (d) and bone windows (e), respectively. They show numerous small (<3 mm) pulmonary nodules with basal and peripheral predominance in the interstitial spaces, producing a branching 'dendriform' appearance. The calcific density of these nodules is more easily appreciated in the bone window.

were patent without focal stenosis or wall calcifications. Heart size was normal and pulmonary vasculature was not dilated. DPO was considered as one of the primary differential diagnoses but the young age at presentation and scarcity of prior case reports hindered a definitive radiological diagnosis.

Upon further inquiry, the patient recalled a 1-minute episode of heavy fume exposure after lighting firecrackers during Chinese New Year at the age of 8 years. Otherwise, he could recollect no other occasion of potential hazardous inhalation. He worked indoors as an accountant and considered occupational risks unlikely. He was also a non-smoker. Barring occasional snoring, he experienced no breathing difficulties and had normal exercise tolerance.

Lung function tests were normal but polysomnography revealed mild-to-moderate obstructive sleep apnoea (OSA) [sleep efficiency = 69%, respiratory disturbance index = 9.1, and oxygen desaturation index = 13.3].

Blood tests, including complete blood count, coagulation profile, immunoglobulin patterns, liver, renal, and endocrine functions were all within the normal reference range. Biological markers for rheumatic diseases, such as rheumatoid factor, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibody, C3, and C4, were negative.

Microbiological examination showed past varicella zoster virus infection with positive anti–varicella zoster virus immunoglobulin G antibody. Sputum, serum and urine cultures were negative. Bronchoalveolar lavage was negative for acid-fast bacilli, fungi, ova, and cysts. Reverse transcription polymerase chain reaction of throat saliva for coronavirus disease 2019 was negative. Antibodies to human immunodeficiency virus were also negative.

No malignant cells were detected on sputum cytology or bronchoalveolar lavage. Transbronchial biopsy of the right lower lobe was unable to establish a pathological diagnosis.

The patient was referred to the cardiothoracic team for lung biopsy. Video-assisted thoracoscopic wedge resections of the left upper and left lower lobes were performed 6 months after the initial CT study. Gross examination of the biopsied specimens showed lung tissue with calcific gritty cut surfaces. Microscopic sections revealed interstitial foci of ossification with mature bony trabeculae and bone marrow tissue (Figure 3), consistent with DPO. There was no evidence of alveolar microlithiasis. Congo red stain showed no amyloid deposition. Ziehl-Neelsen stain for acid-fast bacilli and Grocott methenamine silver stain for fungi were negative.

Since the patient was asymptomatic for DPO, he opted for observation. He was also put on continuous positive airway pressure machine for his OSA. Regular consultation at medical specialist outpatient clinic and follow-up chest radiograph at 6-month intervals were arranged. He had no new complaints. The latest chest radiograph performed over 1 year after the lung biopsy showed no significant interval disease progression (Figure 1c).

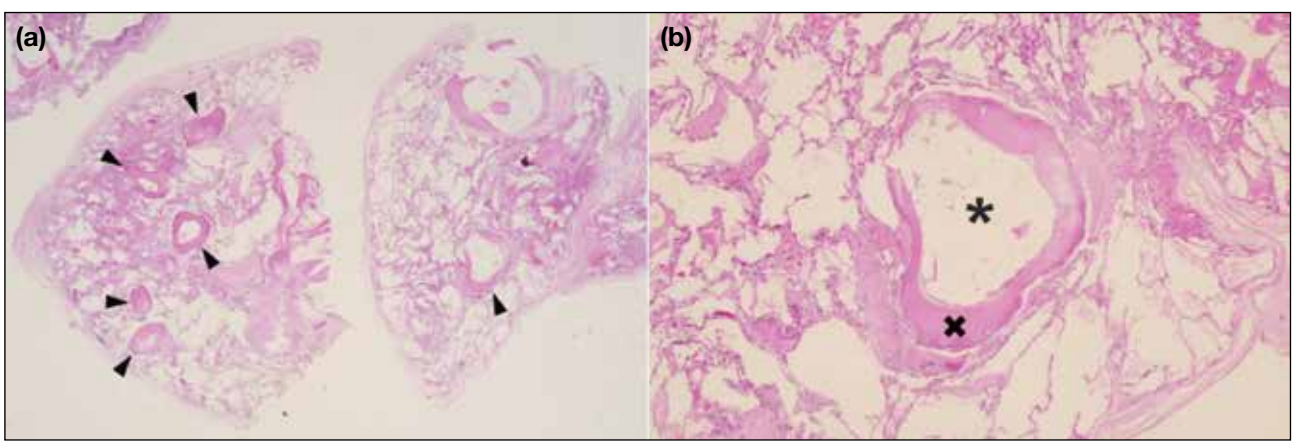

Figure 3. Micrographs of the specimen from wedge resection of left lung tissue with haematoxylin and eosin stain showing (a) foci of ossification (arrowheads) in lung interstitium (×100) and (b) an ossified focus showing mature bony trabeculae (cross) and bone marrow tissue (asterisk) [×400].

DISCUSSION

To the best of our knowledge, this is the youngest reported case of DPO in the literature. On chest radiograph, there are reticulonodular shadows in both lungs, usually with basal predominance.[4] There may be slow interval disease progression.[5] The underlying pathological bony deposition in the alveolar interstitium can be better delineated by CT. Numerous small (usually <3 mm) pulmonary nodules, typically with basal and peripheral predominance, are seen in the interstitial spaces and create the unique tree branch–like morphology of DPO. The calcific density of these nodules can be more easily appreciated in the bone window.[6]

One major diagnostic challenge to recognising DPO lies in distinguishing it from concurrent pulmonary disease. In several case reports, patients had concurrent interstitial lung disease (ILD), especially usual interstitial pneumonia.[1,3] Although the pathophysiology of DPO remains to be elucidated, pulmonary ossifications are often found in areas with more extensive fibrosis.[6] It has been hypothesised that in injured lung tissue, pulmonary fibroblasts and macrophages will undergo metaplasia into osteoblasts and osteoclasts. This may give rise to ectopic ossification.[7] ILD shares some common radiological features with DPO, such as involvement of the alveolar interstitium with basal and peripheral predominance.[8] Reviewing the lung fields after adjusting to the bone window is helpful to reveal the dendriform ossifications amongst the labyrinthine reticulations in ILD.

Another challenge in reaching an unequivocal radiological diagnosis of DPO is related to the long list of differentials for diffuse hyperdense pulmonary nodules. They include, but are not limited to, pulmonary alveolar microlithiasis, previous infections (such as healed varicella pneumonia, tuberculosis, and fungal infections), pneumoconiosis, metastasis, hypercalcaemia, sarcoidosis, and amyloidosis.[9] Although the branching interstitial involvement in DPO is a key distinguishing radiological feature,[10] it may not always be convincingly identified. Other radiological features, e.g., the fine sand–like microcalcifications in pulmonary alveolar microlithiasis,[11] the random scatter and coalescence of nodules in healed varicella pneumonia,[12] the presence of mediastinal lymphadenopathy or calcified lymph nodes in tuberculosis, histoplasmosis and sarcoidosis, can provide clues to the correct diagnosis.[9] In addition, the patient's demographics, occupational risks, inhalation exposure and medical history are often helpful to reduce the possible differentials.

The biggest hurdle to a conclusive radiological diagnosis for this patient was his young age of onset. In a retrospective study by Gruden et al,[13] the mean age of 52 patients with DPO was 78 years (range, 58-96). The authors also proposed some potential risk factors, two of which were present in our patient—OSA and gender. OSA was found in 15 patients (28.8%) in this study.[13] It was hypothesised that aspiration could be the underlying pathogenic pathway for DPO, since other possible risks factors included gastroesophageal reflux disease and debilitating neurological conditions. As for gender, DPO has a strong male predilection. In past studies, the proportion of males ranged from >85%[3] to 100%[13]. Nonetheless while OSA is not uncommon in young men, DPO is rare, if not unprecedented. A case series by Baddini Martinez and Ramos[14] of three patients diagnosed with DPO >20 years after transitory inhalation of hydrocarbon combustion products may offer some insight into our case. Our patient recounted a brief episode of heavy fume exposure after lighting firecrackers during his formative years. Baddini Martinez and Ramos[14] hypothesised that these combustion products could initiate an inflammatory process in lung tissue, causing deposition of collagen and dystrophic calcification, and subsequently inducing bone and marrow precursor cells.

There is no specific management guideline for DPO. Some patients are asymptomatic while others require symptomatic relief of respiratory complaints. Follow-up monitoring by interval imaging may be helpful.[3,10]

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