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Diffuse pulmonary meningotheliomatosis☆

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ABSTRACT

We report the case of an 80-year-old woman presenting with randomly distributed ground glass nodules in the lungs. Since this imaging appearance can be confusing and can mimic other disease processes, it is important to have an organized approach. In this specific case, the distribution and appearance of nodules, their presence for a prolonged period as well as the clinical context were clues to the diagnosis of diffuse pulmonary meningotheliomatosis (DPM). The final diagnosis was established by surgical biopsy. This article reviews the current literature on DPM, imaging appearance, and an algorithmic approach to the presented case.

1. Introduction

Minute pulmonary meningothelial-like nodules (MPMN) are a benign entity, often found incidentally in pathologic specimens following surgical resection or at autopsy [1]. MPMNs are mostly asymptomatic and often found as a single nodule. Although less frequently reported, MPMNs can be multiple, termed diffuse pulmonary meningotheliomatosis (DPM) manifesting as diffuse micro-nodules in a random distribution [2]. This imaging appearance can mimic malignant or infectious lesions on high-resolution computed tomography (HRCT). To broaden the understanding of this entity, we present a case of DPM confirmed by surgical biopsy and review existing literature with emphasis on the radiologic findings.

2. Case report

An 80-year-old woman presented to pulmonary clinic with dry cough and progressive dyspnea over 10 months. The patient denied fever or chest pain. Her past medical history was significant for hypertension and type 2 diabetes mellitus, chronic kidney disease (CKD) and gastroesophageal reflux disease (GERD). Surgical history was significant for resection of benign colon polyps following colonoscopy 5-year-ago. She denied any form of smoking, recent travel history, or known lung disease. In pulmonary clinic, physical examination was unremarkable and revealed a hemodynamically stable, well-nourished woman in no apparent distress. She was afebrile, with blood pressure of 140/76 mmHg, pulse rate of 106 beats/min, respiratory rate of 10/min, and 97% oxygen saturation on room air at rest. Basic laboratory tests including complete blood count and differential, electrolytes, kidney and liver function profiles were normal. Serologic markers were positive for ANA, SSA, however there were no clinical signs or symptoms of autoimmune disorder. Microbiological studies were negative for infectious disease. Pulmonary function testing showed lung mechanics suggestive of a restrictive ventilatory defect with an FEV1 of 1.55 L (84%), FVC of 1.89 L (70%), FEV1/FVC ratio of 0.82 and a diffusing capacity for CO2 of 15.70 mL/mmHg/min (79%).

High resolution chest CT showed multiple bilateral 2–4 mm sub-solid (predominantly groundglass) lung nodules (Fig. 1.A–1.B). Some of these nodules were also seen along the fissural surfaces and had a mild predilection for the lower lobes and peripheral lungs. There were no significantly enlarged lymph nodes, pleural effusions or other abnormalities in the thorax. No significant air trapping was noted on the expiratory images. The patient had two abdominal CTs done 1 year and 4 years prior to chest CT, although images were not available for direct comparison. Reports of both abdominal CTs indicated presence of ground glass nodules in lower lungs. A diagnostic video-assisted thoracoscopic (VATS) lung wedge biopsy of right upper and lower lobes was performed for definitive diagnosis.

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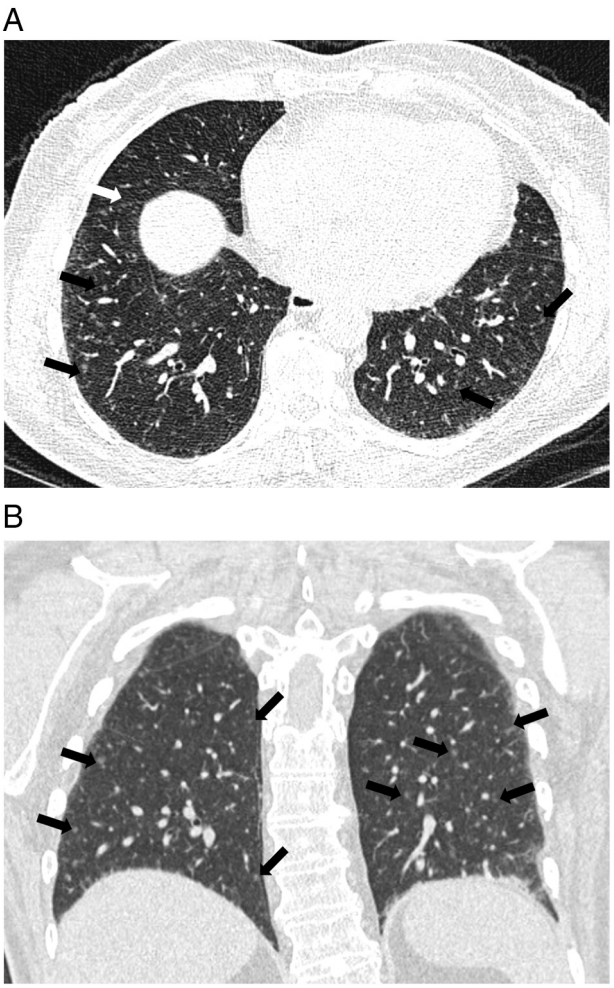

Fig. 1. A–B. Lung window of axial (A) and coronal (B) high resolution chest CT images show multiple sub-solid (predominantly ground glass) lung nodules with a few representative examples indicated by arrows. These range in size from 2 to 4 mm and some are also seen along fissural surfaces (white arrow). Note the mild predilection for lower and peripheral lungs.

The hematoxylin and eosin stain of the lung wedge biopsy showed numerous nodules measuring 0.5 mm to 3 mm in a random distribution. Each nodule was composed of a population of bland epithelioid cells forming small nests within the interstitium with associated variable amount of fibrosis (Fig. 2.A and 2.B), consistent with DPM. In addition, there was patchy small airway abnormality characterized by mild chronic bronchiolitis and prominent peribronchiolar metaplasia (Fig. 2. C). The accompanying interstitium was focally expanded by a mild chronic inflammatory infiltrate (not shown), which did not reach the diagnostic threshold of cellular interstitial pneumonia. Rare non-necrotizing granulomas were present predominantly in the peribronchiolar air spaces (Fig. 2.D). No aspirated particulates were identified and special stains (AFB and GMS) were negative for acid-fast bacilli and fungi.

3. Discussion

MPMNs were first described as “chemodectomas” by Korn et al. in 1960 based on their morphology and close relationship with blood vessels [3]. Later, immunohistochemical, ultrastructural and fluorescence in situ hybridization studies showed no evidence of neuroendocrine differentiation but rather found these to be meningothelial in origin [4–7]. MPMNs are benign often asymptomatic and incidental lesions that are seen on autopsies or surgical lung resections performed for unrelated reasons [8]. MPMNs have been described in the 12–92 years of age range but are most common in the sixth to seventh decade. A female predominance has been reported with female to male ratio ranging from 1.8:1 to as high as 9:1 [1,3,5,9]. Though often presenting as solitary nodules, MPMNs can rarely be multiple and confined to a lobe or may be distributed diffusely in which case they are called “DPM”, a term coined by Suster in 2007 [2]. DPM is usually asymptomatic as well, but can present with respiratory symptoms and mild restrictive lung disease on pulmonary function tests, as seen in our case. The exact etiology remains uncertain, despite various studies reporting potential associations with thromboembolism, smoking-related interstitial lung disease and neoplasm [5,8,10]. Clonal and mutational studies support a reactive rather than neoplastic process for the solitary MPMNs [5,11]. When discovered on imaging studies either incidentally or due to clinical symptoms, definitive diagnosis requires surgical lung biopsy or rarely transbronchial biopsy [12–14]. Management is conservative with surveillance imaging. In the presented case, the patient has remained stable in the 6-month follow-up after VATS biopsy.

Imaging approach to a case of diffuse lung nodules requires assessment of the predominant distribution (craniocaudal, central-peripheral and location in the secondary pulmonary lobule) as well as nodule characteristics. Nodules can be located in a centrilobular, perilymphatic or random distribution. Centrilobular nodules are typically ill defined and ground glass in attenuation (although not exclusively) and spare subpleural and fissural surfaces due to their location in the center of the lobule. In the presented case, the ground glass nodules are seen to sporadically involve the subpleural and fissural surfaces (Fig. 1A) making centrilobular distribution unlikely. Also, lack of propensity for peribronchovascular or interlobular septal location rules out perilymphatic distribution. Findings are consistent with a random distribution.

Groundglass lung nodules (as seen in this case) can have a wide range of differential diagnoses including respiratory bronchiolitis interstitial lung disease (RB-ILD), hypersensitivity pneumonitis (HP), vasculitis and infection. However, all these entities pertain to the airways or vessels located in the center of the secondary pulmonary lobule and hence typically present with centrilobular distribution in contrast to the random distribution seen in this case. Additionally, imaging findings of air trapping and upper lung predilection in HP and RB-ILD respectively are not seen in this case. Lack of history of smoking, antigen exposure and clinical features of infection also make RB-ILD, HP and infectious processes unlikely. For randomly distributed nodules, differential diagnostic considerations include metastatic disease, and infectious processes (miliary pattern). Metastatic disease is excluded as this is usually encountered in the context of a known underlying primary malignancy and the nodules on imaging are discrete and well defined rather than ground glass in attenuation. Miliary tuberculosis or fungal infection is also unlikely given the clinical setting and chronicity of imaging findings.

Radiologic features of DPM described in other studies in literature include randomly distributed ground glass attenuation nodules [1,2,12,15] or discrete micronodules. In our case, micro-nodules were sub-solid and predominantly ground glass in attenuation. Kraushaar et al. have reported that some DPM nodules can have a near-solid appearance through compression of the alveolar airspaces on microscopic examination [1]. Few authors have also reported nodules with predominantly centrilobular [2] or peripheral predominance [2]. Zonal predominance is variable and has been described as upper lobe [9,15] lower lobe (Fig. 1B) [16] or no zonal predominance [1]. Rarely, some DPM nodules show central cavitation [1], which could be confused for infection inflammatory processes or granulomatous disease. Though a definitive diagnosis on imaging can be difficult to make prospectively, this should be considered in the differential, particularly when findings are atypical for other processes. Definitive diagnosis requires tissue confirmation.

The histologic findings of MPMNs and DPM are similar and both

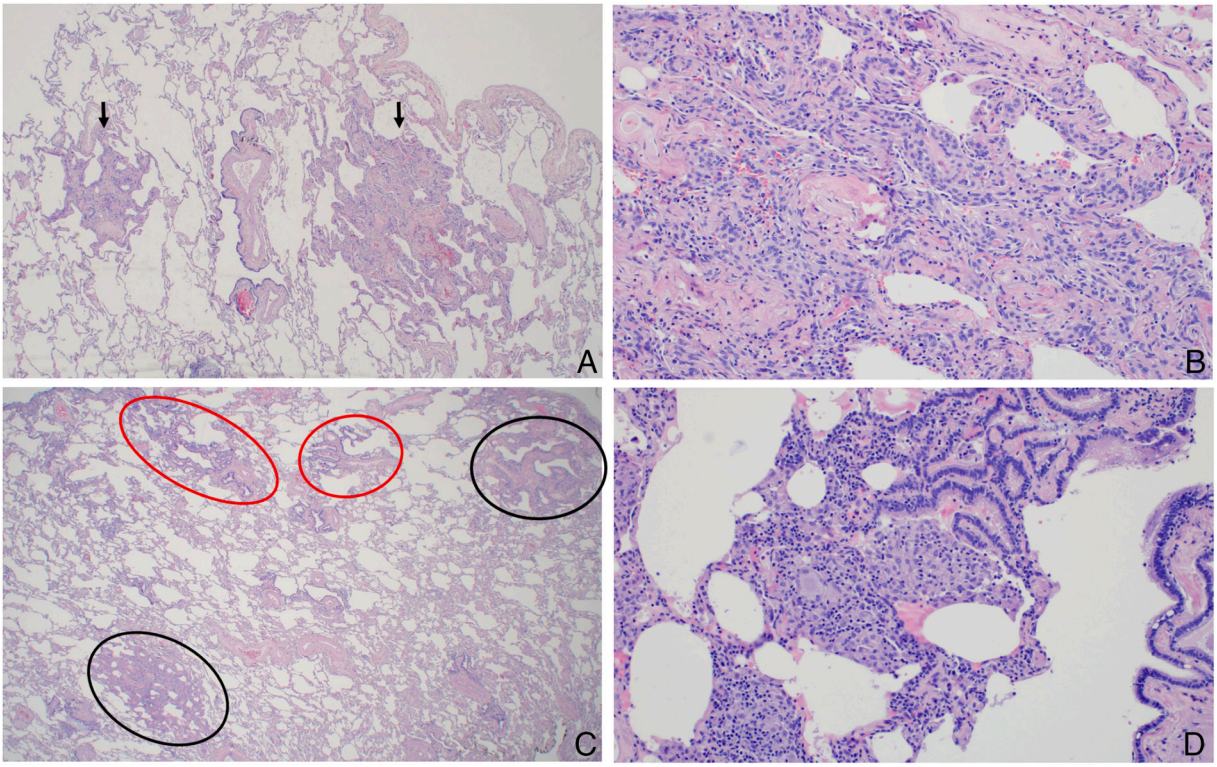

Fig. 2. A. Low power magnification (4×) shows multiple (2) meningothelial-like nodules (MLNs) (arrows) distributed within the interstitium in a random fashion.
B. At higher magnification (20×), the MLN is composed of a population of cytologically bland oval cells arranged in nested pattern.
C. The scanning power shows multiple (2) MLNs (black circle) associated with small airway abnormality including chronic bronchiolitis and peribronchiolar metaplasia (red circle).
D. Rare non-necrotizing granulomas are present in the peribronchiolar air spaces (magnification: 20×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

show small nodule(s) ranging in size from 100 μm–3 mm, which are composed of a population of cytologically bland oval cells arranged in nested pattern and randomly distributed within the interstitium. MPMN can be multiple and mimics DPM histologically, therefore its distinction from DPM requires correlation with additional clinical information (such as presence of associated respiratory symptoms and/or restrictive ventilatory defect on pulmonary functional tests) and radiographic findings of diffuse involvement of the pulmonary parenchyma.

4. Conclusion

DPM is a rare disease more commonly encountered in women and characterized by randomly distributed micro-nodules. Although these may be clinically innocuous, awareness of this entity is important as it can be confused for other disease processes like metastatic disease, infections or interstitial lung diseases. Differentiation from metastatic disease can be difficult in patients with historical or concomitant malignancy. Definitive diagnosis requires surgical lung (and rarely transbronchial) biopsy and correlation with additional clinical and radiologic findings.

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