Diffuse Pulmonary Meningotheliomatosis: A Diagnostically Challenging Entity on Fine-Needle Aspiration Cytology

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Diffuse pulmonary meningotheliomatosis (DPM) is an exceedingly rare entity consisting of multiple minute pulmonary meningothelial-like nodules profusely involving the lungs. To the best of our knowledge, we present the first cytologic description of this uncommon lesion from a 57-year-old nonsmoking woman. Computerized tomographic-guided fine-needle aspiration cytology from a left upper lobe nodule showed whorled/nested clusters of elongated cells with oval nuclei, clear pseudonuclear inclusions, nuclear grooves/indentations, smooth nuclear contours, fine granular chromatin, inconspicuous nucleoli, and abundant fibrillary cytoplasm with indistinct cell borders. The subsequent pulmonary wedge resections confirmed the diagnosis of DPM. As this condition is exceptionally rare, familiarity with these cytologic features is of the essence to accurately establish this challenging diagnosis. Diagn. Cytopathol. 2015;43:727–730.

Key Words: diffuse pulmonary meningotheliomatosis; minute pulmonary meningothelial-like nodules; fine-needle aspiration; cytology

Minute pulmonary meningothelial-like nodules (MPMNs) were first described by Korn et al.[1] in 1960 and were thought to resemble chemodectomas. However, later studies by electron microscopy, immunohistochemistry, and mutational analysis demonstrated the lack of neuroendocrine differentiation and supporting evidence for meningothelial origin.[2–5] In addition, it has been further suggested that primary pulmonary meningioma may have arisen from MPMNs.[6] Histologically, these nodules consist of whorls/nests of moderately sized elongated/spindled cells with oval nuclei, finely granular chromatin, inconspicuous nucleoli, and abundant granular and eosinophilic cytoplasm with indistinct cell borders.[2] MPMNs have a female predominance and are usually present as asymptomatic, solitary, or multiple nodules that are incidentally found during pathologic evaluation of lung specimens.[2,7] In a rare subset of patients, however, these lesions are sufficiently profuse to cause diffuse radiologic abnormalities and occasionally a syndrome of restrictive lung disease, which has been referred to as diffuse pulmonary meningotheliomatosis (DPM).[8–10] To the best of our knowledge, this is the first cytologic description of DPM from a fine-needle aspiration (FNA) sample.

Case Report

Clinical History

This patient is a 57-year-old nonsmoking female with a history of obesity, hypertension, asthma, and hypercholesterolemia, who underwent a left knee replacement. Her postoperative course was complicated by a pulmonary embolus, which was successfully treated with Coumadin. During a follow-up computerized tomographic (CT) evaluation, she was found to have incidental bilateral pulmonary nodules/densities. No intervention was done at the time given the status of her embolus. She experienced a similar episode 3 months later, and a repeat CT scan showed resolution of the pulmonary embolism, but

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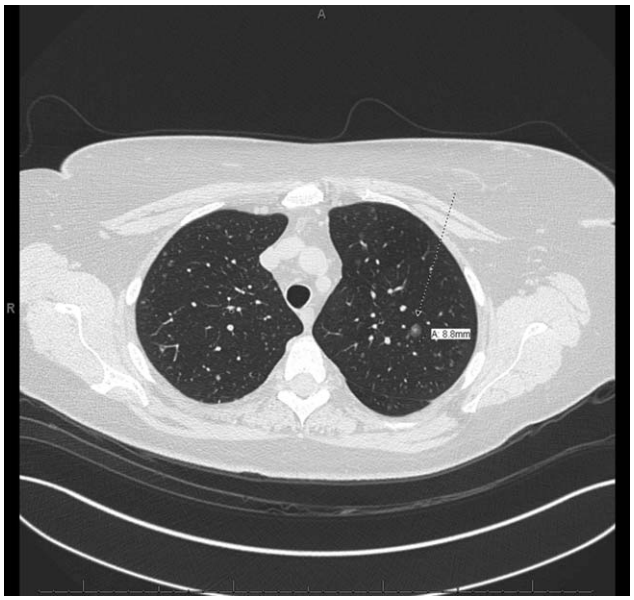

Fig. 1. Chest computerized tomographic scan showing multiple lung nodules. The arrow is pointing at the largest nodule (8.8 mm) located at the left-upper lobe.

increased and diffuse bilateral pulmonary nodules/densities ranging in size from 2 to 9 mm (Fig. 1). Radiographically, many of these nodules have ground glass appearance, but others are more solid, with few of them containing calcifications. Pulmonary function test revealed mild obstructive changes, normal lung volume, and a preserved diffusing capacity for carbon monoxide. Aside from her usual allergic symptoms, she has been asymptomatic and denied shortness of breath. A bronchoscopy was performed that demonstrated normal appearing airways and the bronchoalveolar lavage collected contained benign appearing bronchial columnar cells and alveolar macrophages. Subsequently, CT-guided FNA biopsy was performed.

Cytologic Features

An FNA was performed on the largest nodule from the left upper lobe (three passes including three papanicolaou-, and three giemsa-stained smears). The aspirates yielded predominantly acellular smears with only one sparsely cellular papanicolaou-stained smear, which showed bland appearing elongated cells in clusters or whorls. These cells have oval nuclei, smooth nuclear membranes, finely granular chromatin, inconspicuous nucleoli, and abundant fibrillary cytoplasm without distinct cell borders (Fig. 2A). Nuclear overlapping was frequently observed. Occasional clear pseudonuclear inclusions (Fig. 2B, arrow) and nuclear grooves/indentations were noted (Fig. 2B, arrowheads). No mitosis, necrosis, or apoptosis was identified. Cell block contained

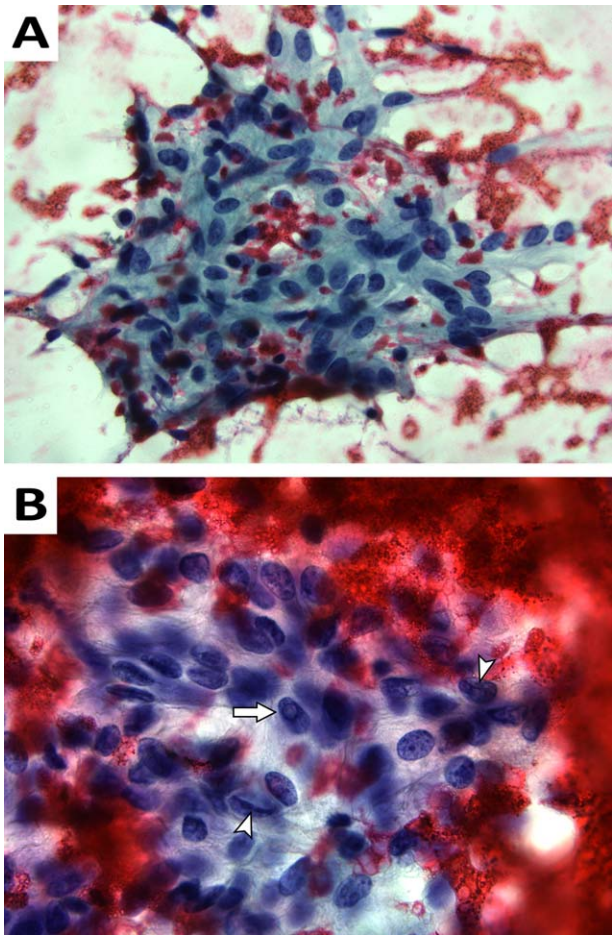

Fig. 2. FNA cytology shows (**A**) a whorled/nested cluster of elongated cells with oval nuclei, smooth nuclear contours, fine-granular chromatin, inconspicuous nucleoli, and abundant fibrillary cytoplasm with indistinct cell borders (Papanicolaou stain, 600×). (**B**) Occasional clear pseudonuclear inclusions (arrow) and grooves/indentations (arrowheads) can be identified (Papanicolaou stain, 1,000×). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

insufficient material for ancillary study. A diagnosis of "aggregates of histiocytes" was rendered with a comment, suggesting that this may represent an inflammatory process or pulmonary Langerhans cell histiocytosis (PLCH).

Histologic Findings

Subsequent pulmonary wedge resections were obtained from the right upper, middle, and lower lobes. Grossly, there were no identifiable lesions and the specimens were entirely submitted for histologic examination. The sections prepared showed multiple interstitial nodules distributed in a randomized fashion (Fig. 3A). These lesions comprised a population of epithelioid and spindle cells arranged in a vaguely nested growth pattern. The individual cells show centrally located oval-shaped nuclei with

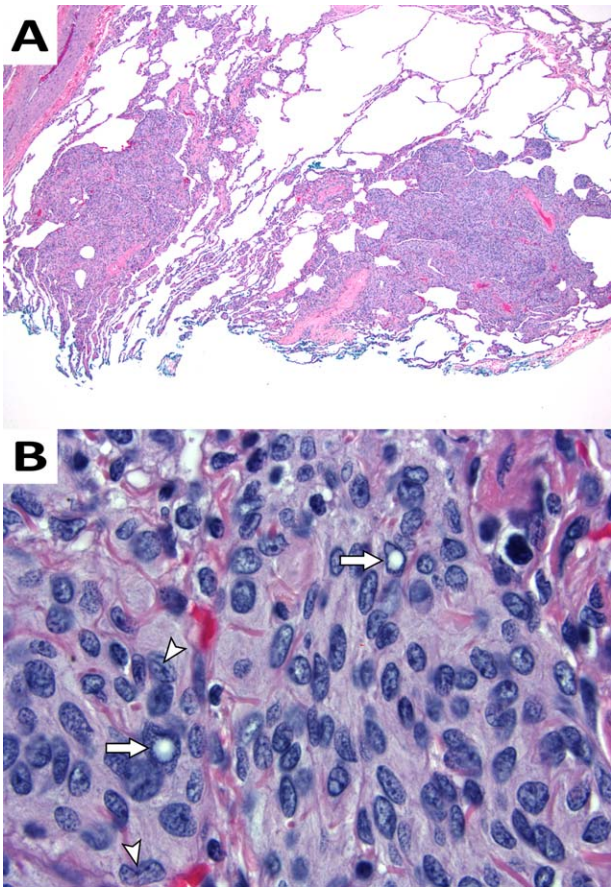

Fig. 3. Pulmonary wedge resection demonstrates (**A**) two adjacent parenchymal nodules (H&E stain, 40×). (**B**) The nodules consist of epithelioid and spindle cells arranged in a vaguely nested growth pattern with cytologic features similar to FNA cytology. Clear pseudonuclear inclusions (arrows) and grooves/indentations (arrowheads) can be seen (H&E stain, 1,000×). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

finely dispersed chromatin, inconspicuous nucleoli, and variably abundant eosinophilic cytoplasm with indistinct cytoplasmic borders (Fig. 3B), similar to the findings of FNA. Occasional clear pseudonuclear inclusions (Fig. 3B, arrows) and grooves/indentations (Fig. 3B, arrowheads) were noted. Immunohistochemical profile of the lesional cells was diffusely positive for vimentin, epithelial membrane antigen (EMA), and progesterone receptor (PR), and negative for cytokeratin (AE1/AE3), smooth muscle actin, S-100, HMB-45, CD31, and CD34. A definitive diagnosis of DPM was established.

Discussion

DPM is an exceedingly rare condition where MPMNs profusely involve the lungs, causing symptoms of mild restrictive lung disease.[8–10] Its radiographic findings mimic metastatic tumors; thus, early recognition of this entity, particularly for FNA cytology in the appropriate clinical setting, could prevent further unnecessary procedures. Here, we report the first FNA case of DPM and describe the cytologic characteristics of this uncommon disease.

Our patient was initially treated for pulmonary embolism. Interestingly, MPMNs have been associated with thromboembolism.[7,11–13] Most MPMNs are small (100 μm to 3 mm) and randomly distributed throughout the lungs, but has a tendency to be located in the peripheral zone.[2,9,14] One study has suggested that MPMNs may be present in all abnormal lungs if extensively sampled.[7] As these lesions are tiny, CT-guided FNA can be technically challenging. In the current case, majority of the smears were virtually acellular and the cell block was inadequate for ancillary tests. One smear consisted of cell clusters with cytomorphology similar to DPM and MPMNs.[2,7,10] The previous reports have noted that the cytoplasm of these meningothelial-like lesions is usually pink and eosinophilic. Although this cytoplasmic feature was present in the hematoxylin and eosin (H&E) stain from the pulmonary wedge resections, it was difficult to appreciate this quality on the papanicolaou stain of the FNA sample. Instead, we noted a fibrillary texture to the cytoplasm on the papanicolaou stain, which may be what others have described as granular cytoplasm on the H&E stain (Figs. 2 and 3). Concordant with Suster and Moran,[10] occasional clear pseudonuclear inclusions were observed on both the FNA and the wedge resection specimens (Figs. 2B and 3B, arrows). Additional feature noted is the presence of nuclear grooves/indentations (Figs. 2B and 3B, arrowheads). The positivity for vimentin, EMA, and PR in the pulmonary wedge resections supports the diagnosis of DPM.[4,7,10,15]

Histiocytes typically have oval and occasionally folded nuclei with granular or vacuolated cytoplasm. Therefore, the bland elongated cell clusters with oval nuclei and nuclear grooves/indentations observed in DPM can cytologically mimic aggregates of histiocytes. Hence, an inflammatory process or PLCH was suggested in the original FNA diagnosis. PLCH is an isolated form of Langerhans cell histiocytosis affecting the lungs of primarily young adults with a history of current or prior cigarette smoking.[16] Chest CT usually demonstrates a mixture of nodules and cysts in the upper-middle lobes.[17] Our patient does not fit this classic profile for PLCH as she is a nonsmoker and presented with diffuse bilateral nodules involving all lobes. When immunohistochemical results are available, PLCH can be easily distinguished from DPM as it expresses CD1a, langerin, and S-100, whereas DPM expresses vimentin, EMA, PR, and CD56.[4,7,10,15,18]

DPM is a challenging diagnosis to make on FNA cytology. The main cytomorphologic features are whorled/nested clusters of bland elongated cells with oval smooth nuclei, fine granular chromatin, inconspicuous nucleoli, and abundant fibrillary cytoplasm with indistinct cell borders. Occasional clear pseudonuclear inclusions and nuclear grooves/indentations can be seen. In the presence of these features, pathologists should be aware of this uncommon entity in the clinical setting of multiple pulmonary micronodules. As these nodules are minute and difficult to aspirate, adequate material for additional ancillary studies may not always be feasible. Therefore, recognizing these important cytologic characteristics in the appropriate clinical context is imperative to accurately diagnose this unusual lesion.

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