Minute Pulmonary Meningothelial-Like Nodules: A Case of Incidentally Detected Diffuse Cystic Micronodules on Thin-Section Computed Tomography

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Abstract: Minute pulmonary meningothelial-like nodules are common incidental pathologic findings but are sparsely described in the radiology literature. They are of uncertain origin and significance, but they can occasionally manifest as mild restrictive lung disease or as incidental micronodules on computed tomography. We present a case of multiple incidentally detected, randomly distributed, cavitating micronodules with pathologic correlation. Awareness of the rare presentation of this entity is important because it may simulate neoplastic or other nonneoplastic diseases.

Key Words: minute pulmonary meningothelial-like nodules, meningotheliomatosis, micronodules, pulmonary chemodectoma, computed tomography

(*J Comput Assist Tomogr* 2010;34: 780–782)

CASE REPORT

A 54-year-old woman was found to have iron deficiency anemia on screening blood work at routine office visit. Results of upper and lower gastrointestinal endoscopy were unremarkable. Computed tomographic (CT) enteroclysis was then performed, showing normal small bowel but multiple, small, bilateral, basal pulmonary nodules. Therefore, spiral chest CT with 1-mm reformations was performed for further evaluation. This demonstrated multiple, bilateral, randomly distributed 1- to 4-mm nodules, many of which had thin-walled cavities. No zonal predominance was noted (Figs. 1 and 2). No other parenchymal, hilar, mediastinal, or pleural abnormality was evident. Differential diagnostic considerations included metastatic disease, atypical infections, and pulmonary Langerhans cell histiocytosis.

The patient was generally well. Her anemia responded to iron therapy. She denied fatigue, shortness of breath, or other respiratory symptom. The patient had no known malignancy. She was a nonsmoker with no recent significant travel history. Past medical history revealed hypertension and gastroesophageal reflux. Given the concern for metastatic lung disease, and absence of known primary malignancy, the patient underwent a minimally invasive thoracoscopic lung biopsy for tissue diagnosis.

A single-wedge biopsy from the right upper lobe demonstrated multiple indistinct, pale, tan, small nodules with an appreciation of some central tissue loss in the larger examples (Fig. 3). On microscopic examination, numerous minute pulmonary meningothelial-like nodules (MPMNs) were identified. The nodules ranged in size from barely detectable microscopic interstitial cellular proliferations to many that were 3.0 to 3.5 mm in diameter. The largest nodule was 4.0 mm in diameter.

The microscopic appearance of the nodules conforms to classic descriptions of an interstitial proliferation of cytologically bland oval to blunted spindle ("epithelioid") cells imparting a variable widening to the alveolar septa (Fig. 4). Some slight whorling of cell clusters imparted a vague meningotheliomatous appearance. The lesions were typically juxtaposed to the pleura, interlobular septa, and perilobular venous tributaries. Large nodules sometimes spanned the lobule to contact both the septum and the bronchovascular bundle. Although some nodules were close to having a near-solid appearance through compression of the alveolar airspaces, many were associated with loss of or enlargement of alveolar tissue in a manner that would suggest the process of "traction emphysema" (Fig. 4). This feature is the correlate of the central radiological lucency identified in many of the nodules on CT scan. The immunohistochemical profile of the lesions was consistent with previous descriptions (positive for vimentin, epithelial membrane antigen, progesterone receptor, and CD56; negative for pankeratin, synaptophysin, S-100 protein, bombesin, CD34; rare cells were positive for the nuclear proliferation antigen MIB1).[1]

DISCUSSION

First described in 1960, MPMNs are nests of epithelioid cells centered on small pulmonary veins and arranged in a "zellenballen" pattern.[2] Initially, their morphology, cytologic structure, and proximity to veins resulted in the incorrect notion that they were neuroendocrine-differentiated cells that functioned as chemoreceptors and thus were referred to as pulmonary chemodectomas.[2] Subsequent reports demonstrated immunohistochemical similarities to meningiomas, which was further supported by positive staining with vimentin and epithelial membrane antigen.[3–5] In addition, ultrastructural analysis demonstrated both a lack of neuroendocrine differentiation that would be expected in paragangliomas and strong similarities to meningothelial cells with cytoplasmic interdigitations and desmosomes.[3,5–7] These features prompted renaming the lesions MPMNs.[3]

Most reports on MPMNs in the literature are derived from incidental discovery of these lesions during routine pathologic examination. The rate of detecting MPMNs varies depending on the source of the lung tissue examined. Studies on multiple autopsy specimens have demonstrated an incidence of 0.07% to 4.9%,[2,3,6,8] which was shown to increase more than 10-fold when the examining pathologists were requested to specifically look for them.[6] By comparison, a higher detection rate of 7% to 13.8% was observed in studies that examined surgical resection specimens.[1,4,9] In addition, a detection rate of 48% was

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Received for publication April 11, 2010; accepted April 13, 2010.
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The authors have no financial disclosures.

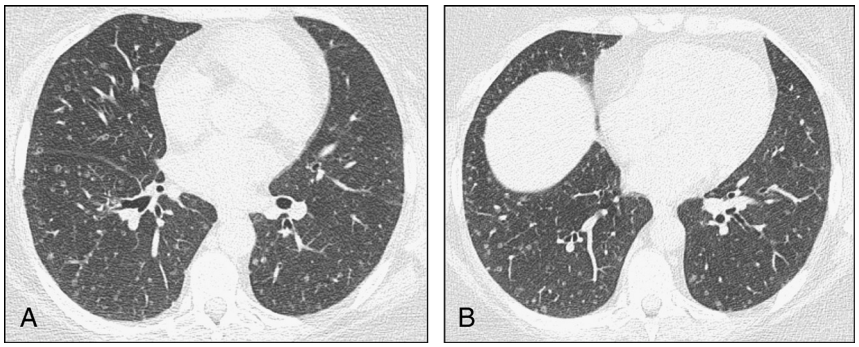

FIGURE 1. A, Thin-section, 1-mm, transaxial, unenhanced CT image in standard lung windows (L −700 Hounsfield unit; W 1500) at the level of the aortic valve showing multiple bilateral randomly distributed micronodules. Many nodules show central cavitation. B, More inferior section with the same technique showing slight asymmetry with greater concentration of nodules in the right lung. The nodules favor the lung periphery.

seen in a subgroup of extensively sampled lobectomy specimens.[1] They are most frequent in the sixth decade and have a 1.8–9:1 female-to-male ratio.[1–10] This female preponderance may relate in part to the presence of immunoreactivity for progesterone receptors in many MPMNs.[4,10]

Although multiple MPMNs may be detected in lung specimens, there are only a few reports that consider the number of lesions to be numerous or diffuse. This condition are alternatively termed *diffuse pulmonary meningotheliomatosis*,[7] *pulmonary chemodectomatosis*,[11] or *MPMN-omatosis*.[12] The precise distinction between the terms multiple and diffuse has not been determined. Suster and Moran[7] documented 5 cases in which middle-aged patients presented with respiratory symptoms and mild restrictive lung disease suggestive of interstitial lung disease. Computed tomographic imaging in these patients showed a diffuse reticulonodular pattern with ground glass nodules that measured up to 8 mm in size. Pathological examination showed multiple MPMNs. This is the only report that has considered MPMNs as the direct cause of a patient's symptoms (restrictive lung disease in this series).

Multiple MPMNs have been associated with a variety of pulmonary abnormalities. The strongest association has been in patients with pulmonary thromboembolism, with MPMNs occurring in 24% to 42% of these patients.[1,6,8] Several studies have shown an association with neoplasia, particularly pulmonary adenocarcinoma, with MPMNs occurring in 9% to 10% in this cohort.[4,9] Associations with smoking-related interstitial lung disease, atypical adenomatous hyperplasia, and cardiac disease have been suggested as well.[1,6,9]

The origin and significance of MPMNs are still uncertain. Genetic analysis of these structures suggests a reactive rather than a neoplastic origin,[4] and their absence in pediatric lung

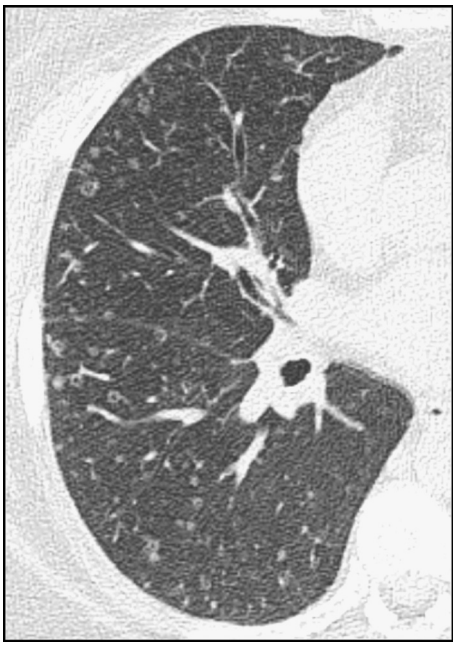

FIGURE 2. Magnified transaxial image of right lower lung better demonstrates the central lucency in several of the micronodules.

FIGURE 3. Gross photograph of 3 formalin-fixed lung biopsy sections. The 3 white arrows point to small, ill-defined tan nodules within the parenchyma. In the middle slice, the 2 nodules give an impression of slight central cavitation. Other vague-appearing nodules of several millimeters may be seen in the background. Scale marks, 1.0 mm.

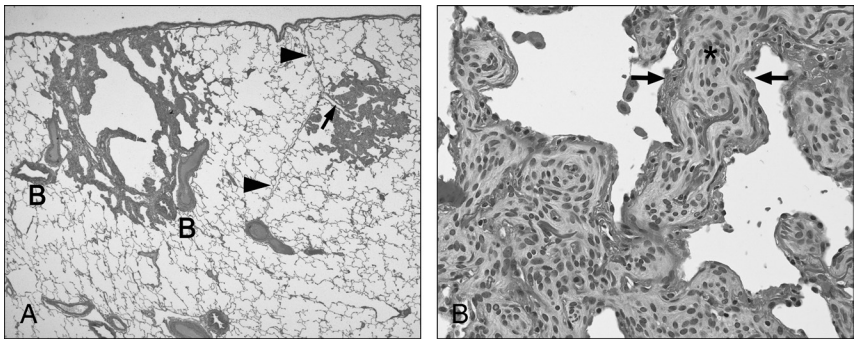

FIGURE 4. A, Low-power photomicrograph of 2 MPMNs. The nodule on the left abuts the visceral pleura and extends onto 2 bronchovascular bundles (B). The central tissue loss, correlating with the central lucency on high-resolution CT, is apparent. The nodule on the right is more compact and juxtaposed to a secondary lobular septum (arrowheads) and, in particular, a small venous tributary (arrow; hematoxylin and eosin). B, Medium-power photomicrograph demonstrating the typical histological features of a MPMN. Cytologically bland epithelioid cells (asterisk) infiltrate between 2 leaves of alveolar epithelium supported by collagen fibers and envelope the alveolar septal capillary. Slight whorling of the cells contributes to the appearance of meningothelium (hematoxylin and eosin).

specimens argues against a congenital origin.[1] Some have suggested that MPMNs may be present in all abnormal lungs if sufficiently sampled and that chronic lung disease stimulates the formation of these nodules.[1] The significance of so-called meningotheliomatosis is similarly uncertain. Using loss of heterozygosity–based genotyping analysis, Ionescu et al[12] demonstrated increased genetic instability in cases with multiple MPMNs and raised the possibility that cases with multiple MPMNs might represent a transition between a reactive and a neoplastic process.

The imaging literature contains little regarding MPMNs. One case study examined a 55-year-old woman being evaluated for a 2-cm right upper lobe nodule with multiple adjacent ground glass nodules. On resection, a diagnosis of pulmonary papillary adenocarcinoma was made. The small nodules noted elsewhere were MPMNs. Follow-up high-resolution CT showed randomly distributed bilateral nodules of ground glass attenuation.[13] Sellami et al[14] reported a 64-year-old woman with a radiographically detected solitary pulmonary nodule. Chest CT scan in this patient showed upper lobe–predominant, randomly distributed, sharply circumscribed solid micronodules. Pathologic evaluation of the largest nodule revealed an adenocarcinoma, whereas the micronodules corresponded to MPMNs. A recent review referred to a 73-year-old patient with uterine cancer and multiple pulmonary nodules on radiographs that corresponded to MPMNs.[1] The Japanese literature reports a case of a 56-year-old woman with a past history of breast cancer. A chest CT scan revealed multiple lower lobe predominantly subpleural nodules, subsequently proven to be MPMNs.[15] These cases illustrate the importance of maintaining a high level of suspicion for this rare entity, especially in association with lung adenocarcinoma. If the pulmonary nodules in these cases had been deemed metastatic disease with no further pathologic correlation, options for curative surgical therapy for the primary malignancy may have been erroneously delayed or denied.

In conclusion, we present a case of pathologically proven MPMNs presenting as incidentally detected cystic micronodules on thin-section CT in a patient with no respiratory symptoms. Knowledge of the imaging manifestations in cases of multiple MPMNs is important given the association of these nodules with malignancy. Curative surgical options could conceivably be denied or delayed if multiple pulmonary micronodules are erroneously assumed to be metastatic disease.

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