Diffuse Pulmonary Meningotheliomatosis

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Abstract: Minute pulmonary meningothelial nodules are rare lesions histologically composed of small nests of epithelioid cells located within the interstitium of the lung. These nodules are generally asymptomatic and are usually found incidentally at autopsy or in surgical specimens resected for unrelated causes. The lesions are most often single, although multiple lesions with unilateral involvement of one or even all lobes of the same lung have been described. To our knowledge, cases of meningothelial nodules with disseminated bilateral pulmonary involvement associated with clinical symptoms of restrictive pulmonary disease and radiologic evidence of diffuse reticulonodular pulmonary infiltrates have not been previously documented. We have studied 5 patients presenting with diffuse bilateral pulmonary involvement by numerous minute pulmonary meningothelial nodules. The patients were 4 women and a man aged 54 to 75 years who presented clinically with dyspnea and shortness of breath and the lesions were discovered on open lung biopsies performed for the evaluation of diffuse bilateral interstitial lung infiltrates found on chest x-rays and computed tomography scans. In 3 patients, there was a previous history of malignancy and the radiologic findings were suspected of representing diffuse metastatic disease. Histologically, the lesions were composed of small clusters of epithelioid cells with round to oval nuclei devoid of atypia and surrounded by abundant eosinophilic cytoplasm. Immunohistochemical studies showed positivity of the tumor cells for epithelial membrane antigen and vimentin, and negative staining for cytokeratin, actin, S-100 protein, CD34, chromogranin, and synaptophysin. Electron microscopic examination in 1 case confirmed the ultrastructural features of meningothelial cells, including complex cytoplasmic interdigitations joined by well-developed desmosomes and abundant intracytoplasmic intermediate filaments. The diffuse bilateral involvement of lung parenchyma in the present cases can lead to confusion on clinical and radiologic grounds with a variety of interstitial pulmonary processes, including idiopathic interstitial pneumonia and lymphangitis carcinomatosa. Diffuse pulmonary meningotheliomatosis should be considered in the clinical differential diagnosis of diffuse interstitial pulmonary infiltrates.

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Minute pulmonary meningothelial-like nodules (MPMN) were first identified by Korn et al[8] in 1960 and initially interpreted as minute pulmonary chemodectomas. Subsequent studies by Kuhn and Askin,[9] Churg and Warnock,[4] and Gaffey et al[5] demonstrated that the lesions actually had immunohistochemical and ultrastructural features of meningothelial cells. Until now, these lesions have represented a curiosity without any clinical significance and are regarded as an embryologic aberration found incidentally at autopsy or in lung specimens resected for various unrelated causes. Although in the majority of cases the lesions are single and incidental, multiple lesions can sometimes be encountered, usually restricted to one lobe and, in rare instances, involving multiple lobes in a single lung. Diffuse, bilateral pulmonary meningothelial nodules associated with clinical symptoms and radiographic findings suggestive of interstitial lung disease or disseminated metastatic malignancy have, to our knowledge, not been described.

We report 5 patients presenting with signs and symptoms of mild restrictive lung disease and radiographic evidence of diffuse, bilateral reticulonodular lung infiltrates in whom open lung biopsies revealed multiple meningothelial-like nodules in the absence of interstitial fibrosis, carcinomatosis, or other obvious pathologic abnormalities that could account for the radiologic findings. The clinicopathologic features of these patients and a review of the literature on the topic are presented.

MATERIALS AND METHODS

The cases were retrieved from the Surgical Pathology files of the Ohio State University Medical Center, Columbus, OH, the University of Texas M.D. Anderson Cancer Center, Houston, TX, and from one of the authors' personal files (C.A.M.) between the years 1996 and 2006. Clinical information on these patients was abstracted from their medical records. Imaging studies and radiology reports were available in all 5 patients. All patients underwent video-assisted thoracoscopic biopsies with multiple sampling involving the right upper and lower lobes. For histologic examination, the sampled tissues were fixed in 10% buffered formalin, embedded in

paraffin and routinely processed for histology. Sections stained with hematoxylin and eosin were available in all cases, ranging from 3 to 7 slides per case. Representative paraffin-embedded tissue blocks were available for immunohistochemical staining in all cases. Immunohistochemical stains were performed using the standard avidin-biotin immunoperoxidase technique in a DAKO Autostainer. The antibodies tested included: cytokeratin cocktail (AE1/AE3, Boehringer-Manheim, Indianapolis, IN; 1:1000); low-molecular weight cytokeratin (CAM5.2, Beckton-Dickinson, San Jose, CA; 1:100); vimentin (V9, Dako, Carpinteria, CA); S-100 protein (polyclonal, Dako, 1:3000); muscle specific actin (HHF-35; Enzo, New York, NY; 1:32,000); smooth muscle actin (Dako, 1:75); chromogranin A (Dako, 1:15); synaptophysin (Dako; 1:100); epithelial membrane antigen (EMA) (Dako, 1:200); and CD34 (Dako, 1:300). Heat-induced epitope retrieval was employed on selected markers using a pressure steamer for 24 minutes with Dako target retrieval solution. Appropriate positive and negative controls were run concurrently for all antibodies tested.

In case no. 2, fresh tissue samples were diced into 1 mm^3 cubes, fixed in 2.5% glutaraldehyde, embedded in EPON and routinely processed for transmission electron microscopy. Thin sections were stained with uranyl acetate and lead citrate and viewed in a Zeiss 900 TEM.

RESULTS

Clinical Findings

The clinical findings in our patients are summarized in Table 1. Four patients were women and 1 was a man. The ages ranged from 54 to 75 years. All patients presented with dyspnea, shortness of breath, and fatigue. None of the patients had a history of smoking or of occupational exposure to carcinogens, asbestos, coal, silica, or other substances. Results of pulmonary function tests showed a pattern of mild restrictive lung disease. Chest x-rays and computed tomography (CT) scans showed diffuse bilateral reticulonodular infiltrates or ground-glass opacities, with multiple small nodules measuring 2 to 3 mm in diameter diffusely scattered throughout both lung fields (Figs. 1A–C). A few of the nodules appeared larger and measured up to 8 mm in greatest diameter. The number of nodules ranged from 30 to > 100 per lung. There was no evidence of hilar adenopathy. Multiple lung biopsies were performed in 2 patients for the evaluation of suspected interstitial lung disease. Three patients had a history of previously resected malignant neoplasms of internal organs and were biopsied for suspected pulmonary metastases. Patient no. 1 had a history of adenocarcinoma of the colon infiltrating through the bowel wall into the serosa with 2 positive regional lymph node metastases removed 9 years previously. Patient no. 2 had a history of uterine leiomyosarcoma resected 7 years previously. On her present admission, she was seen for spontaneous pneumothorax and on chest x-ray showed diffuse bilateral reticulonodular infiltrates in addition to a single 1.5 cm nodule located subpleurally in the right middle lobe. Patient no.5 had a history of papillary thyroid carcinoma resected 27 years previously, an invasive ductal carcinoma of the left breast treated by modified radical mastectomy 18 years previously, and a stage 1 well-differentiated adenocarcinoma of the lung for which she underwent a left lower lung resection 9 years previously. She underwent open lung biopsy for miliary bilateral lesion on chest x-ray and CT scans suspicious for metastases.

Pathologic Findings

Gross Findings

The gross specimens in all cases consisted of wedge resections of lung that measured from 2 to 4 cm in maximum dimension. Cut sections of all lung wedge biopsies showed multiple small gray white nodules scattered randomly throughout the lung parenchyma.

TABLE 1. Clinical Summary in 5 Patients With Diffuse Pulmonary Meningotheliomatosis

Case	Sex/Age	Clinical Presentation	Radiographic Findings	Other Clinical History
1	F/75	Dyspnea, shortness of breath, fatigue	Diffuse bilateral pulmonary reticulonodular infiltrates on CXR and CT scans	Ischemic heart disease, hypertension. History of colon carcinoma 9 y previously
2	F/54	Spontaneous pneumothorax, dyspnea	Diffuse bilateral pulmonary reticulonodular infiltrates plus discrete 1.5 cm nodule in right middle lobe on CXR and CT scans	History of uterine leiomyosarcoma 7 y previously
3	M/51	Progressive cough, shortness of breath	Diffuse bilateral pulmonary reticulonodular infiltrates on CXR and CT scan	N/A
4	F/63	Progressive cough, shortness of breath	Diffuse bilateral pulmonary reticulonodular infiltrates on CXR and CT scan	Coronary artery disease, hypertension
5	F/71	Dyspnea, shortness of breath, fatigue. Patient on surveillance CT scans for metastatic disease	Diffuse bilateral pulmonary reticulonodular infiltrates on CXR and CT scan	Prior papillary thyroid carcinoma, invasive ductal breast carcinoma, and adenocarcinoma of lung

CXR indicates chest x-ray.

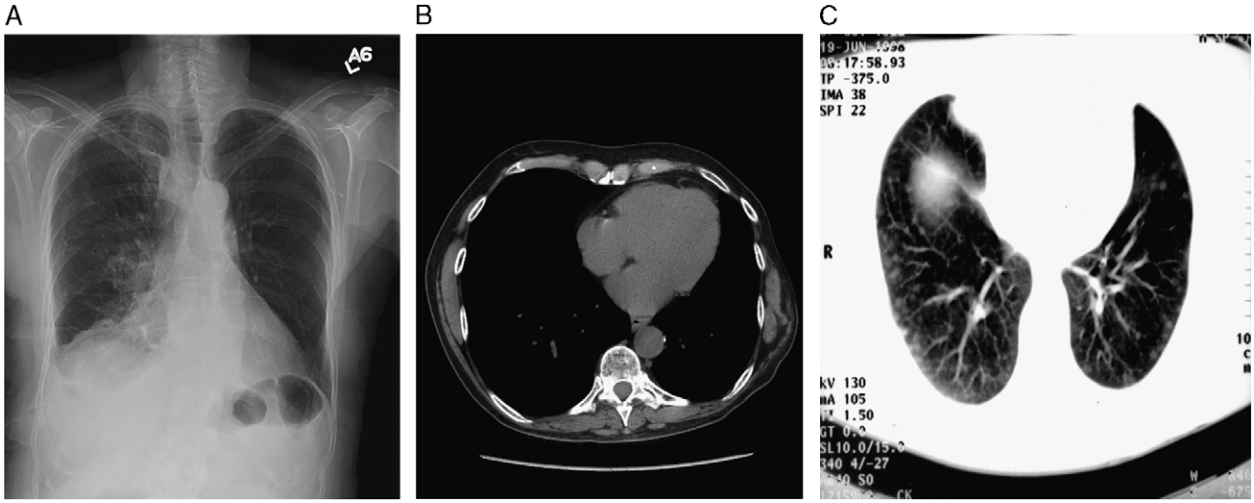

FIGURE 1. Imaging studies. A, (case 5) antero-posterior chest x-ray film with bilateral reticulo-nodular pattern; B, (case 5) chest CT scan with contrast (2.5 mm slices) shows multiple, tiny nodules scattered throughout both lungs; C, (case 1) conventional chest CT scan (lung window) showing multiple ground-glass peripheral bilateral pulmonary nodules with centrilobular distribution.

The nodules measured form 1 to 5 mm in greatest diameter. They were located both subpleurally and deep, but tended to be more numerous in subpleural location. There were no areas of necrosis or hemorrhage associated with the nodules. In case 2, a wedge resection from the right middle lobe also contained a single larger, white, firm, well-circumscribed subpleural nodule 1.5 cm in diameter.

Histologic Findings

Histologic examination demonstrated multiple small interstitial nodules mainly distributed in perivenular location and sometimes along the walls of alveolar septae or surrounding ectatic vascular spaces. The density of the nodules varied from biopsy to biopsy; a few of the specimens contained only 2 or 3 meningothelial nodules per slide; others showed up to 8 discrete nodules per histologic section (Fig. 2). The nodules ranged in size from microscopic deposits composed of 2 or 3 small clusters of cells to lesions that measured 5 mm. in greatest diameter (Fig. 3). A few of the nodules were slightly larger and measured up to 8 mm in greatest diameter as measured on the glass slide with a micrometer. In some instances, the nodules adopted a dense, nodular configuration, and were sharply demarcated from the surrounding pulmonary parenchyma (Fig. 4). Other nodules were

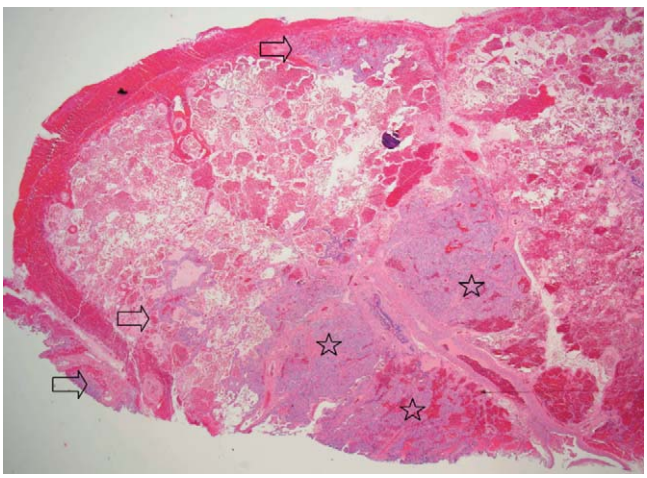

FIGURE 2. Scanning magnification of lung biopsy (case 1) showing multiple foci of meningothelial-like nodules. Three confluent large nodules are seen located towards the center of the field (stars), and 3 smaller ones are present towards the periphery (arrowheads).

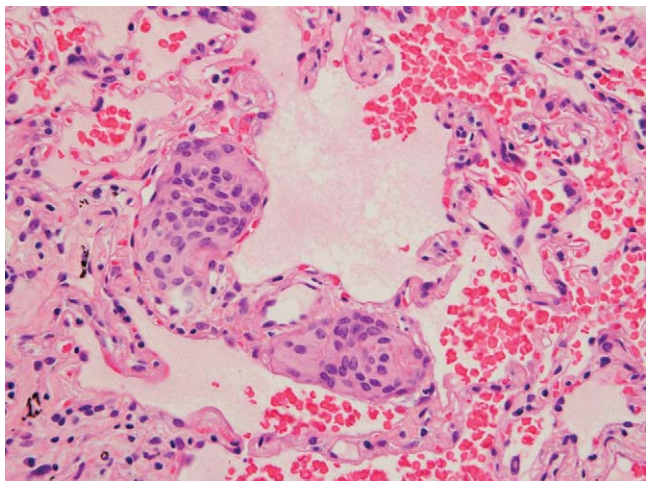

FIGURE 3. Incipient, early focus of meningothelial-like nodule (<1 mm diameter) (case 2) composed of 2 small clusters of meningothelial cells in perivenular location (center).

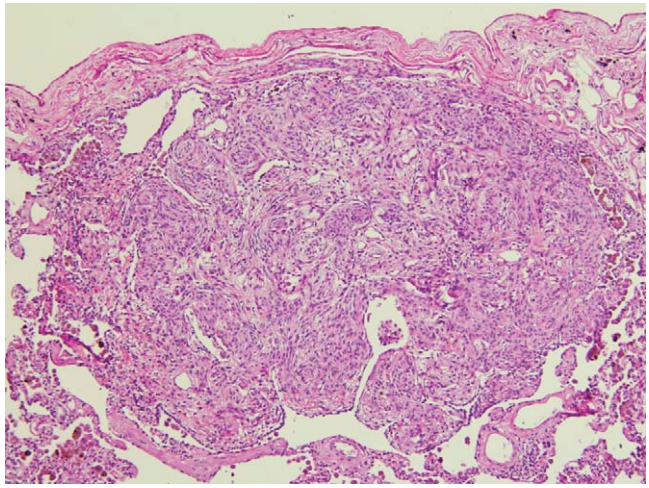

FIGURE 4. Larger focus of MPMN (3 mm diameter) (case 1) showing subpleural, well-circumscribed, nodular proliferation sharply demarcated from the surrounding pulmonary parenchyma.

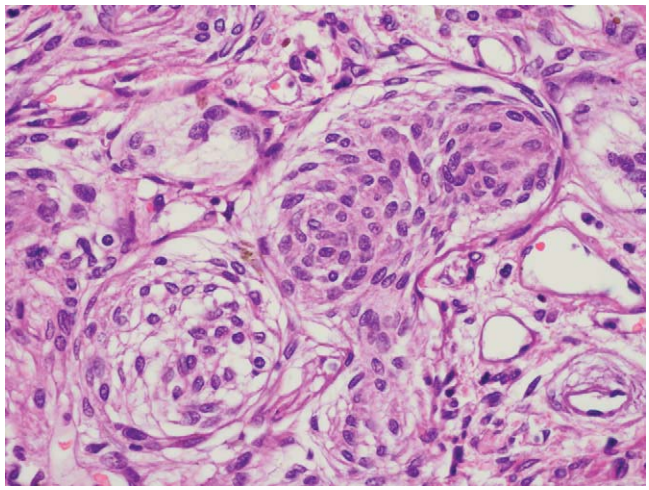

FIGURE 6. Cluster of cells showing a marked whorled appearance within MPMN (case 5).

ill-defined and the tumor cells appeared to be irregularly distributed in perivenular location (Fig. 5). Cytologically the nodules were composed of oval to spindle cells with abundant pink cytoplasm, indistinct cellular borders, and uniform oval nuclei with finely dispersed chromatin. Some of the cells showed clear pseudonuclear inclusions. Whorling of the tumor cells could also be appreciated focally in some areas (Fig. 6). In some nodules, prominent hyalinization of the vessel walls was observed creating a superficial resemblance to glomus tumor (Fig. 7). There was no evidence of necrosis or mitotic figures. The surrounding lung parenchyma showed congestion with mild subpleural fibrosis and occasional accumulation of hemosiderin-laden histiocytes within alveolar lumens. There was no evidence of interstitial fibrosis, inflammation, dysplastic changes of bronchial or alveolar epithelium, organisms, or other pathologic process that would account for the reticulonodular densities observed radiographically. No asbestos bodies could be identified on routine microscopy, and there was no evidence of lymphangitis carcinomatosa. Histologic examination of the 1.5 cm nodule of the right middle lobe in patient no. 2 showed metastatic leiomyosarcoma histologically similar to that of the previously resected uterine specimen.

Immunohistochemical Findings

The cells comprising the nodules showed strong immunoreactivity with vimentin and EMA (Fig. 8). There was no immunoreactivity observed for cytokeratin AE1/AE3, CAM 5.2 low-molecular weight keratin, S-100

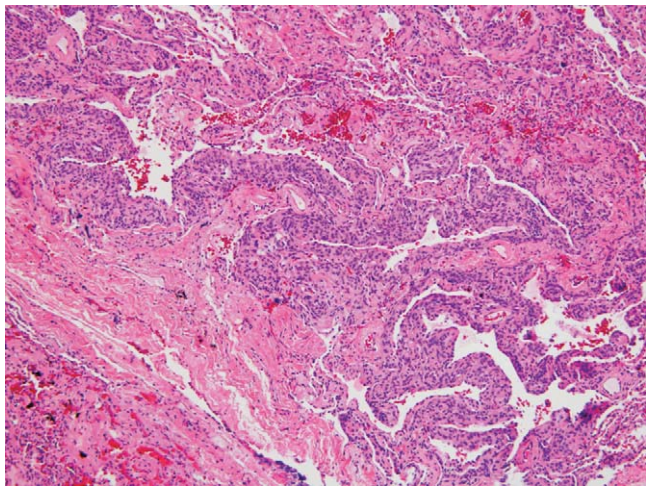

FIGURE 5. Scanning magnification of larger MPMN (case 3) showing elongated, irregular proliferation of meningothelial cells with perivenular distribution.

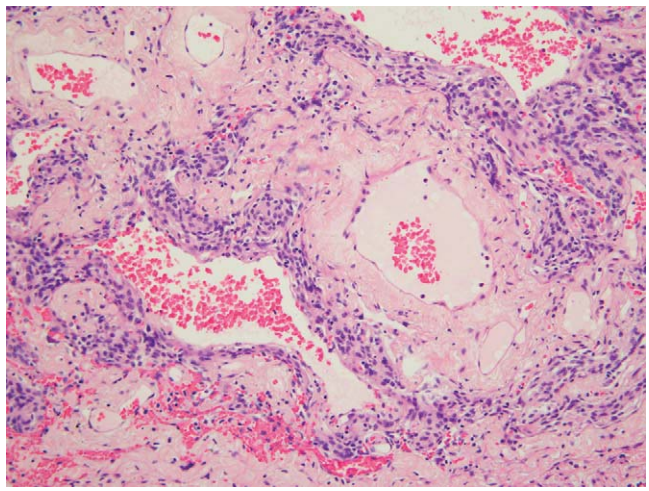

FIGURE 7. MPMN showing prominent perivascular hyalinization surrounded by a concentric layer of meningothelial cells simulating glomus tumor (case 4).

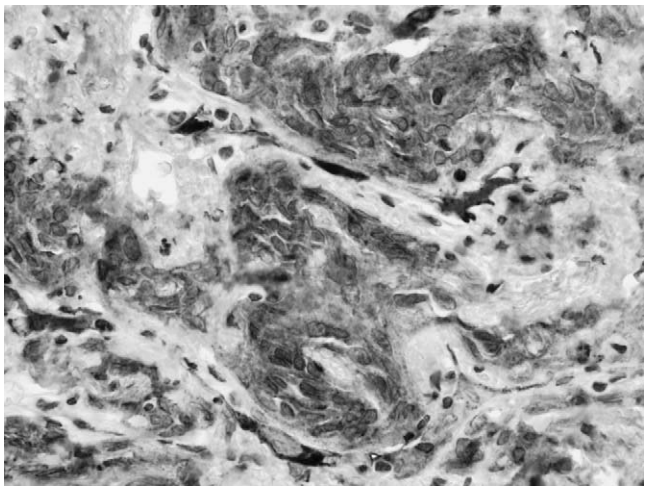

FIGURE 8. Immunohistochemical stain for EMA showing cytoplasmic positivity of the meningothelial cells (case 1).

protein, muscle specific actin (HHF-35), smooth muscle actin, chromogranin, synaptophysin, and CD34.

Ultrastructural Findings

Electron microscopic examination of the nodules in case no. 2 showed cells with complex interdigitating cell processes that were joined by frequent desmosomes (Figs. 9, 10). No basement membrane material could be identified on the cell membranes. The cytoplasm contained abundant intermediate filaments. No dense-core neurosecretory granules, mucin or zymogen granules, microvilli, or other distinctive organelles could be identified.

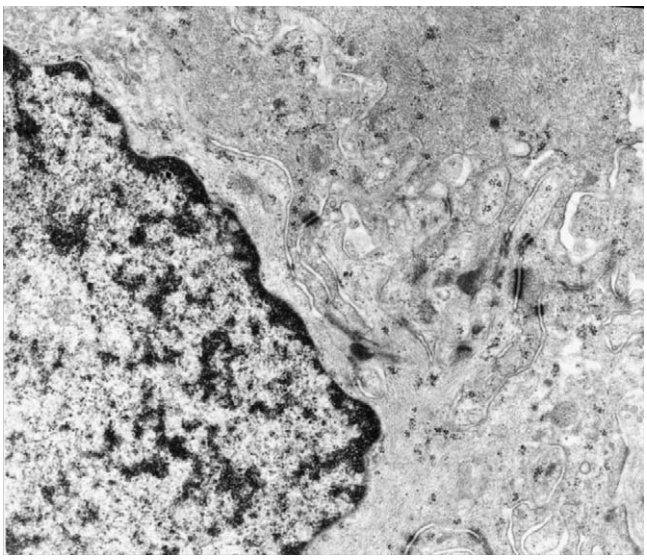

FIGURE 9. Ultrastructural appearance of meningothelial nodule (case 2). Notice complex cytoplasmic interdigitations joined by numerous well-developed desmosomes.

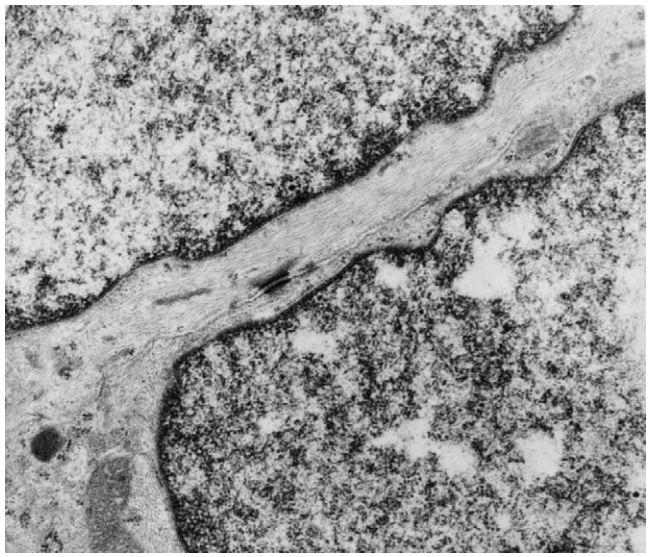

FIGURE 10. Higher magnification showing 2 meningothelial cells joined by a desmosome-type junction and containing abundant cytoplasmic intermediate filaments.

Clinical Follow-up

Three patients were lost to follow-up (cases 1, 3, and 4). The patient from case no. 2 developed multiple additional metastases of uterine leiomyosarcoma to other organs over the ensuing 8 years, including the spine, posterior mediastinum, and base of skull. At last follow-up, 92 months after her open lung biopsy, a surveillance CT scan showed stabilization of the lesions and no evidence of additional growth or metastatic disease to the lungs. The patient has been lost to follow-up since. The patient in case no. 5 with a clinical history of multiple malignancies was placed on surveillance with periodic CT scans and, 1 year before admission, was found to have scattered ground-glass opacities in both lungs in addition to small liver and renal cysts. The lung lesions were described as nonspecific but had started to increase in number in recent months and the patient slowly began to develop respiratory symptoms, for which she underwent wedge lung biopsies. The latter patient is a recent case and no additional follow-up is available.

DISCUSSION

MPMN were first identified by Korn et al in 1960[8]; on the basis of their morphologic features and the close relationship with blood vessels they were initially interpreted as chemoreceptors and designated as ''minute pulmonary tumors resembling chemodectomas.'' Subsequent ultrastructural and immunohistochemical studies demonstrated that they shared features with meningothelial cells and the term ''minute pulmonary meningothelial-like nodules'' was proposed by Gaffey et al in 1988.[5] In their extensive immunohistochemical analysis, these

authors demonstrated strong immunoreactivity of the lesions for vimentin and EMA, 2 markers that are closely associated with cranial and extracranial meningiomas, and no immunoreactivity with antibodies directed against cytokeratins, S-100 protein, neuron-specific enolase, and actin. In the authors' opinion the immunohistochemical findings supported the meningothelial origin of these structures. Most subsequent studies employing immunohistochemical analysis of meningothelial-like nodules have shown similar results.[6,12,18,22] Ultrastructural studies of these lesions have also supported their meningothelial nature by demonstrating cells with complex cytoplasmic interdigitations that were joined by frequent desmosomal junctions.[4,5,9,22] The majority of current studies thus clearly demonstrate histologic, immunohistochemical, and ultrastructural features indistinguishable from those of pia-arachnoid or meningothelial cells in these lesions.

The exact origin and nature of MPMN is still controversial. Demonstration of these lesions in patients with pulmonary thromboemboli led to the initial suggestion that they were related to ischemia secondary to vascular occlusion.[6,18] An immunohistochemical and clonal analysis of these lesions by Niho et al[12] showed monoclonal expansion in 7/11 lesions by the X-chromosome-linked human androgen receptor gene assay (HUMARA). The authors concluded that since not all lesions showed clonal expansion, they most likely represented a reactive proliferation rather than a clonal neoplastic process. More recently, Ionescu et al,[7] using mutational analysis to compare minute pulmonary meningothelial nodules with intracranial meningiomas found loss of heterozygozity alterations at different chromosomal loci between the 2 conditions, thereby concluding that the 2 processes were unrelated and that the former represents a reactive condition. The role of MPMN as a possible neoplastic precursor to meningioma in the lung has also been questioned by other authors who have commented on the fact that these lesions are hardly ever identified in the vicinity of pulmonary meningiomas.[2,5,11] In fact, review of the literature shows only one case reporting the association of pulmonary meningioma with meningothelial-like nodules.[19]

Fewer than 200 cases of MPMN have been reported in the English literature. Approximately 65% of the cases reported have been identified at autopsy and 35% from surgically resected specimens. The lesions are more frequent in the sixth decade of life and show a marked female predilection.[5] The clinical conditions that are most commonly associated with meningothelial nodules include chronic ischemic heart disease, pulmonary thromboemboli, and various malignancies. Pulmonary meningothelial-like nodules are usually single and found incidentally during the course of histologic examination of lungs resected for other conditions. However, the lesions can be multiple; approximately 40% of the reported cases have been multiple. In the original report by Korn and colleagues,[8] one of the patients presented with multiple lesions involving all lobes. In the majority of instances, however, multiple lesions are mostly localized rather than diffuse and distributed bilaterally throughout the lung parenchyma.

Zak and Chabes[24] in 1963 published a study of 3 patients who at autopsy presented with multiple lung lesions for which they proposed the designation of "pulmonary chemodectomatosis." The lesions depicted in their illustrations are in-keeping with minute meningothelial-like nodules and, in fact, the authors make reference to Korn et al's[8] study to indicate their belief that they corresponded to the same lesions. Unfortunately, no details regarding the gross morphologic or radiographic findings in those patients or the number and distribution of the lesions is provided in the manuscript, except for a mention in their table that their third patient showed 3 lesions.[24] In a more recent study of MPMN by Ionescu et al,[7] the authors reported 4 out of 35 patients with multiple lesions in which a similar presentation to our cases was described, except for the fact that none of the patients were symptomatic. The main reason for lung surgery in those patients was carcinoid tumor in 2, hypersensitivity pneumonitis in 1 and metastatic carcinoma in 1. The patients were said to show bilateral lesions measuring < 1 cm on CT scans. The authors proposed the designation of "MPMN-omatosis syndrome" for such cases. Although a syndromic connotation was suggested, no consistent or specific clinical associations were recognized in the study in those patients. The authors, however, found that the patients with multiple lesions showed a greater genetic instability with multiple loss of heterozygozity per nodule than single MPMN, suggesting that when the lesions are multiple and diffuse, they might represent a transitional stage between a reactive and a neoplastic process.[7]

There is very little in the radiologic literature regarding the imaging findings in MPMN. A case study from Japan reported the findings on high-resolution CT scan and routine contrast-enhanced chest CT in a 55-year-old nonsmoking woman who was being staged for suspected lung cancer. The patient had a 2 cm nodule in her right upper lobe and also showed multiple ground-glass opacities 1 to 3 mm in diameter randomly distributed in the peripheral zones of both lungs, which upon histologic examination corresponded to MPMN.[10] A report of a case studied by thin-section CT scans in a 64-year-old woman showed numerous bilateral micronodules < 3 mm in diameter with a random distribution in the upper lobes.[17] A 1.2 cm noncalcified nodule was also identified on chest x-ray, which corresponded to a moderately-differentiated adenocarcinoma; histologic examination of the micronodules was consistent with MPMN. In the present study, all of our patients were evaluated radiologically. The findings were generally those of an interstitial pneumonia pattern, which often overlaps with fine linear, reticular, and mixed reticulonodular patterns. The clinicopathologic entities that would correspond to the above mentioned radiologic patterns include idiopathic interstitial pneumonia, bronchiolitis obliterans, silicosis, coal workers' pneumoconiosis, miliary tuberculosis, Langerhans cell

histiocytosis, and a lymphangitic pattern of metastatic cancer. Two of our patients underwent open biopsy for the evaluation of suspected idiopathic interstitial pneumonia based on the clinical symptoms and radiologic findings. The other 3 patients underwent tissue diagnosis procedures for the suspicion of disseminated metastatic disease. Although 3 patients had a history of cancer, only in 1 were the lesions discovered during routine surveillance studies; the rest were found incidentally on chest x-rays or CT scans performed for the evaluation of respiratory symptoms.

Pulmonary meningothelial-like nodules must be histologically distinguished from pulmonary tumorlets.[3] Pulmonary "tumorlets" represents collections of neurosecretory cells adjacent to terminal bronchioles, which on scanning magnification can be confused with meningothelial nodules. Cytologically the cells of tumorlets, however, display higher nuclear-cytoplasmic ratios, have more stippled chromatin pattern, and are more elongated, rather than having an epithelioid appearance. Immunohistochemically tumorlets show weak cytoplasmic reactivity for cytokeratin and also are immunoreactive with neuroendocrine markers such as chromogranin, synaptophysin, and neuron-specific enolase, allowing for accurate distinction from meningothelial nodules.[3]

Rare cases of multinodular miliary metastatic spread of true chemodectomas to the lung have been described in the literature. The case reported by Tu and Bottomley[23] was a patient with a left carotid body tumor in whom multiple lesions in the lung < 2 mm in diameter were found. Although the lesions closely resembled histologically MPMN, more obvious pleomorphism and large round cells were identified. A case reported by Pinsker et al[14] in a 20-year-old woman with a prior history of carotid body tumor also showed multiple minute bilateral lung nodules that were histologically consistent with disseminated carotid body tumors. A case of multiple bilateral pulmonary chemodectomas in a 15–year-old girl without any prior history of carotid body tumor or other extrapulmonary primary lesion was reported by Chow et al.[1] The lesions in this patient varied in size from minute, miliary nodules to coarse nodules several centimeters in diameter. Immunohistochemical studies demonstrated positivity of the tumor cells for chromogranin and synaptophysin, confirming their neuroendocrine nature. MPMN can be readily distinguished from such rare cases of miliary spread of chemodectoma by their lack of reactivity for neuroendocrine markers and positive immunohistochemical reaction with EMA and vimentin.

Another condition that needs to be distinguished from diffuse meningothelial nodules is metastatic tumors, particularly carcinoma with prominent lymphangitic spread.[20,21] The absence of marked nuclear atypia, mitotic activity, intraluminal plugging of lymphatics by tumor cells, and negative cytokeratin stains will help distinguish meningothelial nodules from pulmonary metastases with lymphangitic spread.[21]

The cases reported herein differ from previously described cases because of their widespread bilateral distribution, which was radiographically suggestive of interstitial lung disease or miliary metastatic spread of internal malignancy, and their association with clinical symptoms of restrictive lung disease. A somewhat related phenomenon has been also described involving the leptomeninges and cerebral cortex, designated as meningioangiomatosis.[15] This condition is regarded as a hamartomatous proliferation of capillary-sized vessels, meningothelial cells and fibroblasts that may be single or diffuse, and may be associated with neurofibromatosis type 2.[13,16] We believe the present cases may represent the pulmonary counterpart of the latter condition. Because of their diffuse and multifocal distribution, the process is best termed "meningotheliomatosis." This rare condition needs to be considered in the differential diagnosis of patients with unexplained radiographic evidence of diffuse bilateral interstitial nodular lung infiltrates.

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