The Korean Journal of Pathology 2011; 45(S1): S32-35
DOI: 10.4132/KoreanJPathol.2011.45.S1.S32

Diffuse Pulmonary Meningotheliomatosis – A Case Report –

Jungsuk An · Heejung Park
Joungho Han · Tae Sung Kim[1]
Yong Soo Choi[2] · Moon Seok Choi[3]
Sang-Won Um[3]

Departments of Pathology, [1]Radiology, [2]Thoracic Surgery, and [3]Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Received: March 4, 2010
Accepted: May 20, 2010

Corresponding Author
Joungho Han, M.D.
Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-2800
Fax: +82-2-3410-0025
E-mail: hanjho@skku.edu

*Current address of Jungsuk An is Department of Pathology, Gachon University Gil Hospital, Incheon, Korea. Current address of Heejung Park is Department of Pathology, Yonsei University Severance Hospital, Seoul, Korea.

Diffuse pulmonary meningotheliomatosis (DPM) is an extremely rare condition. We herein report a unique case of DPM in a 54-year-old woman with a previous history of hepatocellular carcinoma. A chest computed tomography showed diffuse bilateral nodular infiltration, suggesting miliary spread of metastatic hepatocellular carcinoma. The patient underwent a video-assisted thoracoscopic surgery for diagnostic purposes. The cut surface of the lung specimen showed multiple dispersed small nodules, consisting of variably sized nests or whorls of bland epithelioid cells often along the walls of alveolar septa or in a perivascular network within the alveolar interstitium. The tumor cells showed immunoreactivity for epithelial membrane antigen, vimentin, and progesterone receptor. DPM should be included in the differential diagnosis of diffuse multiple small nodules or a reticular pattern in the radiologic studies.

Key Words: Lung; Meningioma; Lung neoplasms

Pulmonary meningothelial-like nodules (PMLNs) were first described by Korn *et al.*[1] in 1960 and were originally described as "minute pulmonary tumors resembling chemodectomas." PMLNs are composed of ovoid to spindle cells forming small perivenular, interstitial nests in a "Zellballen"-like pattern and are often detected incidentally on light microscopic studies of surgically resected lung specimens or at autopsy. Because of a belief that PMLN cells originate from a chemoreceptor whose function is oxygen monitoring and due to their close relationship to the small vessels, they were initially known as chemodectoma. But later, electron microscopic studies revealed that PMLN cells have no neuroendocrine granules but show ultrastructural features of meningothelial cells such as prominent desmosomes and interdigitating cytoplasmic processes.[2,3] Additionally, it was demonstrated that PMLN cells were immunoreactive for vimentin and epithelial membrane antigen (EMA). Based on these ultrastructural and immunohistochemical similarities with meningothelial cells, the term "minute pulmonary meningothelial-like nodules" was proposed by Gaffey *et al.*[4] in 1988 and was then widely accepted.

PMLNs usually present as an asymptomatic nodule in the majority of cases. Diffuse pulmonary involvement by PMLNs is extremely rare. Zak and Chabes[5] also reported cases of three patients with multiple lung lesions for which they proposed the designation of "pulmonary chemodectomatosis" at autopsy, but no details regarding the pathological and radiological findings in these patients are available. Recently, Suster and Moran[6] reported five cases of diffuse pulmonary meningotheliomatosis (DPM) with clinicopathologic features. Herein, we describe a case of DPM in a 54-year-old woman. To the best of our knowledge, this is the first reported case of DPM in Korea.

CASE REPORT

A 54-year-old woman was diagnosed with hepatocellular carcinoma 5 months ago, and she underwent transarterial chemoembolization for the tumor. After 4 months, follow-up abdominal computed tomography (CT) showed multiple small nodules in the subpleural areas of both lungs, which were not seen in the previous abdominal CT. A subsequent chest CT showed diffuse bilateral nodular infiltration with occasional cavitation, which was interpreted as multinodular miliary spread of metastatic hepatocellular carcinoma (Fig. 1). The patient underwent a video-assisted thoracoscopic surgery along the lower edge of the lower lobe of the right lung for diagnostic purposes. The cut surface of the lung specimen showed multiple scattered small (1 to 3 mm) gray nodules. Microscopically, the multiple nodules consisted of variably sized nests or whorls of bland epithelioid cells often along the walls of alveolar septa or in a perivascular network within the alveolar interstitium with edematous intervening or surrounding stroma (Fig. 2A, B). The PMLN cells were elongated or spindle-shaped, with oval nuclei, finely granular chromatin, and inconspicuous nucleoli. Cytoplasm was ab-

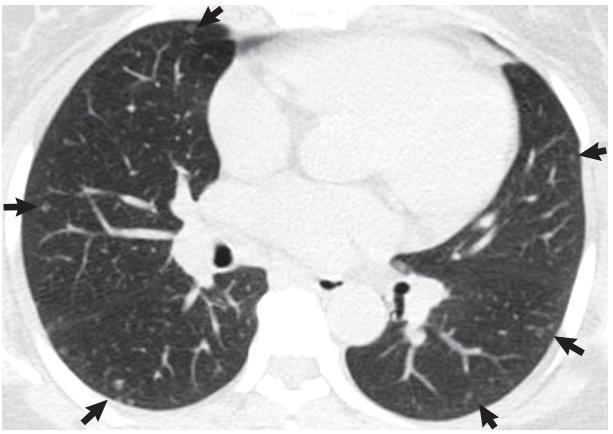

Fig. 1. Chest computed tomography shows bilateral multiple small nodules (arrows).

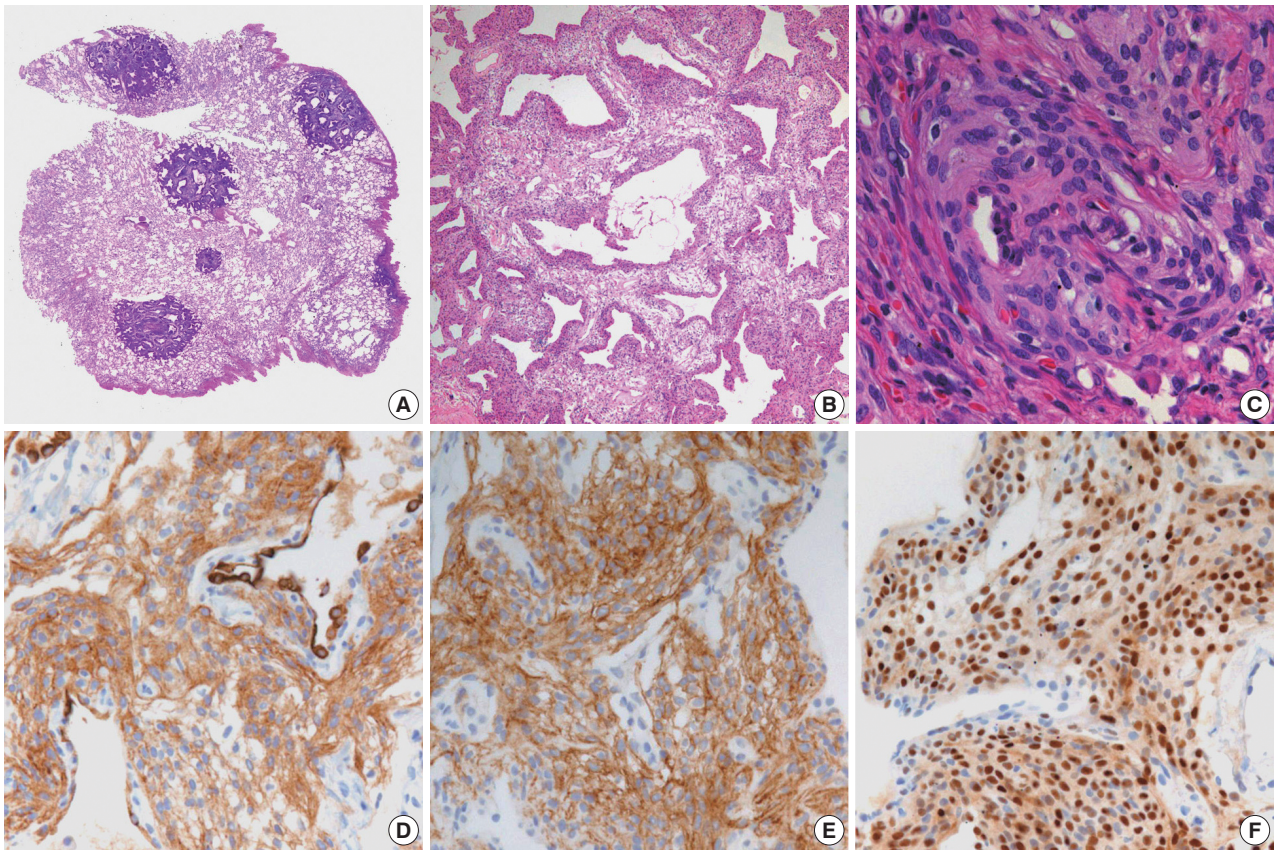

Fig. 2. Scanning magnification of lung biopsy specimen shows multiple nodular proliferation of meningothelial-like nodules, which are sharply delineated from the neighboring normal lung (A). The nodules are mainly distributed within the alveolar interstitium (B) and whorling of tumor cells is also found in some areas (C). The cells comprising the nodule show strong immunoreactivity for epithelial membrane antigen (D), vimentin (E), and progesterone receptor (F).

undant, granular, and eosinophilic, with indistinct cell borders (Fig. 2C). Mitotic figures were not seen. Immunohistochemically, PMLN cells showed a diffuse and intense immunoreactivity for vimentin, EMA and progesterone receptor (PR) (Fig. 2D-F).

DISCUSSION

PMLNs are small (100 μm to a few mm) asymptomatic nodules, often discovered as incidental findings on microscopic studies of either resected lung samples or at autopsy. Pathologic characteristics of PMLN suggested by Gaffey *et al.*[4] included 1) interstitial location, 2) organization of epithelioid cells in a nesting pattern, 3) lateral capillary displacement secondary to expansive growth within the alveolar septa, and 4) close association with pulmonary venules. Although PMLNs have been reported for more than four decades under several different nomenclatures, their exact origin and pathogenesis as well as their incidence and clinical significance are not still clear. Clinically, PMLNs have been found in patients ranging in age from 12 to 91 years, mostly in the seventh decade of life with a marked female predilection.[4,7,8]

Our immunohistochemical stain results were similar with those of previously published studies and support the meningothelial nature of PMLNs. From a point of view of the pathogenesis of PMLNs, several studies were concerned with the results of immunohistochemical staining for PR and its role in the pathogenesis. Since the time, Niho *et al.*[9] have demonstrated immunoreactivity for PR in half of the cases, subsequent studies have shown similar results in almost all the cases.[8,10] In 2002, Pelosi *et al.*[10] documented that PMLN cells were positive for PR immunohistochemically, reinforcing their close resemblance to arachnoid cells and suggesting a role for sex hormones in their pathogenesis.

In a recent large series of PMLN cases including surgical lung biopsy specimens from various unrelated conditions, the incidence of PMLNs in surgical lung biopsy specimens was 13.8%, considerably higher than the incidence of 0.07% to 4.9% reported in previous autopsy series.[8] The authors postulated that the difference in the incidence might be related to underlying lung disease present in all the lung biopsy specimens. They thereby concluded that chronic lung disease could contribute to the formation of PMLNs, perhaps via providing physical and chemical stimuli such as stretching or stiffening of the alveolar septa, or hypoxia, ischemia, parenchymal destruction, or some combination of these factors.

As mentioned, most PMLNs are usually solitary and found incidentally without related clinical manifestations during testing for other diseases. However, multiple lesions can be encountered and have occurred in up to 41% of all patients with PMLNs.[8] There have been several series of DPM (Table 1). Recently, Ionescu *et al.*[7] reported multiple PMLNs in four asymptomatic patients and proposed the term "minute pulmonary meningothelial-like nodule-omatasis syndrome" for such cases. If these lesions are numerous, functional impairment and radiographic abnormalities could develop in patients who have no other underlying lung disease.[6,8] More recently, Suster and Moran[6] reported cases of five patients presenting with symptoms of mild restrictive lung disease such as shortness of breath and impaired pulmonary function. Radiographically, multiple bilateral

Table 1. Literature review of the published cases

Reference (No. of cases)	Sex	Age (yr)	Radiologic finding	Reason for surgery or major non-pulmonary disease
Zak and Chabes[5] (n=3)	F	37	ND	Endocarditis
	F	53	ND	Thymoma
	F	64	ND	Ulcerative colitis
Ionescu *et al.*[7] (n=4)	F	ND	Multiple pulmonary nodules (more than 4)	Carcinoid
	F	ND	Multiple pulmonary nodules (more than 4)	Carcinoid
	F	ND	Multiple pulmonary nodules (more than 4)	Hypersensitivity pneumonia
	F	ND	Multiple pulmonary nodules (more than 4)	Metastatic carcinoma
Suster and Moran[6] (n=5)	F	75	Diffuse bilateral pulmonary reticulonodular infiltrates	Colon carcinoma
	F	54	Diffuse bilateral pulmonary reticulonodular infiltrates	Uterine leiomyosarcoma
	M	51	Diffuse bilateral pulmonary reticulonodular infiltrates	ND
	F	63	Diffuse bilateral pulmonary reticulonodular infiltrates	Coronary heart disease
	F	71	Diffuse bilateral pulmonary reticulonodular infiltrates	Thyroid, breast, and lung carinomas
Mukhopadhyay *et al.*[8] (n=1)	F	ND	Innumarable small pulmonary nodules	Uterine cancer
Our case (n=1)	F	54	Diffuse bilateral pulmonary nodular infiltrates	Hepatocellular carinoma

F, female; M, male; ND, not detected.

reticulonodular infiltrates were seen but open lung biopsies revealed multiple PMLNs in the absence of interstitial lung fibrosis and carcinomatosis. This condition has been termed as "diffuse pulmonary meningotheliomatosis" by the authors. In a molecular study, the small nodules in DPM have been previously demonstrated to show a greater genetic instability and a more frequent loss of heterozygosity than solitary PMLNs, suggesting that this condition may represent the transition between a reactive and a neoplastic proliferation.[7]

In conclusion, DPM should be included in the differential diagnosis of diffuse multiple small nodules or a reticular pattern in the radiologic studies. Especially, this entity should be distinguished from metastatic carcinomas with prominent lymphatic spread in the lungs. To the best of our knowledge, this is the first case of DPM in Korea with a previous history of carcinoma of another organ. We believe that awareness and understanding of the pathogenesis of this entity is helpful for the diagnosis of diffuse multiple small nodules.

REFERENCES

1. Korn D, Bensch K, Liebow AA, Castleman B. Multiple minute pulmonary tumors resembling chemodectomas. Am J Pathol 1960; 37: 641-72.
2. Kuhn C 3rd, Askin FB. The fine structure of so-called minute pulmonary chemodectomas. Hum Pathol 1975; 6: 681-91.
3. Churg AM, Warnock ML. So-called "minute pulmonary chemodectoma": a tumor not related to paragangliomas. Cancer 1976; 37: 1759-69.
4. Gaffey MJ, Mills SE, Askin FB. Minute pulmonary meningothelial-like nodules: a clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 1988; 12: 167-75.
5. Zak FG, Chabes A. Pulmonary chemodectomatosis. JAMA 1963; 183: 887-9.
6. Suster S, Moran CA. Diffuse pulmonary meningotheliomatosis. Am J Surg Pathol 2007; 31: 624-31.
7. Ionescu DN, Sasatomi E, Aldeeb D, *et al.* Pulmonary meningothelial-like nodules: a genotypic comparison with meningiomas. Am J Surg Pathol 2004; 28: 207-14.
8. Mukhopadhyay S, El-Zammar OA, Katzenstein AL. Pulmonary meningothelial-like nodules: new insights into a common but poorly understood entity. Am J Surg Pathol 2009; 33: 487-95.
9. Niho S, Yokose T, Nishiwaki Y, Mukai K. Immunohistochemical and clonal analysis of minute pulmonary meningothelial-like nodules. Hum Pathol 1999; 30: 425-9.
10. Pelosi G, Maffini F, Decarli N, Viale G. Progesterone receptor immunoreactivity in minute meningothelioid nodules of the lung. Virchows Arch 2002; 440: 543-6.