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Original contribution

Minute pulmonary meningothelial-like nodules: clinicopathologic analysis of 121 patients

Eiki Mizutani MD[a,b], Koji Tsuta MD[a,*], Akiko M. Maeshima MD[a], Hisao Asamura MD[b], Yoshihiro Matsuno MD[a]

[a]*Clinical Laboratory Division, National Cancer Center Hospital, Tokyo 104-0045, Japan*
[b]*Thoracic Surgery Division, National Cancer Center Hospital, Tokyo 104-0045, Japan*

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Summary Minute pulmonary meningothelial-like nodules (MPMNs) are generally detected incidentally in resected lung specimens. With the development of diagnostic radiology, MPMNs have occasionally been detected on thin-section computed tomography. Their clinicopathologic background remains unclear because there have been no reports of a large series of patients with them. Among 1724 pulmonary resections during a 4 1/2 year period, 271 MPMNs were identified in 121 patients (7.0%) after pathologic examination. Minute pulmonary meningothelial-like nodules were seen more often in females than in males (10.7% versus 4.5%; odds ratio, 2.01; 95% confidence interval, 1.36-2.97; $P < .001$). Minute pulmonary meningothelial-like nodules were present in all lobes, and the frequency of incidence was not different between lobes. The incidence frequency of MPMNs was not different between age groups. Minute pulmonary meningothelial-like nodules were found more often in patients with malignant pulmonary tumors than in those with benign disease (7.3% versus 2.5%; $P = .044$). In particular, MPMNs were found more often in patients with lung adenocarcinoma than with other primary pulmonary malignant tumors (9.4% versus 4.5%; odds ratio, 2.33; 95% confidence interval, 1.35-4.02; $P < .01$). There was no significant difference in clinicopathologic factors between patients with single and multiple MPMNs, except for the size of each nodule.

1. Introduction

Minute pulmonary meningothelial-like nodules (MPMNs) consist of epithelioid cell nests or whorls in a "Zellballen"-like arrangement centered on small veins [1-3]. From their architecture, cytologic characteristics, and relationship with vessels, MPMNs were believed to have an oxygen-monitoring function, as a chemoreceptor, so Korn et al [3] reported these lesions as "pulmonary chemodectoma" in 1960.

Immunohistochemical studies and ultrastructural analyses of MPMNs have been reported [2,4-6]. Torikata and Mukai [7] described that immunostaining for myosin was positive in all MPMN cells, which suggested that they might originate from muscle cells. Pelosi et al [6] described that immunostaining for progesterone receptor was positive in all 6 patients with MPMN and that sex steroid hormones might have a role in controlling nodule growth. Although the histogenesis of MPMN remains

* Corresponding author.
E-mail address: ktsuta@ncc.go.jp (K. Tsuta).

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unclear, in ultrastructural analysis, MPMN cells exhibited no endocrine granules, were not associated with nerves, and closely resembled meningothelial cells [4,7,8]. Accordingly, a new term, *meningothelial-like nodule*, was proposed by Gaffey et al [4] in 1988 and has been accepted as a minute meningothelioid nodule by the third edition of the World Health Organization [9].

In mutational analysis, Inoescu et al [2] reported that isolated MPMN did not exhibit mutational damage and that MPMN syndrome might represent the transition between reactive and neoplastic proliferation. Niho et al [5] analyzed the clonality of 11 MPMNs in 2 female patients based on an X chromosome-linked polymorphic marker and reported that these MPMNs were nonclonal cell aggregation, implying a reactive rather than neoplastic process based on loss of the pattern showing monoclonality.

The clinicopathologic significance of MPMN remains unclear because only a small number of studies have been reported. Most MPMNs described to date have been very small (100 μm to 3 mm) and were identified incidentally by light microscopic examination either of resected lungs or at autopsy. The reported incidence of these nodules varies among the literature and occurs in 0.3% to 9.5% of cases at autopsy or surgical resection [2,5,10,11]. When examining the incidence of MPMNs by sex, Dail et al [12] described that most patients were female (84%). In some studies, MPMNs were observed 3 times more often in the right lung than in the left [10]. In 1963, Zak and Chabes [13] described the presence of multiple MPMNs in 6 patients and described this condition as chemodectomatosis; therefore, diffuse pulmonary meningotheliomatosis was reported in 2007 [14]. It is not yet clear under what conditions MPMNs frequently occur or whether there is any difference for patients with single or multiple MPMNs.

Recently, with increased use of high-resolution computer tomography, MPMNs have occasionally been detected before surgery. An awareness of the clinicopathologic association of MPMNs with primary bronchogenic carcinoma presenting as ground glass opacity is critically important to determine the appropriate clinical management of patients with detected ground glass opacity [15,16]. In the present study, we analyzed the clinicopathologic and histologic characteristics of MPMN identified in surgically resected lungs.

2. Materials and methods

During the 4 1/2 year period from January 2001 to June 2005, 2057 pulmonary resections were performed at the National Cancer Center Hospital, Tokyo, Japan. Patients with malignant pleural mesothelioma or with preceding chemoradiation therapy were excluded from this study. We examined 1724 patients with MPMNs whose main diagnoses were 976 lung adenocarcinoma, 374 other primary pulmonary malignant tumor, 245 metastatic pulmonary tumor, 122 benign disease, and 7 atypical adenomatous hyperplasia. Resected lung specimens were carefully fixed in the inflated state by transbronchial infusion of 10% formalin and were macroscopically examined extensively by slicing at 5-mm to 10-mm intervals. For a standard lobectomy specimen, 10 to 15 blocks were cut and all examined histologically. They usually consisted of 3 to 4 blocks, including tumor tissue, 1 to 2 resected surgical margins, 1 to 2 peribronchial lymph nodes, and 5 to 10 peripheral lung tissues with or without macroscopic abnormality. All tissue blocks were embedded in paraffin, and 5-μm sections were cut and stained with hematoxylin and eosin.

Clinicopathologic information was obtained by reviewing the medical chart in detail with regard to age, sex, resected lobe, and main pathologic diagnosis. We examined the number, sizes, and location of MPMNs. The number of slides examined per case was recorded to further clarify the correlation with the number of MPMNs.

To compare the frequencies among different groups, χ^2 test, Mann-Whitney U test, and logistic regression were performed with the SPSS 12.0 statistical software program

Table 1 Characteristics of patients with and without MPMN

Characteristic	Patients with MPMN	Patients without MPMN	P [a]
No. of patients	121	1603	
Age (y)			
Mean	62.3	62.0	.51
Range	25-81	9-89	
Sex			
Female	75	624	<.01
Male	46	979	
Resected lobe			
Right	76	1004	.97
Left	45	599	
Main pulmonary disease			
Primary pulmonary malignant tumor	121	1242	[b]<.01
Adenocarcinoma	92	884	[c]<.01
Nonadenocarcinoma	16	358	
Squamous cell carcinoma	13	239	
Other primary pulmonary malignant tumor	3	119	
Nonprimary pulmonary tumor	13	361	
Metastatic tumor	8	237	
Benign disease	3	119	
AAH	2	5	

[a] χ^2 Test and Mann-Whitney U test.
[b] Primary pulmonary malignant tumor versus nonprimary pulmonary malignant tumor.
[c] Adenocarcinoma versus nonadenocarcinoma.

(SPSS, Chicago, IL). All *P* values were reported as 2-sided results, and the significance level was set at <.05.

3. Results

3.1. Clinicopathologic features of the patients

We investigated the relationship between MPMN and the clinicopathologic factors of the patients (Table 1). In this study, 121 patients with MPMNs were identified of 1724 patients undergoing lung resections (7.0%). In univariate analysis, the factors of female sex and primary lung adenocarcinoma were significantly associated with MPMN. Minute pulmonary meningothelial-like nodules were seen significantly more often in females than in males (10.7% versus 4.5%; $P < .001$).

To determine the influence of aging on MPMN, we examined the age distribution of the patients. The mean age with and without MPMNs was 62.3 years (range, 25-81 years) and 62.0 years (range, 9-89 years), respectively. The frequency of MPMNs was not different between age groups ($P = .51$).

Minute pulmonary meningothelial-like nodules were present in all lobes (right upper lobe, 41/560; right middle lobe, 2/140; right lower lobe, 33/380; left upper lobe, 26/385; left lower lobe, 19/259). Although MPMNs were found slightly less often in the right middle lobes, the frequency was not statistically different between lobes.

Minute pulmonary meningothelial-like nodules were observed in 7.3% of patients with pulmonary malignant tumors (116/1595 patients), whereas benign diseases exhibited MPMNs in 2.5% (3/122 patients). Minute pulmonary meningothelial-like nodules were found significantly more often in patients with malignant pulmonary tumors than in those with benign diseases ($P = .044$). In particular, MPMNs were seen in 9.4% of patients with lung adenocarcinoma (92/976 patients), compared with 3.9% in patients with other diseases (29/748 patients). Minute pulmonary meningothelial-like nodules were found significantly more often in patients with lung adenocarcinoma than other diseases ($P < .001$).

Atypical adenomatous hyperplasia (AAH), which is a putative precursor lesion for adenocarcinoma, was the primary disease in 7 patients and an accessory disease in 201 patients. Minute pulmonary meningothelial-like nodules were observed in 12.0% of patients with AAH (25/208 cases). Without AAH, MPMNs occurred in 6.3% (96/1516 cases). Minute pulmonary meningothelial-like nodules were observed significantly more often with AAH than without AAH ($P < .01$). Minute pulmonary meningothelial-like nodules were observed significantly more often in cases of lung adenocarcinoma or AAH than without (99/928; $P < .01$).

Some patients had MPMN in areas showing lepidic growth of the adenocarcinoma (Fig. 1). Multivariate analysis with "age," "sex," and "main pulmonary disease;" "female sex" (odds ratio, 2.01; 95% confidence interval, 1.36-2.97; $P < .001$); and "adenocarcinoma" (odds ratio, 2.33; 95% confidence interval, 1.41-3.39; $P < .01$) exhibited significant relationships with MPMNs (Table 2).

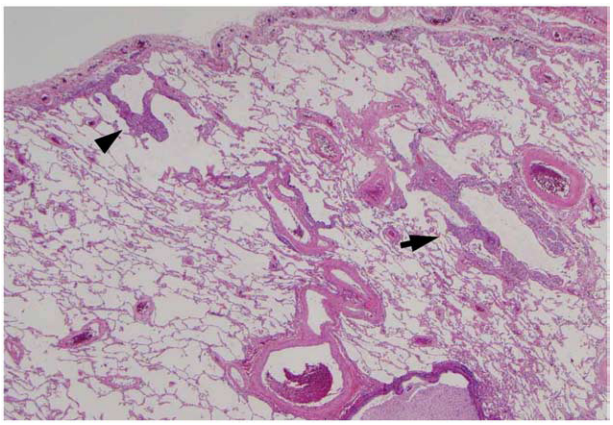

Fig. 1 Photomicrograph of multiple MPMNs, in which one MPMN was located around a capillary vessel (arrow) and the other was located in the subpleural space (arrowhead) (hematoxylin and eosin stain, original magnification ×12.5).

Table 2 Multivariate analysis of the presence of MPMN

Characteristic	Patients with MPMN	Patients without MPMN	Odds ratio (95% confidence interval)	*P*
No. of patients	121	1603		
Age (y)				
>65	63	775	1.06 (0.73-1.54)	.78
<65	58	828		
Sex				
Female	75	624	2.01 (1.36-2.97)	<.01
Male	46	979		
Main pulmonary disease				
Adenocarcinoma	92	884	2.19 (1.41-3.39)	<.01
Nonadenocarcinoma	29	719		

Table 3 Comparison between patients with single and multiple MPMNs

	Patients with single MPMN (n = 76)	Patients with multiple MPMNs (n = 45)	*P* [a]
No. of nodules	76	195 (2-25)	
Age	62.4 ± 10.4	62.5 ± 7.3	.84
Sex	Male, 31; female, 45	Male, 15; female, 30	.67
Location	CV, 64; SP, 12	CV, 161; SP, 34	.75
Size (mm)	0.86 ± 0.51 (0.2-2.3)	1.06 ± 0.65 (0.1-3.2)	.02
No. of slides	10.9 ± 6.4 (4-46)	12.1 ± 6.3 (4-38)	.16

Abbreviations: CV, capillary vessel, SP, subpleura.
[a] χ^2 Test and Mann-Whitney *U* test.

3.2. Comparison between patients with single MPMN and multiple MPMNs

The comparison between patients with single MPMN and multiple MPMNs is shown in Table 3. The average of number of nodules was 4.33 in patients with multiple MPMNs. The most frequent number of nodules was 2 (18 patients) and the maximum was 25. The number of slides for patients with single and multiple MPMNs were 10.9 ± 6.4 and 12.1 ± 6.3, respectively (P = .16), and there was no significant difference between the 2 patient groups. Minute pulmonary meningothelial-like nodules were located around capillary vessels in about 80% of cases, with the rest located in the subpleural area in both patients with single and multiple MPMNs. In Fig. 2, MPMNs were present both around capillary vessels and in the subpleura. No significant differences were observed for the age and location of MPMNs. Each MPMN was significantly larger in multiple MPMN cases than in single MPMN cases (1.06 ± 0.65 mm versus 0.86 ± 0.51 mm; P = .02).

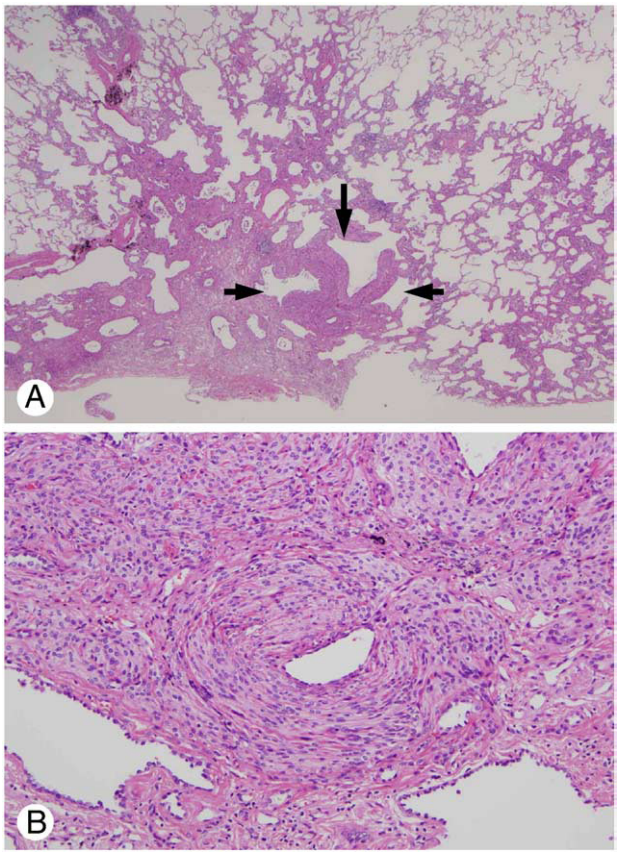

Fig. 2 A, Photomicrograph of an MPMN within a bronchioloalveolar carcinoma (arrow) (hematoxylin and eosin stain, original magnification ×12.5). B, Photomicrograph showing the characteristic "Zellballen" in an MPMN (hematoxylin and eosin stain, original magnification ×100).

4. Discussion

In the present study, we examined 1724 pulmonary resections and found 271 lesions of MPMNs in 121 patients (7.0%). The frequency of MPMNs in autopsy-based analyses ranged from 0.3% to 0.5%, whereas the frequency in operation-based analysis ranged from 1.1% to 9.5% [3,5,6,10,11]. One reason the frequency of MPMNs in operations was higher than in autopsies might be the different main diseases of study groups. We found MPMNs more often in patients with malignant pulmonary tumors than benign diseases. In particular, MPMNs were observed more often in patients with primary lung adenocarcinoma than in those with other diseases (P < .001). Niho et al [5] stated that MPMNs were seen in 10% of patients with lung adenocarcinoma. On the other hand, only a few patients had pulmonary malignancies in autopsy-based analysis [3,10,11]. This was probably because patients with pulmonary adenocarcinoma had a different frequency of MPMNs. As another reason, the difference in the number of slides might have influenced the frequency of MPMNs. The number of slides could not differentiate patients with single MPMN and multiple MPMNs in our study, but we examined about 10 slides in most patients with MPMNs; however, Spain [11] analyzed only 3 to 6 random sections of formalin-fixed lung tissue in autopsies, and it was clearly less than in patients undergoing surgical resection.

Minute pulmonary meningothelial-like nodules were observed more often in females than in males in our study (P < .001). Conventional reports have also suggested that MPMNs were frequently detected in females [3,5,6,10,11]. One possible reason that MPMNs are observed more frequently in females and with pulmonary adenocarcinoma may be the correlation between MPMNs and progesterone receptors. In 1999, Niho et al [5] reported that about half of MPMNs exhibited immunoreactivity for the progesterone receptor. In 2002, Pelosi et al [6] also reported that MPMNs in 6 patients exhibited immunoreactivity for the progesterone receptor using highly sensitive detection kits based on dextran polymer technology. Recently, Ishibashi et al [17] reported that progesterone receptor positivity occurred in 56.3% of patients with pulmonary adenocarcinoma and 61.9% of females with nonsmall cell lung cancer. These reports suggest that progesterone stimulation may provide a cellular growth advantage both to pulmonary adenocarcinoma and to MPMNs, which may in turn result in the frequent coincidence of the 2 conditions in female patients [18].

Zak and Chabes [13] originally described MPMNs as multiple nodules and termed this condition *chemodectomatosis* (minute pulmonary meningothelial-like nodulomatosis). In our examination, multiple MPMNs occurred in 37.2% of all patients with MPMN. There were no significant differences between patients with single and multiple MPMNs in the number of slides (tissue blocks) examined, implying that the difference between these 2 groups of patients cannot be attributed to the extent of investigation.

However, no significant differences were found in the clinicopathologic factors examined in the present study, except for the size of each nodule. Patients with single MPMN might have residual MPMNs in their lungs. We have no experience of cases of diffuse pulmonary meningotheliomatosis, and the condition of the disease is very interesting because it may be connected with the origin of MPMN [14].

In conclusion, MPMNs were identified in 7.0% of patients after pathologic examination. Minute pulmonary meningothelial-like nodules were seen more often in females than males. Minute pulmonary meningothelial-like nodules were present in all lobes and the incidence was not different between lobes or between age groups. Minute pulmonary meningothelial-like nodules were found more often in patients with lung adenocarcinoma than those with other primary pulmonary malignant tumors. There was no significant difference in clinicopathologic factors between patients with single and multiple MPMNs, except for the size of each nodule.

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