Constant expression of somatostatin receptor 2a in minute pulmonary meningothelial-like nodules

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Received 18 April 2019
Revised 24 May 2019
Accepted 29 May 2019
Published Online First 17 June 2019

To cite: Tao LL, Chen Y, Huang Q, *et al*. *J Clin Pathol* 2019;**72**:525–528.

ABSTRACT

Aims Although ultrastructural studies showed that minute pulmonary meningothelial-like nodules (MPMNs) cells closely resembled meningothelial cells, their immunophenotype has not been well characterised, partly due to their rarity.

Methods Somatostatin receptor 2a (SSTR2a) and other markers of meningioma, including epithelial membrane antigen (EMA), progesterone receptor (PR) and S100, were analysed retrospectively in 19 MPMN cases from two institutions in China.

Results The median age of patients with MPMNs was 62.5 years (32–73 years), with a male-to-female ratio of 1:8.5. Most (15/19) patients with MPMNs had coexisting diseases, including adenocarcinomas (12 cases), bronchiectasis (1 case) and tuberculosis (2 cases). Just over half of the cases (10/19) were multifocal lesions (2–5 lesions). An additional 53 cases with 123 lesions from the literature were reviewed with reported immunophenotype information. In total, 162 lesions were included in the analysis. The size of nodules was 1–4 mm. All MPMN lesions (39/39) in the 19 cases showed strong and diffuse cytoplasmic expression of SSTR2a. The expression rate of SSTR2a was higher than that of conventional markers of meningioma, including EMA (86/138), PR (32/68) and S100 (1/125).

Conclusions Our observations expand the spectrum of recognised SSTR2a-positive lesions and once again demonstrated that MPMNs show immunohistochemical characteristics similar to meningothelial cells.

INTRODUCTION

Minute pulmonary meningothelial-like nodules (MPMNs) refers to 0.1–3 mm nodules that often represent incidental microscopic findings in lung specimens. They were first reported by Korn *et al*[1] in 1960. Those researchers described a new pulmonary tumour consisting of nests (Zellballen) of cells located in the interstitial tissue near small veins. Largely on the basis of cytology and the characteristic arrangement of the cells, they named these lesions 'minute pulmonary tumors resembling chemodectomas'. The tumour was initially proposed to be a pulmonary microparaganglioma.[2 3] However, further investigation failed to reveal cytoplasmic granules in the lesions as would be expected in a paraganglioma.[4] Additional reports confirmed that these lesions were inconsistent with the morphology of previously reported paragangliomas but that there was a resemblance at the light and electron microscopic levels to meningeal arachnoid cells and the cells of meningiomas.[5 6] In 1988, 'minute pulmonary meningothelial-like nodules' was proposed by Gaffey *et al*.[7 8]

Due to its rarity, only a few studies on the immunophenotype of MPMNs have been reported. These demonstrated similarities with meningothelial cells, that is, reactivity with vimentin and epithelial membrane antigen (EMA).[7] Recently, somatostatin receptor 2a (SSTR2a) was reported as an important marker of meningioma.[9 10] However, the expression of SSTR2a in MPMNs remains unknown with only one 'letter to the editor' showing that SSTR2a was expressed in five MPMN cases.[11] In an attempt to expand the current knowledge of the clinicopathological features and immunophenotype of MPMNs, focusing on the expression of SSTR2, we retrospectively analysed 19 cases of MPMNs from two institutions in China and an additional 53 cases from the literature.

MATERIALS AND METHODS

Case selection

A total of 19 MPMN cases were obtained retrospectively from the files of the Department of Pathology, Peking University, Shenzhen Hospital, Shenzhen, China, and Sun Yat-sen University Cancer Center, Guangzhou, China. These cases were among 8019 cases of pulmonary lobectomy or segmental resection from January 2015 to January 2018. Diagnostic criteria for MPMNs were established according to the report of Gaffey *et al*.[7]

Clinical data collected for analysis included age, gender, clinical history, initial presentation, imaging data, single or multiple lesions and tumour size. All patients provided written informed consent for the collection and publication of their medical information during the first visit to the hospital.

H&E and immunohistochemical staining

Specimens of these 19 cases were formalin fixed and paraffin embedded and then sectioned at 4.0 mm thickness. The sections were stained with H&E or used for immunohistochemical examination. Immunohistochemical staining was performed using a Leica Autostainer (BOND-MAX, M495644) with a Bond Polymer Refine Detection Kit (Leica Biosystems Newcastle, Newcastle upon Tyne, UK). Appropriate negative and positive controls were generated with satisfactory staining. Immunohistochemical findings were rated as positive when at least 5% of the tumour cells were unequivocally stained in the nucleus for the progesterone receptor (PR) (1E2, Roche Diagnostics, Tucson, Arizona, USA), in the cytoplasm for EMA (Linked-Biotech,

Table 1 Clinicopathological characteristics of 19 cases of MPMNs in present study

Case #	Age	Gender	Major pulmonary disease	Number of lesions	Size (mm)	Immunophenotype						
						SSTR2a	EMA	PR	S-100	CK	Syn	CgA
1	54	M	AIS	1	1.5	+	+	+	–	–	–	–
2	32	F	Bronchiectasis	1	3	+	+	–	–	–	–	–
3	73	F	AIS with microinvasive	3	1–3	+	–	–	–	–	–	–
4	60	F	None	1	2	+	+	–	–	–	–	–
5	63	F	None	2	2–4	+	+	+	–	–	–	–
6	63	F	None	1	4	+	+	–	–	–	–	–
7	66	F	AC	1	1	+	+	–	–	–	–	–
8	62	F	AC	1	1	+	+	–	–	–	–	–
9	40	F	AIS with microinvasive	3	1–3	+	+	–	–	–	–	–
10	52	F	TB	1	1	+	+	+	–	–	–	–
11	64	F	TB	1	1.5	+	+	–	–	–	–	–
12	64	F	AC	1	2	+	+	–	–	–	–	–
13	72	F	AIS with microinvasive	5	1–2	+	+	–	–	–	–	–
14	63	F	AIS with microinvasive	2	2	+	+	–	–	–	–	–
15	63	F	AIS with microinvasive	3	1–2	+	–	–	–	–	–	–
16	63	M	None	2	1–2	+	+	–	–	–	–	–
17	56	F	AIS	3	1.5	+	+	–	–	–	–	–
18	53	F	AC	3	1–2	+	+	+	–	–	–	–
19	46	F	AC	4	1–3	+	–	+	–	–	–	–

AAH, atypical adenomatous hyperplasia; AC, adenocarcinoma; AIS, adenocarcinoma in situ; CgA, chromogranin A; EMA, epithelial membrane antigen; F, female; M, male;MPMNs, minute pulmonary meningothelial-like nodules; PR, progesterone receptor; SSTR2a, somatostatin receptor 2a; Syn, synaptophysin; TB, tuberculosis.

Guangzhou, China), SSTR2A (ZSGB Biotech, Beijing, China), synaptophysin (Linked-Biotech) and chromogranin A (CgA) (Maixin Biotech,Fuzhou,China), and in the cytoplasm and/or nucleus for S100 (Linked-Biotech).

Literature review

We performed an extensive literature search for reported cases of MPMNs (http://www.ncbi.nlm.nih.gov/pubmed/) using different combinations of key words in the title/abstract field, including 'minute pulmonary chemodectoma', 'minute pulmonary meningothelial-like nodules' and 'immunohistochemistry'. Cases in the English language literature were reviewed carefully to extract essential clinicopathological data and to combine those that were studied repeatedly in different papers. Only cases with available immunohistochemical information were included. A total of 53 cases of MPMNs with 123 lesions were retrieved from the literature and included in our review.

RESULTS

Patient clinical characteristics

MPMNs accounted for 0.2% (19/8019) of all pulmonary lobectomy or segmental resection specimens during the study period in the two institutions in China. The major clinicopathological features of the 19 cases of MPMNs are summarised in table 1. The median age of patients with MPMNs was 62.5 years (range 32–73 years). There was a female predominance with a male-to-female ratio of 1:8.5. The sites of occurrence were located in each lobe including five cases of right upper lung, five cases of right lower lung, seven cases of left upper lung, one case of left lower lung and one case of right upper and right lower lung, simultaneously. Most (15/19, 78.9%) MPMN cases had coexisting diseases including adenocarcinomas (12 cases), bronchiectasis (1 case) and tuberculosis (2 cases).

Histomorphology

Just over half of the current cases (10/19, 52.6%) were multifocal lesions (2–5 lesions in each case) (figure 1A). In total, 39 lesions (nodules) were found in these 19 cases. The size of the nodules was 1–4 mm. All lesions were located within the lung. As previous reports described,[7] the lesions were composed of interstitially located cellular nests, often closely associated with or in proximity to small vessels (figure 1B). Most of the lesions were large with multiple cell nests interconnected by variably

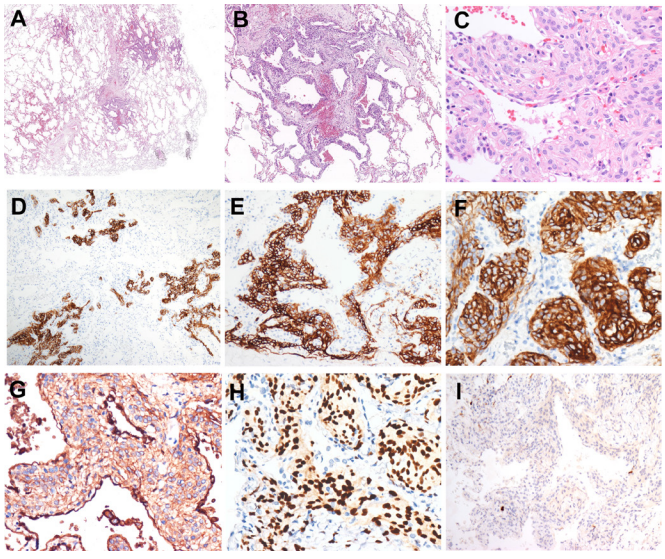

Figure 1 Morphology and immunophenotype of minute pulmonary meningothelial-like nodules. (A) Multifocal nodules/lesions are evident within the lung in one tissue slide. (B) The lesions are composed of interstitially located cellular nests. (C) Tumour cells are moderately sized, elongated or spindle shaped and have eosinophilic cytoplasm with fine chromatin and indistinct nucleoli. (D–F) Tumour cells show diffuse and strong cytoplasmic expression of SSTR2a. (G) Epithelial membrane antigen expression isseen in the lesion. (H) Partial neoplastic cells arepositive for the progesterone receptor. (I) The lesion is negative for S100. SSTR2a, somatostatin receptor 2a.

Table 2 Summary of the brief clinicopathological features of MPMNs in present study and the literature

Characteristics	Present study	Literature	Total
Total cases (total number of nodules/lesions)	19(39)	53(123)	72 (162)
Median age (range)	62.5 (32–73)	NA*(34-94)	NA*(34-94)
Gender (male/female)	2/17	11/42	13/59
Coexisting diseases (yes/no)	15/4	60/9	75/13
Number of lesions (single/multiple)	9/10	23/29	32/39
Size of the lesion (mm)	1–4	0.5–4	0.5–4
Immunophenotype†			
SSTR2apositive/negative)	39/0	NA ‡	39/0
EMA (positive/negative)	29/10	57/42	86/52
PR (positive/negative)	11/28	21/8	32/36
S100 (positive/negative)	0/39	11/85	1/124
CK (positive/negative)	0/39	0/105	0/144
CgA (positive/negative)	0/39	1/40	1/79
Syn (positive/negative)	0/39	0/59	0/98

*Not all detailed age of every cases are rendered in the literature, so it is unable to calculate median age.
†Immunophenotype was evaluated according to nodules/lesions but not according to cases.
‡Since the details of the clinicopathological features were unavailable, a report of five cases of MPMNs showed SSTR2a expression in 'Letters to the Editor'[11] was not included.
CgA, chromogranin A; EMA, epithelial membrane antigen; MPMNs, minute pulmonary meningothelial-like nodules; NA, not available; PR, progesterone receptor .

dense bands of collagen. Tumour cells were moderately sized, elongated or spindle shaped and had eosinophilic cytoplasm with indistinct cell borders. Nuclei were oval with fine chromatin and indistinct nucleoli. Mitotic figures were not found (figure 1C).

Immunohistochemical results

All 39 lesions (nodules) in the19 current MPMN cases showed diffuse and strong cytoplasmic expression of SSTR2a (figure 1D–F). EMA expression was seen in 74.4% (29/39) of the lesions (figure 1G). Variable expression of PR was found in 28.2% (11/39) of the cases (figure 1H). All lesions were negative for S100 (figure 1I), cytokeratin and neuroendocrine markers (synaptophysin and CgA) (table 2).

Review of 72 MPMN cases with available immunohistochemical information

After an extensive search of the English literature, an additional 53 cases with 123 lesions were reviewed with reported immunophenotype information.[7 12–15] In total, 72 cases with 162 lesions from the literature and the present study were included in the analysis. The clinicopathological features of these cases are summarised in table 2. The age of MPMN patients from the literature ranged from 34 years to 94 years. Because age was not available for all cases, a median could not be calculated. Similar to the current cases, there was a predominance of females, with a male-to-female ratio of 1:5. Most MPMN cases (60/68, 88.2%) ware detected incidentally in resected lung specimens for other diseases, including adenocarcinomas (22/68, 32.4%) and infectious diseases (12/68, 17.6%). More than half of the cases (29/52, 55.8%) were multifocal lesions (2–6 lesions in one case). The nodule size was 0.5–4 mm. Information about the expression of SSTR2a in the 53 literature cases was not available. Considering the 19 current cases, the 100% expression rate of SSTR2 was higher than that of conventional markers of meningioma including EMA (86/138), PR (32/68) and S100 (1/125). Lesions from both patient cohorts were negative for CK (0/144), synaptophysin (0/98) and CgA (1/80). The numbers of reviewed cases described above are inconsistent because immunohistochemistry was not performed in all cases and, in some immunohistochemistry cases, the lesions disappeared in serial sections.

DISCUSSION

MPMNs are generally detected incidentally in resected lung specimens, and the detection rate varies from study to study. In 1971, Ichinose *et al*[12] found 10 cases of MPMNs among 1828 necropsies, representing a detection rate of 0.9%. However, Niho *et al*[13] reported a detection rate of MPMNs up to 9.5% (34/357) through routine pathological examinations of lung cancer. Our present study showed that the detection rate of MPMNs in pulmonary lobectomy or segmental resection specimens was only 0.2% (19/8019) during the study period, indicating MPMNs were rare. However, we believe that the actual occurrence rate of MPMNs is higher than what we found because the MPMN lesions are usually small, and insufficient sampling will result in missing some cases.

Clinicopathologically, our results showed that most (15/19, 78.9%) MPMNs are detected incidentally in resected lung specimens, consistent with previous study.[13] No evidence of meningioma in the lung and meninges was found by CT scans for all cases, indicating that MPMNs are not related to meningiomas or metastasis from meningioma. Interestingly, we found that MPMNs in the current patients showed a female predominance, with a male-to-female ratio of 1:8.5. Therefore, MPMNs tend to occur in women. Previous studies reported that MPMNs were 0.1–3 mm in diameter. In the present study, the largest lesion was 4 mm in diameter. Because MPMN lesions are small, sufficient sampling and careful histopathological examination are needed to confirm the existence of this disease.

Somatostatin is a hormone secretion inhibitor that is widely expressed in multiple organs. Somatostatin exerts its biological function through its receptor, SSTR, with five subtypes (SSTR1-5).[16] After somatostatin is activated, it plays proapoptotic, antiangiogenic and antiproliferative roles. More recently, SSTR2a was considered to be expressed specifically in neuroendocrine tumours[17] and meningioma.[9] It was reported that SSTR2a is the most sensitive (95.2%) and specific (92%) marker for the diagnosis of meningioma and achieves the best sensitivity (100%) if combined with EMA.[9] In addition, our recent research shows it is also expressed in follicular dendritic cells and related tumours.[18] This receptor subtype mediates the antiproliferative and antiangiogenic effects of somatostatin. SSTR2a expression is

associated with the entity of neo-angiogenesis in meningiomas, thus providing a basis for the use of somatostatin analog-based therapies that have an antiangiogenic effect in the treatment of these tumours.[19]

The origin of MPMNs is controversial. In 1990, Torikata *et al*[14] found pulmonary meningothelial-like nodules to be EMA negative and vimentin- and myosin positive. This was suggestive of a myogenic rather than meningothelial origin of these curious tumours. However, Kuhn and Askin[5] considered that the tumour cells resembled meningeal-arachnoid cells. Gaffey *et al*[7] demonstrated further similarities to meningothelial cells including reactivity with vimentin and EMA and lack of reactivity with cytokeratin, actin, S100 and neuron-specific enolase. Based on these latter observations, the name 'minute pulmonary meningothelial-like nodules' was proposed. To date, most studies suggest MPMNs have a meningothelial origin.[5–7 15] Because MPMNs is a rare disease, very few studies concerning the immunophenotype of MPMNs have been published, and these studies have been mainly presented as a small series of cases.[7 13 20 21] In the present study, we analysed the expression of SSTR2a in 19 cases of MPMNs, which included 39 nodules/lesions. All lesions showed diffuse and strong expression of SSTR2a. These results add to the evidence of a meningothelial origin for MPMNs. The expression rate of SSTR2a was higher than that of conventional markers of meningioma, including EMA, PR and S100. Our observations expand the spectrum of recognised SSTR2a-positive lesions. MPMNs show immunohistochemical characteristics similar to those of meningioma, suggesting that MPMNs show immunohistochemical characteristics similar to meningothelial cells.

The current study had some limitations. As MPMNs are generally detected incidentally in resected lung specimens, age and other clinical features are prone to sampling bias. Although all MPMNs lesions showed diffuse and strong expression of SSTR2a, our observations expand the spectrum of recognised SSTR2a-positive lesions. Since most typical MPMNs were diagnosed on routine H&E stain and do not pose a diagnostic challenge, SSTR2a immunostaining would be helpful but not critical in routine pathological diagnosis.

In summary, SSTR2a and other markers of meningioma (including EMA, PR and S100) were analysed retrospectively in 19 cases of MPMNs from two institutions in China. In addition, 53 cases from the literature, with reported immunophenotype information, were reviewed in the present study. All MPMN lesions in the 19 cases showed constant expression of SSTR2a. The expression rate of SSTR2a was higher than that of conventional markers of meningioma, including EMA, PR and S100. Our observations expand the spectrum of recognised SSTR2a-positive lesions and once again demonstrated that MPMNs show immunohistochemical characteristics similar to meningothelial cells.

Take home message

- Minute pulmonary meningothelial-like nodules (MPMNs) tend to occur in older women with coexisting diseases and multifocal lesions.
- Somatostatin receptor 2a (SSTR2a) is the most sensitive marker for diagnosing MPMNs. All MPMN lesions showed strong and diffuse cytoplasmic expression of SSTR2a.
- Our observations expand the spectrum of recognised SSTR2a-positive lesions and once again demonstrated that MPMNs show immunohistochemical characteristics similar to meningothelial cells

Handling editor Runjan Chetty.

Contributors These authors have contributed equally to the work.

Funding This project was supported by the Science and Research Foundation of Peking University, Shenzhen Hospital (JCYJ2017010), the Natural Science Foundation of Guangdong Province (2018A030313663), and the Medical Science and Technology Foundation of Guangdong Province (A2018001).

Competing interests None declared.

Patient consent for publication All patients provided written informed consent for the collection and publication of their medical information during the first visit to the hospital.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as supplementary information.

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