Is Primary Pulmonary Meningioma a Giant Form of a Meningothelial-Like Nodule? A Case Report and Review of the Literature

Katsuhiro Masago Waki Hosada Eiichi Sasaki Yoshiko Murakami Masato Sugano Toru Nagasaka Mai Yamada Yasushi Yatabe

Department of Pathology and Molecular Diagnostics, Aichi Cancer Center, Nagoya, Japan

Key Words
CD56 · Primary pulmonary meningioma · Pulmonary meningothelial-like nodule

Abstract
Minute pulmonary meningothelial-like nodules (PMNs) are asymptomatic, small nodules that are occasionally detected in surgical or autopsy specimens. Recent improvements in tumor imaging and the increased use of computed tomography (CT) scans of the chest have led to the early detection of these pulmonary nodules in various clinical settings, often before surgery or health examinations. However, large PMNs have rarely been observed. In this study, we report a patient with a large PMN, which was almost identical to so-called ‘primary pulmonary meningioma’. A CT scan of his chest revealed a small, well-circumscribed nodule. Immunohistochemical analysis of the tumor revealed that the tumor cells were positive for CD56, epithelial membrane antigen, and progesterone receptor. Given the similarity of these results to the staining pattern of minute PMNs in previous reports, we suggest that the primary pulmonary meningiomas reported to date are, in fact, a giant form of PMN.

Introduction

Minute pulmonary meningothelial-like nodules (PMNs) are asymptomatic, small nodules often representing incidental microscopic findings in surgical or autopsy specimens of the lung. In recent years, minute PMNs have been detected with the
increased use of high-resolution computed tomography (CT) scans. The clinicopathological and histological characteristics of minute PMNs have also been analyzed in several reports [1, 2]. However, large PMNs have rarely been observed.

The present case is of a 76-year-old man diagnosed with a rare, large PMN. The tumor was detected during a 3-year follow-up period after surgical resection of a primary gastric cancer. The patient was diagnosed with pulmonary metastasis from the primary gastric malignancy. Subsequently, the patient underwent a partial resection of the pulmonary nodule.

**Case Presentation**

The patient was a 76-year-old Japanese man with an asymptomatic left upper lung nodule. The pulmonary nodule was incidentally discovered on a CT scan of his chest, which was performed during the staging of his gastric cancer (fig. 1a). The patient underwent a segmental gastrectomy with lymph node dissection. Histopathological examination of the explanted stomach revealed a poorly differentiated adenocarcinoma with submucosal invasion, and no lymph node metastasis (type 2, 30 × 25 mm in size, pT1N0M0). Preoperative measurements of carcinoembryonic antigen (CEA, <0.05 ng/ml; normal value: <0.5 ng/ml) and CA19-9 (2.5 U/ml; normal value: ≤37 U/ml) levels were within normal limits.

During an annual follow-up CT scan, the pulmonary nodule was found to have increased in size from 6 to 8 mm (fig. 1b, c). Subsequently, a partial pulmonary resection of the nodule was performed. Based on the surgical specimen, the nodule was well circumscribed, 10 mm in diameter, and tan-white in color (fig. 2a). The specimen was fixed in neutral, buffered formalin and routinely processed by embedding tissue sections in paraffin. The sections were cut 4 μm thick and stained with H&E. Immunohistochemical stains were performed with the antibodies listed in table 1.

Upon further examination, the nodule was found to contain cytologically bland, rounded, and spindled cells with abundant pale eosinophilic cytoplasm, lying in dense collagenous stroma (fig. 2b, c). Scattered psammoma bodies were noted within the tumor, and no mitotic activity, cytological atypia, or necrosis was identified (fig. 2d).

The tumor cells were diffusely positive for CD56, epithelial membrane antigen (EMA), and progesterone receptor (PR, fig. 3a–c). The Ki-67 labeling index was 4% (fig. 3d). The cells were negative for cytokeratin, microphthalmia-associated transcription factor (MITF), human melanin black 45 (HMB45), estrogen receptor (ER), S-100, actin, thyroid transcription factor (TTF-1), anaplastic lymphoma kinase (ALK), CD34, chromogranin, and synaptophysin.

**Discussion**

PMNs are interstitial cellular proliferations that were first identified in 1960 [3]. To date, the exact origin and pathogenesis of these curious lesions is still unknown. Currently, PMNs are considered to be reactive and to have histological, immunohistochemical, and ultrastructural features similar to meningiomas [4]. PMNs are asymptomatic, small (100 μm to 3 mm) nodules often representing incidental microscopic findings in lung specimens [5]. Large PMNs such as the one reported in our case are rare.

Most PMNs are incidental findings of no clinical significance. The reported incidence of these nodules varies in the literature from 0.3 to 9.5% of cases at autopsy or surgical resection [5–8]. The recent development of high-resolution CT scans has provided the
means of detecting these minute lesions. The increased use of high-resolution CT scanning has also led to the occasional detection of PMNs before surgery.

Because PMNs are microscopic lesions, it is generally rare for PMNs to be found prior to surgery. However, such tumors may be interpreted as ground-glass opacity on high-resolution CT scans [9, 10] in cases where PMNs constitute multiple lesions. Such findings often draw clinical attention. In contrast, a solitary giant nodule such as the one found in our case is quite rare. However, it is critically important to determine the appropriate clinical management of patients with these nodules before surgery of the primary malignancy [11, 12]. If the pulmonary nodules in these cases had been deemed as metastatic disease with no further pathologic correlations, options for curative surgical therapy for the primary malignancy may have been erroneously delayed or denied.

Unlike pulmonary metastases from intracranial or intraspinal meningiomas, primary pulmonary meningiomas have rarely been observed [13]. It may be difficult to distinguish PMNs from primary pulmonary meningiomas because of their morphologic similarity, with exception of their size. In a recent report, a wide range of immunohistochemical stains was performed to clarify the histogenesis of minute PMNs. The nodules were found to be positive for PR and CD56 [1, 14], in addition to the classical immunohistochemical markers, such as vimentin and EMA. The detection of PR and CD56 has potential implications for the histogenesis of minute PMNs. We suggest that primary pulmonary meningiomas reported to date are a giant form of PMN. In previous reports on solitary primary pulmonary meningiomas [13, 15–35], newer markers such as PR and CD56 had not been evaluated (table 2). Given the similarity of the immunohistochemical results of our case to reported minute PMNs, including the positive PR and CD56 staining [1, 14], these previously reported primary pulmonary meningiomas may include a similar disease entity. Interestingly, Ionescu et al. [5] reported that meningiomas had their own lineage-specific genetic pathways involving molecular genetic events on chromosomes 22q, 14q, and 1p, which were not shared by minute PMNs. This finding may support our hypothesis based on our findings in this study.

**Conclusion**

In this study, we report a rare case of a giant PMN that was almost identical to so-called primary pulmonary meningioma. In a recent report, PMNs were examined using newly developed markers, and the resulting immunophenotype was identical to that seen in this tumor. Based on the results of our study, we suggest that primary pulmonary meningioma is a giant form of PMN.

**Disclosure Statement**

The authors declare no competing interests.
Acknowledgement

Prof. Andrew G. Nicholson, Honorary Professor of Respiratory Pathology, National Heart and Lung Institute, UK, is acknowledged for his insightful comments and suggestions.

Table 1. Antibodies used

| Antibody        | Clone   | Source         | Dilution |
|-----------------|---------|----------------|----------|
| CD56            | 123C3   | Dako           | Predilute|
| PR              | SP2     | Neomarkers     | 1/100    |
| EMA             | E29     | Dako           | 1/50     |
| S-100           | S100    | Dako           | 1/600    |
| Cytokeratin     | OSCAR   | Signet         | 1/40     |
| MITF            | D51     | Dako           | 1/50     |
| HMB45           | HMB45   | Dako           | 1/50     |
| ER              | SP1     | Dako           | Predilute|
| TTF-1           | 8G7G3/1 | Neomarkers     | 1/100    |
| Chromogranin A  | SP12    | Nichirei       | 1/200    |
| Actin           | 1A4     | Santa Cruz     | Predilute|
| ALK             | 5A4     | Dako           | 1/1000   |
| CD34            | QBEND10 | Dako           | 1/1000   |
| Synaptophysin   | SP11    | Neomarkers     | 1/100    |
| Ki-67           | SP6     | Neomarkers     | 1/100    |
Table 2. Immunohistochemical study

| References first author | Patients’ age (years (gender)) | Tumor size, cm | Vimentin | EMA | CD56 | PR | Other positive findings |
|--------------------------|-------------------------------|----------------|----------|-----|------|----|-------------------------|
| Kemnitz [27]             | 59 (F)                        | 4.0            | NR       | NR  | NR   | NR | NR                     |
| Chumas [16]              | 58 (M)                        | 4.0            | NR       | NR  | NR   | NR | NR                     |
| Zhang [35]               | 58 (F)                        | 2.5            | NR       | NR  | NR   | NR | NR                     |
| Kodama [28]              | 53 (F)                        | 2.6            | NR       | NR  | NR   | NR | NR                     |
| Drlicek [20]             | 41 (M)                        | 2.5            | P        | P   | P    | P  | NR                     |
| Flynn [22]               | 63 (F)                        | 3.0            | P        | P   | P    | P  | NR                     |
|                         | 74 (F)                        | 1.7            | P        | P   | NR   | NR | NR                     |
| Maiorana [30]            | 68 (M)                        | 1.8            | P        | P   | NR   | NR | Cytokeratins (focal)    |
| Lockett [29]             | 65 (M)                        | 0.8            | NR       | P   | NR   | NR | CEA                     |
| Kaleem [25]              | 45 (F)                        | 1.2            | P        | P   | NR   | NR | NR                     |
| de Perrot [19]           | 57 (F)                        | 0.9            | P        | P   | NR   | NR | NR                     |
| Spinelli [13]            | 71 (F)                        | 1.5            | NR       | P   | NR   | NR | NR                     |
| Falleni [21]             | 59 (M)                        | 2.5            | P        | N   | NR   | NR | S-100 (focal)           |
| Cesario [15]             | 56 (M)                        | 2.0            | P        | P   | NR   | NR | NR                     |
| Cura [18]                | 58 (F)                        | 2.0            | NR       | NR  | NR   | NR | NR                     |
| Comin [17]               | 37 (M)                        | 2.0            | P        | P   | NR   | P (focal) | NSE; ER (focal) S-100 (focal) |
| Rowsell [33]             | 51 (M)                        | 4.0            | P        | P   | NR   | NR | NR                     |
| Picquet [32]             | 54 (F)                        | 1.4            | NR       | P   | NR   | NR | NR                     |
| Kaneda [26]              | 49 (F)                        | 1.4            | P        | P   | NR   | NR | S-100 (focal)           |
| Meirelles [31]           | 48 (M)                        | 1.5            | P        | P (focal) | NR | NR | NR                     |
| Incarbone [23]           | 24 (M)                        | 2.4            | P        | P   | NR   | NR | NR                     |
| Izumi [24]               | 18 (F)                        | 3.3            | P        | NR  | NR   | NR | S-100; CD68             |
| Satoh [34]               | 74 (F)                        | 3.0            | P        | P   | NR   | P (focal) | CD68 (focal) |
| Present report           | 76 (M)                        | 1.0            | NR       | P (focal) | P | P  | none                   |

NSE = Neuron-specific enolase; P = positive; N = negative; NR = not reported.

Fig. 1. Chest CT revealing a pulmonary nodule (white arrows) before surgery (a). In subsequent CT scans taken after 1 year (b) and 2 years (c), the nodule slightly increased in size.
**Fig. 2.** Surgical specimen showing a well-circumscribed, tan-white nodule (a). H&E staining showing that the nodule is well circumscribed (b), and contains cytologically bland, rounded, and spindled cells when examined under high-power magnification (c). Scattered psammoma bodies are noted (d).
Fig. 3. High-power magnification of immunohistochemical analysis of a tumor specimen of the left lung nodule. The tumor was positive for CD56 (a), weakly positive for EMA (b), positive for PR (c), and the Ki-67 labeling index was 4% (d).

References

1. 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;33:487–495.
2. Mizutani E, Tsuta K, Maeshima AM, Asamura H, Matsuno Y: Minute pulmonary meningothelial-like nodules: clinicopathologic analysis of 121 patients. Hum Pathol 2009;40:678–682.
3. Korn D, Bensch K, Liebow AA, Castleman B: Multiple minute pulmonary tumors resembling chemodectomas. Am J Pathol 1960;37:641–672.
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;12:167–175.
5. Ionescu DN, Sasatomi E, Aldeeb D, Omalu BI, Finkelstein SD, Swalsky PA, Yousem SA: Pulmonary meningothelial-like nodules: a genotypic comparison with meningiomas. Am J Surg Pathol 2004;28:207–214.
6. Niho S, Yokose T, Nishiwaki Y, Mukai K: Immunohistochemical and clonal analysis of minute pulmonary meningothelial-like nodules. Hum Pathol 1999;30:425–429.
7. Churg AM, Warnock ML: So-called ‘minute pulmonary chemodectoma’: a tumor not related to paragangliomas. Cancer 1976;37:1759–1769.
8. Spain DM: Intrapulmonary chemodectomas in subjects with organizing pulmonary thromboemboli. Am Rev Respir Dis 1967;96:1158–1164.
9. Kraushaar G, Ajlan AM, English JC, Muller NL: Minute pulmonary meningothelial-like nodules: a case of incidentally detected diffuse cystic micronodules on thin-section computed tomography. J Comput Assist Tomogr 2010;34:780–782.
10 Kuroki M, Nakata H, Masuda T, Hashiguchi N, Tamura S, Nabeshima K, Matsuzaki Y, Onitsuka T: Minute pulmonary meningothelial-like nodules: high-resolution computed tomography and pathologic correlations. J Thorac Imaging 2002;17:227–229.

11 Sellami D, Gotway MB, Hanks DK, Webb WR: Minute pulmonary meningothelial-like nodules: thin-section CT appearance. J Comput Assist Tomogr 2001;25:311–313.

12 Park HY, Nishi Y, Tabi K, Yamamoto H, Shibasaki M, Sakata K, Nagata M, Kuramitsu K, Nakamura S, Morita R, Kaneko K, Shimizu Y, Sakamoto Y: Minute pulmonary meningothelial-like nodules: a case report (in Japanese). Nihon Kokyuki Gakkai Zasshi 2002;40:499–502.

13 Spinelli M, Claren R, Colombi R, Sironi M: Primary pulmonary meningioma may arise from meningothelial-like nodules. Adv Clin Path 2000;4:35–39.

14 Pelosi G, Maffini F, Decarl N, Viale G: Progesterone receptor immunoreactivity in minute meningothelial nodules of the lung. Virchows Arch 2002;440:543–546.

15 Cesario A, Galetta D, Margaritara S, Granone P: Unsuspected primary pulmonary meningioma. Eur J Cardiothorac Surg 2002;21:553–555.

16 Chumas JC, Lorette CA: Pulmonary meningioma. A light- and electron-microscopic study. Am J Surg Pathol 1982;6:795–801.

17 Comin CE, Caldarella A, Novelli L, Janni A: Primary pulmonary meningioma: report of a case and review of the literature. Tumori 2003;89:102–105.

18 Cura M, Smoak W, Dala R: Pulmonary meningioma: false-positive positron emission tomography for malignant pulmonary nodules. Clin Nucl Med 2002;27:701–704.

19 de Perrot M, Kurt AM, Robert J, Spiliopoulos A: Primary pulmonary meningioma presenting as lung metastasis. Scand Cardiovasc J 1999;33:121–123.

20 Drlicek M, Grisold W, Lorber J, Hackl H, Wuketic M: Meningioma of lung: first report with light and electron microscopic study. Am J Surg Pathol 1986;10:515.

21 Falleni M, Roz E, Dessy E, Del Curto B, Braidotti P, Gianelli U, Pietra GG: Primary intrathoracic meningioma: histopathological, immunohistochemical and ultrastructural study of two cases. Virchows Arch 2001;439:196–200.

22 Flynn SD, Yousem SA: Pulmonary meningiomas: a report of two cases. Hum Pathol 1991;22:469–474.

23 Incarbone M, Ceresoli GL, Di Tommaso L, Cappuzzo F, Inzirillo F, Infante M, Alloiso M: Primary pulmonary meningioma: report of a case and review of the literature. Lung Cancer 2008;62:401–407.

24 Izumi N, Nishiyama N, Iwata T, Nagano K, Tsukiioka T, Hanada S, Suhiro S: Primary pulmonary meningioma presenting with hemothysis on exertion. Ann Thorac Surg 2009;88:467–468.

25 Kaleem Z, Fitzpatrick MM, Ritter JH: Primary intrathoracic meningioma: histopathological, immunohistochemical and ultrastructural study of two cases. Virchows Arch 2001;439:196–200.

26 Kuroki M, Nakata H, Masuda T, Hashiguchi N, Tamura S, Nabeshima K, Matsuzaki Y, Onitsuka T: Minute pulmonary meningothelial-like nodules: high-resolution computed tomography and pathologic correlations. J Thorac Imaging 2002;17:227–229.

27 Kemnitz P, Spormann H, Heinrich P: Meningioma of lung: first report with light and electron microscopic findings. Ultrastruct Pathol 1982;3:359–365.

28 Kodama K, Doi O, Higashiyama M, Horai T, Tateishi R, Nakagawa H: Primary and metastatic pulmonary meningioma. Cancer 1991;67:1412–1417.

29 Lockett L, Chiang V, Scully N: Primary pulmonary meningioma: report of a case in [Japanese]. Kyobu Geka 2005;58:512–515.

30 Maiorana A, Ficarra G, Fano RA, Spagna G: Primary solitary meningioma of the lung. Pathologica 1996;88:457–462.

31 Meirelles GS, Ravizzini G, Moreira AL, Akhurst T: Primary pulmonary meningioma manifesting as a solitary pulmonary nodule with a false-positive PET scan. J Thorac Imaging 2006;21:225–227.

32 Picquet J, Valo I, Jousset Y, Enon B: Primary pulmonary meningioma first suspected of being a lung metastasis. Ann Thorac Surg 2005;79:1407–1409.

33 Rowsell C, Sirbovan J, Rosenblum MK, Perez-Ordonez B: Primary chordoid meningioma of lung. Virchows Arch 2005;446:333–337.

34 Satoh Y, Ishikawa Y: Primary pulmonary meningioma: Ten-year follow-up findings for a multiple case, implying a benign biological nature. J Thorac Cardiovasc Surg 2008;139:e39–e40.

35 Zhang FL, Cheng XR, Zhang YS, Ding JA: Lung ectopic meningioma. A case report. Chin Med J (Engl) 1983;96:309–311.