

Localized malignant pleural mesothelioma arising in the interlobar fissure: a unique surgical case masquerading clinicopathologically as primary lung adenocarcinoma

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Abstract

An 80-year-old male with previous workplace exposure to asbestos presented with a history of an increase in the pulmonary-to-hilar mass, measuring more than 50 mm in diameter, likely in the right lower lobe. We first interpreted it as suspicious of primary lung adenocarcinoma with direct invasion to the right hilar lymph node. A right middle and lower lobectomy with partial resection of upper lobe was performed, and gross examination showed a hilar tumor lesion, involving the middle/lower lobe to hilar lymph node and looking whitish to yellow-grayish, partly adjacent to the right pulmonary artery. On microscopic examination, the tumor was located on the extrapulmonary, interlobar pleural fissure, predominantly composed of a proliferation of atypical epithelioid cells, often arranged in an irregular and fused tubular growth pattern with an involvement of pulmonary artery. Immunohistochemically, these atypical cells are positive for several mesothelial markers, including calretinin, cytokeratin 5/6, and WT-1, whereas negative for thyroid transcription factor 1. Furthermore, p16 deletions were specifically detected by fluorescence in situ hybridization, and electron microscopy showed numerous, significantly elongated microvilli. Taken together, we finally made a diagnosis of localized malignant pleural mesothelioma, epithelioid-type, arising in the right interlobar fissure between lower and middle lobes. We should be aware that, owing to its characteristic features, clinicians and pathologists might be able to raise interlobar fissure localized malignant pleural mesothelioma as one of the differential diagnoses, based on careful clinicopathological examinations.

Keywords

Malignant pleural mesothelioma, interlobar pleural fissure, asbestos, localized malignant pleural mesothelioma, p16

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Introduction

Among malignant pleural mesothelioma (MPM), which is the most common primary tumor of the pleura cavity, one original paper reported that, in contrast to diffuse MPM characterized by a macroscopic pattern of diffuse spread across the pleural surface, an extremely rare subtype of sharply demarcated solitary MPM has been identified, designated as localized malignant pleural mesothelioma (LMPM).¹ Indeed, Klemperer and Rabin first reported the classification of mesothelioma, as diffuse (maximum) and localized (minimum) tumors, in 1931.^{2,3} To date, the number of “true” cases reported as LMPM in the English literatures is not large, less than 70 cases, and most recent reference is from 2015, within our thorough investigation.^{3–7} Yao et al.⁶ and Nakas et al.² have recently described that the patients of LMPM reveal variable clinical symptoms, as follows: pain; cough; dyspnea; pleural thickening; pleural effusion; and lung and/or rib involvement, likely showing different biological behaviors with various histological subtypes, including epithelioid, biphasic, and sarcomatoid, and varying in better-to-worse disease-specific survival.^{1–7} Hence, it would be critical to establish an accurate pre-operative diagnosis by computed tomography (CT)-guided biopsy. Although it is well known that most of the MPM have a close relationship with occupational and environmental exposure to asbestos, some LMPM patients showed no history of it.^{1–7} Furthermore, the gross findings of LMPM are capable of showing multiple forms, as follows: pulmonary to extrapulmonary, lobulated and/or smooth mass with or without destruction of the ribs.^{1–7} Taken together, LMPM often poses a pre-operative diagnostic challenge to clinicians and pathologists, since it is difficult to determine whether LMPM is a separated clinicopathological entity from MPM and whether LMPM is one part of diffuse MPM diagnosed at an early stage,¹ at least in part.

We herein report a quite unique surgical case of LMPM, epithelioid-type, arising in the right interlobar pleural fissure between lower and middle lobes. The transbronchial lung biopsy specimens were too small to be diagnostic. Based on the clinical examination, we pre-operatively interpreted it merely as highly suspicious of primary lung adenocarcinoma.

Materials and methods

The patient was an 80-year-old Japanese man. Bronchial brushing and washing cytology, and transbronchial lung biopsy from the mass were performed, followed by a right middle and lower lobectomy with partial resection of upper lobe. The tumor specimens after fixation in 10% neutral buffered formalin were embedded in paraffin for histological, immunohistochemical, or fluorescence in situ hybridization (FISH) examinations.⁸ All immunohistochemical stainings were carried out using Dako Envision kit (Dako Cytomation Co., Glostrup, Denmark) according to the manufacturer’s instructions, and using commercially available pre-diluted monoclonal antibodies against the following antigens (Dako

Cytomation Co.): calretinin, cytokeratin (CK5/6), WT-1, Ber-EP4, thyroid transcription factor 1 (TTF-1), synaptophysin, claudin-4, MOC31, carcinoembryonic antigen (CEA), and D2-40 (podoplanin). Although all tumor specimens were fixed in formalin, transmission electron microscopy was performed. For electron microscopy, dehydrated specimens were embedded in epoxy resin. Silver-gold sections produced with a diamond knife were transferred to copper grids and stained with uranyl acetate for viewing on a transmission electron microscopy (HF5000; Hitachi, Ltd, Tokyo, Japan).

Case presentation

The patient had a history of urothelial carcinoma in the urinary bladder 3 years ago. He was a heavy smoker over 45 years with previous workplace exposure to asbestos. There was no history of immunosuppressive disorders, use of immunosuppressive medications, or unusual infections.

During a follow-up of his bladder carcinoma, a chest X-ray showed a recent increase in the mass shadow in pulmonary-to-hilar mass, measuring more than 50 mm in diameter, before the surgery. There was no apparent pleural effusion. Laboratory data, including blood cell count and chemistry, were almost within normal limits, except for high levels of C-reactive protein (CRP; 3.16 mg/dL). CEA (3.62 ng/mL) and squamous cell carcinoma antigen (SCC; 1.0 ng/mL) levels as tumor markers were within normal limits, but cytokeratin 19 fragment (CYFRA; 27.1 ng/mL) level was overtly increased. A chest CT scan revealed a relatively well-demarcated pulmonary mass involving the right hilar lymph node, measuring approximately 50 mm × 40 mm in diameter, presented likely in the right lower lobe (Figure 1(a)). Pleural effusion was not recognized. CT scans of the head and abdomen disclosed no definite evidence of metastases in the lymph nodes or other organs. To date, this patient has been followed for 1 year since surgery, and he remains well without any sign of recurrence. He did not undergo any post-surgical chemotherapy or adjuvant radiotherapy.

Pathological findings

The bronchial brushing/washing cytology specimens were inadequate, and the transbronchial lung biopsy specimens from the mass were also too small to be diagnostic. Despite that, based on all clinical findings, we first interpreted it as highly suspicious of carcinoma, such as primary lung adenocarcinoma, and a right middle and lower lobectomy with partial resection of upper lobe was performed.

On gross examination, the cut surface revealed a relatively well-demarcated, solid firm, and lobulated hilar mass, measuring 55 mm × 43 mm × 40 mm, which involved the right middle/lower lobe to hilar lymph node and looked whitish to yellow-grayish, partly adjacent to the right pulmonary artery (Figure 1(b)). The background of the lung had no remarkable change, that is, not emphysematous (Figure 1(b)). There were no other lung carcinoma components within our thorough investigation.

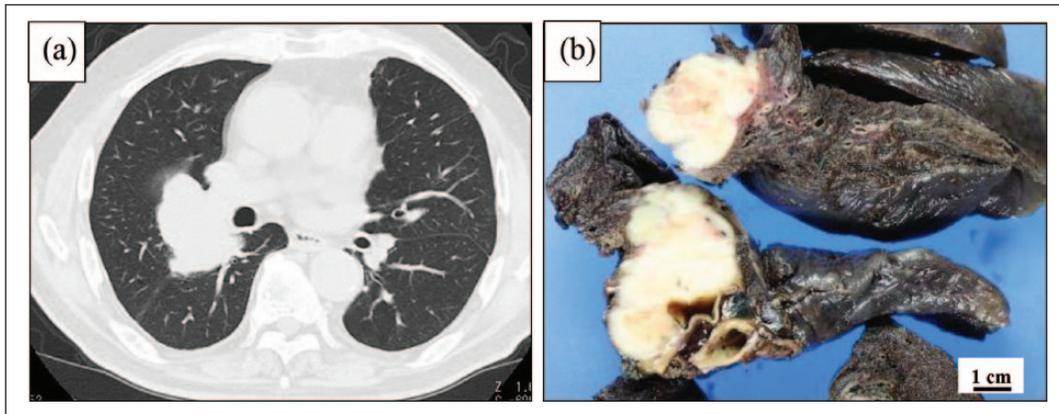


Figure 1. Imaging findings of LMPM and gross examination of the resected specimen. (a) A chest CT scan shows a relatively well-demarcated pulmonary mass involving the right hilar lymph node, measuring approximately 50 mm × 40 mm in diameter, presented likely in the right lower lobe. Pleural effusion is not recognized. (b) On gross examination, the cut surface shows a relatively well-demarcated, solid firm, and lobulated hilar mass, measuring 55 mm × 43 mm × 40 mm, which involves the right middle/lower lobe to hilar lymph node and looked whitish to yellow-grayish, partly adjacent to the right pulmonary artery. The background of the lung has no remarkable change, that is, not emphysematous (Bar = 1 cm).

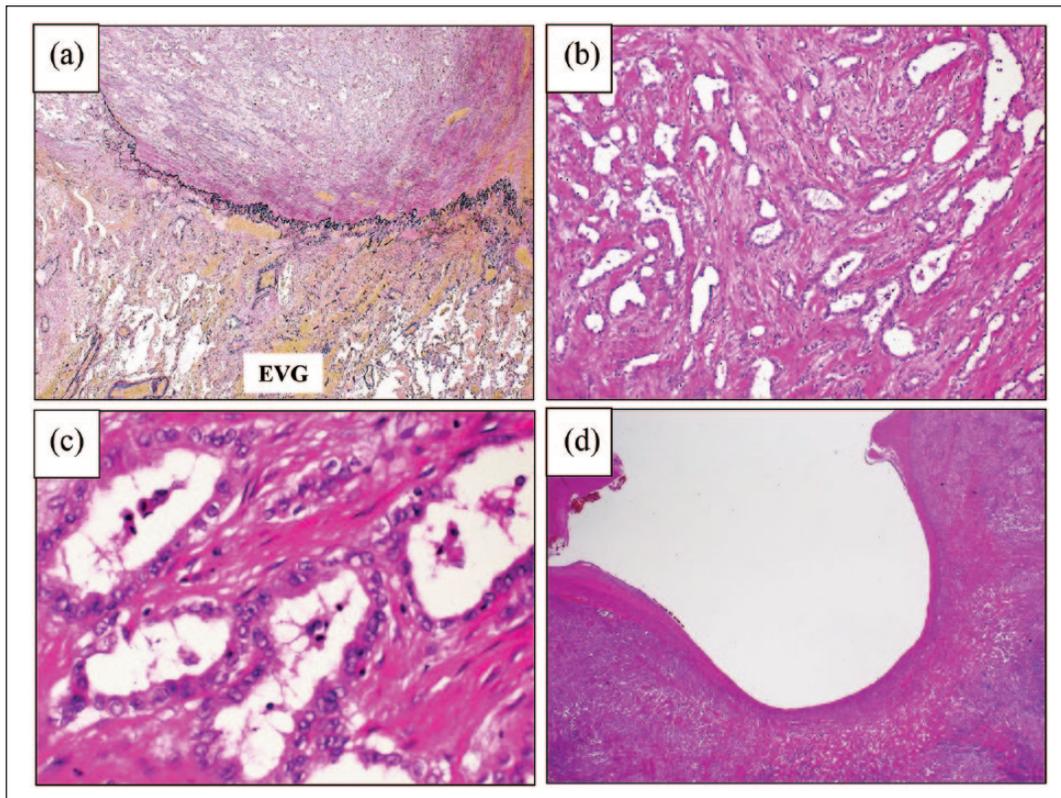


Figure 2. Microscopic examination of the epithelioid-type LMPM arising in the interlobar pleural fissure. (a) Low-power view shows that the extrapulmonary tumor is located on the outer layer of elastic membrane in the interlobar visceral pleura (EVG staining). (b) The tumor is predominantly composed of a proliferation of atypical epithelioid cells, often arranged in an irregular and fused tubular growth pattern with prominent desmoplastic fibrosis (H&E stains). (c) High-power view shows that the atypical cells have enlarged and hyperchromatic nuclei, prominent nucleoli, and possible cilia (H&E stains). (d) The tumor between the right middle and lower lobe partly involves the right pulmonary artery (H&E stains).

On low-power view of microscopic examination, the extrapulmonary tumor was located on the outer layer of elastic membrane in the interlobar visceral pleura, confirmed by

elastica van Gieson (EVG) staining (Figure 2(a)). The tumor was predominantly composed of a proliferation of atypical epithelioid cells, often arranged in an irregular and fused tubular

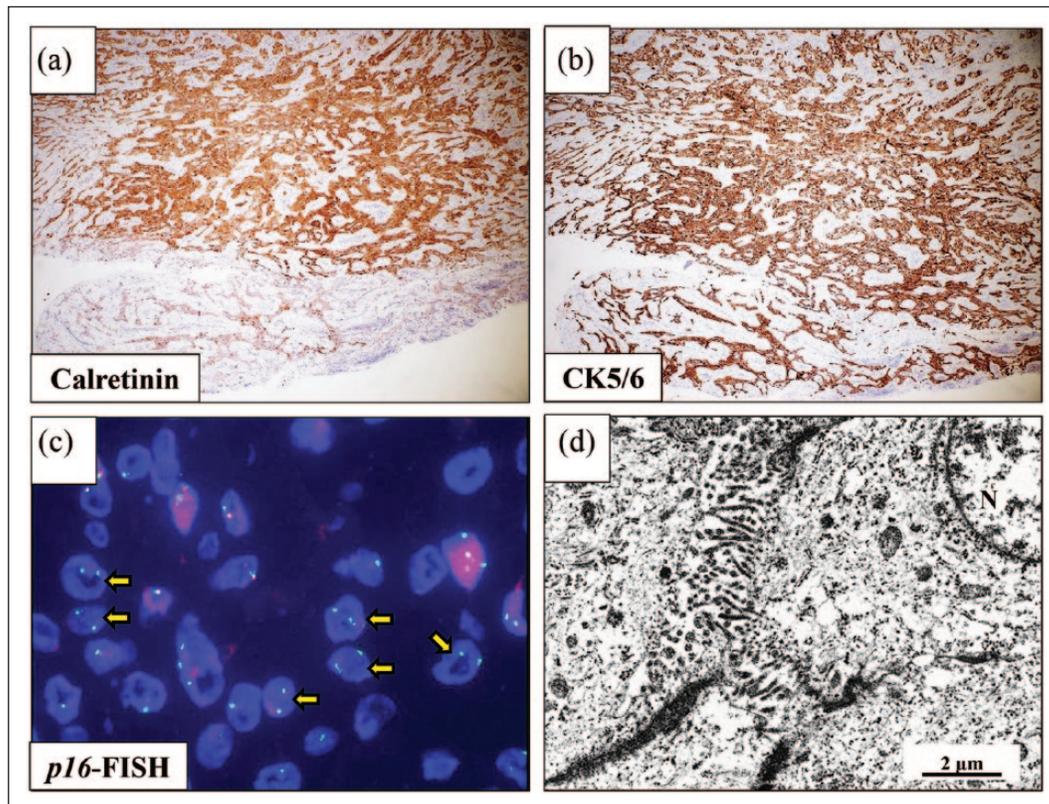


Figure 3. Immunohistochemical, FISH, and ultrastructural examinations of the epithelioid-type LMPM arising in the interlobar pleural fissure. (a, b) Immunohistochemically, the mesothelioma cells of LMPM are specifically and diffusely positive for calretinin (a) and CK5/6 (b). (c) p16 deletions (arrows) are specifically detected by FISH. (d) Electron microscopy shows numerous, significantly elongated microvilli (N = Nucleus. Bar = 2 μ m).

growth pattern with prominent desmoplastic fibrosis (Figure 2(b)). On high-power view, the atypical cells had enlarged and hyperchromatic nuclei, prominent nucleoli, and possible cilia (Figure 2(c)). There was no intracytoplasmic mucin with Alcian blue staining. The tumor between the right middle and lower lobes extended into the hilar lymph node and partly involved the right pulmonary artery (Figure 2(d)). Immunohistochemically, the tumor cells were specifically and diffusely positive for calretinin (Figure 3(a)), CK5/6 (Figure 3(b)), and WT-1, known as mesothelial markers, and unexpectedly, focally positive for Ber-EP4. However, they were completely negative for TTF-1, synaptophysin, claudin-4, MOC31, CEA, and D2-40. All immunohistochemical profiles of the MPM cells are summarized in Table 1. Furthermore, p16 deletions were specifically detected by FISH (Figure 3(c)), but electron microscopy also showed numerous, significantly elongated microvilli (Figure 3(d)). Based on all these features, we finally made a diagnosis of LMPM, epithelioid-type, arising in the right interlobar pleural fissure between lower and middle lobes.

Discussion

It is suggested that MPM is a highly aggressive neoplasm associated with asbestos exposure, leading to confer a significantly poor prognosis with median survival time of merely less than

Table 1. Immunohistochemical profile of the mesothelioma components in our case of interlobar fissure epithelioid-type LMPM.

Positive	Negative
Calretinin	TTF-1
CK5/6	Synaptophysin
WT-1	Claudin-4
Ber-EP4 (focal)	MOC31
	CEA
	D2-40

LMPM: localized malignant pleural mesothelioma; TTF-1: thyroid transcription factor 1; CEA: carcinoembryonic antigen.

20 months as well as 5-year survival rate of less than 5% with best supportive care.¹⁻⁹ Thus, it could be critical to establish an accurate pre-operative diagnosis by percutaneous CT-guided tumor biopsy, the clinical utility of which in diagnosing pulmonary to pleural malignancies has been generalized.

It is very likely that our case report is clinicopathologically remarkable for one reason at least: imaging and gross findings together with H&E histological features tremendously mimicked a primary lung adenocarcinoma. Accordingly, primary lung adenocarcinoma is the most important differential diagnosis in such LMPM cases, including ours; however,

LMPM can be easily distinguished from lung cancer, by immunohistochemical profile of several specific mesothelial markers including calretinin, CK5/6 and/or WT-1, as shown here. Furthermore, the other useful method for discriminating LMPM was presented as the detection of homozygous deletion of p16 using FISH.⁸ It is well known that p16 is located on 21.3 region of the short arm of chromosome 9 (9p21.3), and the homozygous deletion of p16 has been identified in up to 86% of epithelioid-type MPM cases.^{8,10,11} Finally, based on the classic ultrastructural features, it has been reported that MPM cells have a significantly greater microvillus length/diameter ratio (>7) than that of adenocarcinoma of the lung,¹² strongly supporting our final diagnosis of LMPM, epithelioid-type, arising in the right interlobar fissure between lower and middle lobes.

Conclusion

We herein reported an extremely rare case of LMPM, epithelioid-type, arising in the right interlobar fissure. The presented case was tentatively diagnosed as highly suspicious of primary lung adenocarcinoma, since our clinicopathological features mimicked it at least in part. All clinicians/pathologists should be aware that its clinicopathologically characteristic findings from extensively careful examination might induce one of the differential diagnoses and possibly a correct diagnosis. LMPM of the interlobar fissure may be more common than generally considered.

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S.Y., X.G., J.W., H.I., and H.U. participated in conception of the idea and writing of the manuscript. S.Y., X.G., J.W., K.T., N.K., Y.S., and H.U. performed the histological and immunohistochemical interpretation of the tumor tissue. K.T. performed surgery, and K.N. analyzed fluorescence in situ hybridization (FISH). All authors have read and approved the final manuscript.

Availability of data and materials

The data set supporting the findings and conclusions of this report is included within the article.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review with the Editor-in-Chief of this journal.

Declaration of conflicting interests

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References

- Allen TC, Cagle PT, Churg AM, et al. Localized malignant mesothelioma. *Am J Surg Pathol* 2005; 29: 866–873.
- Nakas A, Martin-Ucar AE, Edwards JG, et al. Localised malignant pleural mesothelioma: a separate clinical entity requiring aggressive local surgery. *Eur J Cardiothorac Surg* 2008; 33(2): 303–306.
- Takahashi H, Harada M, Maehara S, et al. Localized malignant mesothelioma of the pleura. *Ann Thorac Cardiovasc Surg* 2007; 13(4): 262–266.
- Tanzi S, Tiseo M, Internullo E, et al. Localized malignant pleural mesothelioma: report of two cases. *J Thorac Oncol* 2009; 4(8): 1038–1040.
- Hayashi H, Notohara K, Yoshioka H, et al. Localized malignant pleural mesothelioma showing a thoracic mass and metastasizing to the stomach. *Intern Med* 2010; 49(7): 671–675.
- Yao W, Yang H, Huang G, et al. Massive localized malignant pleural mesothelioma (LMPM): manifestations on computed tomography in 6 cases. *Int J Clin Exp Med* 2015; 8(10): 18367–18374.
- Nakano T, Hamanaka R, Oiwa K, et al. Localized malignant pleural mesothelioma. *Gen Thorac Cardiovasc Surg* 2012; 60(7): 468–474.
- Hida T, Hamasaki M, Matsumoto S, et al. Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: comparison with 9p21 FISH and BAP1 immunohistochemistry. *Lung Cancer* 2017; 104: 98–105.
- Hasegawa S, Okada M, Tanaka F, et al. Trimodality strategy for treating malignant pleural mesothelioma: results of a feasibility study of induction pemetrexed plus cisplatin followed by extrapleural pneumonectomy and postoperative hemithoracic radiation (Japan Mesothelioma Interest Group 0601 Trial). *Int J Clin Oncol* 2016; 21(3): 523–530.
- Chiose S, Krasinskas A, Cagle PT, et al. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. *Mod Pathol* 2008; 21(6): 742–747.
- Hida T, Hamasaki M, Matsumoto S, et al. BAP1 immunohistochemistry and p16 FISH results in combination provide higher confidence in malignant pleural mesothelioma diagnosis: ROC analysis of the two tests. *Pathol Int* 2016; 66(10): 563–570.
- Warhol MJ, Hickey WF and Corson JM. Malignant mesothelioma: ultrastructural distinction from adenocarcinoma. *Am J Surg Pathol* 1982; 6(4): 307–314.