

**Localized Malignant Pleural Mesothelioma  
Arising in the Interlobar Fissure:  
A Unique Surgical Case  
Masquerading Clinicopathologically as Primary Lung  
Adenocarcinoma**

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	and electron microscopy showed numerous, significantly elongated microvilli. Taken together, we finally made a diagnosis of localized malignant pleural mesothelioma (LMPM), epithelioid-type, arising in the right interlobar fissure between lower and middle lobe. We should be aware that, owing to its characteristic features, clinicians and pathologists might be able to raise interlobar fissure LMPM as one of differential diagnoses, based on careful clinicopathological examinations.

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## Case Report

### **R1: Localized Malignant Pleural Mesothelioma**

#### **Arising in the Interlobar Fissure:**

#### **A Unique Surgical Case**

### **Masquerading Clinicopathologically as Primary Lung Adenocarcinoma**

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Short running title: LMPM of the interlobar fissure.

Word count: 1,415 words (Abstract 232 words); References: 12; and 3 Figures & 1

Table.

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## Abstract

**An 80-year-old male with previous workplace exposure to asbestos presented**  
**with a** history of an increase in 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 (LMPM), epithelioid-type, arising in the right **interlobar fissure** between lower and middle lobe. We should be aware that, owing to its characteristic features, clinicians and pathologists might be able to raise **interlobar fissure** LMPM as one of differential diagnoses, based on careful clinicopathological examinations.

Key Words: Malignant pleural mesothelioma (MPM), **interlobar pleural fissure**, asbestos, localized MPM (LMPM), p16.

## 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 MPM (LMPM) [1]. Indeed, Klemperer and Rabin first reported the classification of mesothelioma, as **diffuse** (maximum) and localized (minimum) tumor, 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, 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 CT-guided **biopsy**. Although it is well known that most of 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 lobe. **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 prediluted 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 of 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 x 40 mm in diameter, presented likely in the right lower lobe (Figure 1A). 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 x 43 x 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 (Fig. 1B). The background of the lung had no remarkable change, i.e., not emphysematous (Fig. 1B). There were no other lung carcinoma components within our thorough investigation.

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 (Fig. 2A). The tumor was predominantly composed of a proliferation of atypical epithelioid cells, often arranged in an irregular and fused tubular growth pattern with prominent desmoplastic fibrosis (Fig. 2B). On high-power view, the atypical cells had enlarged and hyperchromatic nuclei, prominent nucleoli, and possible cilia (Fig. 2C). There was no intracytoplasmic

mucin with Alcian-Blue staining. The tumor between the right middle and lower lobe extended into the hilar lymph node and partly involved the right pulmonary artery (Fig. 2D). Immunohistochemically, the tumor cells were specifically and diffusely positive for calretinin (Fig. 3A), CK5/6 (Fig. 3B), 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 profile of the MPM cells is summarized in Table 1. Furthermore, *p16* deletions were specifically detected by FISH (Fig. 3C), but electron microscopy also showed numerous, significantly elongated microvilli (Fig. 3D). Based on all these features, we finally made a diagnosis of localized pleural malignant mesothelioma (LMPM), epithelioid-type, arising in the right **interlobar pleural fissure** between lower and middle lobe.

**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 20 months **as well as 5-year survival rate of less than 5% with best supportive care [1–7,9]**. 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* by 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 lobe.

**Conclusion**

We herein reported an extremely rare case of LMPM, epithelioid-type, arising in the right interlobar fissure. The present 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 differential diagnoses, and possibly a correct diagnosis. LMPM of the interlobar fissure may be more common than generally considered.

**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 by the Editor-in-Chief of this journal.

### **Competition interests**

The authors declare that they have no competing interests.

### **Authors' contributions**

SY, GX, JW, HI and HU participated in conception of the idea and writing of the manuscript. SY, GX, JW, KT, NK, YS and HU performed the histological and immunohistochemical interpretation of the tumor tissue. KT performed surgery, and KN analyzed FISH.

All authors have read and approved the final manuscript.

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## Figure Legends

**Figure 1. Imaging finding 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 x 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 x 43 x 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, i.e., 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).

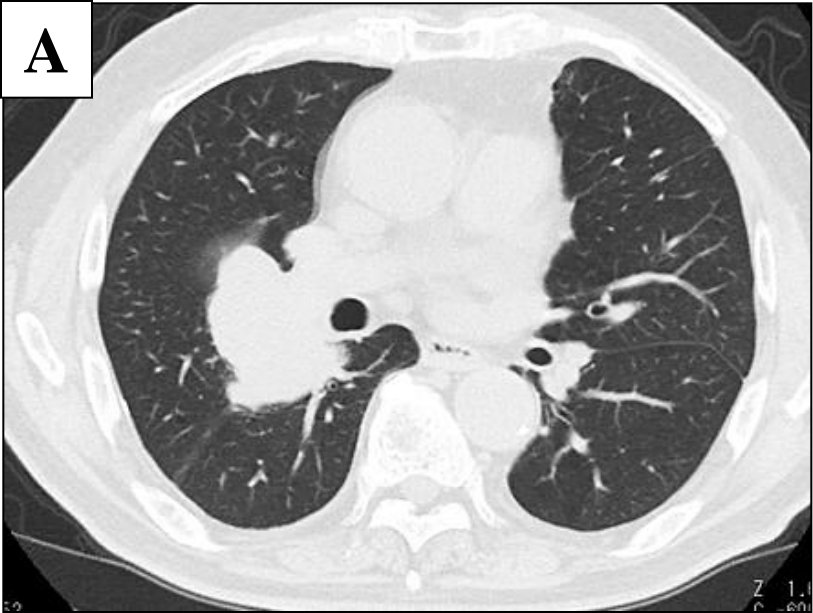
**Figure 3. Immunohistochemical, FISH and ultrastructural examinations of the epithelioid-type LMPM arising in the interlobar pleural fissure. (A, B)** Immunohistochemically, the mesothelioma cells of LMPM are specifically and diffusely positive for calretinin (A) and CH5/6 (B). (C) *p16* deletions (arrows) are specifically detected by FISH. (D) Electron microscopy shows numerous, significantly elongated microvilli. N = Nucleus. Bar = 2  $\mu$ m.

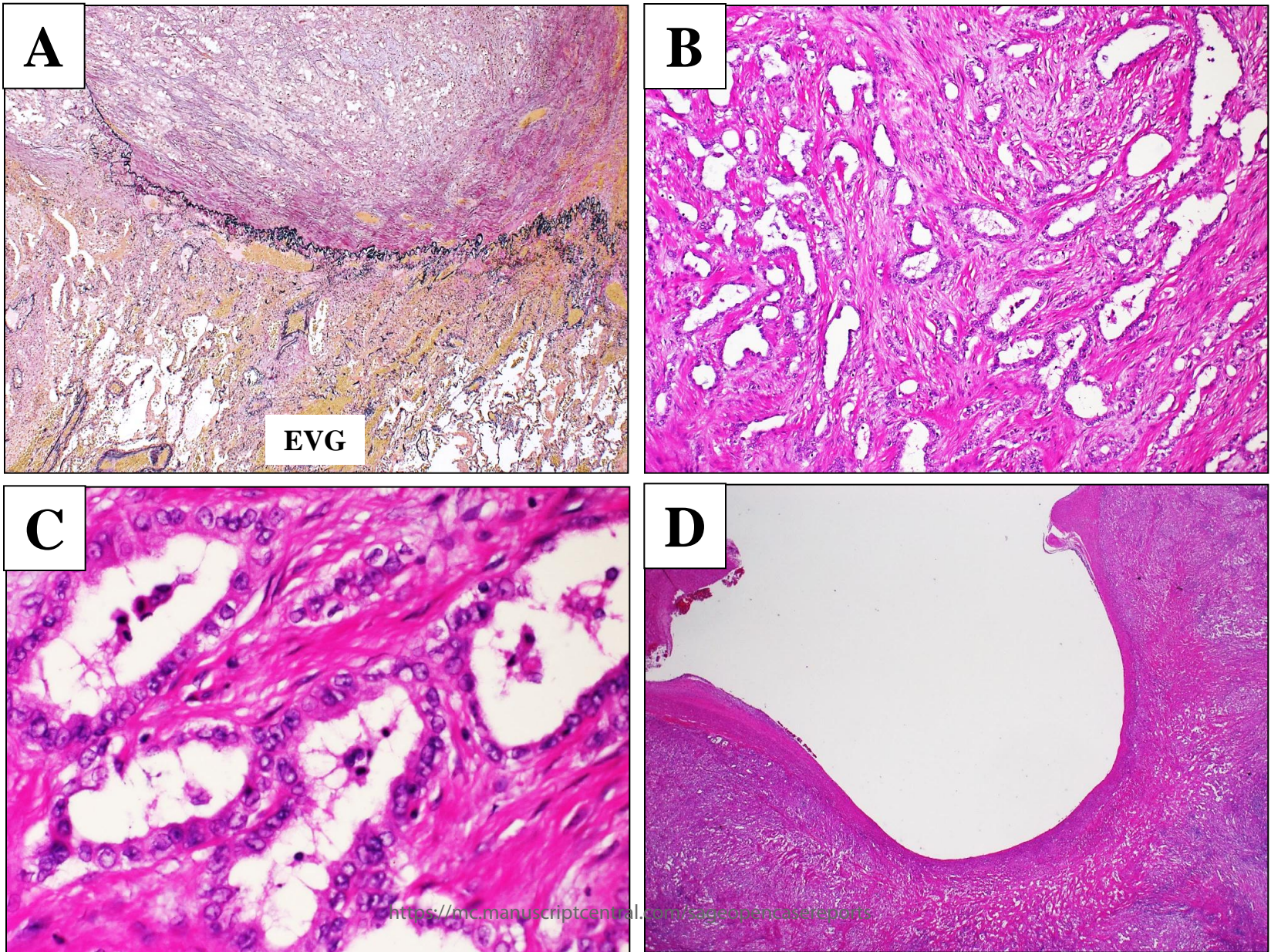
**Table 1. Immunohistochemical profile of the mesothelioma components in our case of interlobar fissure epithelioid-type LMPM.**

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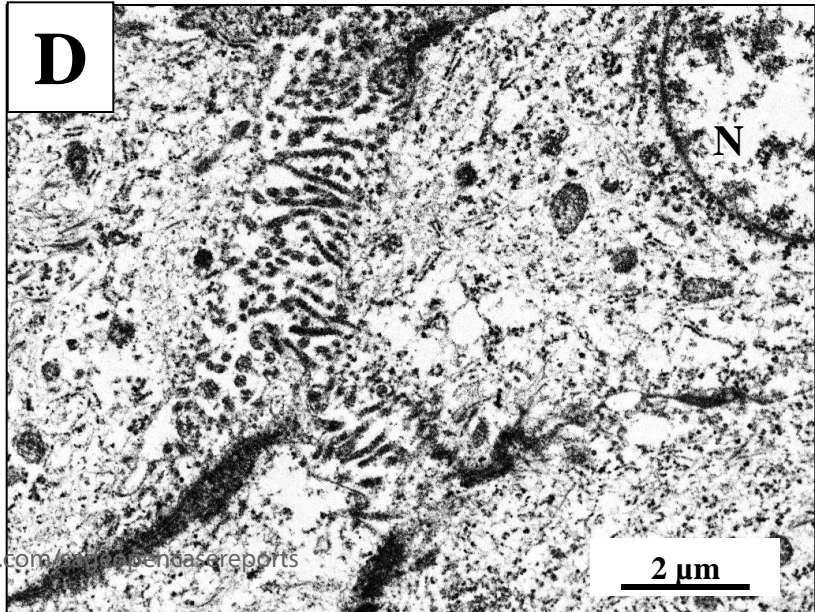
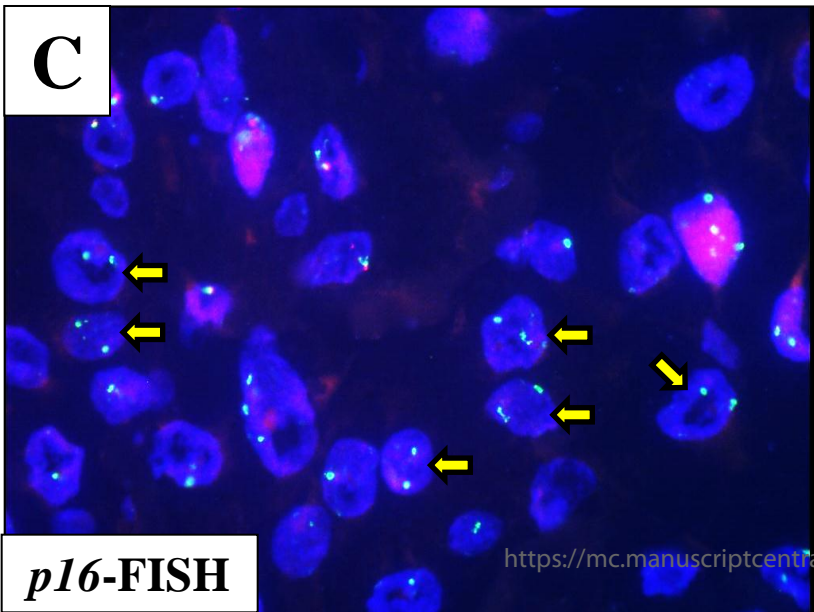
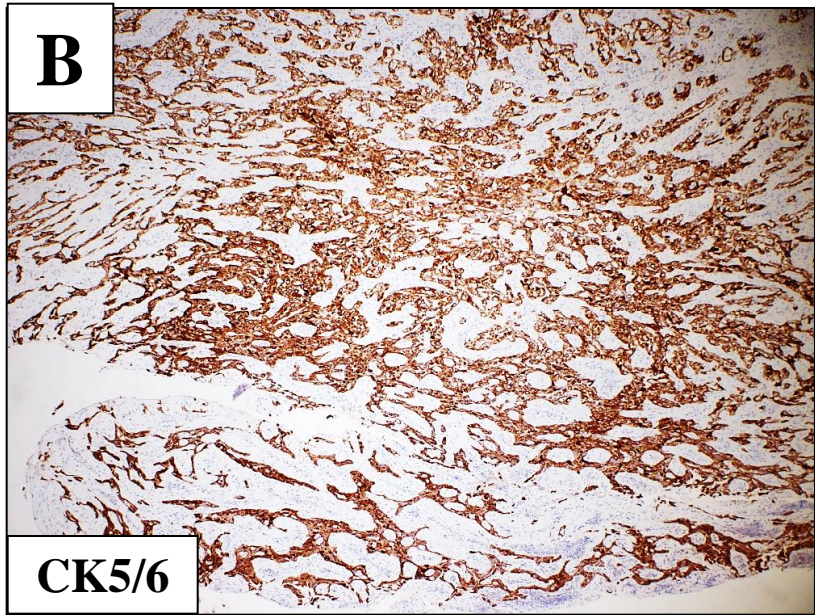
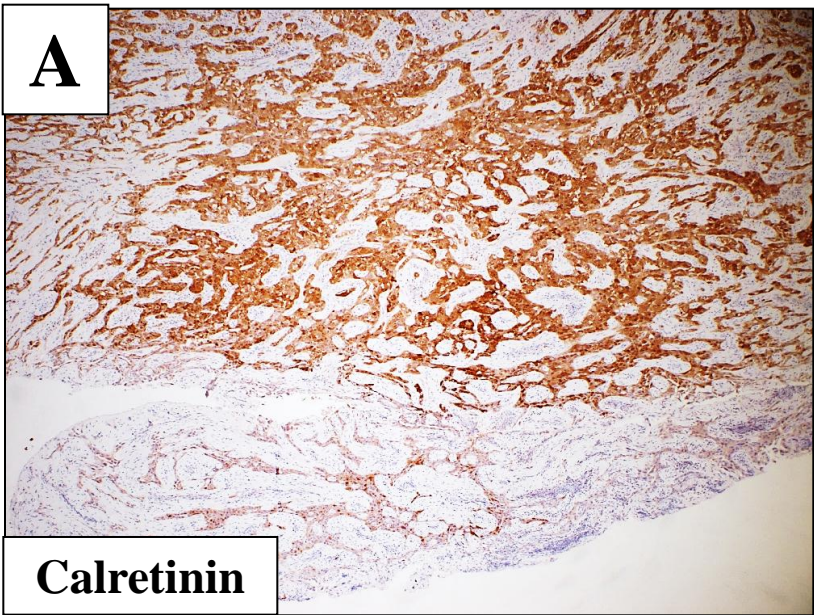
Positive	Negative
Calretinin	TTF-1
CK5/6	Synaptophysin
WT-1	Claudin-4
Ber-EP4 (focal)	MOC31
	CEA
	D2-40

# Figure 1





# Figure 3



## **Declarations**

### **Ethics approval and consent to participate.**

Not applicable.

### **Consent for publication**

Written informed consent was obtained from the patients and their families on admission for the publication of this report and any accompanying images.

### **Availability of data and materials**

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

### **Competing Interests**

The authors declare no conflicts of interest in association with this study.

### **Funding**

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Organization, Fukuyama Medical Center, Fukuyama, Japan.

**Authors' contributions**

SY, GX, HI and HU participated in conception of the idea and writing of the manuscript. SY, GX, JW, KT, NK, YS and HU performed the histological and immunohistochemical interpretation of the tumor tissue. KT and TH performed surgery, and KN analyzed FISH.

All authors have read and approved the final manuscript.