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CASE REPORT

Clinicopathological characteristics and molecular analysis of primary pulmonary mucoepidermoid carcinoma: Case report and literature review

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Keywords
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Abstract

Primary pulmonary mucoepidermoid carcinoma (PMEC) is extremely rare. Herein, we report a case of a 71-year-old male patient with high-grade PMEC involving the right upper lobe that was successfully resected via lobectomy. As a result of invasion into the pleural and paratracheal lymph nodes, four cycles of adjuvant chemotherapy with paclitaxel and carboplatin were administered. There were no signs of relapse during 10 months of follow-up. Furthermore, we reviewed the literature and summarized the surgical approaches, prognostic factors, and underlying genetic mechanisms of PMEC, which will benefit clinical treatment.

Introduction

Smetana *et al.* first described pulmonary mucoepidermoid carcinoma (PMEC) in 1952.[1–4] It is an extremely rare malignant neoplasm of the lung that accounts for approximately 0.1–0.2% of all lung malignancies.[3–7] PMEC is a salivary gland-type tumor of the lung,[5,8] deriving from the minor salivary glands of the tracheobronchial tree[9] and has been reported to occur over an age range of 3–78 years.[3,10,11] Compared to other salivary gland-type tumors of the lung, there is no gender predilection in PMEC.[5,12] According to the 2015 World Health Organization classification of lung cancer, PMEC is a mucoepidermoid carcinoma.[13] Histologically, PMEC consists of mucous-forming, epidermoid, and intermediate cells that are divided into high-grade and low-grade variants.[2,5,8,13–15] As opposed to high-grade PMEC, the prognosis of low-grade PMEC is excellent, with very good five-year survival rates.[16]

Case Report

A 71-year old man with a long smoking history presented for evaluation of an asymptomatic lung mass in the right upper lobe (Table 1, patient 1). On physical examination, his vital signs were normal and there were no abnormalities on auscultation of the chest. Enhanced chest computed tomography (CT) showed a solitary mass with

Table 1 Detailed clinical features of eight cases of surgically resected PMEC at our institution

No.	Age	Gender	Smoking index	Symptom	Location	Location 2	Surgical procedure	Grade	pTNM	Adjuvant treatment	Outcome	OS (months)	DFS (months)
1	71	M	2000	None	RUL	Segmental bronchus	Lobectomy	High	T2N1M0	Yes	Alive	9	9
2	29	F	0	Dyspnea	RUL	Lobar bronchus	Sleeve lobectomy	Low	T1N0M0	No	Alive	77	77
3	39	M	400	Hemoptysis	Trachea	Trachea	Sleeve resection of trachea	Low	T1N0M0	No	Alive	83	83
4	74	M	1200	None	RLL	Segmental bronchus	Wedge resection	Low	T1N0M0	Yes	Alive	14	14
5	69	F	0	Cough	RUL	Lobar bronchus	Sleeve lobectomy	High	T1N0M0	No	Alive	6	6
6	76	M	800	Dyspnea	RUL	Lobar bronchus	Sleeve lobectomy	High	T4N1M0	No	Alive	17	14
7	43	F	0	Cough	LUL	Lobar bronchus	Sleeve lobectomy	Low	T2N0M0	No	Alive	36	36
8	39	M	1600	Cough	RUL	Lobar bronchus	Sleeve lobectomy	Low	T1N0M0	No	Alive	35	35

DFS, disease-free-survival; LUL, left upper lobe; OS, overall-survival; PMEC, primary pulmonary mucoepidermoid carcinoma; pTNM, pathological tumor node metastasis; RLL, right lower lobe; RUL, right upper lobe.

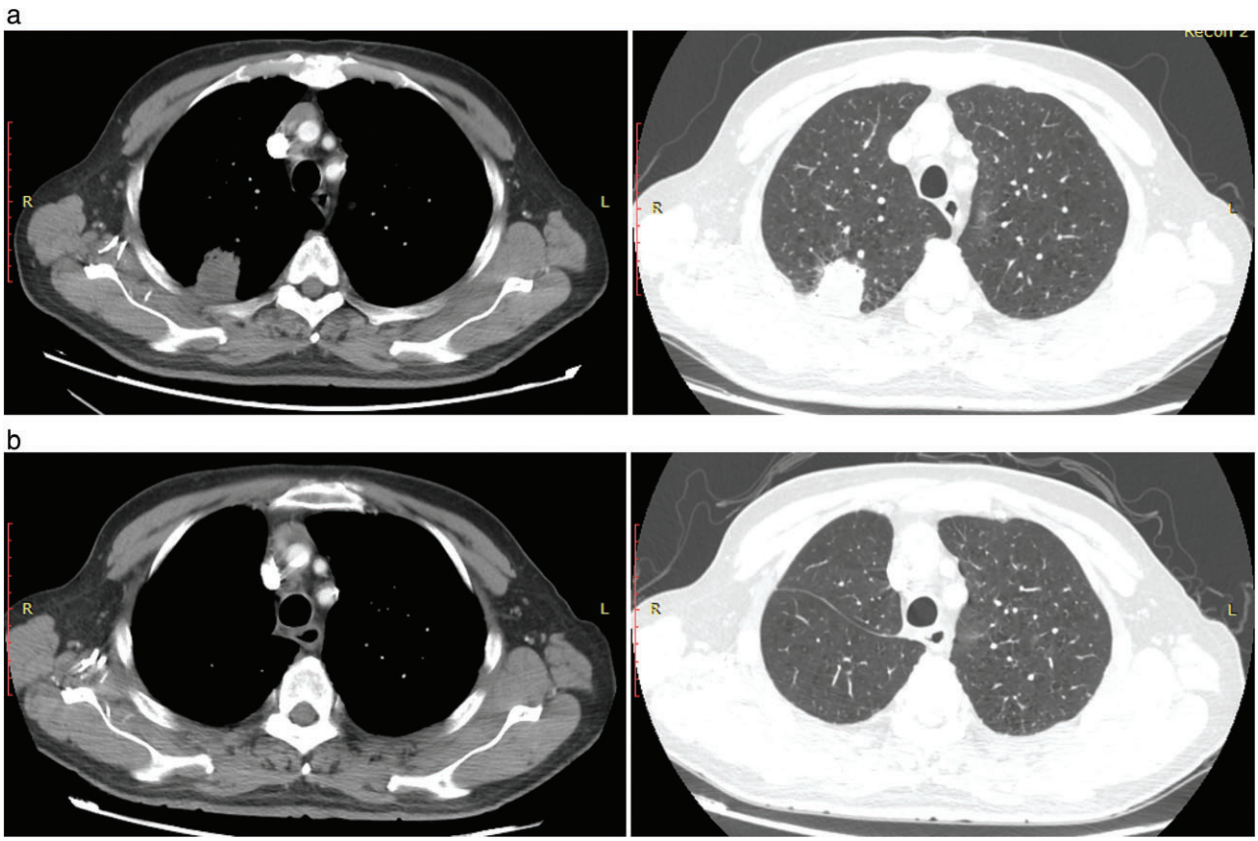

Figure 1 Chest computed tomography (CT) scans. (**a**) Enhanced CT shows a solitary mass with heterogeneous enhancement in the apico-posterior segment of the upper lobe of the right lung, approximately 3.5 × 3.4 × 2.7 cm in size. (**b**) CT taken two months postoperatively shows good recovery.

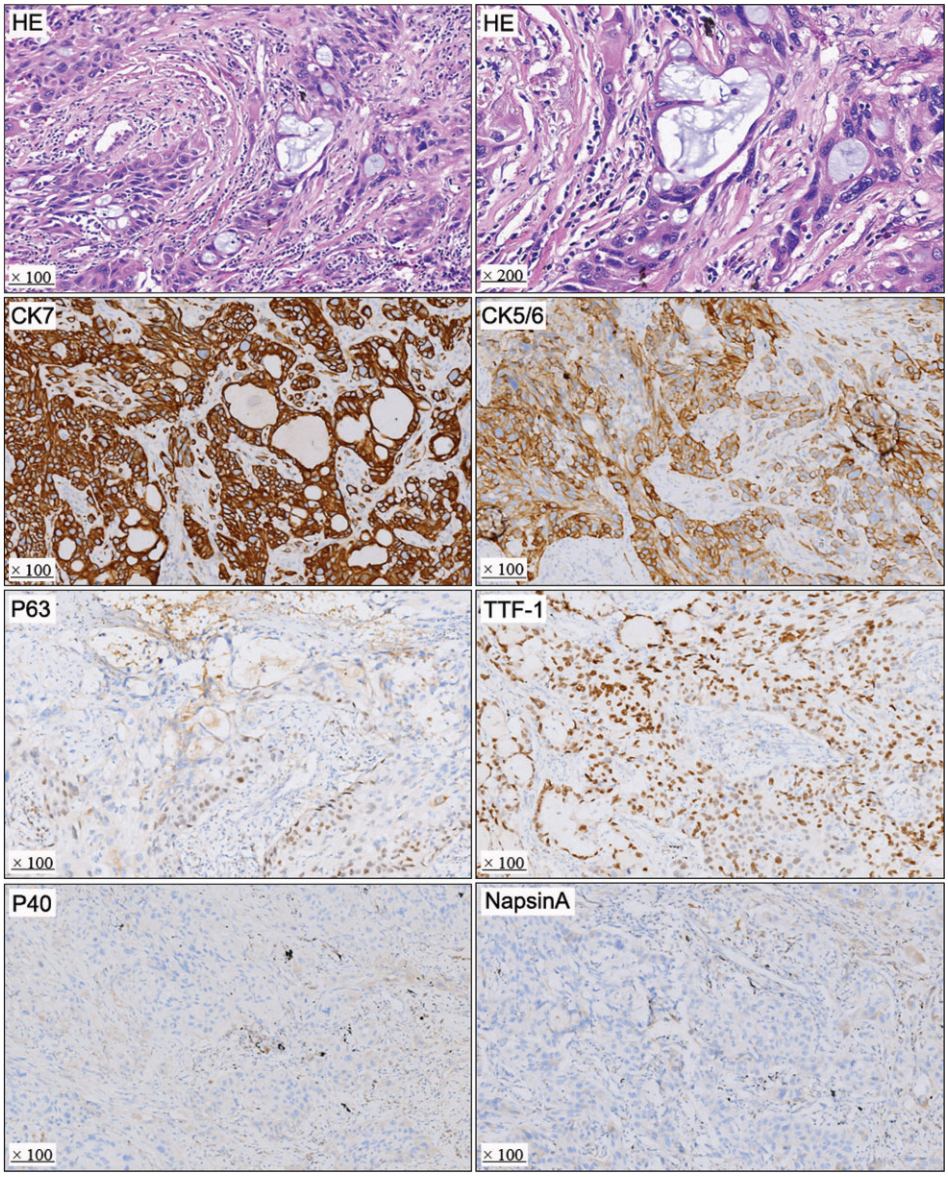

Figure 2 Hematoxylin–eosin (HE) staining and immunohistochemistry. The tumor cells were diffusely positive for CK 7; partially positive for CK 5/6, p63, and TTF-1; and negative for p40, NapsinA, SOX-2, and SPA.

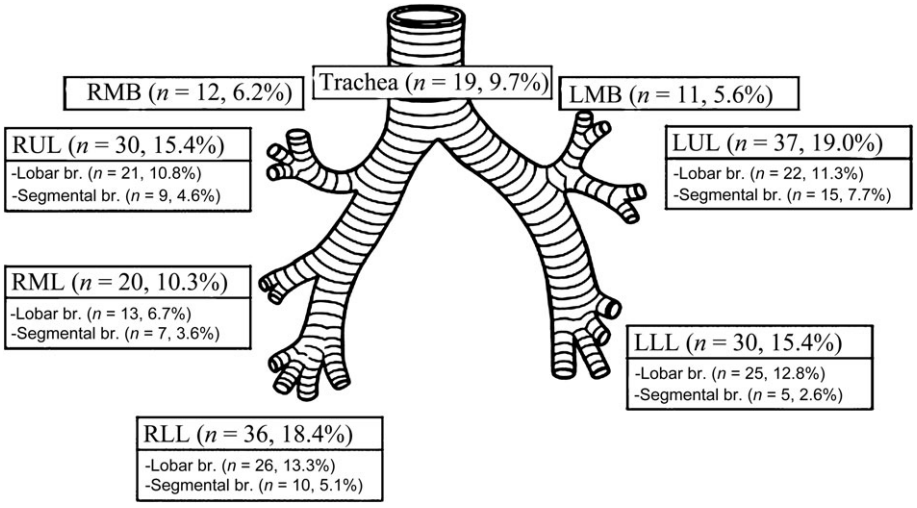

Figure 3 Tumor localization in 695 patients with primary pulmonary mucoepidermoid carcinoma. Tumors had no particular location tendency and were distributed almost equally among the trachea, right main bronchus (RMB), left main bronchus (LMB), and all lobes of both lungs. Br, bronchus; LLL, LUL, left upper lobe; left lower lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

Table 2 Clinicopathological characteristics and outcomes of literature review

Reference	Year (period)	Country	Number of cases	Age (years)	Gender (%)	Size (cm)	Treatment	TNM stage (%)	LN involvement (%)	Intrathoracic invasion (%)	Survival data	Prognostic factors
Jiang *et al.*[2]	2014 (2001–2013)	China	34 (L 25, H 9)	H: Median age 65 (24–78) L: Median age 40 (16–76)	M 19 (44.1) F 15 (55.9)	H: 3.5 (1.5–5.0) L: 2.5 (0.6–6.0)	Surgery 34 Postoperative Treatment Radiotherapy 2 Chemotherapy 7	H: I–IIA 3 (33.3) IIB–IV 6 (66.7) L: I–IIA 22 (88.0) IIB–IV 3 (12.0)	H: Yes 6 (66.7) No 3 (33.3) L: Yes 1 (4.0) No 24 (96.0)	NA	5 YSR OS 84.6% 5 YSR DFS 81.6%	Age TNM stage Grade LN metastasis
Hsieh *et al.*[4]	2017 (1991–2015)	China (Taiwan)	41 (L 10, H 31)	≤ 65 19 (46.3%) > 65 22 (53.7%)	M 30 (73.2) F 11 (26.8)	≤ 3 cm 25 (61.0%) > 3 cm 16 (39.0%)	Surgery 41	I 21 (51.2) II 11 (26.8) III–IV 9 (22.0)	Yes 15 (36.6) No 26 (63.4)	NA	Stage I: 5 YSR 7.0% II: 5 YSR 70.7% III–IV: 5 YSR 0% Grade L: 5 YSR 66.7% H: 5 YSR 53.2%	Disease stage pT status pN status ALI
Zhu *et al.*[9]	2014 (2004–2011)	China	42 (L/INT 33, H 9) MAML2 rearrangement (+) (*n* = 21) MAML2 rearrangement (–) (*n* = 21)	MAML2 rearrangement (+) Median age 33 (14–73) MAML2 rearrangement (–) Median age 60 (27–76)	MAML2 rearrangement (+) M 13 (61.9) F 8 (38.1) MAML2 rearrangement (–) M 12 (57.1) F 9 (48.3)	MAML2 rearrangement (+) 3.0 (0.5–6.5) MAML2 rearrangement (–) 3.0 (0.5–10.0)	NA	MAML2 rearrangement (+) I–IIA 19 (90.5) IIB–IV 2 (9.5) MAML2 rearrangement (–) I–IIA 17 (81.0) IIB–IV 2 (19.0)	MAML2 rearrangement (+) Yes 2 (9.5) No 19 (90.5) MAML2 rearrangement (–) Yes 5 (23.8) No 16 (76.2)	MAML2 rearrangement (+) Yes 4 (19.0) No 17 (81.0) MAML2 rearrangement (–) Yes 6 (28.6) No 15 (71.4)	MAML2 rearrangement (+) 5 YSR OS 94.7% 5 YSR DFS 88.4% MAML2 rearrangement (–) 5 YSR OS 64.6% 5 YSR DFS 53.0%	MAML2 rearrangement
Huo *et al.*[10]	2015 (2000–2014)	China	26 (L 18, H 8)	Mean age 46.5 (12–79)	M 13 (50.0) F 13 (50.0)	NA	Surgery 23 Chemotherapy 3	NA	Yes 1 (3.8) No 21 (80.8) NA 4 (15.4)	Yes 2 (7.7) No 20 (76.9) NA 4 (15.4)	5 and 10 YSR OS 72.1%	Age, peribronchial growth pattern, tumor size grade Ki-67 labeling index
Lee *et al.*[12]	2014 (2000–2010)	Korea	23 (L 5, INT 12, H 6)	H: Median age 57 (24–75) INT: Median age 32 (10–62) L: Median age 32 (12–54)	M 13 (56.5) F 10 (43.5)	H: 3.0 (2.0–4.0) INT: 2.35 (1.0–3.0) L: 1.4 (0–3.7)	Surgery 23	I–IIA 22 (95.7) IIB–IV 1 (4.3) NA 2 (9.5)	Yes 0 (0) No 23 (100)	NA	5 YSR DFS 100% 8 YSR OS 100% 8 YSR DFS 90.9%	NA

Table 2 Continued

Reference	Year (period)	Country	Number of cases	Age (years)	Gender (%)	Size (cm)	Treatment	TNM stage (%)	LN involvement (%)	Intrathoracic invasion (%)	Survival data	Prognostic factors
Zhu *et al.*[14]	2013 (2001–2013)	China	69 (L 45, INT 11, H 13)	Median age 47.5 (7–73)	M 38 (55.1) F 31 (44.9)	2.65 (0.5–10)	Surgery 66 Chemotherapy 3 Radiotherapy 4	I 48 (69.6) II 12 (17.4) III 8 (11.6) IV 1 (1.4)	Yes 12 (17.6) No 57 (82.6)	Yes 16 (23.1) No 53 (76.8)	Stage I–IIA: 5 YSR 90.8% IIB–IV: 5 YSR 54% Grade L-INT: 5 YSR 95% H: 5 YSR 41.7%	TNM stage, intrathoracic invasion, LN metastasis, margin status
Komiya *et al.*[16]	2016 (1973–2012)	United States	423 (L 226, H 73, unknown 124)	≥ 39 130 (30.7%) 40–69 219 (51.8%) ≥ 70 74 (17.5%)	M 232 (54.8) F 191 (45.2)	NA	Surgery alone 274 Surgery + Radiation 30 Radiation alone 64 Neither 55	NA	NA	NA	Stage Localized: 5 YSR 97% Regional: 5 YSR 56.9% Distant: 5 YSR 8.2% Grade L: 5 YSR 90.6% H: 5 YSR 28.6%	Age, distant stage, grade
Salem *et al.*[20]	2017	United States	16 (L 14, H 2)	Median age 40.4 (7.4–82.9)	M 7 (43.6) F 9 (56.3)	Median tumor size 2.6 (0.6–10)	Surgery 14 Radiation 6 Chemotherapy 3	II 10 (62.4) III 3 (18.8) IV 3 (18.8)	Yes 3 (18.8) No 13 (81.2)	Yes 1 (6.3) No 15 (93.7)	Median follow-up months 40.7 (1.7–120.1) Died 3 (18.8) Alive 13 (81.2)	

ALI, angiolymphatic invasion; H, high-grade tumors; INT, intermediate-grade tumors; L, low-grade tumors; LN, lymph node; NA, not assessed; PMEC, primary pulmonary mucoepidermoid carcinoma; TNM, tumor node metastasis; YSR, year survival rate.

Table 3 Summary of molecular analyses of PMECs from previous studies

Reference	Year (period)	Country	Number of cases	Age (years)	Sex (%)	Size (cm)	TNM stage (%)	LN involvement (%)	Intrathoracic invasion (%)	MAML2 rearrangement	EGFR mutation	Outcome
Behboudi *et al.*[8]	2006	Sweden Finland	Case 1: L Case 2: L Case 3: L	Case 1: 6 Case 2: 35 Case 3: 32	Case 1: F Case 2: M Case 3: F	Case 1: 1.3 Case 2: 1.0 Case 3: NA	NA	NA	NA	Case 1: Positive Case 2: Positive Case 3: Positive	NA	Case 1: 14 years Case 2: 11 years Case 3: 5 years
Zhu *et al.*[9]	2014 (2004–2011)	China	42 (L/INT 33, H 9)	MAML2 rearrangement (+) Median age 33 (14–73) MAML2 rearrangement (–) Median age 60 (27–76)	MAML2 rearrangement (+) M 13 (61.9) F 8 (38.1) MAML2 rearrangement (–) M 12 (57.1) F 9 (48.3)	MAML2 rearrangement (+) 3.0 (0.5–6.5) MAML2 rearrangement (–) 3.0 (0.5–10.0)	MAML2 rearrangement (+) I–IIA 19 (90.5) IIB–IV 2 (9.5) MAML2 rearrangement (–) I–IIA 17 (81.0) IIB–IV 2 (19.0)	MAML2 rearrangement (+) Yes 2 (9.5) No 19 (90.5) MAML2 rearrangement (–) Yes 5 (23.8) No 16 (76.2)	MAML2 rearrangement (+) Yes 4 (19.0) No 17 (81.0) MAML2 rearrangement (–) Yes 6 (28.6) No 15 (71.4)	Positive 21 L/INT 21 H 0 Negative 21 L/INT 12 H 9	NA	MAML2 rearrangement (+) 5 YSR OS 94.7% 5 YSR DFS 88.4% MAML2 rearrangement (–) 5 YSR OS 64.6% 5 YSR DFS 53.0%
Achcar *et al.*[21]	2009 (1997–2008)	United Kingdom	17 (L 10, H 7)	MAML2 rearrangement (+) Median age 39.5 (33–51) MAML2 rearrangement (–) Median age 59 (23–82)	MAML2 rearrangement (+) M 2 (15.4) F 11 (84.6) MAML2 rearrangement (–) M 3 (75.0) F 1 (25.0)	NA	NA	NA	NA	Positive 13 L 10 H 3 Negative 4 L 0 H 4	NA	NA
Yu *et al.*[22]	2012 (2001–2009)	China	20 (L 17, H 3)	H: Median age 65 (25–74) L: Median age 48 (8–73)	M 11 (55.0) F 9 (45.0)	H: 2.4 (1.5–3.5) L: 2.1 (0.5–4.5)	NA	NA	NA	NA	L861Q 5 I760I 1 None 14	Recurrence: L861Q 1 I760I 0 None 1

H, high-grade tumors; INT, intermediate-grade tumors; L, low-grade tumors; LN, lymph node; NA, not assessed; PMEC, primary pulmonary mucoepidermoid carcinoma; TNM, tumor-node-metastasis; YSR, year survival rate.

heterogeneous enhancement in the apicoposterior segment of the upper lobe of the right lung (Fig 1a). Laboratory evaluation showed elevated carcinoembryonic antigen levels (5.86 μg/L; normal range 0–5 μg/L) but no other abnormalities. The patient underwent video-assisted thoracic surgery with right upper lobectomy and lymph node dissection. Grossly, the mass measured 4 × 3.5 × 2.5 cm and was grey-white in color. On microscopic examination, all three typical cell types of mucoepidermoid carcinoma were observed (Fig 2). Immunohistochemistry revealed that the tumor cells were diffusely positive for CK 7; partially positive for CK 5/6, p63, and TTF-1; and negative for p40, NapsinA, SOX-2, and SPA. Ki-67 was approximately 70%. The final diagnosis was high-grade PMEC with pleural and paratracheal lymph node invasion (T2aN1M0, stage II b). All resection margins were negative. Postoperative CT showed good recovery (Fig 1b). The patient had four cycles of postoperative adjuvant chemotherapy with paclitaxel and carboplatin, and there were no signs of relapse during 10 months of follow-up.

Written informed consent was obtained from all patients for the publication of this case report and accompanying images.

Discussion

Several published reviews confirm that complete surgical resection remains the best treatment choice for PMEC and can result in better long-term survival compared to non-surgical treatment.[4–6,12] Advanced disease at the time of initial diagnosis may make complete resection difficult, especially in cases of high-grade PMEC. Because PMEC is a type of non-small cell lung cancer, adjuvant therapy should be administered when complete resection is not possible, although the utility of chemotherapy and radiotherapy in these cases remains controversial.[5–7,14,17,18]

We searched medical records from Tianjin Medical University General Hospital from January 2010 to April 2017 and identified a total of eight surgically resected cases of PMEC. Table 1 displays the characteristics of the eight patients and the surgical results. Patient 6, who had advanced high-grade disease (T4N1M0; stage IIIa) underwent extensive resection but refused chemotherapy, and experienced recurrence at 14 months. Patient 4, who had poor cardiovascular status, underwent a wedge resection with a final diagnosis of low-grade PMEC with positive margins. Thus, he received two cycles of pemetrexed and nedaplatin and one cycle of gemcitabine and nedaplatin and showed no sign of relapse during 14 months of follow-up.

In addition to our in-house review, we reviewed 695 cases of PMEC from nine previous studies. Most PMECs are low/intermediate grade, and tumor locations indicate no particular tendency (Fig 3). Complete resection of PMEC, whether high-grade or low-grade, in the absence of lymph node metastasis, yielded good prognosis, and prognostic factors predicting aggressive behavior included age, histological grade, tumor-node-metastasis stage, lymph node metastasis, and complete resection (Table 2).

The *MECT1/3* fusion gene is common in PMEC.[8–10] In 62 patients analyzed in our systemic review, *MAML2* rearrangement was much more common in low-grade (73.9%) compared to high-grade (18.8%) PMEC cases (Table 3). Five-year overall survival was also better in the *MAML2* rearrangement-positive group (94.7% vs. 64.6% in patients without *MAML2* rearrangement). Thus, *MAML2* rearrangement may signal a better prognosis in cases of PMEC.

Finally, in a study by Han *et al.*, gefitinib administration was attempted to treat a case of PMEC after metastasis to the chest wall and contralateral lung.[8,19] CT follow-up indicated that the metastatic lesions had responded to the treatment, although there was no *EGFR* tyrosine kinase mutation detected in the chest wall tumor. These findings suggest that PMECs with the *MECT1-MAML2* fusion gene may be a valid target for tyrosine kinase inhibitor therapy. However, this hypothesis requires further investigation in a clinical setting.

In summary, complete surgical resection remains the mainstay of treatment for PMEC and can result in long-term survival. Adjuvant chemotherapy may be useful in patients with high-grade PMEC, especially in cases of lymph node involvement or intrathoracic invasion. The current literature indicates that the *MECT1-MAML2* fusion gene is common in PMEC and is specific to this tumor. Identifying *MAML2* rearrangement might be helpful to differentiate PMEC from other epithelial lung malignancies. *MAML2* rearrangement seems to be associated with a favorable clinical outcome and PMEC cases with the *MECT1-MAML2* fusion gene may exhibit a good response to tyrosine kinase inhibitor therapy.

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Disclosure

No authors report any conflict of interest.

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