

CASE REPORT

Spindle cell subtype of pulmonary clear cell tumor with prominent calcification and malignant potential

Yinghua Song¹, Fangfang Chen¹, Caiqing Zhang¹ & Xiaoyan Lin²¹ Department of Respiratory Medicine, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, China² Department of Pathology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China**Keywords**

Clear cell tumor; malignant potential; perivascular epithelioid cell tumor; spindle cells.

Correspondence

Xiaoyan Lin, Department of Pathology, Shandong Provincial Hospital Affiliated to Shandong University, 324 JingWu Road, Jinan 250021, China.

Tel: +86 531 6877 6430

Fax: +86 531 8790 1265

Email: linxiaoyan@163.com

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Thoracic Cancer **8** (2017) 530–534**Abstract**

Perivascular epithelioid cell tumor of the lung, also known as clear cell “sugar” tumor, is a rare benign tumor arising from perivascular epithelioid cells. Herein, we present a case of spindle cell subtype of pulmonary perivascular epithelioid cell tumor with prominent calcification and malignant potential in a 49-year-old woman. Histologically, the striking feature of this lesion was attributed to the presence of spindle cells arranged in a diffuse pattern, which is a pitfall for diagnosis. However, some of the lesion contained polygonal tumor cells with clear abundant cytoplasm surrounded by thin-walled vascular spaces. The size of the tumor and its Ki-67 index suggested malignant potential, and calcification was another rare characteristic. Immunostaining indicated that the tumor cells were positive not only for HMB-45 and Melan A, but also for CD34 and CD1a. This tumor should be distinguished from tumors with rich spindle cells such as sarcoma, clear cell carcinoma, or metastatic tumors. The patient in this case was alive with no tumor recurrence or metastasis six months after lobectomy.

Introduction

As a new classification category, perivascular epithelioid cell tumors (PEComas) are defined as “mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells.”¹ (p.252) PEComas of the lung, also called “sugar” or clear cell tumors (CCTL), are rare benign neoplasms that consist of clear cells with high glycogen levels in the cytoplasm. They are positive for HMB-45 and Melan A, but negative for cytokeratin (CK). Definitive preoperative diagnosis is difficult because of the rarity of this tumor, with only 50 reported cases in the literature.² Herein, we present a case of PEcoma of the lung in a female patient treated by surgical resection. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Case report

A 49-year-old female presented with a 10-month history involving a vague chest tumor, and was admitted to

Shandong Provincial Hospital, China for further treatment. A pulmonary mass was first detected in the patient’s right lower lung during preoperative examination of an ovario-cystectomy. The mass was observed with a clear boundary but without mediastinal lymph node enlargement, indicating the possibility that it was benign. Ten months later, the patient presented with a cough and chest pain and returned to the hospital. A new lung computed tomography (CT) examination was conducted, revealing a solitary circular pulmonary nodule with a smooth edge in the lower lobe of the right lung, but without obvious changes compared to that in the 10 months previously. A contrast-enhanced CT scan of the chest showed that the mass was 4.5 × 4 cm in size, with obvious enhancement and abundant vascularity (Fig 1a,b), which meant that the possibility of malignancy could not be excluded. A carcinoid in particular could not be completely ruled out because it is a low-grade malignant tumor with relatively slow growth. Physical examination revealed no abnormalities with the exception of cough and chest pain. Therefore, it was decided to perform surgical thoracoscopic right lower

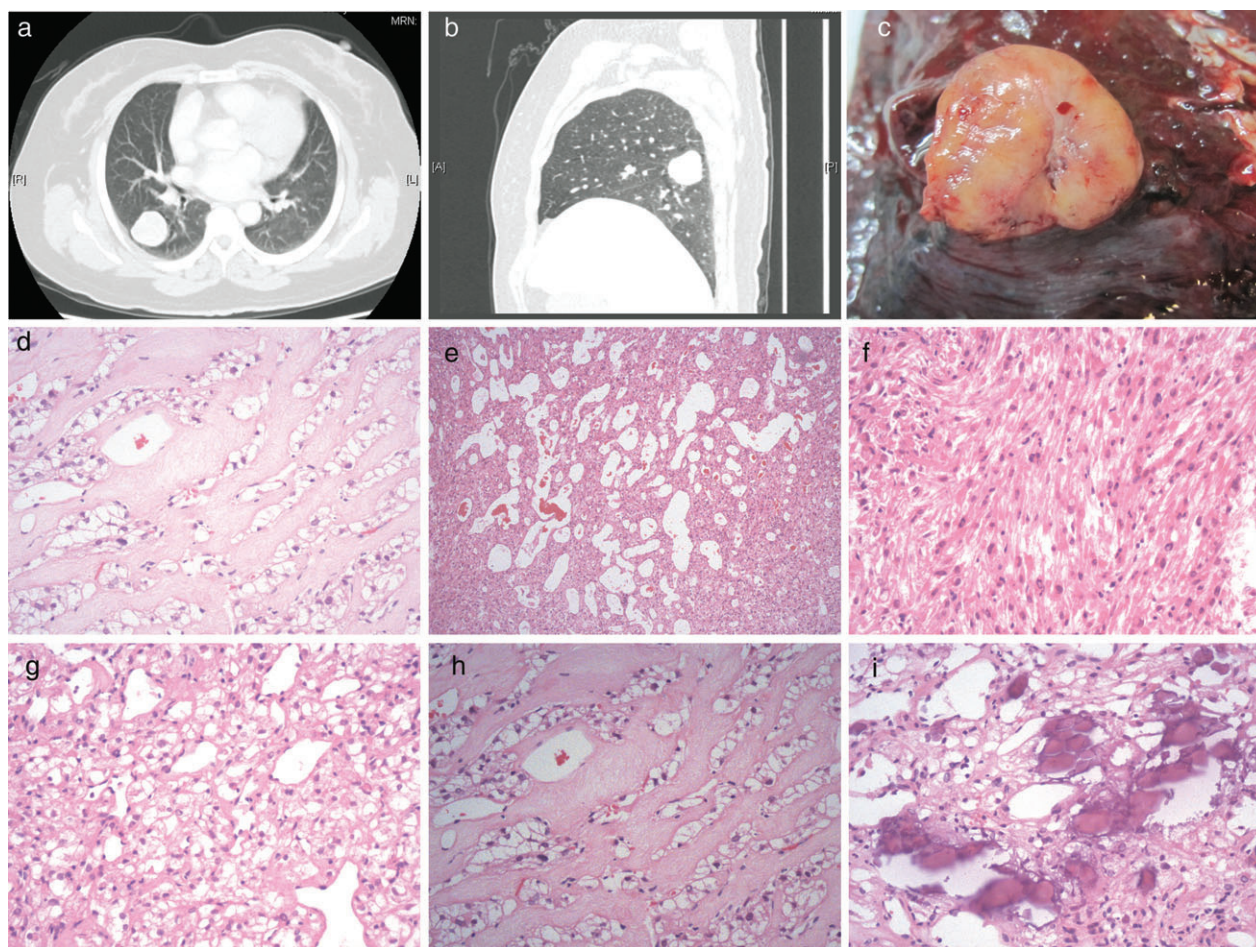


Figure 1 Computed tomography features and histological characteristics of perivascular epithelioid cell tumors in the lung. (a, b) Contrast-enhanced computed tomography thorax-axial and coronal section showing a mass in the right lower lobe. (c) Gross pathological examination shows a mass >4 cm. (d) The tumor does not have a fibrous capsule and presents with a solid cellular growth pattern. (e) Abundant stroma with thin walled blood vessels. (f) The tumor is predominantly composed of spindle and histiocytoid shaped cells. (g) Perivascular epithelial cells are arranged around the vessels. (h) Hyaline degeneration. (i) Calcification is another characteristic of the tumor (hematoxylin & eosin, original magnification $\times 200$).

lobectomy, as the patient refused pathological biopsy and the mass was potentially malignant.

A solid mass was found in the parenchyma of the right lower lung lobe, with parietal adhesion to the middle lobe and pleura. The tumor was approximately $4 \times 3 \times 2 \text{ cm}^3$ in size, and was located 2 cm from the bronchial tangent. It had well-defined margins and was grayish-pink on the cut surface (Fig 1c).

The resected specimens were fixed with 10% neutral buffered formalin and embedded in paraffin blocks. Tissue blocks were cut into 4 μm slides, deparaffinized in xylene, rehydrated with graded alcohols, and stained with hematoxylin and eosin or immunostained with the following antibodies: CK, Vimentin, HMB45, Melan A, CD34, CD99, desmin, actin (SM), CD1a, S-100, thyroid transcription factor-1, surfactant protein A, epithelial membrane antigen (EMA), synaptophysin, CD56, calretinin, CD31, mucin,

CK7, CD117, and Ki-67. Sections were stained with a streptavidin-peroxidase system (PV-6000, Beijing Zhong-Shan Biotech Corp., Beijing, China). Diaminobenzidine tetrahydrochloride substrate (DAB kit; Beijing ZhongShan Biotech Corp.) was used, slightly counterstained with hematoxylin, dehydrated, and mounted. For the negative controls, the primary antibody was replaced with phosphate buffered saline.

Histopathological examination showed that the neoplasm was demarcated from the surrounding lung tissues with a relatively clear boundary. The tumor did not have a fibrous capsule, and presented with a solid cellular growth pattern and abundant vascularity (Fig 1d). It was made up of two cell components, spindle and perivascular epithelial cells. The tumor was composed of cells with a sheeted appearance and scant stroma interspersed with thin walled blood vessels (Fig 1e). The tumor cells were spindle and

histiocytoid in shape, with clear to pale eosinophilic cytoplasm, a low nuclear to cytoplasmic ratio, small central nucleoli, and inconspicuous mitotic activity without any necrosis (Fig 1f). These cells, with more of a spindle shape made up >75% of the tumor. However, other tumor cells arranged along the vessels showed prominent typical characteristics of perivascular epithelial cells (Fig 1g). The cells had clear abundant cytoplasm, with indented polygonal tumor cells, and pleomorphic nuclei with a distinct cell border, surrounded by thin-walled vascular spaces and sinusoid-type vessels. No necrosis, hemorrhage or cyst formation was observed in the tumor. Hyaline degeneration had occurred in the mesenchyme (Fig 1h), and calcification was another characteristic of the tumor (Fig 1i).

Periodic acid–Schiff staining was positive in the tumor cell cytoplasm, which could be digested by amylase (Fig 2a). Reticular fiber staining revealed reticular fibers surrounding each tumor cell. Immunohistochemical analysis indicated that the tumor cells were positive for HMB-

45, Melan A, CD34, vimentin, CD1a, and partially positive for smooth muscle actin (SMA) (Fig 2b–g). However, the tumor cells were negative for CK (Fig 2h), EMA, synaptophysin, chromogranin, S-100, thyroid transcription factor-1, surfactant protein A, CD31, desmin, mucin, CK7, and CD117. The Ki-67 index was 3–5% (Fig 2i). The overall characteristics of the tumor favored a pathological diagnosis of PEComa (CCTL) with calcification in the lower lobe of the right lung and malignant potential. The patient was alive with no tumor recurrence or metastasis after six-months of follow-up.

Discussion

PEComas are a group of mesenchymal neoplasms that are all characterized by the presence of perivascular epithelioid cells.³ Regardless of their location, the tumors in this family include angiomyolipoma, lymphangiomyomatosis, CCTLs, and a set of similar visceral and soft tissue lesions. CCTLs,

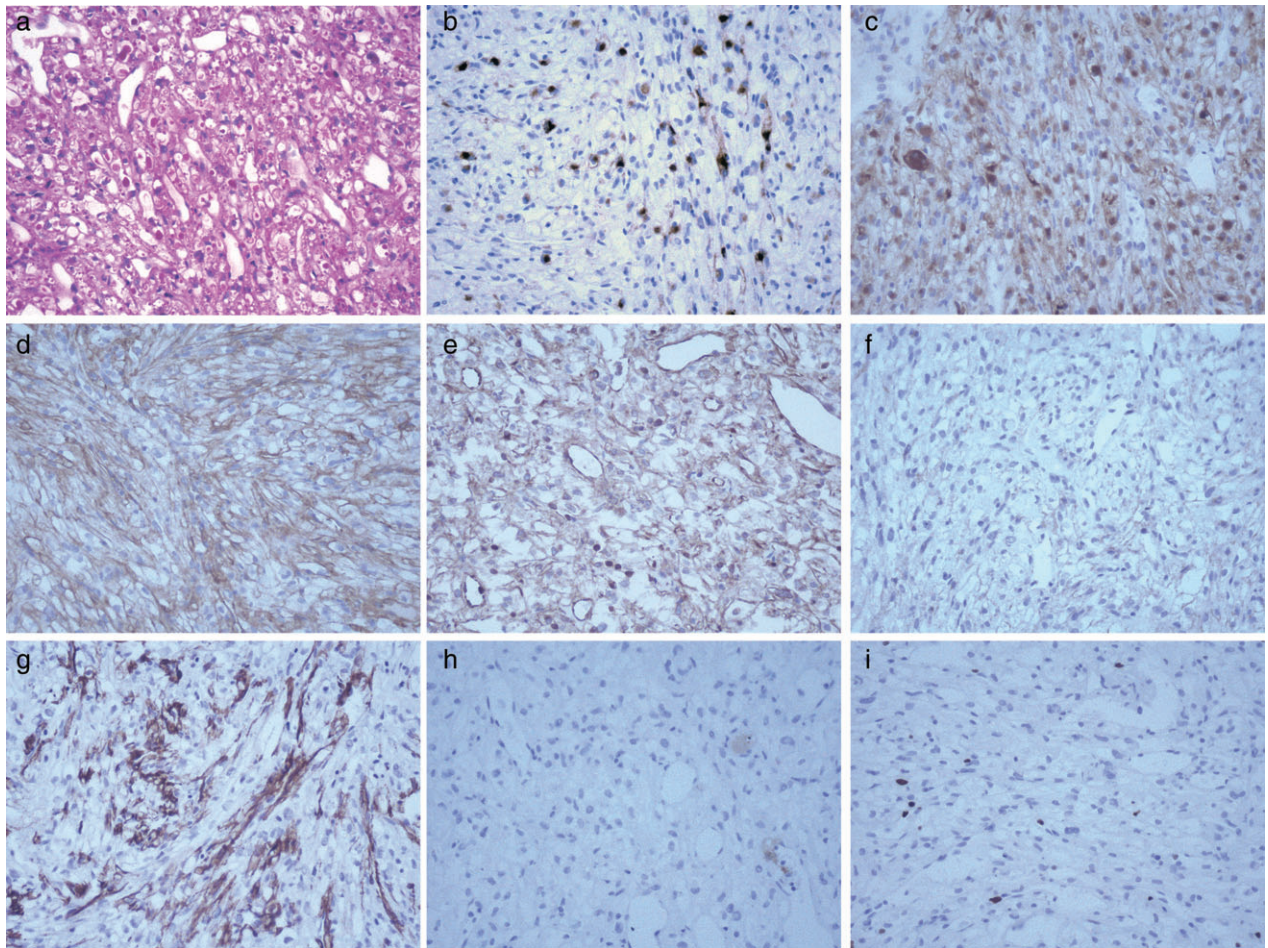


Figure 2 Histochemistry and immunohistochemistry staining of the perivascular epithelioid cell tumor in the lung. (a) Periodic acid–Schiff staining indicates abundant glycogen in the cytoplasm. The tumor cells stained positive for (b) HMB-45, (c) Melan A, (d) CD34, (e) Vimentin, (f) CD1a and (g) smooth muscle actin and negative for (h) cytokeratin. (i) Ki-67 is about 3% (original magnification of a–i $\times 400$).

a member of the PEComa family occurring in the lung, are very rare. Although CCTLs can occur in any age group (range 8–73 years), they are usually found in adults aged 40–50, and there is a slight predominance in women.⁴ Most lesions are solitary, asymptomatic, located within the peripheral lung, and are difficult to diagnose. Cough, chest pain, hemoptysis, and high fever are rare presenting symptoms of CCTLs. Our female patient had symptoms including cough and chest pain, which are unusual for such a tumor. Radiographically, CCTLs present as round, peripheral parenchymal nodules with no evidence of cavitation or calcification. On contrast-enhanced CT scans, these lesions might show intense post contrast enhancement because of their rich vascular stroma.

Macroscopically, a CCTL appears as a pink nodule of approximately 2 cm (range 1–6.5 cm) that is well demarcated from the lung parenchyma, unencapsulated, and without necrosis or bleeding. Microscopic study typically shows large cells with clear abundant cytoplasm, without atypia or mitoses, consistent with a benign tumor. In this case, the striking feature was the prominent spindle cell area, which occupied more than 70% of the tumor, making it difficult to diagnose. The first diagnosis that came to mind was a spindle cell tumor, such as leiomyoma, sarcomatoid carcinoma, solitary fibrous tumor, and metastatic tumor. We reviewed the case carefully and found that there were perivascular epithelioid cells with clear cytoplasm present that were arranged around the thin-walled vessels, which indicated a diagnosis of CCTL. Another pathological characteristic in this case was the presence of calcifications, the first time they have been reported in this type of tumor. CCTL is characterized immunohistochemically by immunoreactivity for HMB-45, Melan A and non-reactivity for CKs and EMA, which is consistent with reported immunohistochemical staining patterns. In our case, the tumor cells were positive not only for HMB-45 and Melan A, but also for CD1a, CD34 and SMA. Adachi *et al.* reported a case of benign clear cell tumor of the lung positively stained for CD1a in a 60-year-old man, and they also confirmed CD1a expression in 19 cases with PEComa.⁵ These results suggested that CD1a expression could be an additional marker for PEComas, and also indicates that this tumor is a distinct and integrated disease entity.⁶ CD34 is usually absent or scattered in PEComas that occur in other organs; however, it stains strongly and is diffusely distributed in lung CCTLs. Positive staining of CD34 may be important for the diagnosis of pulmonary CCTL.⁷ Recently, a novel type of interstitial cell called a telocyte has been discovered, which might be the cell of origin for both PEComas and gastrointestinal and extragastrintestinal stromal tumors, according to the immunohistochemistry expression pattern.⁸

Clear cell tumors should be distinguished from other primary or metastatic pulmonary tumors, especially those with prominent clear cells, such as clear cell carcinoid in the lung, metastatic renal cell carcinoma, metastatic melanoma, granular cell tumors, oncocytoma, and acinic cell carcinoma. In addition, CCTLs should also be distinguished from other tumors in the lung with prominent spindle cells, such as leiomyoma, sarcomatoid carcinoma, metastatic tumor, and solitary fibrous tumor. A careful search for the features of perivascular epithelioid cells, combined with special immunohistochemical staining is helpful in achieving a differential diagnosis.

According to World Health Organization guidelines, excision is the treatment of choice for CCTLs and no adjuvant therapy is recommended. CCTLs have previously been reported to behave in a benign fashion, although one study reported a case of fatal recurrence and metastasis.⁹ Tumors with characteristics including size >2.5 cm, necrosis, a mitotic index in 1/50 high-power fields, marked pleomorphism, and nuclear atypia could be considered as having malignant potential.¹⁰ In our case, necrosis and a mitotic index were not found, but the tumor was 40 mm in diameter and the Ki-67 labeling index was 3–5%, which suggested malignant potential. Careful long term follow-up of this patient is recommended. The patient was alive with no tumor recurrence or metastasis after six months of follow-up.

In conclusion, our report describes a case of CCTL of the lung with prominent spindle cells and calcification. This variant of PEComa should be recognized and misdiagnosis avoided, because other malignant tumors, such as pulmonary clear cell carcinoma or sarcoma, require an active treatment regimen. Positive staining of CD34, melanin marker, CD1a, and SMA are factors that may be helpful in the diagnosis of this rare pulmonary tumor. Our case will require long-term follow-up.

Acknowledgment

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Disclosure

No authors declare any conflict of interest.

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