Primary proximal epithelioid sarcoma of the lung: a case report and review of the literature

Authors: Jiay Li, Yehan Zhou and Yang Liu
Title: Primary proximal epithelioid sarcoma of the lung: a case report and review of the literature

Author Names: Jiayu Li¹; Yehan Zhou§; Yang Liu¹ *

Authors’ Affiliations: 1. Department of Pathology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China.

Co first author: §Yehan Zhou

Corresponding author: *Yang Liu

Department of Pathology, Sichuan Cancer Hospital & Institute, No.55, section 4, Renmin South Road, 610041, China.

Tel: +86-28-85420341

Mail: Yang Liu (liuyang_secancer@sina.com); Jiayu Li (lijiayu1011@163.com);

Yehan Zhou (247222637@qq.com)

Reference: 28
Abstract

Epithelioid sarcoma (ES) is a rare mesenchymal tumor that can be divided into proximal/axial type and classical/distal type. Primary proximal epithelioid sarcoma of the lung is extremely rare. So far, no more than five cases have been reported. We reported a case of primary pulmonary ES and reviewed the literature to summarize its clinicopathological features. A 51-year-old man presented with hemoptysis and cough. Chest computed tomography (CT) showed a nodule located in the apical and posterior segments of the left upper lobe of the lung. The patient underwent a lobectomy, and a pathologic diagnosis of epithelioid sarcoma was made. Histologically, most tumors are composed of epithelioid cells with evidence of bidirectional expression of epithelium and mesenchyma. The SMARCB1 stain of tumor cells was negative, and a pathogenic mutation of SMARCB1 p.E115* (exon 3) were identified by the next-generation sequencing. Two months after surgery, positron emission tomography/computed tomography (PET/CT) indicated tumor recurrence, and the patient received a round of adjuvant chemotherapy combined with immunotherapy. After 11 months of follow-up, the patient died.

We reported in detail the primary proximal epithelioid sarcoma of the lung treated with immunotherapy for the first time, providing ideas for diagnosis and treatment.

Keywords

Epithelioid sarcoma, Lung, SMARCB1, INI-1
Introduction

Epithelioid sarcoma (ES) is a relatively rare and aggressive soft tissue tumor first named by Enzinger, which accounts for <1% of all soft tissue sarcomas (Enzinger, 1970). According to its location, two different types of ES have been described, namely the classical/distal type and the proximal/axial type. Classical ES involves the skin, subcutaneous tissue or deeper soft tissue in the extremities of young adults, while proximal ES is more seen in axial locations and deep-seated lesions over a wide age range and has a worse prognosis (Thway et al., 2016).

Recently, several reports have described that proximal ES might occur in visceral tissues such as the kidney, adrenal gland, uterine, esophagus and so on (Jeney et al., 2003; Maggiani et al., 2007; Alikhan et al., 2017). Primary pulmonary ES is extremely rare, and no more than five cases have been reported in the literature.

We herein report a case of a primary pulmonary proximal-type ES along with relatively detailed clinicopathological information to provide more data for rare diseases.

Materials and methods

Case report

A 51-years-old man was admitted to our hospital due to the symptoms of cough and hemoptysis for 3 months. A computed tomography (CT) scan of the chest revealed a 2 cm-sized nodule in the left upper lobe of the lung. CT value was 36Hu, and the enhanced scan showed a mild to moderate non-uniform enhancement (Fig. 1). Moreover, the tumor was shown to invade the mediastinum and thoracic vertebrae. The patient has a history of smoking but has no additional tumors. A lobectomy was subsequently performed, and a diagnosis of poorly differentiated carcinoma was initially considered.
No lymph node metastasis was found. The diagnosis of ES was eventually made by consultation with immunohistochemical and genetic tests.

Two months after the surgery, positron emission tomography/computed tomography (PET/CT) showed a soft tissue mass in the left hilum of the lung and uneven thickening and enhancement of the left pleura (Fig. 2). A suspicion of recurrence and pleural metastasis was made. Therefore, the patient received five cyclic treatments of adjuvant chemotherapy with albumin-bound paclitaxel (175mg d1, 200mg d8) and cisplatin (50mg d1, d8) combined with Pembrolizumab (200mg). Implantable radiotherapy was also performed once during this period. However, imaging still indicated progression of the disease. Therefore the chemotherapy drugs were later replaced by vinorelbine and carboplatin and were administered once. Unfortunately, the patient died of severe myelosuppression nine months after his initial diagnosis. Multiple examinations found no other visceral and skin lesions in the patient's whole body.

Methods

Formalin-fixed paraffin-embedded (FFPE) tissues were cut into 3µm-thick sections then stained with haematoxylin and eosin (H&E) and immunohistochemically stained for CD34, Pan-Cytokeratin (CKpan), Vimentin, Smooth muscle actin (SMA), Desmin, MyoD1, Myogenin, WT-1, Calretinin, Melan-A, HMB45, TdT, CD117, ERG, Sall4, P63, thyroid transcription factor-1 (TTF-1), NapsinA, LCA, S100, Syn, CD68, SMARCB1, SMARCA4, Ki67 and PD-L1 (clone 22C3). These antibodies were applied on Zhongshan Golden Bridge Biotechnology Development according to the EnVision method.
DNA of FFPE was extracted using a QIAamp DNA FFPE Tissue Kit (Qiagen) according to the manufacturer’s instructions. Extracted DNA was purified and qualified to employ the Nanodrop2000 (Thermo) and then quantified by Qubit3.0 (Life Technology) with a dsDNA HS Assay Kit (Life Technology) according to the manufacturer’s protocols. DNA Libraries were subjected to PCR amplification and purification before targeted enrichment. Libraries from different samples were marked with unique indices during library preparation, and up to 2µg of different libraries were pooled together for targeted enrichment. Library quantification was analyzed by the KAPA Library Quantification kit (KAPA Biosystems). The size distribution of libraries was measured by Agilent Technologies 2100 Bioanalyzer (Agilent Technologies). The enriched libraries were sequenced on Novaseq NGS platforms (Illumina) to coverage depths of at least 1000x for FFPE. Finally, various types of DNA gene fusion mutations, gene copy number changes, point mutations, base insertion and deletion mutations in tumor tissues were comprehensively analyzed by bioinformatics.

Results

Histologically (Figure 3), the tumor cells were composed of epithelioid cells arranged in a sheet or solid pattern. However, the loose cohesion of tumor cells in some areas differed from the tight connection of epithelial-derived tumors. Stromal fibrosis, hyalinization and focal necrosis could be seen. At high magnification, the epithelioid cells showed moderate eosinophilic cytoplasm and vacuolated nuclei. There were conspicuous nucleoli and mitoses. Focal rhabdoid features were evident. There was no significant geographic necrosis.

Immunohistochemical stains are shown in Figure 4. The malignant cells were diffuse and had strong cytoplasmic reactivities for CD34, Pan-Cytokeratin (CKpan) and Vimentin, while additional
immunoreactivity was negative for smooth muscle actin (SMA), Desmin, MyoD1, Myogenin, WT-1, Calretinin, Melan-A, HMB45, TdT, CD117, ERG, Sall4, P63, thyroid transcription factor-1 (TTF-1), NapsinA, LCA, S100, Syn and CD68. In addition, the proliferative index Ki-67 was about 30%. Most importantly, the SMARCB1 stain of tumor cells was negative, and SMARCA4 was positive. The immune checkpoint pathway biomarker programmed death-ligand 1 (PD-L1: clone 22C3) expression was positive (tumor proportion score 60%; combined positive score 60).

Molecularly (Fig. 5), a pathogenic mutation of SMARCB1 p.E115* (exon 3) and unknown significance mutations of BRCA2 and ZFHX3 were identified by the next-generation sequencing. Microsatellite instability was not detected. No positive results were detected for these genes (ALK, BRAF, BRCA1, EGFR, ERBB2, FGFR2, FGFR3, KIT, KRAS, MET, NRAS, NTRK1, NTRK2, NTRK3, PDGFR2, PIK3CA, RET, ROS1).

Discussion

Epithelioid sarcoma is a malignant tumor. The proximal type, first reported as a unique subtype of epithelioid sarcoma in 1997, has an aggressive biological behavior with a higher recurrence rate, early metastasis, and higher mortality rate than the classical type. Five and ten-year survival rate is between 80% and 50%, respectively (Bos et al., 1988). There were also very few reports of primary pulmonary epithelioid sarcoma. This paper introduced the relevant case and reviewed the literature in the hope of providing more detailed clinicopathological information.
Clinical manifestation

There are no characteristic symptoms. Patients can present with chest pain, chest tightness, cough and other symptoms, but also no significant symptoms. In this case, there are unspecific symptoms such as cough and hemoptysis. Imaging examination often indicates pulmonary masses which are similar to other lung neoplasms.

Pathological features

Histologically, tumors are mainly composed of spindle-shaped cells and large ovoid or polygonal epithelioid cells with abundant cytoplasms and prominent nuclei, some of which may be similar to rhabdoid cells. This is consistent with our case. Epithelial and mesenchymal markers, including cytokeratin, epithelial membrane antigen and vimentin are co-expressed. It has been reported positive CD34 expression in 50-60% of tumors (Naik et al., 2011). Significantly, an inactivation of SMARCB1 (also known as INI1, BAF47, SNF5) is helpful in diagnosis (Hornick et al., 2009). CD34 was positive, and SMARCB1 was negative in our case, following the reports above. SMARCB1 is a well-known tumor suppressor gene related to cell growth and development. It locates at 22q11.23 and encodes a significant core subunit in the SWitch/Sucrose Non-Fermentable(SWI/SNF) complex, whose products are expressed in the nucleus of almost all normal tissues in the body. The mechanisms of SMARCB1 inactivation include chromosomal abnormalities or loss of heterozygosity and point mutations (Le Loarer et al., 2014).
Differential diagnosis

To the best of our knowledge, primary pulmonary sarcoma is extremely rare. Therefore it is undoubtedly a huge challenge to think of such tumors and make a proper diagnosis. The most common histological type of lung neoplasm is non-small cell lung cancer (NSCLC), which is bound to be problematic in the differential diagnosis. Noticeably, loss of expression of the \textit{SWI/SNF} complex has been identified in a significant proportion of lung cancer (Yoshimoto et al., 2015). \textit{SWI/SNF} chromosome remodeling complex is a polyprotein related to chromosome remodeling. It can combine the critical cell proteins and transcription factors into the corresponding DNA domain by moving the histone position in the chromosome and finally realize the regulation of gene expression (Reisman et al., 2009; Wilson and Roberts., 2011). It includes ATPase-catalyzed homologous \textit{SMARCA4}, \textit{SMARCA2} (\textit{BRM}) and extremely conserved core subunits \textit{SMARCB1}. Nevertheless, it has been reported that \textit{SMARCB1} gene alterations were the least common among \textit{SWI/SNF} - mutant NSCLCs (Alessi et al., 2021). The histomorphology and mesenchymal immunohistochemistry in our case are more suitable for diagnosing epithelioid sarcoma. Emori et al. (Emori et al., 2017) also reported that a 58-year-old male with primary pulmonary epithelioid sarcoma suggested to have a pulmonary mass with mediastinal invasion and peripheral lymph node metastasis by imaging examination was misdiagnosed as NSCLC. In a similar situation, the initial diagnosis of poorly differentiated carcinoma was encountered in our case, and it was difficult to distinguish and classify other types of tumors because of the nonspecific immunohistochemistry. There may be similarities as follows: (1) The clinical manifestations are not specific. Non-characteristic symptoms such as cough, hemoptysis, chest pain and so on may happen. It has been reported that people with no history of smoking should be alerted to the possibility of sarcoma (Emori et al., 2017). The biological behavior of lymph node metastasis found by imaging
examination is more favorable to epithelial-derived malignancies. However, what is neglected is proximal epithelioid sarcomas, unlike most soft tissue sarcomas, which often have lymph node metastasis. It was reported that up to 50% of ES is prone to metastasis to the lung and regional lymph nodes (Baratti et al., 2007). (2) The patients have no history of other tumors. Imaging examinations, including PET/CT and CT, indicated no lesions except for the pulmonary mass. Primary epithelioid sarcoma of the lung is extremely rare. Most of the pulmonary epithelioid sarcomas reported in the literature were metastatic lesions (Jeon et al., 2016; Hoshi et al., 2018). The correct diagnosis could be made based on the systemic condition and medical history. In our case, there was no ulcer or damage to the whole body of the patient. (3) There is an ambiguous pathological morphology. ES is a mesenchymal tumor with epithelioid cell morphology, as its name implies. Microscopically, epithelioid cells are distributed in sheets, but other epithelioid arrangements, such as silk and nests, may be seen. On the other hand, the immunohistochemical expression of the epithelium may also be confused with NSCLCs.

Secondly, SMARCA4 - deficient thoracic sarcomatoid tumors recently reported also need to be considered. About 10%~35% of non-small cell lung cancers, such as large cell carcinoma and solid adenocarcinoma, have been found to show an absence of SMARCA4 expression, which is called SMARCA4 - deficient lung cancer (Imielinski et al., 2012; Seo et al., 2012, 2014). Recently, Le Loarer et al. (Le Loarer et al., 2015) have reported a rare and highly malignant primary thoracic sarcoma named SMARCA4-deficient primary thoracic sarcoma. This group of tumors related to the SMARCA4 gene has an invasive biological behavior showing compressive growth and often involving the mediastinum, chest wall and lung. The solid structure of adhesive or non-adhesive epithelioid cells with rhabdoid morphology might also overlap with epithelioid sarcoma. However, immunohistochemistry of
SMARCA4 in our case made a distinction.

On the one hand, some primary pulmonary tumors can also take the form of epithelioid cells, which must be distinguished. (1) Pleural malignant mesothelioma: some cases have similar morphological characteristics to epithelioid tumor cells, but mesothelial markers such as WT-1 and calretinin are almost positive. There were some reports about SMARCB1-deficient pleural malignant mesothelioma with rhabdoid features (Kimura et al., 2018). This is worthy of our identification. (2) Epithelioid angiosarcoma: the poorly differentiated ones have solid patches, necrosis and haemorrhage. CK and CD34 can also be expressed in about half of the cases. It is helpful to identify the areas of vascular differentiation and positive immunohistochemical markers such as ERG, FLI-1 and CD31. (3) Synovial sarcoma: relatively specific genetic changes can be distinguished. (4) Melanoma: the positive expressions of TIMF, HMB45, and MART-1 markers are helpful in indicating melanoma. (5) Rhabdomyosarcoma: It is easy to occur in infants and children but rare in adults. Myogenic immunohistochemical markers such as desmin, Myogenin and MyoD1 are mostly positive. SMARCB1 is positively expressed in most of the above tumors, which is an important differentiation from epithelioid sarcoma.

On the other hand, it should be emphasized that a group of malignant tumors with inactivation of the SMARCB1 gene, such as renal medullary carcinoma, atypical teratomatoid/rhabdomyosarcoma, undifferentiated sarcoma, myoepithelial carcinoma, epithelioid malignant peripheral neurilemmoma and extraosseous myxoid chondrosarcoma, is often associated with rhabdomyoid features and lack of INI nuclear stain. Clinical information and pathological features should be integrated for comprehensive analysis.
Prognosis and treatment

The prognostic factors of epithelioid sarcoma include sex, age, location, etc. Young women, tumor size (less than 5cm) are good prognostic indicators, while elderly men, multi-focal lesions, the deeper depth of tumor invasion, high mitotic activity, necrosis, vascular infiltration and inadequate resection may predict poor prognosis (Chbani et al., 2009).

Owing to the rarity of the tumor, the treatment for ES is very limited. Extensive surgical resection is still considered to be the most common method for pulmonary sarcoma. The chemotherapy regimens are similar to those commonly used in soft tissue sarcomas, that is, the combination of ifosfamide and adriamycin (Guillou et al., 1997). It has been reported that in patients with primary pulmonary epithelioid sarcoma 4 cycles of adjuvant chemotherapy were well tolerated, including ifosfamide and adriamycin. Follow-up PET at 3 and 10 months showed no signs of metastatic disease (Saha et al., 2016). In a large retrospective study, anthracycline and gemcitabine-based regimens were moderately active in ES, while pazopanil had a low value (Frezza et al., 2018). However, some studies have found that ES was resistant to chemotherapy and the effect of adjuvant chemotherapy was still unclear (Emori et al., 2017). We tried to adopt the treatment of chemotherapy and immunotherapy after surgery because of good expression of PD-L1. Unfortunately, the disease progressed, and eventually the patient died possibly due to the side effects of chemotherapy. It is worth noting that immunotherapy has been reported for the first time in pulmonary epithelioid sarcoma.

With the development of research, Food and Drug Administration (FDA) approved Tazemetostat for the treatment of locally advanced or metastatic epithelioid sarcoma patients who are not eligible for surgical resection. Tazemetostat, a potent, selective, orally available EZH2 inhibitor, has shown clinical activity in INI1-negative tumors including durable objective responses and disease stabilization.
Therefore, comprehensive molecular analysis of tumors should be expected to better understand molecular driving forces and guide more accurate and personalized treatment decisions.

Abbreviations

ES: Epithelioid sarcoma; CT: Computed tomography; PET/CT: Positron emission tomography/computed tomography; PD-L1: The immune checkpoint pathway biomarker programmed death-ligand 1; NSCLC: Non-small cell lung cancer; SWI/SNF: SWitch/Sucrose Non-Fermentable; FDA: Food and Drug Administration

Acknowledgements

Not applicable.

Authors’ contributions

Jiayu Li and Yehan Zhou wrote the main manuscript text and prepared figures 1-5.

Yang Liu provided the case and writing ideas.

All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Sichuan Cancer Hospital, Chengdu, China
Duplicate publication

The manuscript has not been formally published in any journal or in any other citable form.

Funding

This study has no funding source.

Competing interests

The authors declare that they have no conflicts of interest.

References


epithelioid sarcoma and in a subset of myoepithelial carcinomas can be reliably detected by FISH in archival material. Genes Chromosomes Cancer. 53, 475-486.


### Table S1. The detailed clinical features of the other three reported cases of primary pulmonary ES are listed.

<table>
<thead>
<tr>
<th>Case N.</th>
<th>Age/sex</th>
<th>Medical history</th>
<th>Position</th>
<th>Tumor size (cm)</th>
<th>Symptoms</th>
<th>Stage</th>
<th>Initial diagnosis</th>
<th>Treatment</th>
<th>Prognosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41/male</td>
<td>HIV infection</td>
<td>right perihilar mass</td>
<td>4.4</td>
<td>haemoptysis, chest CT, HIV/AIDS</td>
<td>cT2bN0M0</td>
<td>poorly differentiated carcinoma and adjacent chemotherapy with docetaxel and doxorubicin</td>
<td>pneumonectomy and adjuvant chemotherapy</td>
<td>remission 36 months after initial treatment</td>
<td>A typical presentation of primary pulmonary epithelioid sarcoma misdiagnosed as non-small cell lung cancer.</td>
</tr>
<tr>
<td>2</td>
<td>56/male</td>
<td>non-smoker</td>
<td>right upper lobe</td>
<td>2.8</td>
<td>hemoptysis</td>
<td>cT4N1M1a</td>
<td>poorly differentiated malignancy</td>
<td>four cycles of systemic chemotherapy with the CDDP + PEM regimen (cisplatin 75 mg/m², pemetrexed 500 mg/m²) was administered, and five cycles of carboplatin (AUC 6) were administered, intensity-modulated radiation therapy (60 Gy/30 fractions)</td>
<td>Three and a half years after initial treatment, the patient noticed a 20 to 30 mm-sized painless firm nodule. Four years after initial treatment, PET-CT revealed metastatic involvement in the left lung, right ribs, and thoracic vertebrae, right axillary lymph node. The patient later died due to left pulmonary metastases and pneumonia.</td>
<td>Primary pulmonary epithelioid sarcoma misdiagnosed as non-small cell lung cancer.</td>
</tr>
<tr>
<td>3</td>
<td>27/male</td>
<td>never-smoker</td>
<td>large left pleural effusion and multiple hypermetabolic pleural nodules</td>
<td>unknown</td>
<td>cough and SOB</td>
<td>cT4N1M1</td>
<td>poorly differentiated malignancy</td>
<td>He was initially treated with first-line combination chemotherapy with the MAI regimen (doxorubicin 25 mg/m² × 3 days, ifosfamide with 25% dose reduction at 1,875 mg/m² × 5 days, mesna support). He subsequently expired 2 months after his initial diagnosis.</td>
<td>Primary pulmonary epithelioid sarcoma of the proximal type: a diagnostic and therapeutic challenge.</td>
<td></td>
</tr>
</tbody>
</table>

Table S1. The detailed clinical features of the other three reported cases of primary pulmonary ES are listed.
A contrast-enhanced CT scan showed the solid nodule with heterogeneous enhancement (A.B).

CT showed a solid nodule in the left upper lobe of the lung located in the mediastinal window and lung window, respectively (C.D).

A PET/CT showed that a soft tissue mass in the left hilum of the lung and uneven thickening and enhancement of the left pleura, some of which were fused, had increased metabolism in varying degrees.

The tumor cells were composed of epithelioid cells arranged in a sheet or solid pattern (A). The loose cohesion of tumor cells in some areas (B). (H&E stain, ×5, ×10)

The epithelioid cells showed moderate amounts of eosinophilic cytoplasm and vacuolated nuclei (C).

There were prominent nucleoli (D). (H&E stain, ×20, ×40)

The malignant cells were diffuse and had strong cytoplasmic reactivities for pan-cytokeratin (A), Vimentin (C), CD34 (D) and SMARCA4 (E). (immunohistochemical stain, ×20)

They were negative for P63 (B) and INI-1 (F). (immunohistochemical stain, ×20)