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CASE REPORT

Rare Primary Pulmonary Primitive Neuroectodermal Tumor: A Case Report and Literature Review

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Abstract: Primitive neuroectodermal tumors (PNETs) arising from the lung without thoracic wall involvement are extremely rare and particularly aggressive neoplasms. Herein, we present the case of a 41-year-old woman with pulmonary PNET diagnosed following histopathological, immunohistochemical, and molecular pathological examination of a surgical biopsy specimen. The case report is accompanied by a literature review of primary pulmonary PNETs.

Keywords: primitive neuroectodermal tumor, pulmonary, differential diagnosis

Introduction

Peripheral primitive neuroectodermal tumors (PNETs) are rare malignancies that occur most commonly in extraskeletal and soft tissues during childhood or adolescence. Pathologically, PNETs are part of the small round cell sarcoma family, which are characterized by neuroectodermal differentiation. Kushner et al first described 54 cases of PNET in 1991.[1] Such tumors primary in the thoracopulmonary region are commonly known as Askin tumors.[2,3] PNET and Askin tumors are collectively referred to as extraskeletal Ewing sarcomas. As members of the Ewing family, PNET, Askin tumors, and Ewing sarcoma are characterized by *EWRS1* fusion on chromosome 22 and ETS family transcription factors. Most cases (85%) have t (11;22) (q24; q12) translocation and form *EWSR1-FLI1* fusion genes. A previous study demonstrated that the disease may originate from the chest wall (33.3%) and pelvis (22.2%) most commonly, other common sites include paraspinal region (13.0%), retroperitoneum (11.1%), limbs (9.3%), abdomen (7.4%), neck (1.9%), and unknown sites (1.9%),[1] but it rarely arises from the lung. PNETs that arise in the lung parenchyma without chest wall involvement are extremely rare in adults; to the best of our knowledge, only 28 cases have been described in the English literature. Herein, we report a rare case of primary pulmonary PNET and its pathological characteristics.

Case Report

A 41-year-old woman presented with persistent dry cough and low-grade fever (37.5°C) for one week. Pulmonary computed tomography (CT) revealed a localized lesion in the left upper lung lobe. The lesion was close to the pulmonary capsule,

with a maximum diameter of 1.9 cm. We considered the possibility of benign lesions at first.

During further examination, a pathologist performed a fine-needle cytology smear. After hematoxylin-eosin staining, red blood cells were observed throughout the field under the microscope. Moreover, a few scattered heterotypic cells were observed in these red blood cells. The heterotypic cells had naked nuclei and the nucleus chromatin was fine and smooth, resembling those typical of small cell lung cancer (SCLC). However, the wiredrawing phenomenon was not obvious (Figure 1A). Therefore, we provided a descriptive examination without a specific diagnosis at the time.

The patient underwent a mass and partial lung resection with biopsy. A surgeon excised irregularly shaped tissue, which included tumor and surrounding lung tissue, with the following dimensions: 5.6 cm × 5.1 cm × 2.1 cm. Upon sectioning of the tissue, a solid cystic nodule (1.9 cm × 1.5 cm × 0.9 cm) was found close to the pulmonary capsule (Figure 1B). The solid area was grayish red and yellow with fine texture, while the cystic area had hemorrhage and necrosis.

Histopathological examination of the specimen revealed dense neoplastic tissue in the lung tissue margins. The neoplastic cells were composed of small blue round cells (Figure 1C); most tumor cells were in a lamellar arrangement, while some were in a hemangiopericytoma-like arrangement (Figure 1D). The small round blue cells exhibited neuroectodermic differentiation. Homer-Wright chrysanthemum-shaped clusters were present, and their axes were neurofibrillary substances. At high magnification, the tumor cells had round or oval nuclei, clear nuclear membranes, and fine and uniform nuclear chromatin, resembling dust or pepper (Figure 1E, F).

Immunohistochemical staining showed that the tumor cells expressed vimentin (Figure 2A), Fli-1 (Figure 2B), and CD99 (Figure 2C) proteins, while the expression of CgA, Syn, CK5/6, and protein S-100 were negative. One-step reverse transcription polymerase chain reaction showed that the tumor cells had specific heterotopic fusion genes, *EWSR1-FLI1* (Figure 2D). Combining the morphologic, immunohistochemical, and molecular findings, we were able to diagnose the patient with primary pulmonary PNET.

Following diagnosis, the patient did not undergo treatment (eg, radiotherapy or chemotherapy) other than surgical resection. Follow-up visits were scheduled every three months; after 18 months, the patient showed no signs of recurrence.

Discussion

PNET is a highly aggressive soft tissue sarcoma. The tumor is part of the Ewing sarcoma family and occurs

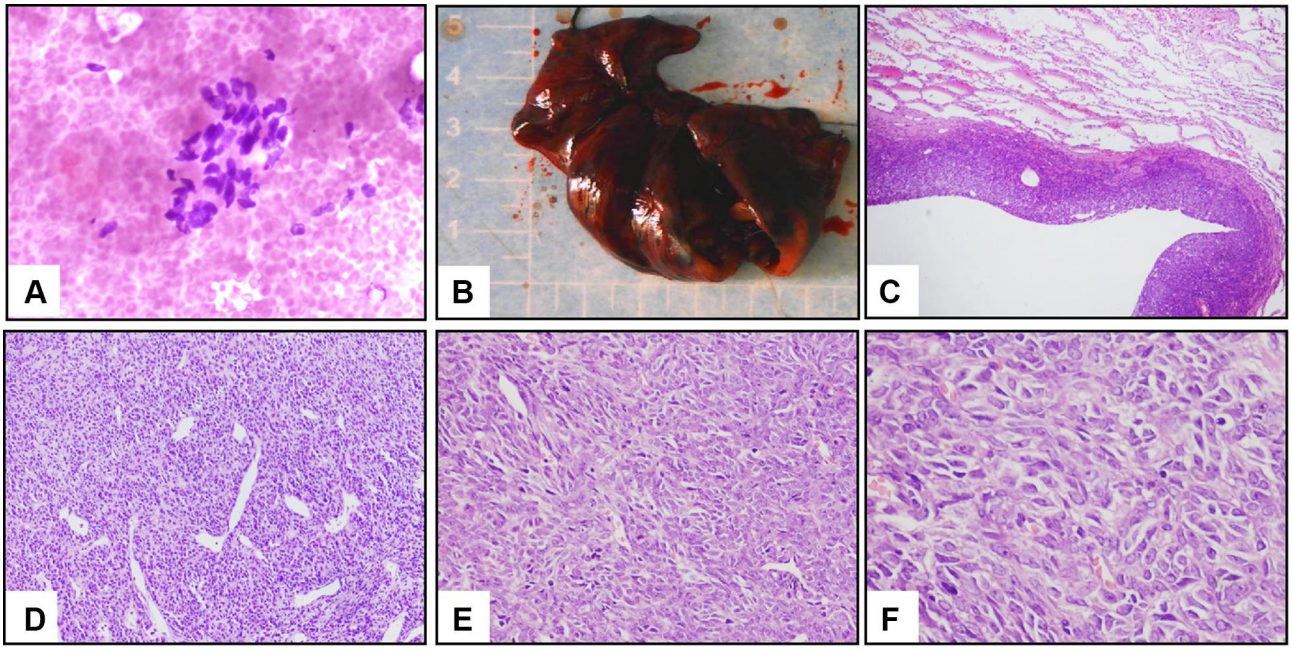

Figure 1 Gross and microscopic histopathological features of the pulmonary primitive neuroectodermal tumor. (**A**) Fine-needle cytology of the tumor (H&E; magnification ×40); (**B**) Gross specimen of the tumor and surrounding lung tissue; (**C**) Location of the tumor in the lung tissue (H&E; magnification ×40); (**D**) Area with tumor cells arranged in a hemangiopericytoma-like pattern (H&E; magnification ×100); (**E**) Homer-Wright chrysanthemum-shaped clusters can be observed in some areas (H&E; magnification ×200); (**F**) In some regions, cells were polygonal (H&E; magnification ×400).

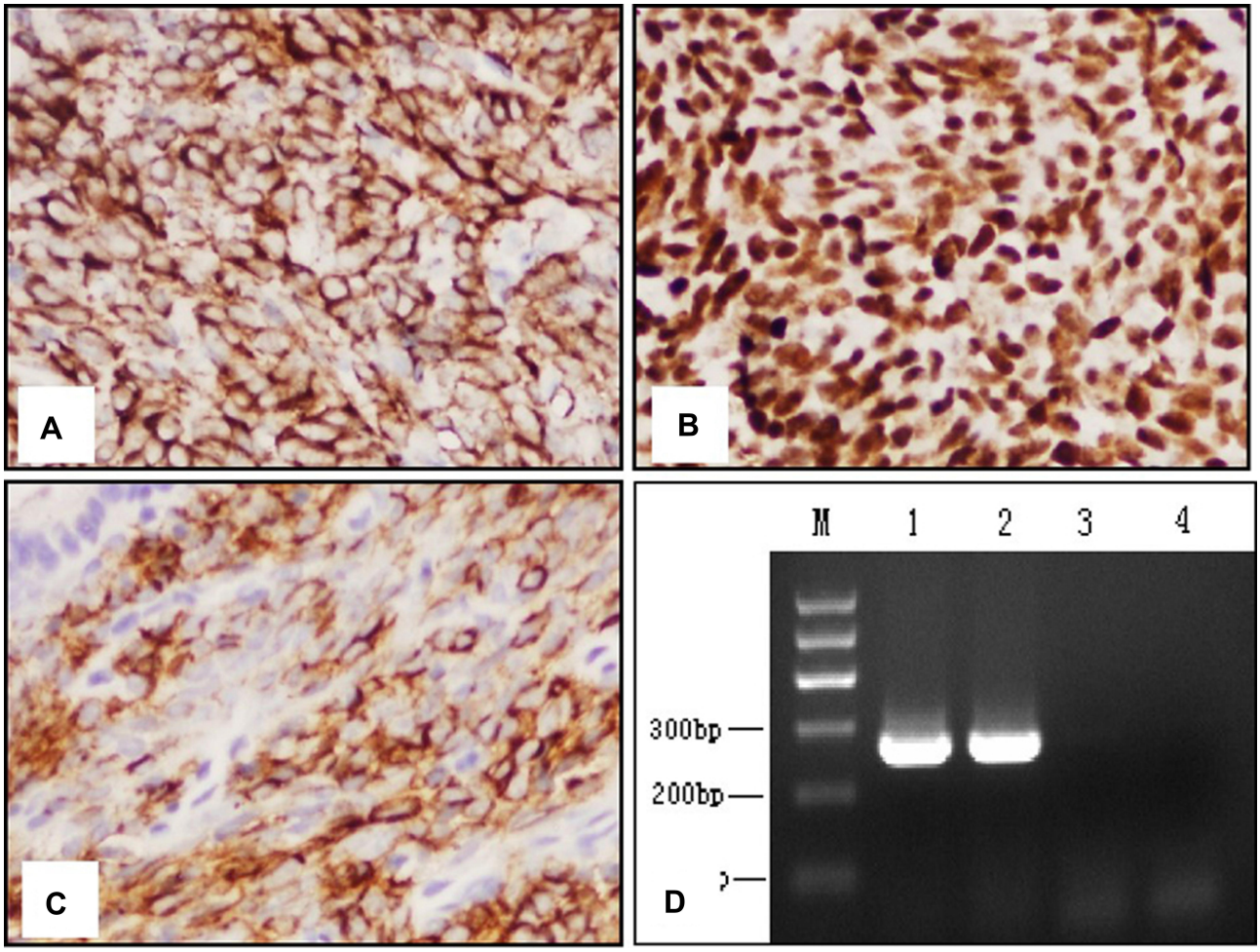

Figure 2 Immunohistochemical and molecular analyses of the pulmonary primitive neuroectodermal tumor. (**A**) Immunohistochemical staining for Vimentin showing diffuse membrane positivity (original magnification ×400); (**B**) Immunohistochemistry image showing cells with diffuse FLI-1 positivity (original magnification ×400); (**C**) Tumor cells showing diffuse membrane positivity for CD99 (original magnification ×400); (**D**) Expression of the EWSR1-FLI-1 fusion gene: (1) a case of Ewing sarcoma, (2) the present case, (3) a case of myxoid liposarcoma (negative control), and (4) blank control.

most commonly in children, adolescents, and young adults (< 35 years old).[4] PNET is widely diagnosed through clinically and histologically identical tumors comprised of small round blue cells; these cells are uncommon entities, accounting for 5% of all small round cell tumor cases.[5] Typically, PNET is a painful and aggressive tumor that may invade the chest wall, lungs, mediastinum, and heart. Despite the lungs being one of the common metastatic areas, cases of primary pulmonary PNETs are extremely rare. In our case, the patient presented with a one-week history of dry cough and low-grade fever without expectoration, fatigue, or other symptoms. CT imaging revealed a mass in the left upper lung lobe. Histopathological examination detected the proliferation of small round blue cells with neuroectodermic differentiation. Immunohistochemical analysis indicated positive expression of CD99, Fli-1, and vimentin. Finally, molecular pathology identified EWSR1-FLI1 fusion gene expression. Taken together, these findings supported the diagnosis of pulmonary PNET.

PNET can involve many parts of the body, Studies have reported that PNET occurs most commonly in the abdomen, kidneys, mediastinum and chest, nasal cavity, maxillary bone, adrenal glands, and retroperitoneal space, etc. Upon searching all available literature published in English journals and reports on primary pulmonary PNETs without thoracic wall involvement, we retrieved 21 studies describing a total of 28 cases (Table 1).[6–26] Among 28 cases, the proportion of male patients was slightly higher than that of female patients (17:11). Of all patients, 87% were younger than 35 years old at disease onset (range, 8–67 years old), which is in accordance with the common characteristics of PNET. Tumor metastasis at diagnosis, large tumor size, and invasion of the heart are indicatives

Table 1 Primary Pulmonary Primitive Neuroectodermal Tumor in Previous Reports

Reference	Year	Age/Sex	Tumor Location	Immunohistochemistry (Positive)	Treatment	Follow-Up
BAŞGÖZ[6]	2017	58/M	RLL	CD99, CD56, Vimentin,	S+CT	A&W
Li Q et al[7]	2017	12/M	RLL	CD99, Vimentin, Syn	CT+RT	A&W at 15 months
Zhang CH[8]	2016	30/F	LLL	Vimentin, CD99, Syn, Fli-1, NSE	S+CT	DOD at 20 months
Narayan R[9]	2016	8/F	RLL	CD99	S+CT	A&W at 60 months
Dong M[10]	2015	16/M	Multiple in both lung	CD99, Vimentin	CT	DOD at 5 months
Gachechiladze[11]	2014	31/F	Right lung	CD99, CD56, Vimentin	CT	DOD at 1 months
Amita[12]	2013	21/F	LUL	CD99, NSE, Vimentin,	S+CRT	A&W at 3 months
Andrei[13]	2013	31/M	Lung	CD99, NSE, Vimentin	S+CRT	DOD at 36 months
Lin[14]	2013	19/M	Lung	CD99, NSE, Vimentin,	S	A&W at 4 years
Weissferdt[15]	2012	22/M 27/M 29/F 56/F 29/M 31/M	RUL LUL LUL RLL RUL RML	CD99, NSE, Vimentin CD99, NSE, Vimentin CD99, NSE, Vimentin CD99, NSE, Vimentin CD99, NSE, Vimentin CD99, NSE, Vimentin	S S+CT S+CT CT+S+CT S S+CT	NK DOD at 24 months DOD at 36 months A&W at 11 months NK DOD at 54 months
Mao[16]	2012	28/M	Multiple in both lung	CD99, Vimentin	CT	DOD at 12 months
Ngow[17]	2011	15/M	Lung	CD99, NSE	CT	DOD at 12 months
Antelo[18]	2010	22/F	Lung	CD99, Syn	CT	A&W
Gaude[19]	2009	28/M	L hilum	Syn, CgA	S+CRT	DOD at 4 months
Verfaillie[20]	2009	33/M	Lung	NSE, Vimentin, Syn	S+CRT	DOD at 22 months
Lee[21]	2007	67/M	LLL	CD99, Vimentin, Syn	S+CT	A&W
Mikami[22]	2001	17/F	RLL	CD99	S+CRT	DOD at 9 months
Kahn[23]	2001	18/M	RML	CD99, Vimentin, NSE	S	DOD at 24 months
Baumgartner[24]	2001	26/F	L hilum	CD99	CT+S+CRT	DOD at 8 months
Imamura[25]	2000	30/F 41/M	RLL LUL	CD99, NSE CD99, Vimentin, NSE	CT+S+CT CT+S	A&W at 16 months A&W at 22months
Tsuji[26]	1998	25/F 15/M	LLL LLL	CD99, NSE CD99, NSE	S S	DOD at 24 months A&W at 24 months

Abbreviations: M; male; F, female; RUL, right upper lobe; LUL, left upper lobe; RLL, right lower lobe; LLL, left lower lobe; RML, right middle lobe; NK, not known; CT, chemotherapy; S, surgery; RT, radiotherapy; CRT, chemoradiation; A&W, alive and well; DOD, dead of disease.

of poor prognosis. Regarding treatment options, surgery is the preferred treatment, whereas chemo- and radiotherapy are the main treatment options for patients who are unable to undergo surgery due to tumor location or disease stage, but they are considered ineffective.

Most patients sought medical attention with symptoms of pneumonia, such as cough and low-grade fever, and had pulmonary nodules found on CT examination, which were then sent for biopsy. Pathological and immunohistochemical analyses were used to assist the diagnosis. Almost all cases showed CD99 positivity. Importantly, the disease needs to be distinguished from other small round cell lung tumors, including SCLC, metastatic neuroblastoma, alveolar rhabdomyosarcoma, synovial sarcoma, and non-Hodgkin's

lymphoma. Among these, primary pulmonary PNET and SCLC—the most common small round cell tumor of to occur primarily in the lung—are the most similar. Immunohistochemical staining showed that neuroendocrine markers, such as Syn and CgA expression, were positive in both PNET and SCLC cases. Therefore, we recommend genetic testing to positively identify PNET cases through the detection of (11;22) (q24; q12) translocation, resulting in the fusion gene *EWSR1-FLI1*, which can be detected in most PNET patients.

The National Comprehensive Cancer Network guidelines recommend local treatment (surgery and/or radiotherapy) plus chemotherapy for treating tumors of the Ewing family.[27] Although chemotherapy can improve the survival rate of patients and radiotherapy can provide local control, complications associated with these therapies have reduced their utilization. Rud et al[28] and Qureshi et al[29] have suggested that surgery, especially with a negative surgical margin, may have a more important role in PNET than in skeletal Ewing sarcoma. Therefore, surgery remains the gold standard treatment for PNET. In addition to conventional radio- and chemotherapy, molecular targeted therapy is an option for patients who cannot have surgery. A recent report suggested that pulmonary PNET with copy number loss (CNL) of the Von Hippel-Lindau (VHL) gene benefits from sunitinib treatment; after a four-month treatment with sunitinib, the patient achieved partial response according to the Response Evaluation Criteria in Solid Tumors guideline and the quality of life has improved significantly.[8]

For patients with pulmonary nodules who cannot undergo surgery due to disease stage or other contraindications, lung puncture can be used to detect the nature of the nodules. If the patient has pleural effusion or sputum, these specimens can be embedded in liquid paraffin and used for diagnosis. Under the microscope, these tissues should have few and morphologically atypical cells. Moreover, both PNET and SCLC cells are small round cells and have naked nuclei, and immunohistochemical staining may show positivity for neuroendocrine markers in both cancer types. Therefore, this rare primary pulmonary PNET can be easily misdiagnosed as SCLC. However, while SCLC is sensitive to chemoradiotherapy, PNET is not. Thus, in addition to cellular morphology and immunohistochemistry analyses, fusion gene detection analysis must be performed to accurately diagnose pulmonary PNET cases. For PNET originated in the lung, relevant clinical studies are mostly single-institution and small-scale because of the disease rarity. Moreover, the absence of guidelines for the diagnosis and treatment of primary pulmonary PNET imposes an additional challenge for clinicians in the oncology field.

Conclusion

Herein, we reported a rare case of primary pulmonary PNET. A review of the literature showed that early detection and surgical resection can greatly improve the survival of patients with PNET. Regarding pathological diagnosis, immunohistochemistry analysis should be combined with fusion gene detection to ensure an accurate diagnosis. The most reliable marker of PNET, including those of pulmonary origin, is the translocation or amplification of the *EWSR1* gene. Moreover, early diagnosis is important for performing a radical surgical resection of the tumor and for administering a chemotherapeutic regimen with less intensity and side effects.

Ethics and Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. The images did not contain the patient records and information. This study was approved by the Clinical Research Ethics board of the First Affiliated Hospital, Shihezi University School of Medicine.

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Disclosure

The authors have no conflicts of interest to disclose.

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