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Case Report

Classic biphasic pulmonary blastoma with brain and axillary metastases: a case report with molecular analysis and review of literature

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Abstract: Pulmonary blastoma is a rare series of malignant lung tumor, which contains three categories: classic biphasic pulmonary blastoma, pluropulmonary blastoma, and well-differentiated fetal adenocarcinoma. In this study, a 19-year old female suffering with classic biphasic pulmonary blastoma and metastases in brain and axilla was presented with special interest in clinicopathological presentations, immunohistochemical features, and molecular characterizations. However, this case was misdiagnosed initially with small biopsy specimen. Comprehensive management should be used for the treatment of this malignancy.

Keywords: Pulmonary blastoma, classic biphasic pulmonary blastoma, metastasis, treatment

Introduction

Pulmonary blastoma (PB), a rare primary lung tumor, is considered as a distinct malignancy from others based on pathological features, clinical course, and prognosis. Histologically, pulmonary blastoma is subdivided into three categories: 1) classic biphasic pulmonary blastoma (CBPB), 2) pluropulmonary blastoma (PPB), and 3) well-differentiated fetal adenocarcinoma (WDFA) [1, 2]. Furthermore, classic pulmonary blastoma was also classified as a subtype of pulmonary sarcomatoid carcinoma (PSC) according to the guideline of 2004 WHO classification [3]. The prognosis of classic biphasic pulmonary blastoma is poor and the overall 5-year survival rate is around 15% [2]. Complete resection is the mainstay of the treatment. Meanwhile, adjuvant chemotherapy and radiotherapy should be considered for some patients. Herein, we report a 19-year-old female with classic biphasic pulmonary blastoma, with special interest in the clinical manifestations, pathological features, and treatment strategy.

Case report

The patient was a 19-year-old female nonsmoker who initially presented with a progressively enlarging mass on the right axilla for two months and headache for one month. Two months ago, a mass of 1.5 cm in diameter on the right axilla was found by herself accidentally. Rapidly, it grew up to 8 cm. Physical examination revealed a tough mass at the back of the right axilla which showed an obscure boundary and closely adhered with the surrounding tissue. On the surface of the mass was a 2 cm in diameter of kermesinus plaque. A biopsy of the mass was performed in the local hospital. Then, the pathology was sent to the Department of Pathology of West China Hospital for consultation. Without further information, the pathological consideration was described as a neoplasm with fiber and epithelial components, which possibly derived from the accessory breast. Otherwise, a spiroma derived from eccrine gland could not be excluded from our considerations. Obviously, cell proliferation was active (**Figure 1**).

Later, the patient complained an intermittent pain on her left head with dizziness and seeing things in double images. Magnetic resonance imaging (MRI) was performed, which demonstrated a mass on the brain in the left occipital lobe (**Figure 2A**). Simultaneously, a well-defined lesion in the lung was observed by chest X-ray (**Figure 2B**). The lung mass was further con-

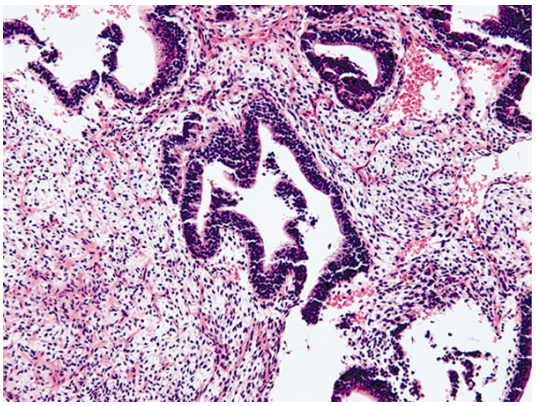

Figure 1. First biopsy from fine needle aspiration tissue: biphasic pattern of epithelial and stromal elements (H&E. magnification ×200).

firmed by computed tomography (CT) showing approximate 4 cm in diameter on the left upper lobe (**Figure 2C**). A clinical diagnosis of lung cancer with metastases in brain and axilla was suspected.

At this time, neurologic examine was implemented, resulting in no paresthesias, numbness, or loss of muscle strength. Laboratory tests were negative except for the syphilis experiment. Due to the severe symptoms of the head, the patient was underwent a debulking surgery of "left pillow leaf resection + left pillow leaf intracranial hematoma clearance + superior sagittal sinus suture". Without any additional treatment, the patient was discharged six days after operation voluntarily and died 46 days later.

Pathology and molecular features

Microscopically, a typical biphasic tumor was revealed. The tumor was consisted of both embryonic epithelium and sarcomatous mesenchyme, which was similar to fetal lung tissue morphologically (**Figure 3A**, **3B**). The epithelial components were composed of infrequent tubular/glandular structures. Lining epithelium of the glands were relatively uniform with round hyperchromatic nuclei and some eosinophilic cytoplasm. Among the glands, some focal nests of squamoid cells could be observed. On the other hand, the stroma of the tumor showed undifferentiated mesenchymal appearance. Necrotic and haemorrhagic foci could be found occasionally (**Figure 3C**, **3D**).

Immunohistochemically, strong activities of CK (AE1/AE3), CAM5.2, CK18 and TTF-1 were detected in epithelial component (**Figure 4A-C**), which was lost of EMA, CK7, CK20, or napsin A expression. Vimentin and bcl-2 were diffuse positive in the stromal cells, in contrast to the patchy and moderate staining of MSA, desmin and myogenin. High proliferation activities were demonstrated in both epithelial and mesenchymal elements by using Ki-67 (up to 50~70%). P53 was partially positive for both components (**Figure 4D-F**). Considering the clinical findings, the conclusive diagnosis was rendered as follows: a metastatic malignant tumor, originating from classic biphasic pulmonary blastoma of the lung.

In addition, immunohistochemical staining of ALK (D5F3) has been done. The result was negative, which implied that there was no translocation of *ALK* gene. Antibodies used in this study were summarized in **Table 1**. We also analyzed the *EGFR* alterations of this case. The epithelial and mesenchymal elements were macro-dissected under the microscope individually, and then mutation analysis of *EGFR* of the both elements was performed in the department of pathology of West China Hospital. Genomic DNA was extracted from the tumor tissue using standard protocols (RNeasy Mini Kit and QiAamp DNA Mini Kit; Qiagen, Hilden, Germany). *EGFR* (exons 18-20) was sequenced using genomic DNA. Cycle sequencing of the purified polymerase chain reaction (PCR) products was carried out with PCR primers using the commercially available ADx Mutation Detection Kits (Amoy Diagnostics Company Ltd., Xiamen, China). The result revealed no *EGFR* mutation in both epithelial and mesenchymal elements.

Discussion

Pulmonary blastoma, first described in 1945 by Barnett and Barnard [4], is a distinctive malignant entity in lung pathology. Although the occurrence is rare [2], existence of PB is well documented. The rarity of these tumors makes pathologists encounter baffle in identification. Furthermore, histopathologic diagnosis by either bronchoscopy or small biopsy is usually absence of a certain amount of specimen. Therefore, small biopsy specimen is not enough to render a final diagnosis. Due to the characteristic biphasic pattern, the case we presented here was misdiagnosed at first. According to

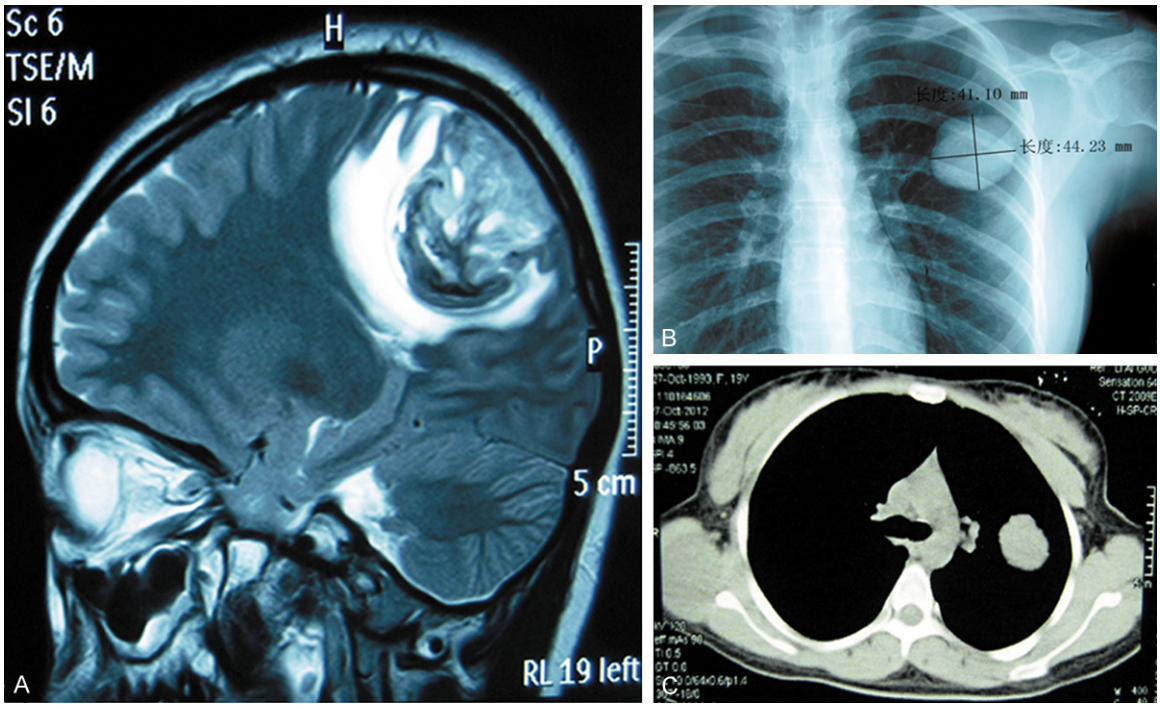

Figure 2. A: MRI of the brain showing a single metastasis in the left occipital lobe. B: Chest radiograph showing a well-circumscribed large 4.1×4.4 cm mass in the left upper lung field. C: Computed tomography scan showing a well-defined mass.

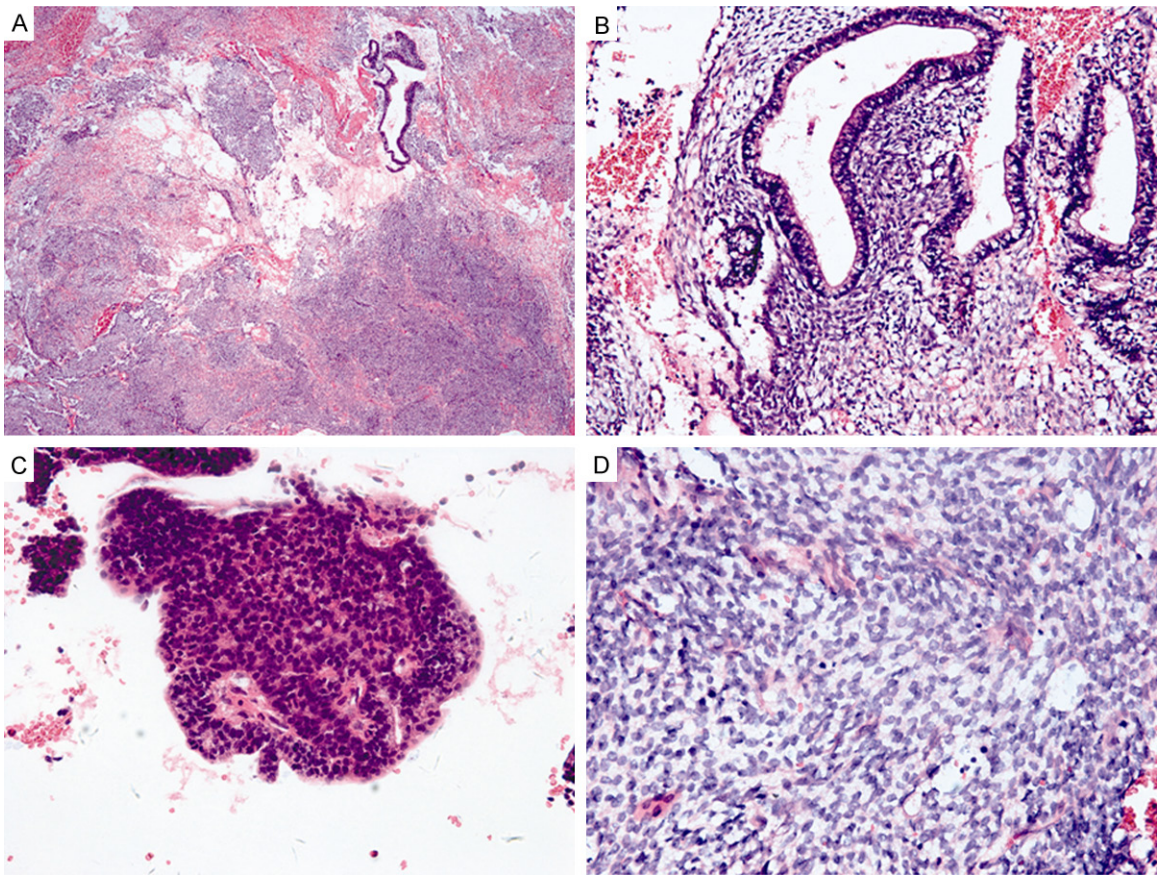

Figure 3. A: Resected specimen of the brain metastasis demonstrating the tumor is predominant with stromal elements and the epithelial elements arranged in a tubular pattern, is embedded (H&E. magnification ×40). B: Lesions with biphasic appearance, containing both neoplastic glands and adult sarcomatous or embryonic mesenchyme (H&E. magnification ×400). C: Focal nests of squamoid cells could be observed (H&E. magnification ×400). D: Abundant in spindle cells, and the mitotic figure can be easily seen (H&E. magnification ×400 right).

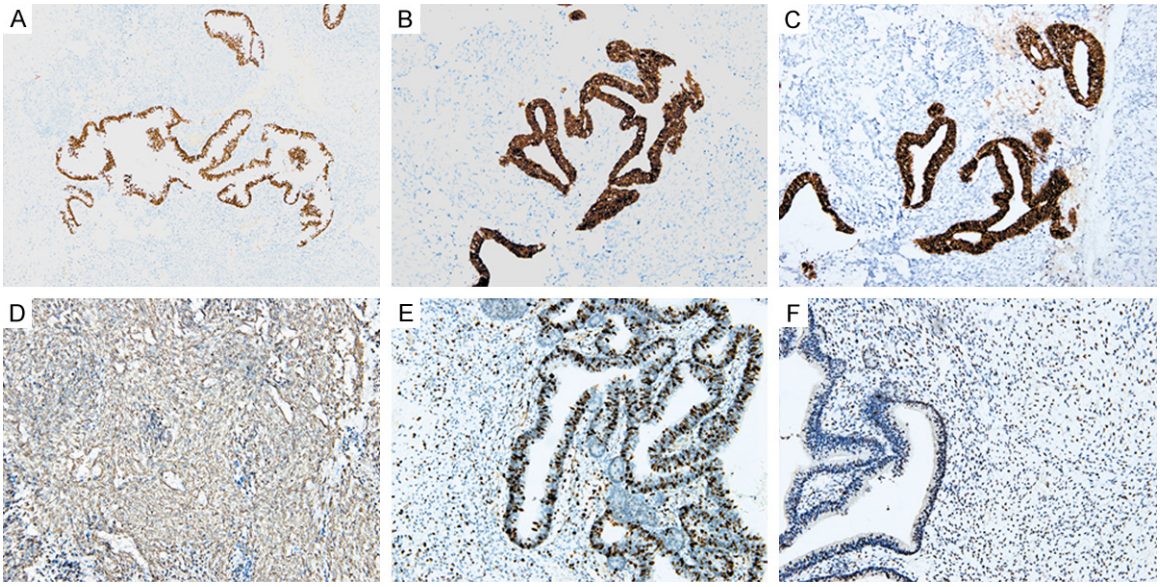

Figure 4. A-C: TTF-1, CK (AE1/AE3) and CK18 are positive in epithelial component (DAB. magnification ×200). D: Vimentin immunostain of stromal elements (DAB. magnification ×200). E: Ki-67 is up to 50~70% in both epithelial and mesenchymal elements (DAB. magnification ×200). F: P53 was partially positive for both components (DAB. magnification ×200).

Table 1. Antibodies used in this study

NO.	Antibody	Manufacturer	Description	Clone
1	CDK1	Abcam	Mouse monoclonal	DCS-280
2	CK (pan)	OriGene	Mouse monoclonal	AE1/AE3
3	CK18	OriGene	Mouse monoclonal	UMAB50
4	TTF-1	OriGene	Mouse monoclonal	8G7G3/1
5	EMA	DAKO	Mouse monoclonal	E29
6	CK7	OriGene	Mouse monoclonal	RN7
7	CK20	OriGene	Rabbit monoclonal	EP23
8	Vimentin	DAKO	Mouse monoclonal	V9
9	bcl-2	DAKO	Mouse monoclonal	13H4
10	MSA	MAIXIN-BiO	Mouse monoclonal	HHF35
11	Desmin	DAKO	Mouse monoclonal	D33
12	Myogenin	OriGene	Mouse monoclonal	F12B
13	p53	OriGene	Mouse monoclonal	BP53.12
14	Ki-67	MAIXIN-BiO	Mouse monoclonal	MIB-1
15	ALK	Roche	Rabbit monoclonal	D5F3

the 2004 WHO classification [3], WDFA is categorized as a variant of adenocarcinoma of the lung. And CBPB is among carcinomas with pleomorphic, sarcomatoid or sarcomatous elements. However, PPB is another distinct clinicopathological entity among sarcomas of the lung, which is a malignant stromal tumor in early childhood and rarely occurs after the age of 5. According to the result in Lee's study [5] and the review by Koss et al. [2], pulmonary blastoma most commonly manifests as a solitary mass in the peripheral lung on chest radiograph. The radiologic differential diagnosis for pulmonary blastoma must be made. These lesions include: a primary or metastatic malignant neoplasm and benign pulmonary parenchymal tumors such as hamartoma, chondroma, and sclerosing hemangioma. For immunohistochemical study and mutation analysis, expression of p53 was detected in this case, which may be consistent with an underlying *TP53* mutation, but no *EGFR* was found in this case.

In the most recent review by Van Loo [4], the average age was 39 years for CBPB, with a gender ratio that favored men by 1.5:1. Cough, chest pain, haemoptysis, dyspnea and respiratory distress are the most common presenta-

Table 2. All 11 cases of CBPB with brain metastasis presented in the literature

Case no.	Reference	Age (yrs)	Sex	Initial presentation	Diagnosis verified by	Treatment	Survival
							Time (month)
1	10	72	M	Hemoptysis	CT scan	RT 50 Gy	12
2	11	57	M	Absent	Autopsy	no treatment	2.5
3	12	45	M	Headache, gait disturbance	CT scan + histology	S + Ch	12
4	13	50	M	Chest pain	Autopsy	no treatment	4
5	14	4	F	Symptom-free	CT scan + histology	S + Ch + RT 40 Gy	9
6	9	51	M	Cough, hemoptysis	CTscan/MRI + histology	S + RT 48.8 Gy	25
7	15	52	F	Symptom-free	CT scan + histology	absent	absent
8	16	27	M	Fever	CT scan + histology	Ch	6
9	17	28	F	Dyspnoea, cough and chest pain	CT scan/MRI + histology	S + Ch + RT 30 Gy	18[a]
10	18	75	M	hemiplegia and aphasia	CT scan/MRI + histology	S + RT 30 Gy	1.5
11	Present case	19	F	headache	CT scan/MRI + histology	S[b]	2

[a]18 months later, the patient still remained well and without evidence of disease recurrence. [b]Only the brain metastasis was resected. Abbreviations: M, Male; F, female; RT, radiotherapy; S, surgery; CT, computed tomography; Ch, chemotherapy.

tion features [6]. CBPB has a recurrence rate of 43% and a propensity for metastasizing to the mediastinum, pleura, diaphragm, liver, heart, adrenal and soft tissues of the extremities [7, 8]. Brain metastasis is extremely rare. Literatures revealed only 6 cases of brain metastasis before 2006, which was concluded by Kouvaris, et al [9]. Based on literatures, a total number of 11 cases of brain metastases, including our case, were reported and listed in **Table 2** [10-18].

The prognosis is very poor for this malignance and its therapy is difficult to determine because of the small number of cases. Adverse prognostic factors for patients with biphasic tumors are tumor recurrence, metastasis at initial presentation and gross size of the tumor (>5 cm) [2]. According to the review by Van Loo [4] with 34 cases of CBPB between 1995 and 2010, the median survival time for CPBP without metastasis at initial TNM stage was 22.5 months. However, as showed in **Table 2**, the median survival time for the patient with brain metastasis is less than 7.5 months.

Until now, there is no standard management for this malignancy. It seems that these patients could benefit from the combination treatment of surgery, radiotherapy and/or chemotherapy (**Table 2**, case 1, 3, 6, and 9). For example, the patient reported in case 6 underwent surgery and radiotherapy resulting in relative long-term survival (25 months). In addition, the patient mentioned in case 9 was in good condition without recurrence 18 months later, following a stereotactic radiosurgery to the brain foci and a whole-brain radiotherapy (30Gy). These cases indicate that long-term survival is possible in this rare disease if an aggressive approach is undertaken.

Since classic biphasic pulmonary blastoma is a rare disease and the strategy of treatment is remained unclear, more clinicopathological data should be needed. Commonly, the primary treatment of such malignancy is surgery resection, especially for the local foci. Comprehensive strategy might be taken into account for treatment for individual patient who in late stage, including surgery, chemotherapy and radiotherapy. For brain metastases, stereotactic radiosurgery and a whole brain irradiation might be an appropriate treatment to prolong the survival time.

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Disclosure of conflict of interest

None.

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