

Case Report

Biphasic pulmonary blastomas in the context of neurofibromatosis 1

Qing Li^{1,3}, Xiao-Yan Su², Dan Gong^{1,3}, Dao-Lin Zeng¹, Jie Yu¹, Qiong-Yu Lan^{1,3}

Departments of ¹Oncology, ²Pathology, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi, China; ³Jiangxi Key Laboratory of Clinical and Translational Cancer Research, Nanchang 330006, Jiangxi, China

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Abstract: Pulmonary blastomas (PB) are rare malignant lung tumors. At present, there is no standard treatment for unresectable pulmonary blastomas. Neurofibromatosis 1 is an autosomal dominant genetic disease, characterized by neural crest cell prosoplasia, causing multi-system damage. To the best of our knowledge, pulmonary blastomas in the context of neurofibromatosis have not been previously examined. A 20-year-old man with a history of neurofibromatosis 1 was diagnosed with a pulmonary blastoma (stage IIIA). Liposomal doxorubicin and ifosfamide were administered for a total of six cycles. Apatinib was given as maintenance treatment. Brain metastasis was found 9 months after presentation. Brain tumors were treated with whole brain radiation, 30 Gy/10 fractions, and gross tumor volume 51 Gy/12 fractions. Relief of neurological symptoms was obtained via radiotherapy. The patient died a little less than 11 months after presentation. Advanced pulmonary blastomas are treated with chemotherapy or alternatively with Apatinib. For brain metastases, whole brain radiation can relieve neurological symptoms and prolong survival times.

Keywords: Pulmonary blastoma, neurofibromatosis 1, brain metastases, apatinib, case report

Introduction

Pulmonary blastomas (PB) are rare malignant lung tumors, accounting for 0.25%-0.5% of all primary pulmonary malignant tumors [1]. PBs have been classified as classic biphasic pulmonary blastomas (CBPB), well-differentiated foetal adenocarcinomas (W DFA), and pleuropulmonary blastomas (PPB). However, according to 2004 World Health Organization (WHO) classifications [2], PBs are a variant of soft tissue tumors and well-differentiated foetal adenocarcinomas. Age of onset is usually between 35-78 years, with an average age of 52 years [3].

Neurofibromatosis I (NF1), also known as von Recklinghausen's disease, is an autosomal dominant genetic disease, characterized by neural crest cell prosoplasia, causing multi-system damage. Its prevalence is about 1/2,500 to 1/3,000 [4]. Main clinical manifestations include alterations of skin pigmentation, Lisch nodules of the iris, and multiple benign neurofibromas. Some people with NF1 also frequently

have learning disabilities. They may develop skeletal abnormalities, vascular disease, central nervous system (CNS) tumors, or malignant peripheral nerve sheath tumors [5]. Criteria for diagnosis of NF1, developed by a National Institutes of Health (NIH) Consensus Conference in 1987, have been generally accepted for routine clinical use. NIH diagnostic criteria are met when two or more of the following features are present, in the absence of another diagnosis: 1) Six or more café-au-lait macules >5 mm in greatest diameter in pre-pubertal individuals, as well as >15 mm in greatest diameter in post-pubertal individuals; 2) Two or more neurofibromas of any type or one plexiform neurofibroma; 3) Freckling in the axillary or inguinal regions; 4) Optic gliomas; 5) Two or more Lisch nodules (iris hamartomas); 6) Distinctive osseous lesions, such as sphenoid dysplasia or tibial pseudarthrosis; and 7) First-degree relative with NF1, as defined by the above criteria [6].

The current study describes a 20-year-old man with NF1 that developed biphasic pulmonary

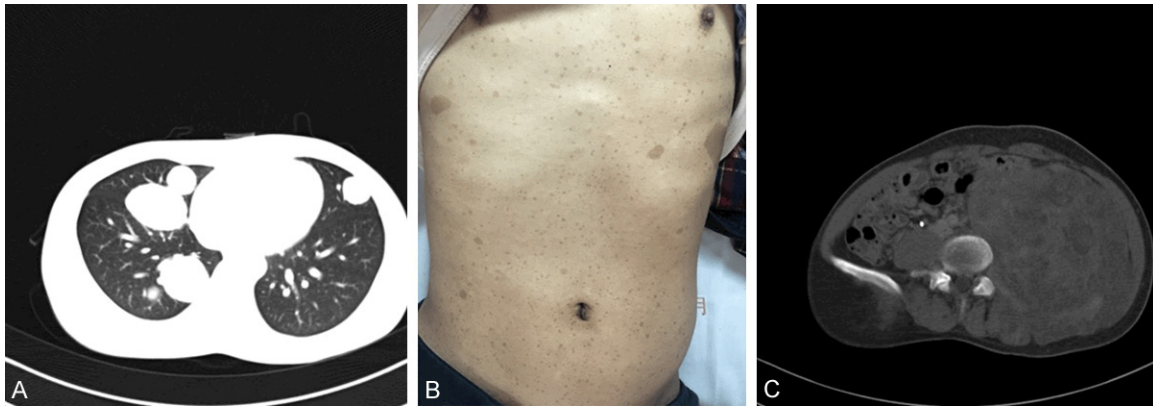


Figure 1. Radiographic findings. A. Chest CT scans revealed multiple mass lesions in both lungs. B. Abdominal skin with a large number of café-au-lait macules >15 mm in greatest diameter. C. CT showing a large mixed density mass (14.8 × 12.0 cm) in the left abdomen and pelvic retroperitoneal area.

blastoma. This study also presents a review of the disease.

Case report

A 20-year-old man was admitted to the hospital with a cough. He denied chest discomfort, showing no fever, dyspnoea, or weight loss. Computed tomography (CT) revealed multiple mass lesions, bilaterally. The largest tumor diameter was 5.0 cm × 3.6 cm, with no mediastinal invasion (**Figure 1A**). Brain magnetic resonance imaging (MRI) revealed no apparent metastasis. Clinical stage was set at T4N0M0 stage IIIA.

The man had no other remarkable items in his medical history, apart from NF1. He had been diagnosed with a lesion in the pelvic cavity at Shanghai Children's Hospital at the age of 12. Upon physical examination, the abdominal skin revealed a large number of café-au-lait macules, >15 mm in greatest diameter (**Figure 1B**). Freckles were noted in the axilla. Imaging revealed a large mixed-density mass (14.8 cm × 12.0 cm) in the left abdomen and pelvic retroperitoneal area (**Figure 1C**). Serum levels of tumor markers, AFP and CEA, were normal throughout the course of treatment.

A CT-guided biopsy of the lung tumor was performed. Haematoxylin and Eosin staining (HE) of the pathological specimen revealed fusiform malignant cells with mixed epithelial and mesenchymal malignant features (**Figure 2A**). Immunohistochemical staining for epithelial marker cell keratin (CK) was positive (**Figure 2B**). Mesenchymal markers, vimentin and nuclear-

associated antigen Ki-67 (Ki-67), were also positive (**Figure 2C, 2D**). Results confirmed the diagnosis of biphasic pulmonary blastomas.

These tumors were considered unresectable because of the multiple locations in both lungs. Chemotherapy with liposomal doxorubicin (20 mg/m² on day one) and ifosfamide (1.2 g/m²/day from day one to three) was administered every 21 days, for a total of 6 cycles. Contrast-enhanced CT was used to monitor his course every 2 cycles. The lung tumors gradually reduced in size. CT images revealed a partial response (PR) after two cycles of chemotherapy (RECIST 1.1). The largest tumor diameter was 4.0 cm × 2.6 cm (**Figure 3A**). After six cycles of chemotherapy, the largest tumor diameter was 3.5 cm × 2.1 cm (**Figure 3B**). Apatinib mesylate tablets were given 500 mg/daily as maintenance treatment. The largest tumor diameter continued to shrink to 2.7 cm × 2.0 cm (**Figure 3C**). After 4 months of apatinib treatment, he reported progressive difficulty in walking and weakness in his right hand. An MRI revealed multiple brain tumors in the left frontal and parietal lobes (**Figure 3D, 3E**). The largest tumor was 3.6 × 1.7 × 2.1 cm, located in the left frontal lobe. These brain tumors were treated with whole brain radiation, clinical target volume (CTV) 30 Gy/10 fractions, and gross tumor volume (GTV) of left frontal lobe 51 Gy/12 fractions. Pulmonary lesions, now classified as progressive disease (PD), were treated with one cycle of liposomal doxorubicin (20 mg/m² on day one) and ifosfamide (1.2 g/m²/day from day one to three). CT findings revealed

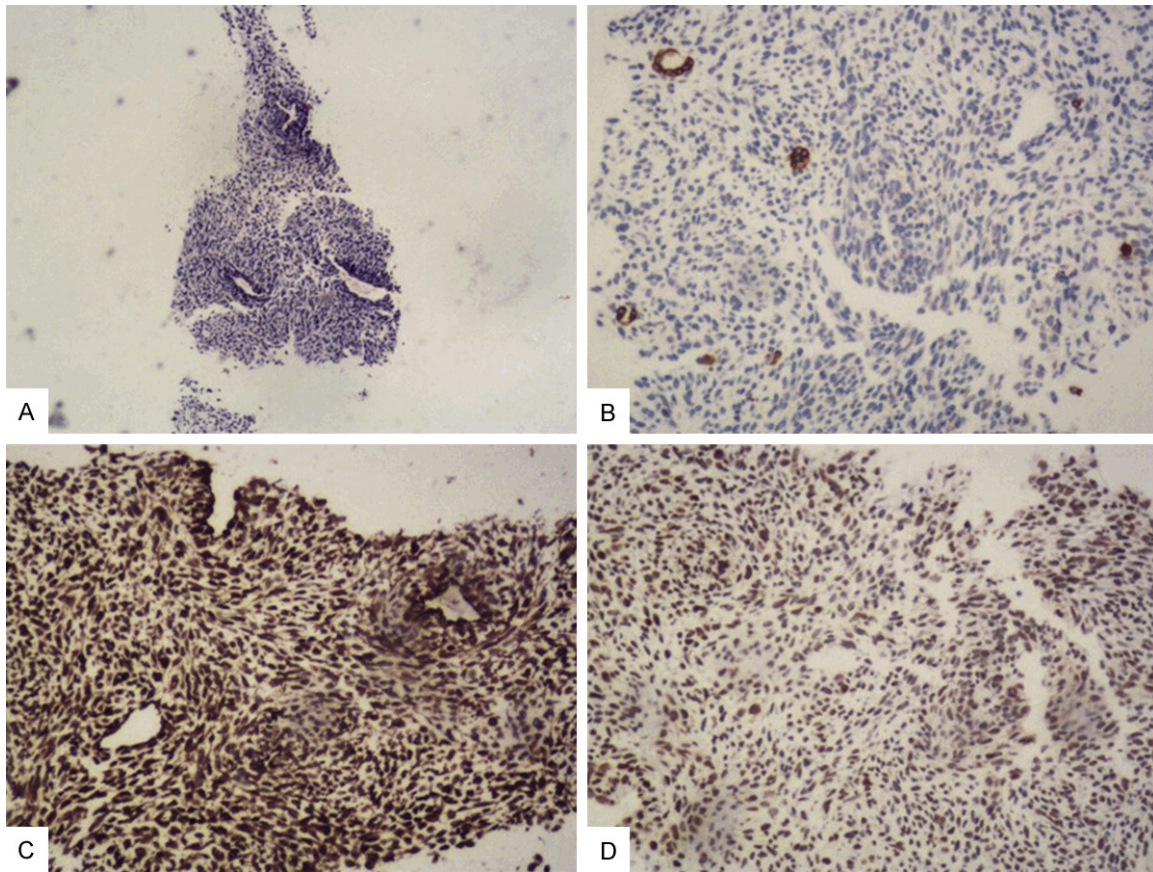


Figure 2. Histological findings. (A) Pathology of the lungs showing fusiform malignant cells mixed epithelial and mesenchymal malignant cells (H&E stain; magnification 40 ×). (B) CK (100 ×) positive in a gland-like structure. (C) Vimentin and (D) Ki-67 (100 ×) are diffusely positive in the mesenchymal cells.

that the neurofibroma in the pelvic cavity was larger than before, with signs of bleeding within the lesion (**Figure 3F**). He felt abdominal mass pain if he stopped apatinib treatment. Because his Karnofsky Performance Scale score was 50, no further chemotherapy was administered. The patient left the hospital in a cachectic state and died on July 15, 2017. Overall survival for this patient was less than 11 months (**Figure 4**).

Discussion

Pulmonary blastomas carry a poor prognosis. They account for 0.25%-0.5% of primary pulmonary malignant tumors [7]. Age at diagnosis ranges from 45 to 76 years old (average age is 53 years) [8]. This disease is extremely rare in children [9]. Nonspecific respiratory symptoms, such as coughing, haemoptysis, chest pain, and shortness of breath, are common symptoms. Other clinical symptoms include fever,

weight loss, pneumothorax, and pleural effusion. However, 40% of cases may be asymptomatic and are detected during incidental chest x-rays or CTs [10]. No characteristic serum tumor markers have been identified. AFP, NSE, and CEA have been shown to be increased in single reports [7, 11]. The current study provides an overview of cases obtained via a Medline-search between 2011 and 2018 (**Table 1**).

NF1 is autosomal dominant disease with a prevalence of approximately 1 in 4,000 [12]. Moreover, 15%-19.87% of patients present with central nervous system tumors or other malignancies [13, 14]. The most common types of cancer are malignant peripheral nerve sheath tumors and intracranial gliomas [15]. Other malignancies include gastrointestinal stromal tumors (GIST), rhabdomyosarcomas, and pheochromocytomas [16]. Howell et al. reported an increased risk of breast cancer at young-

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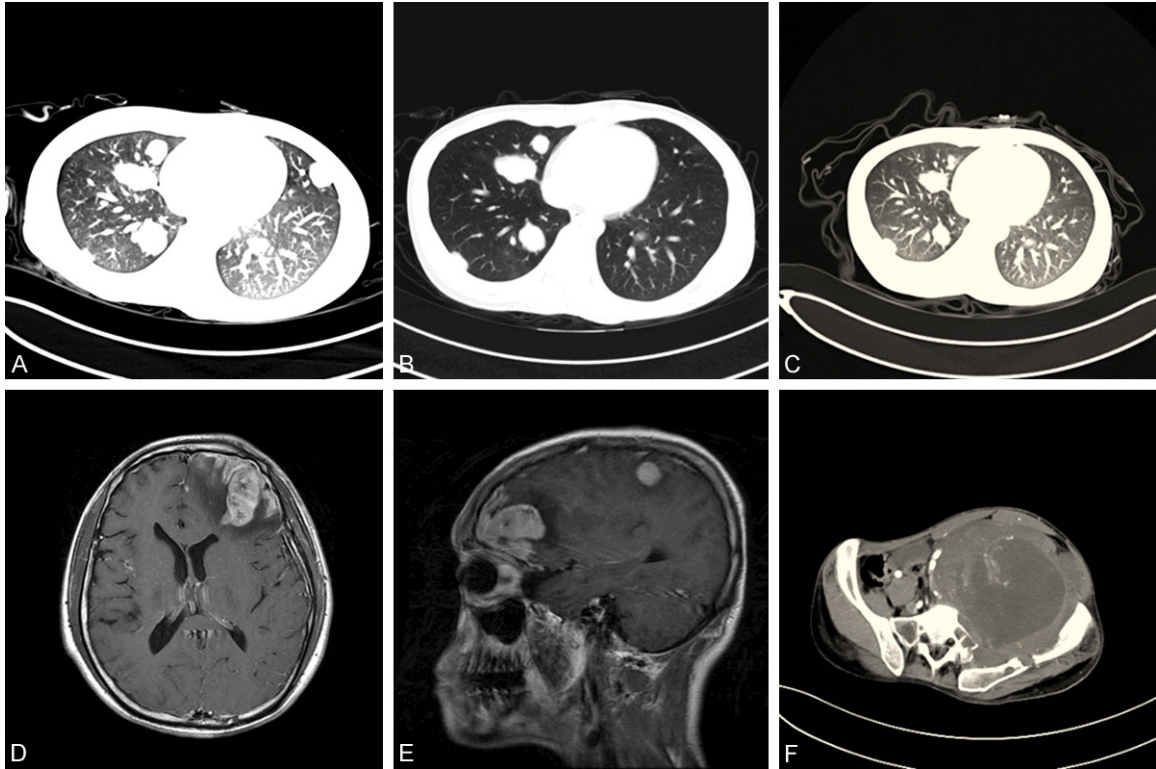


Figure 3. (A) Chest CT revealed tumor shrinkage after two cycles of chemotherapy. The largest tumor diameter was 4.0 cm × 2.6 cm. (B) Chest CT after six cycles of chemotherapy. The largest tumor diameter was 3.5 cm × 2.1 cm. (C) Chest CT after apatinib targeted therapy for 46 days. The largest tumor diameter was 2.7 cm × 2.0 cm. (D, E) MRI of the brain showing multiple metastasis in the left frontal lobe (D) and parietal lobe (E) and parietal lobe (E) Abdominal CT revealing the neurofibroma in the pelvic cavity larger than prior, with signs of bleeding within the lesion. (F) The neurofibroma in the pelvic cavity was larger than prior after apatinib targeted therapy for 46 days, with signs of bleeding within the lesion.

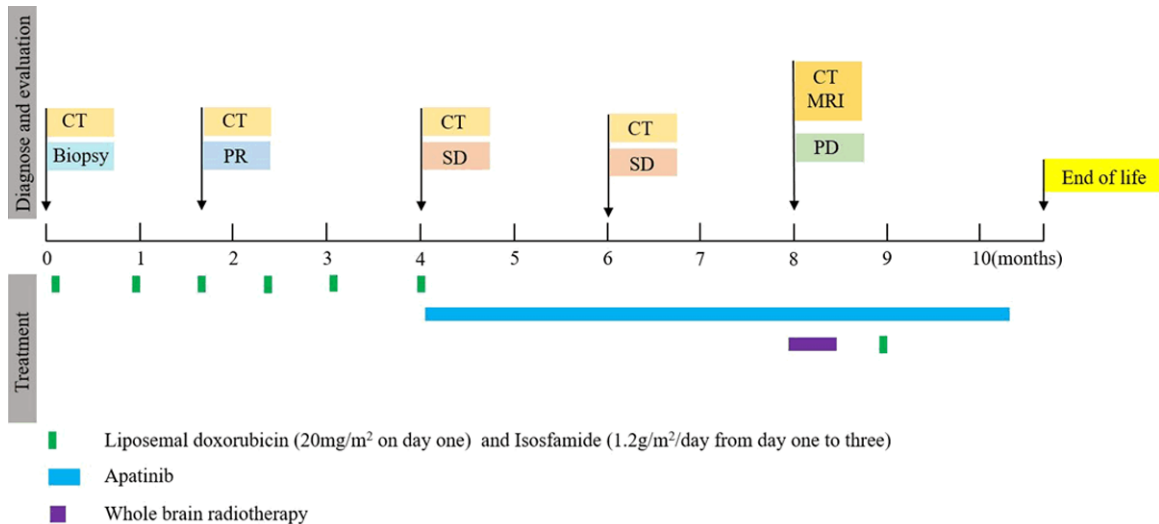


Figure 4. Timeline of representative treatment, imaging tests, and evaluation. CT, Computed tomography; MRI, magnetic resonance imaging; PR, partial response; PD, progressive disease; SD, stable disease.

er ages with poorer outcomes in NF1 patients [15]. In the present case, the patient was diag-

nosed with pulmonary blastomas via needle biopsy. The histology resembles lung fetal tis-

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Table 1. Overview of cases of pulmonary blastomas between 2011-2018

Year	Author	Age (years)/gender	Smoking history	Location	Size	Histology	Stage	Metastasis	Surgery	Chemotherapy/Radiotherapy	Outcome
2011	S. VanLoo [25]	77/Male	Yes	Right upper lobe	6 cm	CBPB	pT3N0M0	Locoregional recurrence, bone, liver metastases	Right upper lobectomy	Sorafenib	Died 1 week after started chemotherapy
2012	Inga-Marie Schaefer [26]	58/Male	Yes	Upper right hemithorax	15 × 9 × 6 cm	Pulmonary carcinosarcoma	pT3N0M0	No	Right-sided pneumectomy	No	Alive and well at 30 months
2013	Anand Sharma [27]	63/Male	Yes	Right lower lobe	15.8 × 9.5 × 10.3 cm	CBPB	pT3N0M0	No	Right lower lobectomy	4 cycles of Cyclo, Doxo and Vds (CAV)	Alive
2014	Ramakant Dixit [10]	68/Male	Yes	Left lung	Large	CBPB	?	Pleura, rib and chest wall	No	RT	Died 1 months after diagnosis
2014	Robert J Smyth [28]	67/Male	Yes	Right lower lobe	9.0 × 5.5 cm	CBPB	T3N0M0	No	Right pneumectomy	No	Alive and well at 23 months
2014	Kenta Kawasaki [29]	75/Male	Yes	Right lung, frontal lobe	2 cm	PB	T1N1M1	Brain, lymph node	Total resection of the left frontal tumor	Whole brain RT (30 Gy)	Died 35 days after discharge
2014	Muthu P [30]	17/Male	?	Right upper and middle lobes	12 × 10 × 10 cm	CBPB	T4N0M0	Extensive skeletal metastases	Right upper and middle lobectomy	3 cycles of DDP and VP-16, local RT	Alive at 24 months
2016	Mohammad Reza Mohajeri Tehrani [31]	58/Male	?	Bilateral pulmonary	Large	PB	T4N0M0	No	Right lung mass resection, then left lung mass resection 2 years later	Chemotherapy	Alive and well at 40 months
2015	Yingjie Xiu [23]	19/Female	No	Left upper lobe	4 cm	CBPB	cT2N1M1	Brain and axilla	Left pillow leaf resection	No	Died 46 days after surgery
2015	Shinya Sakata [7]	68/Male	?	Left upper lobe	5.5 × 4.5 cm	CBPB	cT3N0M0	Spleen, liver, pleura, rib, stomach, duodenum, heart, cervical and lymph nodes	Left upper lobectomy and lymph node dissection	4 cycles of Carbo and Pac and Bev	Died 9.7 months after onset of disease
2015	Joaquim Bosch-barrera [32]	25/Female	Yes	Left upper lobe	4.5 × 5.5 × 5.2 cm	PB	T4N0M0	No	Left pneumectomy	2 cycles of neoadjuvant DDP plus VP-16, RT with weekly DDP (50.4 Gy)	Unknown
2015	Kelsey Gallo [33]	43/Male	No	Mediastinal mass centered in the sub-carinal region	6.7 × 4.7 cm	CBPB	?	No	Unresectable	4 cycles of DDP, If and VP-16 (VIP), RT (40 Gy)	Alive and well at 3 months
2014	Dalokay Killc [34]	68/Male	Yes	Left upper lobe	10.5 × 9 × 5 cm	PB	?	Brain	Cranial mass resection and then left upper lobectomy	Yes	Died 6 months after surgery with multiple metastases to the bone and liver
2016	Dorota Brodowska-Kania [1]	73/Male	?	Right lung's segment 2	5.2 × 3.0 cm	PB	pT2aN0M0	No	A wedge resection of the right lung upper lobe	No	Alive and well at 24 months
2017	Fadi Nemeah [35]	33/Female	Yes	Left lower lobe	7.1 × 6.2 × 6.2 cm	CBPB	?	No	Left lower lobectomy	No	Alive and well at 12 months
2018	Zhaoting Meng [36]	24/Female	No	Left upper lobe	5.8 cm	CBPB	cT3N1M1b	Pleural invasion and rib	No	Crizotinib	A progression-free survival of 3 months.

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2018	H. Le Caer [37]	71/Female	Yes	Right lower lobe	7 cm	Pneumoblastoma	T2N0M0	Bone, Brain, right adrenal, subcutaneous nodule, liver	Right lower lobectomy	3 cycles of DDP, VP-16; 3 cycles of Carbo, VP-16; RT (30 Gy/10 f)	Alive 7 years after diagnosis and 5 years after metastatic progression
2018	Tadashi Sakane [38]	65/Female	No	Right lower lung	5 cm	Blastomatoid variant of pulmonary carcinosarcoma	T3N2M0	Subcarinal lymph node	Right lower lobectomy with lymph node dissection	4 cycles of DDP and Vin	Alive and well at 30 months
2018	Jennifer A. Lewis [39]	38/Female	Yes	Left upper lobe	9.5 cm	CBPB	pT3N2M0	Lymph nodes, brain	Left upper lobectomy	4 cycles of DDP and Vin, thoracic RT (50.4 Gy/28 f), gross total resection of the posterior temporal mass and gamma knife radiosurgery	Alive more than 10 years
2018	Jennifer A. Lewis [39]	29/Female	No	Left lower lobe	9 cm	CBPB	?	Bilateral ovaries	Thoracotomy and resection of the tumor, laparotomy with resection of the ovarian masses.	4 cycles of DDP, If and VP-16 (VIP), RT for positive bronchial margin (59.49 Gy/33 f)	Alive more than 10 years

DDP, Cisplatin; Cyclo, cyclophosphamide; If, ifosfamide; Vin, vinorelbine; Bev, bevacizumab; Carbo, carboplatin; Pac, paclitaxel; Doxo, doxorubicin; Vds, vindesine; VP-16, etoposide; RT, radiotherapy.

sue, containing both epithelial and mesenchymal features. In addition to CK, other epithelial markers may be positive, including EMA and TTF-1 [17]. To the best of our knowledge, this is the first report of a case of PB in the context of NF1.

Prognosis of biphasic PB remains poor, with a median survival time of 19 months [8]. Surgical resection is the main method for treatment, with a 5-year survival rate of 25% in stage I [7]. Chemotherapy and radiotherapy can be administered to unresectable patients. However, there is no agreement regarding standard treatment. Combination chemotherapy with cisplatin and etoposide may be considered [18]. Ifosfamide plus doxorubicin with radiotherapy has been reported for postoperative recurrence [19]. Carboplatin and paclitaxel plus bevacizumab have shown temporary effectiveness [7]. Apatinib is a novel receptor tyrosine kinase inhibitor that selectively targets vascular endothelial growth factor (VEGF) receptor 2. It selectively binds and inhibits VEGFR-2, blocks downstream signalling, prevents VEGF-mediated endothelial cell migration and proliferation, and inhibits neovascularization with potential antiangiogenic and antitumor activity [20]. Feng Li reported that apatinib treatment showed objective efficacy and manageable toxicity in stage IV sarcoma patients that failed using chemotherapy [21]. In the present case, the patient achieved stable disease (SD) within five months of maintenance apatinib. Bleeding in the pelvic neurofibroma attracted attention. It is unusual that the patient felt abdominal mass pain when stopping apatinib treatment. This may be because the drug affected angiogenesis in the neurofibroma synchronously. However, malignant transformation of the neurofibroma cannot be ruled out.

Brain metastases in PB were first reported by Barson et al. [22]. The median survival time for patients with brain metastasis is less than 7.5 months [23]. Surgery, radiotherapy, and chemotherapy can be implemented. There is also no standard regimen for radiotherapy. One patient that was given 50 Gy survived 12 months [24]. In the current case, brain metastases were treated with whole brain radiation at a total dose of 30 Gy and GTV of the left frontal lobe mass at a dose of 51 Gy. Despite relief of neurological symptoms afforded by radiotherapy, there were only two months between the dis-

covery of brain metastases and the death of the patient.

To the best of our knowledge, this is the first reported case of pulmonary blastoma in the context of neurofibromatosis type 1. Treatment with chemotherapy and apatinib was employed for the patient's advanced pulmonary blastoma. For brain metastases, whole brain radiation relieved his neurological symptoms, likely prolonging survival.

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Written informed consent was obtained from all patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qiong-Yu Lan, Department of Oncology, The Second Affiliated Hospital of Nanchang University, 1 Minde Road, Nanchang 330006, Jiangxi, China. Tel: 138-7007-8811; E-mail: flylanhuacao@163.com

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