Case Report

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Classic biphasic pulmonary blastoma: a case report and review of the literature

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Abstract

Pulmonary blastoma (PB) is a very rare malignant lung tumor consisting of classic biphasic PB, well-differentiated fetal adenocarcinoma, and pleuropulmonary blastoma. We herein present an unusual case involving a patient with classic biphasic PB who underwent right upper lobe resection and subsequent treatment. No standard treatment guidelines are available for PB because of its rarity. Our patient received nedaplatin plus paclitaxel as adjuvant chemotherapy. After disease recurrence, the patient received two cycles of etoposide-cisplatin and six cycles of pemetrexed, bevacizumab, and carboplatin. Because of severe adverse effects of the chemotherapy, the patient was finally administered anlotinib, a new oral multikinase inhibitor. Both the tumor size and the serum tumor marker concentration decreased. In conclusion, surgical excision is the treatment of choice for PB. Chemotherapy in the present case resulted in PB activity that was consistent with the literature. Targeted therapies including antiangiogenic agents should be considered as a new treatment option for this rare disease.

Keywords

Pulmonary blastoma, chemotherapy, anlotinib, alpha-fetoprotein, surgical excision, targeted therapy

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Introduction

Pulmonary blastoma (PB) is an exceedingly rare type of lung cancer, comprising only 0.25% to 0.50% of all lung malignancies.[1,2] In the most recent World Health Organization classification, PB is included

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in the category of carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.[3] It can be divided into three separate histologic categories: one biphasic type (classic biphasic PB (CBPB)) and two monophasic types (well-differentiated fetal adenocarcinoma and pleuropulmonary blastoma). CBPB, the most common of the three subtypes, is histopathologically characterized by heterogeneous intermixing of epithelial and mesenchymal malignant cells.[3] Standard treatment of this lung malignancy is surgical excision in the early stages. However, there is not enough data to establish a standard treatment guideline because of the rarity of CBPB. The prognosis of CBPB is poor, and the overall 5-year survival rate is around 15%.[4,5] We herein present an unusual case of CBPB in a patient who received comprehensive treatment in our unit and demonstrate the activity of an oral multikinase inhibitor, anlotinib, for the CBPB. The pertinent literature is also reviewed.

Case report

A 58-year-old man presented with a 10-day history of cough and mild hemoptysis. He had a 20-year history of tobacco consumption, having smoked one pack of cigarettes per day, but he had no additional risk factors. A chest radiograph revealed a gross opacity located in the posterior aspect of the right lung. Contrast-enhanced chest computed tomography (CT) showed a mass of approximately 5 cm in diameter in the right upper lobe complicating a pulmonary infection (Figure 1). The boundary of the lesion was clear and smooth, the enhancement was uneven, and many small patches of necrosis were present.

The patient's physical examination findings were normal, but laboratory tests showed an elevated serum concentration of alpha-fetoprotein (AFP) at 64.6 ng/mL (reference range, 0–9 ng/mL). Bronchoscopy

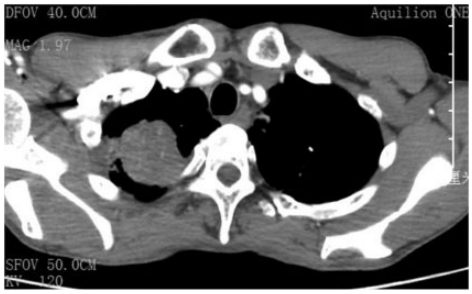

Figure 1. Contrast-enhanced chest computed tomography showed a mass of approximately 5 cm in diameter in the right upper lobe complicating a pulmonary infection.

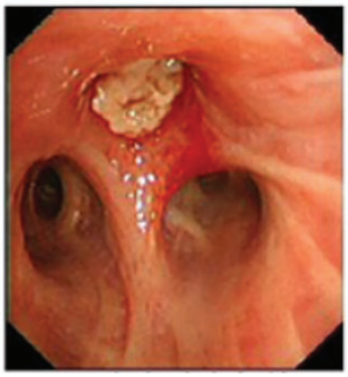

Figure 2. Bronchoscopy showed that the tumor was occluding the right upper apical bronchus.

confirmed that the tumor was occluding the right upper apical bronchus (Figure 2), and biopsy samples were necrotic. Fluorodeoxyglucose positron emission tomography and brain magnetic resonance imaging showed no apparent metastasis, confirming that the disease was enclosed in the right lung.

The preoperative work-up showed no contraindications; therefore, right upper lobectomy and lymph node dissection were performed under electronic thoracoscopy. Definitive histology with hematoxylin and eosin staining demonstrated mixed epithelial and mesenchymal malignancies (typical features of CBPB). The epithelial

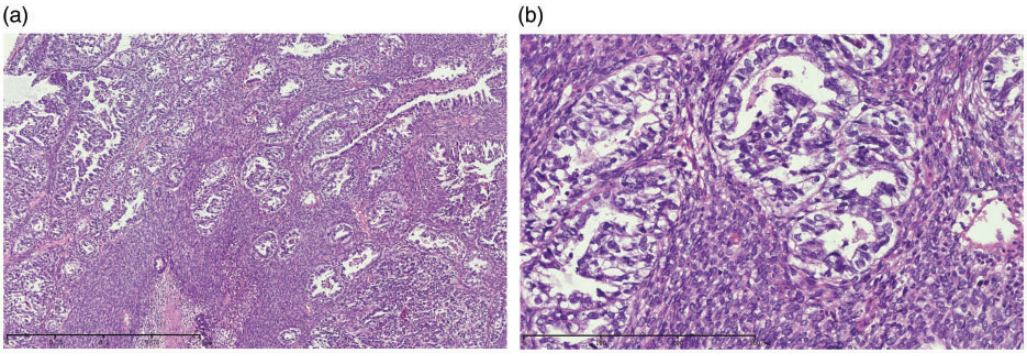

Figure 3. Histopathological examination demonstrated mixed epithelial and mesenchymal malignancies. The epithelial component formed glands composed of columnar cells with clear cytoplasm, whereas the mesenchymal component consisted of round and spindle cells with variable degrees of nuclear atypia. (a) Hematoxylin and eosin, 5×. (b) Hematoxylin and eosin, 20×.

component formed glands composed of columnar cells with clear cytoplasm, whereas the mesenchymal component consisted of round and spindle cells with variable degrees of nuclear atypia (Figure 3(a) and (b)). Immunohistochemical staining showed the following results: CK-7 (+), CK-5/6 and 20 (focally positive), thyroid transcription factor 1 (focally positive), P40 (−), CD56 and vimentin (spindle cell +), desmin (−), CD34 and 99 (−), Ki-67 (epithelial region 70%, spindle cell region 40%), synaptophysin (−), epithelial membrane antigen (−), and calponin (+). The surgical margins and lymph nodes were negative. The tumor was classified as pT3N0M0 according to the 7th TNM classification. A molecular study was performed on the tumor sample. We explored activating mutations of epidermal growth factor receptor (*EGFR*) for exons 18 to 21 and analyzed the rearrangements in anaplastic lymphoma kinase (*ALK*), proto-oncogene receptor tyrosine kinase (*ROS1*), and rearranged during transfection (*RET*), with negative results. The patient subsequently underwent adjuvant chemotherapy with nedaplatin at 80 mg/m^2 and paclitaxel at 200 mg/m^2 every 3 weeks, which was well tolerated. After two courses, the serum concentration of AFP decreased from 64.6 to 11.9 ng/mL.

The patient again presented with cough and chest tightness 2 years later. His AFP concentration had risen to 78.5 ng/mL (Figure 4). Positron emission tomography showed abnormal 18F-fluorodeoxyglucose uptake in the right upper pleura with an elevated standardized uptake value (SUV) of 12, as well as on bilateral lung nodules (SUV = 8.1) and an ipsilateral hilar lymph node (SUV = 5.1). The imaging examination also showed strong fixation on the left liver (SUV = 9.4) (Figure 5). The patient was diagnosed with local recurrence and liver metastases, and the tumor was deemed unresectable. Nedaplatin plus paclitaxel were administered again, but no response was observed. Next, the patient received two cycles of cisplatin and etoposide. The tumor regressed and his AFP concentration decreased. However, his course was complicated by refractory nausea/vomiting, dehydration, and severe neutropenia requiring 2 days of hospitalization. We adjusted the chemotherapy regimen. The patient showed a response to pemetrexed disodium plus bevacizumab plus carboplatin. He completed six cycles with frequent dose reductions; however, the carboplatin

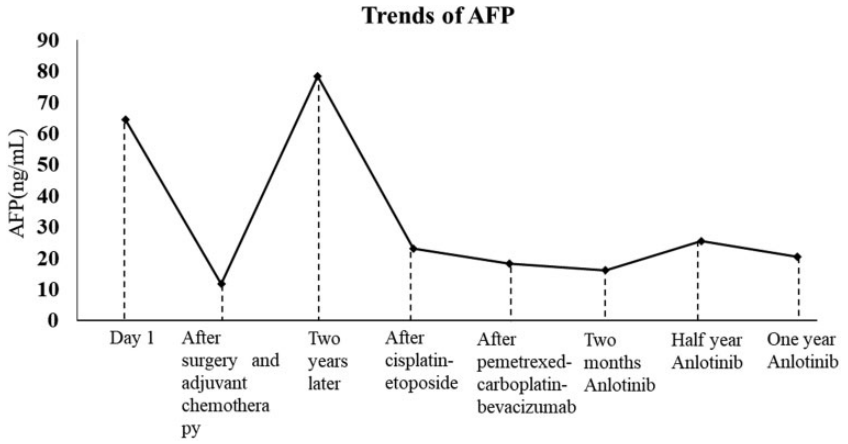

Figure 4. The patient's clinical course showed a decreased alpha-fetoprotein (AFP) concentration after lobe resection and adjuvant chemotherapy with nedaplatin-paclitaxel. After recurrence 2 years later, the AFP concentration rapidly increased. After two cycles of etoposide-cisplatin and six cycles of pemetrexed plus bevacizumab plus carboplatin, the AFP concentration declined again. After the administration of anlotinib, the AFP concentration remained stable and low.

was eliminated from the treatment regimen because of chemotherapy-relevant pneumonia. The effect measurement of CT showed that the tumor was stable, and laboratory testing showed that the AFP concentration decreased (Figure 4). However, the patient refused to undergo chemotherapy again. Finally, we prescribed anlotinib hydrochloride, a novel oral multitarget tyrosine kinase inhibitor, for treatment of the tumor. The patient was still alive at the time of this writing (>4 years after diagnosis and 1.5 years after metastatic progression) and was undergoing regular follow-up with no evidence of recurrence on CT and with a low AFP concentration 1 year after administration of anlotinib (Figure 4). The patient tolerated the treatment well with acceptable and manageable adverse effects.

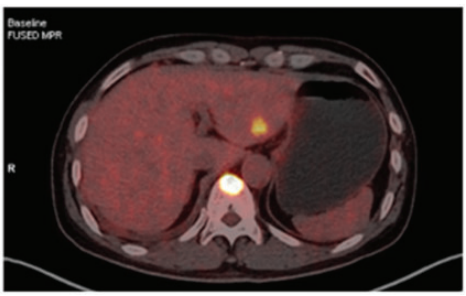

Figure 5. Positron emission tomography scan with liver metastasis.

Discussion

PB is an exceedingly rare but aggressive malignancy with distinctive biological behavior.[6] PB was first described by Barnett and Barnard[7] in 1945, and Barnard[8] subsequently termed it "embryoma." Most of the literature regarding PB is derived from isolated case reports or the experience of multiple centers over several decades. Larsen and Sorensen[9] collected 202 cases from 1962 to 1995 by a Medline search. Van Loo et al.[2] reviewed the literature from 1995 to 2011 and identified only 42 reported cases of CBPB. In the current study, we collected only 31 reported cases of CBPB (Table 1) after reviewing the literature from 2010 to present (2020), emphasizing the rarity of this tumor.

Table 1. Summary of reports of CBPB from 2010 to 2020.

Patient no.	Age (years)	Sex	Size (cm)	Surgery	CT/RT	Outcome	Ref.
1	71	F	7	Right lower lobectomy, multiple metastasectomies	Pt+VP-16; Carbo+VP-16; RT 30 Gy	Alive at 7 years after diagnosis	19
2	38	F	9.5	Lobectomy, craniotomy	adj Vin; adj RT 50.4 Gy; Doc; GKRS+WBRT	Alive at 10 years without recurrence	20
3	29	F	9	Lobectomy, metastasectomies	Pt+If+VP-16; RT 50.49 Gy	Alive at 10 years without recurrence	20
4	29	F	5	Right middle lobectomy with lymph node dissection	Adj Ned+RT	Alive at 6 months	21
5	17	M	12	Right upper and middle lobectomy	Neo Pt+VP-16; adj RT	Death at 2 years after diagnosis	22
6	27	M	15	Unresectable	/	Death at 1 month	23
7	27	M	14	Unresectable	Ble+Pt+VP-16; Pac+Pt+If	Death at 6 months after diagnosis	24
8	70	M	7	Right middle lobectomy with lymph node dissection	/	Alive at 3 years without recurrence	25
9	28	F	Missing data	Left upper lobectomy and mediastinal lymphadenectomy; stereotactic radiosurgery to the brain metastasis	adj If+Vcr+Act+Doxo; Pt+If; WBRT (30 Gy)	Alive at 1.5 years without recurrence	26
10	25	F	5.5	Left pneumonectomy	Neo Pt+VP-16+RT 50.4 Gy	Missing data	27
11	22	F	12	Right pneumonectomy with pericardiectomy; stereotactic radiosurgery	If+Doxo; Carbo+Vcr/Cyclo+Act/Doc+Gem	Death at 2.5 years after diagnosis	28
12	66	F	12	Lobectomy	Pt+VP-16; RT	Death at 6 months after presentation	29
13	67	M	9	Right pneumonectomy	/	Missing data	30
14	16	F	11	Right upper lobectomy	adj If+Carbo+VP-16	Alive after adjuvant chemotherapy	31
15	75	M	2	Brain metastasectomies	WBRT (30 Gy)	Death at 1 month after diagnosis	32

(continued)

Table 1. Continued.

Patient no.	Age (years)	Sex	Size (cm)	Surgery	CT/RT	Outcome	Ref.
16	68	M	5.5	Left upper lobectomy with lymph node dissection	Carbo+Pac+Bev; Pem; Doc	Death at 10 months after presentation	33
17	24	M	7.7	Right upper lobectomy, right pneumonectomy	Carbo+VP-16+RT 60 Gy	Alive after operation	34
18	44	F	5.8	Unresectable	Crizotinib	Missing data	5
19	26	F	17	Left pneumonectomy	adj Pt+VP-16; RT 20 Gy; Doxo+If	Missing data	35
20	36	F	9.2	Left lower lobectomy	Crizotinib	Death at 7 months after diagnosis	36
21	19	F	4	Brain metastasectomies	/	Death at 2 months after presentation	37
22	51	M	Missing data	Unresectable	Carbo+Doc	Alive at 11 months	38
23	51	F	8	Wedge resection of right upper lobe, thyroidectomy	Pt+Doc; RT 37.5 Gy	Death at 33 months after diagnosis	38
24	50	M	5.9	Bilobectomy	/	Alive after operation	38
25	77	M	5	Right upper lobectomy with mediastinal lymph node dissection	Sorafenib	Death at 1 year after presentation	2
26	68	M	Missing data	Unresectable	RT	Death at 1 month after diagnosis	6
27	63	M	15.8	Right lower lobectomy	Cyclo+Doxo+Vcr	Alive after chemotherapy	39
28	68	M	10.5	Left upper lobectomy with lymph node dissection, cranial mass resection	RT+CT	Death at 6 months after diagnosis	40
29	58	M	Missing data	Right and left posterolateral thoracotomy and tumor resection	CT	Alive at 40 months after presentation	41

(continued)

Table 1. Continued.

Patient no.	Age (years)	Sex	Size (cm)	Surgery	CT/RT	Outcome	Ref.
30	62	M	10	Thoracotomy and tumor resection, multiple metastasectomies	Carbo+Cyclo+Adr	Death after operation	42
31	43	M	6.7	Unresectable	If+Pt+VP-16; RT 40 Gy	Missing data	43

F, female; M, male; CT, chemotherapy; RT, radiotherapy; adj, adjuvant; Ned, nedaplatin; GKRS, gamma knife radiosurgery; WBRT, whole-brain radiation; Pt, cisplatin; Gem, gemcitabine; Doc, docetaxel; Act, actinomycin-D; Vcr, vincristine; Cyclo, cyclophosphamide; If, ifosfamide; Vin, vinorelbine; Bev, bevacizumab; Carbo, carboplatin; Pac, paclitaxel; Doxo, doxorubicin; VP-16, etoposide; Pem, pemetrexed; Ble, bleomycin; Adr, Adriamycin.

Cough, hemoptysis, chest pain, and dyspnea are most common presenting features of PB. Approximately 40% of affected patients are asymptomatic,[6] and the tumors are found incidentally on chest radiographs. Our patient's major symptoms were cough and phlegm production accompanied by blood in the sputum. No serum tumor marker is specific for PB.[10] Previously described patients[11] showed increased serum concentrations of AFP, neuron-specific enolase, and carcinoembryonic antigen. In particular, increased numbers of AFP-positive tumor cells have been described in many reports of PB.[11,12] In the present case, we initially found an abnormally high AFP concentration, and the AFP concentration then decreased or increased with the improvement or recurrence of the disease. Therefore, we suggest that AFP may be used as a valuable prognostic indicator. We also recommend the use of AFP as a follow-up biomarker because it can help physicians to determine whether recurrence has developed. However, accumulation of more evidence is needed. Because it is difficult to obtain tissues from a tumor containing both epithelial and mesenchymal components by transbronchial biopsy, the pathological diagnosis in most cases of PB is made through examination of tissues obtained by surgical resection. In the present case, the transbronchial biopsy showed necrotic material with non-malignant cells, and the diagnosis of CBPB was made after surgical resection. Histological examination supplemented with immunohistochemical analysis is the most reliable and conclusive method of diagnosing CBPB and differentiating it from other more frequent primary lung malignancies. In this case study, immunohistochemical examination revealed the following: CK-7 (+), CK-5/6 and 20 (focally positive), thyroid transcription factor 1 (focally positive), CD56 and vimentin (spindle cell +), Ki-67 (epithelial region 70%,

spindle cell region 40%), and calponin (+). These findings are similar to the literature. Microscopically, CBPB is characterized by the presence of biphasic malignant and immature cellular components (epithelial and mesenchymal).

Because of the rarity of this disease, no standard treatment guidelines have been established. Surgery is the cornerstone of curative-intent treatment for localized disease. This has been further supported by numerous case reports and reviews. In 1991, Koss et al.[13] reported that the mean survival duration in patients who underwent surgical resection was 33 months, whereas that in patients with unresected disease was only 2 months. In a more recent case study, Zaidi et al.[14] reported that a patient with locally advanced CBPB underwent lobectomy of the primary tumor after neoadjuvant chemotherapy and was alive at 35 months with no evidence of disease. This compared favorably to patients who did not undergo surgical resection and had a median survival of 5.5 months.[14] The role of adjuvant chemotherapy or/and radiotherapy is still controversial, but it is often administered given the propensity for recurrence.

No standard chemotherapy regimen is available for patients with advanced disease. Table 1 provides a comprehensive list of chemotherapies used in patients with PB from the published studies that we reviewed, including etoposide, platinum, ifosfamide, doxorubicin, docetaxel, cyclophosphamide, vincristine, paclitaxel, and bevacizumab. Interestingly, the multikinase inhibitor sorafenib showed efficacy in a rare case of renal metastasis of biphasic PB.[15] Various combinations of chemotherapeutic drugs have been tried, but no higher-level evidence is currently available to determine which chemotherapeutic drugs are superior to the rest. However, several case reports have described platinum-based treatment.[13,16] Our patient underwent right upper lobe resection and was treated with nedaplatin plus paclitaxel as adjuvant chemotherapy. After disease recurrence, he received two cycles of etoposide-cisplatin and six cycles of pemetrexed, bevacizumab, and carboplatin. The tumor assessment showed a decreased AFP concentration and regressed tumor size, suggesting that these regimens are effective for CBPB. To our knowledge, this is the first reported case demonstrating the activity of an oral multikinase inhibitor, anlotinib, for the treatment of CBPB in an adult patient. Previous research has demonstrated that PB has rich vasculature in the periphery of the tumor[17]; thus, angiogenesis may play an important role in tumor growth. Anlotinib targets vascular endothelial growth factor receptors, fibroblast growth factor receptors, platelet-derived growth factor receptors, and c-kit, which are involved in broad-spectrum inhibition of tumor angiogenesis and growth.[18] Anlotinib has been used as a third-line treatment for refractory advanced non-small cell lung cancer[18] and may also be beneficial in patients with PB. The present case is valuable to establish future treatments for this lung malignancy.

Conclusion

PB is a rare neoplasm lacking clear treatment guidelines. Surgery is the preferred treatment, and no consensus has been reached regarding the role of other therapies. We have herein described an unusual case of CBPB showing a positive response to anlotinib, an oral multikinase inhibitor. This finding could lead to a new treatment option for this rare disease with a poor prognosis. Further accumulation of knowledge and experience is expected.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

This study was approved by the Ethical Review Board of Ningbo First Hospital. Written informed consent was obtained from the patient.

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