

CASE REPORT

Primary pulmonary angiosarcoma: Three case reports and literature review

Yanhong Ren^{1,2,3†}, Min Zhu^{2,3,4†}, Yan Liu^{2,3,4}, Xiaoli Diao² & Yuhui Zhang^{2,3,4}

1 Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China

2 Department of Respiratory Medicine, Capital Medical University, Beijing, China

3 Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing, China

4 Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

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Correspondence

Yuhui Zhang, Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, 8 Gongtinan Road, Chaoyang, 100020 Beijing, China.

Tel: +86 10 8523 1508

Fax: +86 10 8523 1508

Email: zhangyhcy@163.com

†Co-first author.

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Introduction

Angiosarcoma of the lung is a rare tumor that most often presents as metastatic disease. Primary pulmonary angiosarcoma is rarely reported. Because of the rarity of this disease, our understanding of primary pulmonary angiosarcoma is limited. In this report we present three cases of primary pulmonary angiosarcoma with a brief review, to contribute to the sparse literature on this disease.

Case Report

Case 1

A 59-year-old woman presented with increasing dyspnea and bloody sputum, which had occurred over a period of three months before admission. Her past medical history and physical examination were unremarkable, except for

Abstract

Primary pulmonary angiosarcoma is a rare type of malignant vascular tumor with a very aggressive clinical course and a grim prognosis. To date, only a handful of cases have been reported in English literature. Its rarity and consequent low index of suspicion makes clinical diagnosis difficult. In this report we present three cases of primary pulmonary angiosarcoma with cough, hemoptysis, and progressive dyspnea to contribute to the sparse literature on this disease. A review is made of previous reports of primary pulmonary angiosarcomas, and the clinical characteristics, diagnosed method, treatment options, and prognosis of pulmonary angiosarcoma are also discussed.

exposure to tuberculous infection 20 years ago. Computed tomography (CT) pulmonary angiography performed in another hospital revealed a filling defect in the right upper pulmonary artery. She was initially sequentially treated for pulmonary thromboembolism with low molecular weight heparin and warfarin. However, as her shortness of breath worsened, she was admitted to our hospital for further investigation. At admission, her vital signs were stable. A clinical respiratory examination revealed decreased respiratory sounds in the bilateral lung zone. Chest CT showed bilateral pleural effusion and multiple nodules with scattered areas of ground glass opacity in the lung parenchyma (Fig 1a). Pleural fluid was hemorrhagic and exudative by Light's criteria. Repeated cytologic tests of pleural effusion were negative for tumor cells. No extrapulmonary lesions were identified by positron emission tomography (PET) scan; therefore, metastatic disease was excluded. The patient underwent video-assisted thoracoscopy surgery (VATS), which revealed diffuse small nodular lesions on

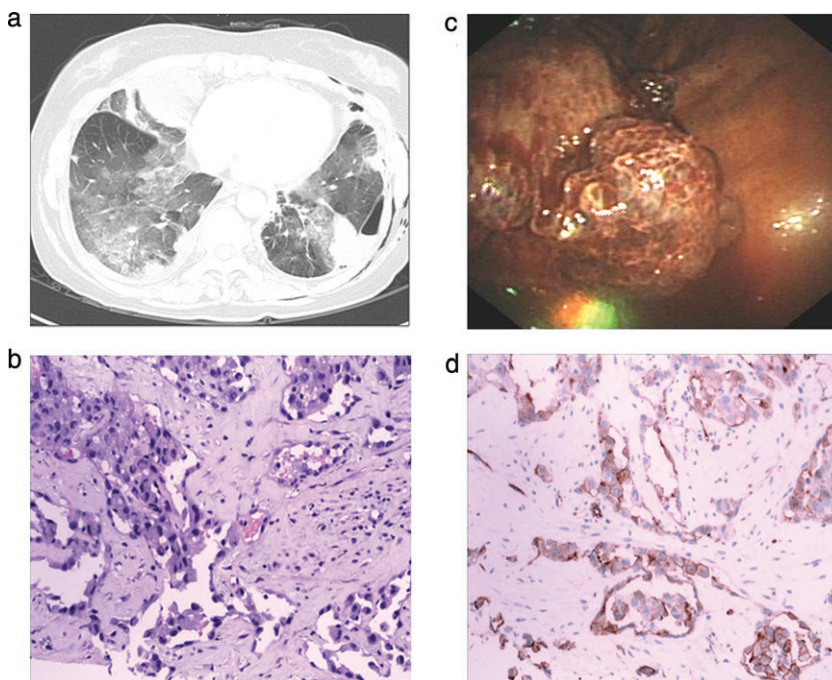


Figure 1 (a) Thoracic computed tomography scan revealed multiple nodules with scattered areas of ground glass opacity in the lung parenchyma. (b) Specimen stained with hematoxylin and eosin showed histological findings of epithelioid angiosarcoma. (c) Video-assisted thoracoscopy revealed diffuse small nodular lesions on parietal pleura with vacuolar changes on the left lung. (d) Histological findings of epithelioid angiosarcoma with CD31.

the parietal pleura with vacuolar changes on the left lung (Fig 1c). Thoracoscopy biopsy revealed malignant cell infiltration (positive for vimentin, CD31, CD34; negative for S100, thyroid transcription factor-1 [TTF-1]/Napsin-A/carcinoembryonic antigen, cytokeratin [CK]7, CK5, CK20, caudal type homeobox 2, gross cystic disease fluid protein-15, D2-40, metastatic carcinoma [MC], calretinin, and periodic acid–Schiff–diastase), consistent with pulmonary primary angiosarcoma (Fig 1b,d). The patient had to abandon further chemotherapy because of physical weakness. After two months of supportive therapy, she died as a result of respiratory failure.

Case 2

A 32-year-old non-smoking female with no past medical history presented to our emergency department with a two-month history of productive cough, intermittent hemoptysis, and progressive dyspnea on exertion. During physical examination, the patient was anxious and appeared ill. She was tachycardic to 130/minute; her BP was 100/70 mmHg; her respiratory rate 32/minute; and her pulse oximetry 90% on room air. A chest examination revealed a reduction in respiratory sounds in the bilateral lower lung zone. Chest CT revealed bilateral pleural effusion, multiple nodules, ground-glass opaque lesions, and large pericardial effusion (Fig 2a). A PET scan failed to reveal any tumors in other locations. Laboratory tests for infection, blood dyscrasia, and connective tissue disease were all negative. After introduction of a pericardium tube,

1000 mL of hematic fluid was drained. A cytological study of the pericardium effusion did not reveal any definite results. The patient underwent a bronchoscopy and trans-bronchial biopsies; however, these did not contribute to a diagnosis. A left medical thoracoscopy with pleural biopsies was performed and showed multiple visceral pleural flat nodules of a dark red color (Fig 2c). Histologic examination of the pleura biopsy specimen showed vascular spaces lined by malignant endothelial cells, some containing vesicular nuclei, which is suggestive of high-grade angiosarcoma (Fig 2b,d). The patient was treated with intermittent Endostar and supportive therapy for two months with little improvement in her shortness of breath. She died as a result of respiratory failure after four months.

Case 3

A 69-year-old, chronic smoking male presented with cough, bloody sputum, and weight loss of a five-month duration. He had a history of hypertension and diabetes. He had consulted a general physician, and chest CT had shown multiple nodules in the central and peripheral portions of both lungs. Many of the nodules were surrounded by a halo of ground-glass haziness (Fig 3a). He had initially been treated for pneumonia with various antibiotics in another medical center but had remained symptomatic. He was admitted to our hospital for further investigation of his condition. The patient's general condition was fair. Inspiratory crackles and wheezing could be heard

Figure 2 (a) Computed tomography of the chest revealed bilateral pleural effusion, multiple nodular, ground glass opaque lesions and large pericardial effusion. (b) Hematoxylin and eosin showed vasoformative architecture in the myxoid matrix, with intracytoplasmic lumina. (c) Medical thoracoscopy showed multiple visceral pleural flat nodules of a dark red color. (d) Immunohistochemical findings of epithelioid angiosarcoma with CD31.

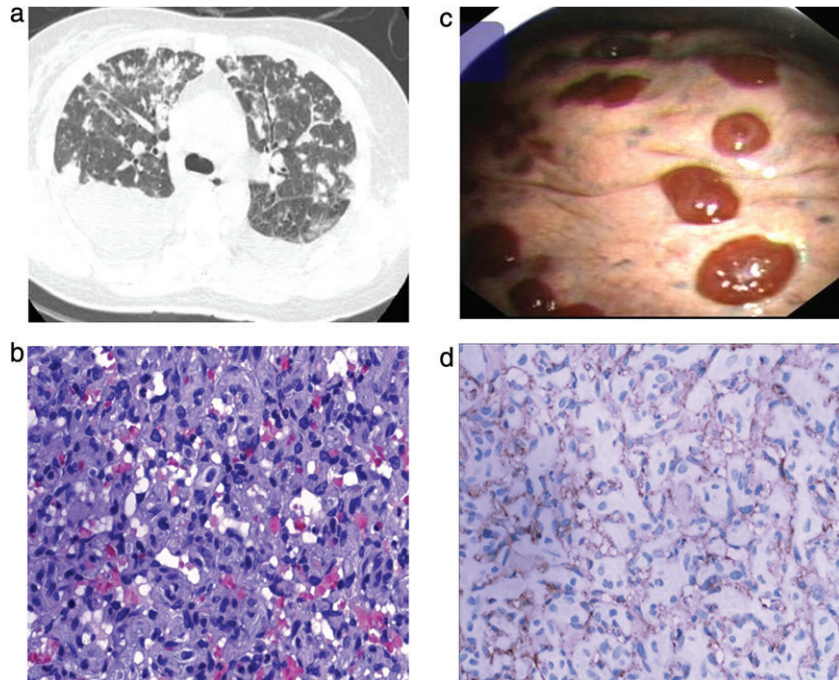
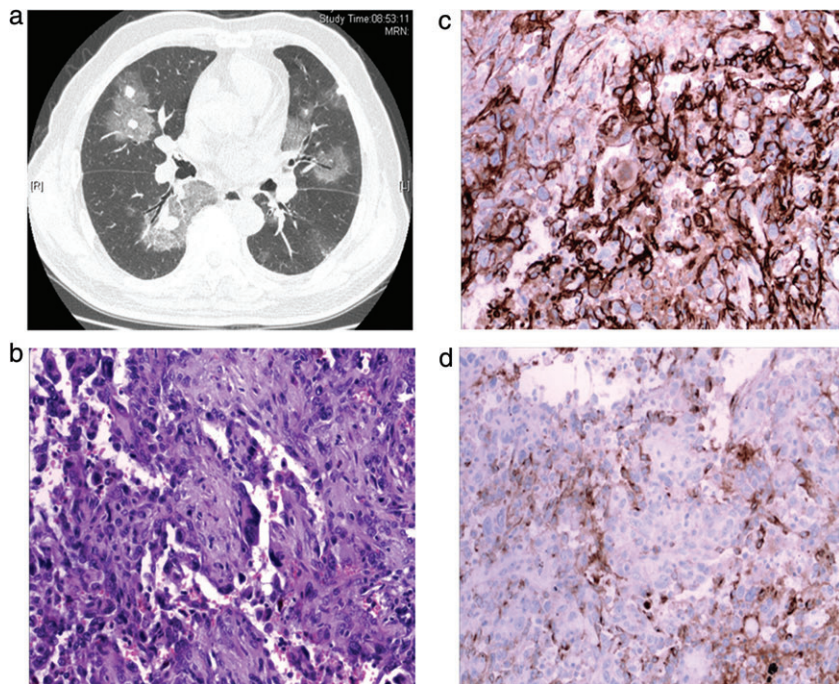


Figure 3 (a) Computed tomography of the chest showed multiple nodules in the central and peripheral portions of both lungs. Many of the nodules were surrounded by a halo of ground-glass haziness. (b) Well-formed anastomosing vessels. The vasoformative areas consist of channels lined by high-grade epithelioid cells, with abundant eosinophilic cytoplasm and significant nuclear atypia. (c,d) Immunohistochemical stain showed tumor cells positive for CD31 and VIII.



bilaterally. Other physical findings were negative. Laboratory data were normal, except for a moderate degree of anemia (hemoglobin, 11 g/dL). To explore the origin of hemoptysis and make a definite diagnosis, the inferior lobe and lingular segment of the superior lobe of the left lung were resected by VATS. A histological pathology examination of the resected specimen revealed well-formed

anastomosing vessels. The vasoformative areas consisted of channels lined by high-grade epithelioid cells, with abundant eosinophilic cytoplasm and significant nuclear atypia (Fig 3b). On immunohistochemical testing, the tumor cells stained positive for endothelial markers factor VIII, CD31, and CD34 (Fig 3c,d) and negative for CK7 and TTF. A PET scan identified no extrapulmonary lesions. A

diagnosis of primary epithelioid angiosarcoma was made. After a month of supportive therapy, the patient died as a result of multiple organ failure.

Discussion

Primary pulmonary angiosarcoma is a rare type of malignant vascular tumor characterized by the proliferation of tumor cells with endothelial features. To the best of our knowledge, only 28 cases, including our patients, have been reported in English literature (Table 1).^{1–24} The mean age of the reported cases was 54.7 years (range 23–85). Of these cases, 18 (64.3%) were men and 10 (35.7%) were women.

There are no symptoms specific to pulmonary angiosarcoma, as the presentation is similar to symptoms found in all lung cancers. Of the 28 cases, hemoptysis and/or hemoptum (16 cases) were the most frequently observed symptoms at the first visit, followed by cough (13) and dyspnea (12).

Reported chest radiograph findings ranged from solitary lesions to multiple nodular densities, with or without pleural effusion. Among the 28 cases, multiple lesions were the most common presentation, occurring in up to 50% (14/28) of patients. Multiple lesions could be expressed as nodules, ground glass opacities, and halo signs. Solitary lesions accounted for 39.3% (11/28). In addition, three cases were described as pulmonary consolidation. Compared with patients with solitary lesions, patients with multiple lesions had a poorer prognosis because of the rapid progression of multiple lesions and less effective clinical treatment. Particular attention should be paid to the three cases with pulmonary consolidation. Median survival in these patients was similar to patients with multiple lesions. Therefore, primary pulmonary angiosarcoma showing multiple infiltration or consolidation suggests a prognostic indicator for an unfavorable outcome.

Early diagnosis of primary pulmonary angiosarcoma is uncommon because of the non-specific respiratory manifestations and consequent low index of suspicion. Definitive diagnosis is made on the basis of histopathological and immunohistochemical findings. The proliferation of variably sized vascular channels with irregular branching, epithelioid-like endothelial lining of vascular spaces, abundant cytoplasm with pleomorphic nuclei and prominent nucleoli, and mitotic figures in atypical fashion are typical pathological features of pulmonary angiosarcoma. Immunohistochemical examination is essential to confirm diagnosis. Among the various immunohistochemical markers used for classification, CD31, CD34, and factor VIII-related antigen are considered specific for diagnosis.

Among the 28 reported patients with primary pulmonary angiosarcoma, bronchoscopy was performed in 13 patients, but only two cases were definitively diagnosed

(positive diagnostic rate 15%). Open lung biopsy was performed in 19 patients (including 11 of the patients who were not definitely diagnosed after bronchoscopy) and a definitive diagnosis was obtained. The total positive diagnostic rate of open lung biopsy was 100%. Percutaneous needle aspiration cytology (PNAC) and pleural biopsy are also effective in the diagnosis of pulmonary angiosarcoma, especially for patients with peripheral pulmonary nodules. Of the 28 patients, four were diagnosed by PNAC and pleural biopsy. In addition, two patients were diagnosed after autopsy; one article did not mention the diagnosis method. Our analysis suggests a low positive diagnostic rate by bronchoscopic biopsy for primary pulmonary angiosarcoma, regardless of the type of radiologic features. Possible reasons for infrequent diagnosis by bronchoscopic biopsy include the fact that the tumors involved few bronchi and the atypical pathological features of primary pulmonary angiosarcoma are difficult to recognize with a small bronchoscopic biopsy sample size. Once clinically suspected, medical thoracoscopy/VATS or open lung biopsy are more effective methods of diagnosis.

There is no standard treatment regimen specifically for pulmonary epithelioid angiosarcoma. Surgical resection, radiation, and chemotherapy have all been attempted. Surgery has been the mainstay for locally confined disease.⁸ Several previous studies have shown that angiosarcoma is radiosensitive.²⁵ Chemotherapy has also been reported to be effective. Two chemotherapeutic combinations have demonstrated partial and full effects: doxorubicin/ifosfamide and docetaxel/gemcitabine.¹³ Systemic administration of high doses of recombinant interleukin 2 (rIL-2) also seems to have been effective.³ However, rIL-2 therapy is usually used with radiotherapy or chemotherapy; therefore, the potential efficacy of rIL-2 alone cannot be assessed. Although many attempts have been made to treat primary pulmonary angiosarcoma, none have proven effective. Of the 28 reported cases, 91% of patients with solitary lesions (10/11) were treated actively, including radiotherapy (1 case), chemotherapy (1), surgery combined with chemotherapy and radiotherapy (3), and surgery (5 cases). The median overall survival was seven months. Only five cases of 14 with multiple lesions accepted chemotherapy, radiotherapy, and palliative surgery. The remaining patients (9/14) had to abandon further therapy because of physical weakness. The median overall survival of patients with multiple lesions was two months. All three cases of our report showing pulmonary consolidation received surgery or chemotherapy. The survival times were one week, two weeks, and six months. Compared with patients with solitary lesions, patients with multiple lesions had a poorer prognosis.

In summary, primary pulmonary angiosarcoma is a very rare type of malignant vascular tumor and its clinicopathologic features are not well known. Definitive diagnosis is

Table 1 Reported cases of pulmonary angiosarcoma

No.	Publication year	Author	Age/gender	Symptoms	Image	Diagnosis	Therapy	Prognosis
1	1954 ¹	Benjamin & Towne	48/M	Blood sputum, shortness of breath, cough	Pleural fluid, multiple nodules	Autopsy	None	12 days
2	1983 ²	Spragg <i>et al.</i>	75/M	Progressive dyspnea, weakness	Diffuse infiltration	Autopsy	None	5 days
3	1987 ³	Palvio <i>et al.</i>	59/M	Chest pain and hemoptysis	Consolidated upper and middle lobes	Thoracotomy	Pneumonectomy	1 week
4	1987 ⁴	Ott <i>et al.</i>	60/M	Shortness of breath, chest pain, cough	Mass involving all three lobes of the right lung with mediastinal invasion	Open lung biopsy	Palliative operation	2 months
5	1988 ⁵	Segal <i>et al.</i>	72/F	Malaise and dyspnea	Bilateral alveolar infiltration	Open lung biopsy	None	2 days
6	1997 ⁶	Sheppard <i>et al.</i>	60/M	Hemoptysis	Diffuse ground glass pattern throughout both lung fields	Autopsy	None	2 days
7	2001 ⁷	Atasoy <i>et al.</i>	50/M	Chest pain, malaise, hoarseness	Hypodense mass with soft tissue attenuation in the LUL	NA	Chemotherapy	9 months
8	2003 ⁸	Kojima <i>et al.</i>	25/M	Chest pain, cough	A solid mass in the left hilar lesion with mediastinal invasion	Bronchoscopic biopsy	Radiation therapy and interleukin-2	> 1 year
9	2004 ⁹	Maglaras <i>et al.</i>	46/M	Hemoptysis	Nodular infiltrates and bilateral hemothorax	Thoracotomy	Chemotherapy	1 month
10	2005 ¹⁰	Pandit <i>et al.</i>	79/F	Shortness of breath, chest pain and cough	Multiple nodules in both lungs	Open wedge biopsy	None	18 months
11	2006 ¹¹	Ozcelik <i>et al.</i>	62/M	Cough, hemoptysis, chest pain, fatigue, weight loss	A nodular lesion in the posterior segment of the RUL	Thoracotomy	Surgery, chemotherapy and radiation therapy	5 months
12	2006 ¹²	Patsios <i>et al.</i>	76/F	Hemoptysis	Soft tissue opacity	Thoracotomy	Surgery	1 month
13	2008 ¹³	Wilson <i>et al.</i>	56/M	Hemoptysis	A LUL mass	Lobectomy	Surgery, chemotherapy and radiation therapy	39 months
14	2009 ¹⁴	Campione <i>et al.</i>	85/F	Cough and dyspnea	Right pleural effusion	Open wedge biopsy	None	3 months
15	2009 ¹⁵	Kuroda <i>et al.</i>	43/M	Cough	A mass in the LLL	Lobectomy	Surgery	15 months
16	2010 ¹⁶	Chen <i>et al.</i>	50/M	Hemoptysis	Multiple nodules in the peripheral of both lungs	Open lung operation	Surgery and chemotherapy	> 6 months
17	2010 ¹⁷	Wan Musa <i>et al.</i>	23/M	Chest pain	Left pleural effusion with consolidation at the lingula area	CT guided biopsy	Chemotherapy	2 weeks

Table 1 Continued

No.	Publication year	Author	Age/gender	Symptoms	Image	Diagnosis	Therapy	Prognosis
18	2011 ¹⁸	Judy <i>et al.</i>	45/M	Weight loss, anorexia, hemoptysis, fatigue	Bilateral pulmonary nodules	Thoracotomy	Chemotherapy	5 months
19	2012 ¹⁹	Kakegawa <i>et al.</i>	45/M	Cough, bloody sputum	A nodule in the left main bronchus, atelectasis of the LUL	Thoracotomy	Surgery	> 12 months
20	2012 ²⁰	Yang <i>et al.</i>	41/M	Productive cough	A solitary pulmonary nodule with bilobulation in the LUL	Thoracoscopic wedge resection	Surgery	< 1 week
21	2013 ²¹	Obeso Carillo <i>et al.</i>	56/F	Hemoptysis	A peripheral nodule in the LLL	Intraoperative biopsy of the pleural lesions	Surgery and chemotherapy	7 months
22	2013 ²¹	Gerado <i>et al.</i>	35/F	Bone and joint pain	A solid lesion in the RLL	Thoracotomy	Radical tumor resection	6 months
23	2014 ²²	Treglia <i>et al.</i>	54/F	Symptomless	A mass in the inferior lobe of the left lung	Lobectomy	None	NA
24	2015 ²³	Tanaka <i>et al.</i>	48/M	Dyspnea on exertion	Nodules involving the lower segments (S8, S9, S10) of the left lung	Bronchoscopy biopsy	Surgery and chemotherapy	1 year
25	2015 ²⁴	Shimabukuro <i>et al.</i>	79/F	Bloody sputum	Consolidation and GGO in the right middle and lower lobes and GGO in the left S1 + 2 and S8	Surgical resections	Palliative operation	3 months
26	2016	Yanhong <i>et al.</i>	59/F	Dyspnea and bloody sputum	Pleural effusion and multiple nodules with GGO in lung parenchyma	Video-assisted thoracoscopy	None	2 months
27	2016	Yanhong <i>et al.</i>	32/F	Productive cough, hemoptysis and dyspnea	Pleural effusion, multiple nodules, GGO lesions, and large pericardial effusion	Medical thoracoscopy	Intermittent Endostar	2 months
28	2016	Yanhong <i>et al.</i>	69/M	Cough, bloody sputum and weight loss	Multiple nodules in the central and peripheral portions of both lungs	Video-assisted thoracoscopy.	None	1 month

F, female; GGO, ground-glass opacity; LLL, left lower lobe; LUL, left upper lobe; M, male; NA, not available; RLL, right lower lobe; RUL, right upper lobe.

made by histopathological and immunohistochemical findings. Once clinically suspected, medical thoracoscopy/VATS or open lung biopsy are reliable diagnostic methods. To date, there have been few reports of an effective

treatment for this condition. Surgical resection, radiation, and chemotherapy have all been attempted; however, these tumors have a very aggressive clinical course and a grim prognosis.

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Disclosure

No authors report any conflict of interest.

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