Chest

Pulmonary epithelioid angiosarcoma responsive to chemotherapy: A case report

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ABSTRACT

Primary pulmonary epithelioid angiosarcoma (AS) is an extremely rare cancer with a poor prognosis. The presenting symptoms and imaging results are nonspecific and hold similarities with more common lung pathology, contributing to missed or delayed diagnosis. Complementing radiological imaging with patient information, such as presenting symptoms and exposures, is important for early consideration of pulmonary epithelioid AS. Even with supportive imaging findings and clinical suspicion for pulmonary epithelioid AS, the most reliable and definitive method for diagnosis is through immunohistochemistry. We describe the case of a 65-year-old patient who presented with dyspnea, cough, and hemoptysis in whom pauci-immune vasculitis was initially suspected before immunohistochemical diagnosis of primary pulmonary epithelioid AS. Due to the rarity of this disease, treatment options have not been well-studied and consist of any combination of surgical resection, chemotherapy, and radiation therapy. Although typically poorly responsive to chemotherapy, our patient achieved a reduction in size of his pulmonary nodules after a course of steroids followed by cyclophosphamide and was later maintained with gemcitabine and docetaxel until his death nearly a year after presentation.

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Introduction

We report the case of a 65-year-old male with primary pulmonary epithelioid angiosarcoma (AS), a lethal neoplasm of extreme rarity that originates from endothelial cells of small vessels and accounts for approximately 0.001% of all cancers. Primary pulmonary epithelioid AS is seen in adults and has a marked predominance in males, occurring 6 to 9 times more often in men than women by some study estimates [1,2]. Presenting signs and symptoms commonly include chest pain, dyspnea, hemoptysis, cough, and weight loss. Among the differential diagnoses for primary pulmonary epithelioid AS are more common pulmonary diseases, such as metastatic disease.

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A 65-year-old male with a past medical history significant for type 2 diabetes mellitus, coronary artery disease status post two-vessel bypass, hypertension, and hyperlipidemia presented to his primary care physician complaining of shortness of breath and cough for which he was prescribed an oral steroid and albuterol. The patient denied a history of smoking or asbestos exposure, intravenous drug use, or human immunodeficiency virus exposure. The patient had worked in a coal mine for approximately 30 years, but past surgical, family, and social histories were otherwise noncontributory. Two days later, he presented to an outside hospital with diffuse alveolar hemorrhage and was electively intubated for bronchoscopy. His initial hemoglobin was 9.4 g/dL. Urinalysis revealed no blood or protein with a creatinine of 0.77 mg/dL. Liver function tests were not performed. Computed tomography (CT) of the chest with contrast was performed as part of the initial workup at an outside hospital and demonstrated bilateral pulmonary nodules (Fig. 1). The largest nodule measured 12-13 mm in the costophrenic sulcus and was concerning for metastatic disease. Bibasilar atelectasis was present and more pronounced in the left than right lower lobe. No other abnormalities were noted. He was extubated but later reintubated for worsening hemoptysis. At this point, he received blood transfusions and underwent emboilization of his left lower lobe by interventional radiology.

Approximately 1 week later, he experienced extensive bleeding from his endotracheal tube that slowed but persisted after embolization. A repeat CT of the chest without contrast revealed worsening bilateral lower lobe atelectasis, left lower lobe mucous plugging with an enlarging focus of cavitation, and bilateral perihilar ground-glass opacities, one of which was new and cavitary. In addition to metastasis, septic emboli and vasculitis were also in the differential. Pulse methylprednisolone was started at 500 mg intravenously every 12 hours for 3 days, and he was extubated approximately 1 week later. A subsequent CT of the chest without contrast demonstrated that the lower lobe cavitary component had resolved, albeit with consolidation concerning for pneumonia and areas of hemorrhage. The bilateral pulmonary nodules were stable, and the previously new cavitary nodule was not evident. These findings indicated a response to treatment and were considered suggestive of granulomatosis with polyangiitis. During hospitalization in the intensive care unit, blood cultures remained negative. Although initial bronchoalveolar lavage (BAL) specimens were negative, subsequent BAL cultures revealed Enterobacter species for which the patient received cefepime. Serology remained negative for an infectious source, and results from antigen testing for Cryptococcus, Histoplasma, Aspergillus, and Coccidioides were negative as well. The (1→3)-β-D-Glucan assay was initially inconclusive but negative on repeat testing. He was believed to have antineutrophil cytoplasmic antibody-negative granulomatosis with polyangiitis given his presentation and aforementioned suggestive findings, and cyclophosphamide at a dose of 150 mg by mouth daily was initiated. He was transferred from the intensive care unit and discharged to home several days later in stable condition with 60 mg oral prednisone.

He attended follow-up appointments with rheumatology and pulmonology and continued cyclophosphamide therapy. The patient was recovering well and experienced only a single episode of hemoptysis. He did complain of intermittent dyspnea upon exertion and was given an albuterol metered-dose inhaler. An outpatient follow-up CT scan of the chest without contrast, approximately 2 weeks after discharge, revealed stable bilateral pulmonary nodules. The most suspicious nodule was in the right lower lobe and measured 2.2 cm with spiculated margins and an irregular shape. A 2.2-cm left lower lobe nodule of fluid density was new and suggestive of a bronchocele, while the ground-glass infiltrates had resolved. By 3 months after discharge, his episodes of blood-tinged saliva progressed to worsening hemoptysis. An outpatient follow-up chest CT without contrast at this time showed multiple persistent nodules with increasing size of the nodules in the upper lobes and decreased size of most of the nodules in the lower lobes. No adenopathy or effusion was evident. A third outpatient CT of the chest without contrast was obtained, revealing relatively stable bilateral pulmonary nodules with an increase in size of the dominant right lower lobe pulmonary mass to 3.4 × 2.7 cm (Fig. 2). The surrounding ground-glass halo was suggestive of hemorrhage.

Bronchoscopy with transbronchial fine needle aspiration from the right upper lobe and core biopsy demonstrated malignant cells suggestive of sarcomatoid carcinoma or epithelioid angiosarcoma. Immunohistochemistry of the biopsy specimen was positive for AE1/3, pan-cytokeratin, CK7, and epithelial and mesothelioma. Imaging and histology of primary pulmonary epithelioid AS are often suggestive but nonspecific, so a strong clinical suspicion followed by immunohistochemical confirmation of the endothelial tumor origin is necessary. This neoplasm is aggressive and often detected late in the disease course, thus associated with a poor prognosis.
membrane antigen – all markers of epithelial differentiation. Plasma cell marker CD138 was also positive. Testing for CD31 and pCEA returned equivocal results. The specimen was negative for CK20, CK5/6, P40, P63, K903, CAM 5.2, CD45, CD21, Ber-EP4, TTF-1, S-100, and CD34. A definitive diagnosis was not made after transbronchial biopsy, and further testing of a resected specimen or additional diagnostic material was recommended. The patient was referred to the hematology-oncology service and started on gemcitabine and docetaxel. He underwent robotic-assisted thoracoscopic surgery for a right upper lobe wedge resection with removal of pleural nodules and bronchoscopy to remove an endobronchial thrombus. The final diagnosis after histological examination of the right upper lobe wedge specimen was epithelioid angiosarcoma (Fig. 3).

The pleural nodules demonstrated hyalinized tissue identified as pleural plaques. Immunohistochemistry was performed on the specimen with results strongly positive for CD31 (Fig. 4) and vimentin while focally positive for AE1/3, CK7, and epithelial membrane antigen. The results were negative for CAM5.2, CK5/6, p63, S-100, desmin, SMA, Factor VIII, TTF-1, napsin-A, CD34, D2-40, and CD21 markers. Additionally, sequencing analysis was performed and showed the tumor to be EGFR negative. The patient’s chest tube was removed on postoperative day 1, and he was discharged to home in stable condition. Postoperatively, a positron emission tomography scan was obtained and showed the remaining right lower lobe pulmonary mass to be intensely hypermetabolic. Most of the bilateral pulmonary nodules were below the positron emission tomography threshold for consideration as metastatic disease. Moderate uptake was evident in the lateral right upper lobe, and given the recent resection, consistent with postsurgical change. The CT scan showed stable, persistent nodules without evidence of hemorrhage or necrosis. The patient elected to receive chemotherapy at an institution closer to his home and continued follow-up until his death nearly 1 year after initial presentation.

**Discussion**

Sarcomas represent 1% of all cancers [3], of which angiosarcomas (AS) comprise only 1% [4]. Even rarer still are angiosarcomas of pulmonary origin, which account for only 10% of AS [5] and thus represent roughly 0.001% of all cancers.

![Fig. 2](image1.png)

**Fig. 2** – Axial computed tomography images of the right lower lobe show increasing size and surrounding ground-glass opacity of the dominant right lower lobe mass. (A) Image from initial hospitalization. (B) Image from 1 month later. (C) Image from 3 months later. Of note, the adjacent satellite nodule in the right lower lobe decreases in size over this time course.

![Fig. 3](image2.png)

**Fig. 3** – (A) Low-power image showing normal alveolar spaces in the top right corner with hemosiderin macrophages within the alveolar spaces. The left half of the image shows a solid nodule with vascular spaces and cells with high N:C ratios. These cells demonstrate large and atypical nuclei with vesicular chromatin and prominent nucleoli. (B) High-power image of the neoplastic cells shows again atypical nuclear morphology with prominent nucleoli.
Pulmonary epithelioid AS is therefore an exceedingly rare malignant vascular neoplasm of the lung, which also includes epithelioid hemangioendothelioma and Kaposi sarcoma, with only a couple dozen cases reported [4]. Primary pulmonary epithelioid AS is an aggressive, high-grade sarcoma that typically has an average survival of 9 months [6]. Other prognostic factors that predict a more aggressive clinical course are older age with a mean age at diagnosis of 58 years [2], size larger than 5 mm, high-grade classification on histology, and a mitotic rate greater than 10 mitotic figures per 10 high-power fields [7].

Commonly reported presenting signs and symptoms of primary pulmonary epithelioid AS are nonspecific and include chest pain, dyspnea, hemoptysis, cough, and weight loss [7]. Our patient demonstrated dyspnea and cough initially and then presented with diffuse alveolar hemorrhage (DAH) 2 days later. While the patient’s older age and male sex fit the epidemiological data from the majority of primary pulmonary epithelioid AS cases reported thus far, he lacked the history of irradiation or asbestos exposure often associated with primary pulmonary epithelioid AS in the West [1,8]. His presentation with DAH and ongoing hemoptysis prompted the investigation of Goodpasture syndrome, which was ruled out by negative antilysosomal basement membrane antibody testing. The absence of renal involvement and antineutrophil cytoplasmic antibody-negative assay results also made granulomatosis with polyangiitis a less likely cause for the DAH and ongoing hemoptysis. Given the bilateral location of pulmonary nodules, metastatic disease was another one of the early working diagnoses. There were no indications of a different primary malignancy as the source of metastasis throughout the course of imaging and laboratory testing, though occult or clinically inapparent malignancy cannot be fully excluded. The potential finding of angiosarcoma elsewhere in the body is an important point to consider as some early case reports of primary pulmonary epithelioid AS are believed to be misdiagnosed metastases due to the presence of multiple bilateral pulmonary nodules without the support of well-documented testing or immunohistochemistry results [4,6,9]. The majority of angiosarcoma metastases to the lung originate from cutaneous or cardiac angiosarcomas, estimated to account for 60% to 80% of cases [3]. Local metastasis from cardiac angiosarcoma is a commonly reported source for bilateral pleural angiosarcoma especially, but the younger average age of 40 years for cardiac angiosarcoma incidence and lack of a right atrial mass on imaging or cardiac symptoms in our patient during this episode make this less likely [7,9,10].

Imaging findings in primary pulmonary epithelioid AS are classically nonspecific. Findings suggestive of angiosarcoma include reticulonodular or alveolar infiltrates, ground-glass opacities, and areas of solid nodules with cavitary lesions [7,11,12]. The presence of ground-glass opacities surrounding nodules, described as a halo sign on CT, indicates areas of hemorrhage from fragile neoplasm vasculature in this context [6,12,13]. Pleural effusions or hemothorax are also seen on radiographic imaging. Almost three-quarters of cases show bilateral nodules [13]. If idiopathic pulmonary hemorrhage is being considered on the list of differential diagnoses, the multinodular pattern on radiographic imaging found in most cases of primary pulmonary epithelioid AS is atypical for idiopathic pulmonary hemorrhage, making it a less likely cause of this patient’s DAH and hemoptysis [7,12]. Our patient’s CT imaging demonstrated many elements characteristic of primary pulmonary epithelioid AS: multiple bilateral peripheral nodules, ground-glass opacities that later resolved, cavitary lesions, and masses with spiculated borders. Since other benign or more common causes of these nonspecific imaging findings are often suggested early in the workup, providing radiologists with clinical information such as presenting symptoms and patient history is important for early consideration of pulmonary AS.

With the more widespread use of immunohistochemistry, misdiagnosis becomes less likely. Factor VIII-related antigen, Ulex europaeus lectin, and CD31 are the most reliable markers indicating endothelial origin in epithelioid angiosarcomas [2,11,13]. Histology of angiosarcoma typically shows areas of hemorrhage, anastomosing vessels, and foci of necrosis in solid regions [11]. Angiosarcoma can also resemble adenocarcinoma histologically, so detection of specific vascular markers such as erythroblast transformation-specific related gene (ERG), CD31, or CD34 helps support a diagnosis of angiosarcoma [14]. Though our patient was negative for factor VIII-related antigen and not tested for Ulex europaeus lectin, immunohistochemistry results showed that the resection specimen was strongly positive for CD31, a very sensitive and specific marker for endothelial differentiation [1,8], supporting the diagnosis of angiosarcoma. Poorly differentiated areas are more often positive for CD31 than factor VIII-related antigen [2,7], possibly explaining the negative factor VIII-related antigen results in our specimen. Epithelial tumors and mesothelioma also rarely stain with CD31 markers, essentially ruling out these 2 tumor sources [7]. The specimen was positive for CK7, a marker of lung tissue. Pancreatobiliary and gastric tissue are also CK7-positive, in addition to ovary and breast tissue [15], which are less concerning for primary cancer or absent, respectively, in our male patient. Symptoms were localized to the pulmonary system, lowering clinical suspicion for extrathoracic primary cancer.
Treatment strategies for primary pulmonary epithelioid AS have not been largely studied, owing to the scarcity of cases and poor patient survival. Often, a multidisciplinary approach with a combination of surgical resection, chemotherapy, and radiation therapy is initiated. Lesions are often multifocal with high recurrence rates, which also favors a multidisciplinary approach to treatment [16]. Among reported cases, surgical resection is the first option to remove larger, localized masses, although with frequent recurrence. The use of radiation therapy has also been suggested, primarily to help control refractory dyspnea and hemoptysis [3]. Chemotherapy is generally not effective and described as an adjuvant to reduce the burden of nodules preoperatively or palliatively. Therefore, the improvement in this patient’s bilateral pulmonary nodules with a course of steroids and cyclophosphamide remains particularly intriguing given the chemotherapy-resistant reputation of epithelioid AS.

Due to the extreme rarity of primary pulmonary epithelioid AS, chemotherapy options for this specific patient population remain understudied. Often, chemotherapeutic results are described in case reports or a small case series with a variety of regimens used to varying effects. For example, one case report documents marked regression of inoperable pulmonary epithelioid AS in a 25-year-old male after an unusual regimen of radiotherapy and intravenous recombinant interleukin-2 [17], while another report mentions the use of a more standard regimen of doxorubicin and ifosfamide in a 56-year-old male smoker with negligible effect [5]. Several promising combinations, such as gemcitabine and docetaxel, are currently under investigation in phase II and III clinical trials [5]. Phase II of the ANGIOTAX study has also shown that weekly paclitaxel demonstrates better response rates for angiosarcoma than doxorubicin, the first-line agent for soft tissue sarcoma. However, no significant difference in progression-free survival between treatment groups is reported, and response rates remain low for angiosarcoma [18,19].

In addition to the paucity of cases, lack of standardized chemotherapeutic regimen, and the malignancy’s resistance to therapy, the older patient population that is typically affected may not be offered chemotherapy due to comorbidities that increase the risk of acute toxicity [8]. Metronomic oral cyclophosphamide with prednisolone, a course similar to that initially given to this patient, may address this issue and has been recently studied for treatment feasibility in patients 65 years or older with inoperable soft tissue sarcoma tumors [20]. The results are promising, showing tumor response with a decreased risk of acute toxicity compared with doxorubicin therapy, the first-line treatment for advanced or recurrent soft tissue sarcomas. The first mention of cyclophosphamide for chemotherapy-resistant angiosarcoma dates from 1961, with an article describing 2 cases that responded after thiotaep and methotrexate had failed [21]. In the more recent feasibility study, only 3 patients with angiosarcoma were included, one of whom received paclitaxel as second-line therapy. The fact that the patient population remains exceedingly small half a century later despite improved diagnostic tests is an obstacle to research. However, the possibility of regression or prolonged, stable disease with better quality of life in a malignancy known for its poor prognosis encourages further study of available chemotherapeutic options. Due to the rarity of this disease, research to delineate effective treatment from incidental improvement is recommended with high-volume trials affiliated with large oncolgic centers.

**Conclusion**

Primary pulmonary epithelioid AS is an aggressive and exceedingly rare vascular tumor that is not commonly considered during the early workup of pulmonary disease. Nevertheless, it belongs on the differential of any adult male patient presenting with diffuse alveolar hemorrhage or intractable hemoptysis, especially if there is a history of irradiation, asbestos exposure, or tuberculous pyothorax. Suggestive findings of primary pulmonary epithelioid AS on radiographic imaging include ground-glass opacities, cavitary lesions, and nodules with spiculated, irregular borders. Due to the nonspecific imaging and histology findings, immunohistochemical markers are required to reliably diagnose primary pulmonary epithelioid AS. Treatment, which is currently understudied due to the aggressiveness and rarity of the disease, involves several modalities, including chemotherapy, radiation therapy, and surgical resection. This aggressive, high-grade malignancy is typically resistant to chemotherapy, and most patients die within 1 year of the onset of symptoms. Once diagnosed, consultation with a high-volume oncology center that has experience treating sarcomas is recommended.

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