Primary pulmonary angiosarcoma mimicking diffuse pulmonary hemorrhage: A case report

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Abstract. Pulmonary angiosarcomas are usually secondary tumors, and a primary angiosarcoma of the lung is extremely rare. The present study reports a case of an elderly patient diagnosed with primary pulmonary angiosarcoma (PPA). A 78-year-old man presented with a 3-month history of cough and blood in phlegm. A computed tomography scan of the chest indicated pulmonary infection with ground-glass opacity in the right upper lobe. The patient underwent lobectomy of the right upper lobe as his clinical symptoms did not significantly improve after anti-infection treatment. The postoperative pathological examination confirmed a diagnosis of PPA. He developed left lung and pelvic metastases 1 month after surgery. After four cycles of liposomal doxorubicin therapy, the patient achieved partial remission. The patient remained in sustained remission after 6 months of follow-up. The present case report is intended to provide diagnostic insight into PPA. In addition, the findings indicate that timely diagnosis and treatment of PPA are very important due to its increased risk of local recurrence and distant metastasis.

Introduction

Angiosarcoma is a rare and aggressive, vascular malignancy accounting for nearly 2% of all sarcomas, with an estimated incidence of 2/10,000,000 worldwide. It typically affects elderly population aged between 60 and 70 years with a poor prognosis (1). Angiosarcomas commonly involve skin, head and neck, and superficial soft tissue. They can also arise in other well-recognized sites, such as liver, spleen, breast, heart, and central nervous system. However, areas previously exposed to irradiation, and bone and lung are rarely affected (2). Angiosarcomas of the lung can be divided into primary pulmonary angiosarcoma (PPA) and metastatic pulmonary angiosarcoma (MPA). MPA is more common than PPA (90% vs. 10%) (3). To date, fewer than 30 cases of PPA have been reported, based on searching PubMed search, especially MEDLINE. This study presents a case of PPA mimicking diffuse pulmonary hemorrhage or pulmonary infection from an imaging perspective. The study introduces the clinical characteristics, diagnosis, and treatment of PPA. The study also reviews the relevant published studies were also reviewed in this study.

Case presentation

A 78-year-old man with a 3-month history of cough and persistent hemoptysis was admitted to the hospital on December 31, 2021. He was a lifelong nonsmoker. The physical examination revealed moist rales in the right lung lobe. Routine laboratory tests, such as blood parameters, C-reactive protein, serum procalcitonin, and tumor marker, were all normal. Tests were negative for Mycobacterium tuberculosis. Fungal antigen tests including G test and GM tests for glucans and galactomannans, respectively, were also negative. The patient underwent chest computed tomography (CT) and abdominal CT. Chest CT showed a hypodense and noncalcified nodule, approximately 5.5x4.8 cm in size, in the right upper lobe (Fig. 1A). No nodular lesions were found in the abdomen. Fiberoptic bronchoscopy indicated hemorrhage of the right upper lobe bronchus. No pathogens were found in the alveolar lavage fluid. The patient's clinical symptoms did not improve following treatment for pulmonary infection with moxifloxacin and meropenem for 7 days (Fig. 1B). He received selective bronchial artery interventional hemostasis with embolization on February 08, 2022. However, the CT scan revealed persistent pulmonary hemorrhage and enlarged pulmonary lesion (Fig. 1C). Pulmonary lobectomy of superior lobe of right lung and mediastinal lymph node dissection were performed on February 25, 2022, to establish a definitive diagnosis for prompt clinical treatment. Hematoxylin and eosin (H&E) staining showed poor cell differentiation, deeply stained nucleus, and karyokinesis (Fig. 2A-B). Immunohistochemical staining revealed weakly positive vascular antigen CD31, negative CD34, and strongly positive ERG and FLI (Fig. 2C-F). The pathological examination confirmed the diagnosis as PPA. The patient received no adjuvant treatment after the surgery due to his old age and poor

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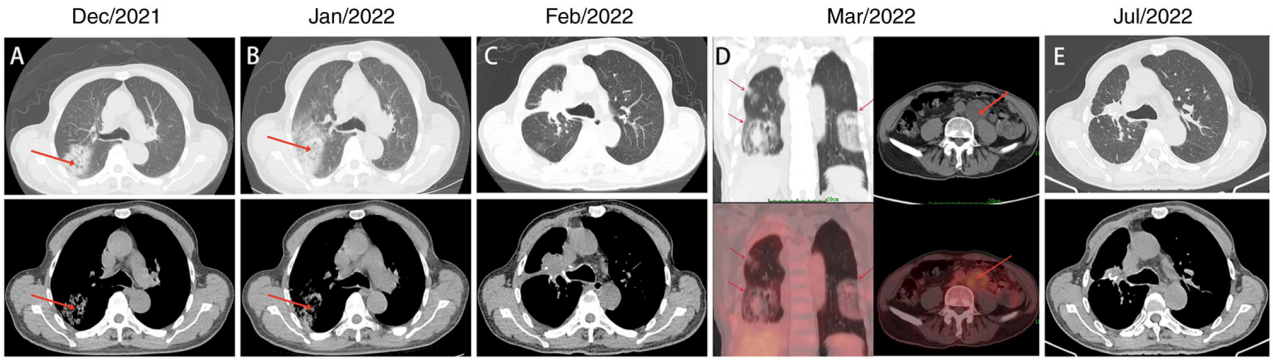

Figure 1. Imaging of the patient during the whole course of treatment. (A-E) imaging findings of lesions at (A) December 2021, (B) January 2022, (C) February 2022, (D) March 2022 and (E) July 2022. The arrows point to the location of pulmonary lesion.

Eastern Cooperative Oncology Group (ECOG) performance status. Unfortunately, hemoptysis persisted after the surgical procedures, and was exacerbated on March 18, 2022. Positron emission tomography-CT (PET-CT) was performed on March 28, 2022. The PET scan showed metabolically active bilateral pulmonary nodules (standardized uptake value, SUVmax, 3.1) and a new pelvic soft tissue mass beside the left common iliac artery (SUVmax, 3.4), suggesting PPA recurrence and metastases (Fig. 1D). The patient underwent percutaneous needle biopsy of pelvic lesion on April 1, 2022, which revealed a pathological diagnosis of PPA. Considering the rapid disease progression and poor ECOG performance of the patient, pegylated liposomal doxorubicin (PLA) was selected as the adjuvant treatment. The patient's symptoms of hemoptysis were significantly relieved after two cycles of chemotherapy (PLA 40 mg/m^2, d1, at an interval of 3 weeks). After the completion of four cycles of chemotherapy, the hemoptysis did not relapse anymore, and the lesions in both lungs obviously diminished (Fig. 1E). Further, the pelvic lesion also contracted (Fig. S1). The patient refused further treatment and was followed up regularly. Currently, the patient exhibits no evidence of disease recurrence after 6 months of follow-up. The detailed diagnosis and treatment procedures are shown in Fig. 3.

Discussion

Angiosarcoma of the lung is a rare malignancy derived from the vascular endothelium with extremely low incidence. MPA is far more common than PPA and is usually the result of metastatic cutaneous and cardiac angiosarcomas, or secondary tumors. Generally, PPA is detected promptly, as most patients present with persistent hemoptysis, chest pain, cough, fatigue and weight loss. However, 20% of cases are asymptomatic and are detected incidentally or during autopsy (4).

Angiosarcoma of the lung can occur at any age. The reported median age of onset is 45 years, with no sex differences (4). PPA may be triggered by risk factors, such as Lucite-ball Plombage, expose to Thorotrast, polyvinyl chloride, and chronic empyema (5). The common CT presentation may be a solitary mass with variable degrees of consolidation or multifocal lesions. Occasionally, it may present as ground-glass opacity, which usually manifests as diffuse pulmonary hemorrhage or pulmonary infection, similar to the case scenario presented in this study. Since PPA tends to spread to different parts of the body by the time of presentation, PET-CT is highly suggestive because of its sensitivity to metastatic disease (6). However, neither CT nor PET-CT can differentiate PPA from other pulmonary malignant neoplasms.

The definitive diagnosis of PPA must be based on histopathological and immunohistochemical findings. Endothelial cell markers, such as CD31, CD34, FLI-1, factor VIII, and epithelial markers (EMA and cytokeratin), are considered to be specific for the diagnosis. A recent study indicated that aldehyde dehydrogenase may be also an important clinical marker for PPA (7).

To date, no standard regimen exists, especially for PPA, because of the limited number of cases. Typically, the treatment options depend on the stage of the disease. Surgery is the mainstay of treatment for local confined diseases. Vascular embolization can be performed before surgery, especially in patients with large tumor size and severe hemorrhage symptoms. Local ablative treatment may also be an alternative for patients with small tumor size (<3 cm), or patients with surgical contraindications (8). Adjuvant radiotherapy and aminolevulinic acid-photodynamic therapy are complementary treatments after the surgery due to the radiosensitivity of the tumor (9,10). In view of the risk of metastasis, anthracycline-based chemotherapy is also recommended (2). Chemotherapy is the primary treatment for advanced-stage disease. The commonly used treatment regimen is doxorubicin with or without ifosfamide. The combination of gemcitabine and docetaxel is also highly efficacious as few patients achieve a complete radiographic response (6). However, in most cases, chemotherapy is exclusively used as a palliative treatment for angiosarcoma in the absence of substantial response (5). Another promising strategy is the use of vascular-targeted drugs. Studies indicated that antiangiogenic molecules, such as bevacizumab and sorafenib, are clinically effective in the control of angiosarcomas (2). Other potential treatments for angiosarcoma are still under investigation clinically. Vascular-disrupting compounds (ASA404) and immune modulators (interleukin-2, interferon-α) might prolong progression-free survival; however, further investigations are needed (11,12). Emerging data also suggest that immune checkpoint inhibitors can be used to treat a subtype of angiosarcoma (13). PPA is an extremely rare sarcoma, less than 30 cases have been described in the English literature to date, and most studies

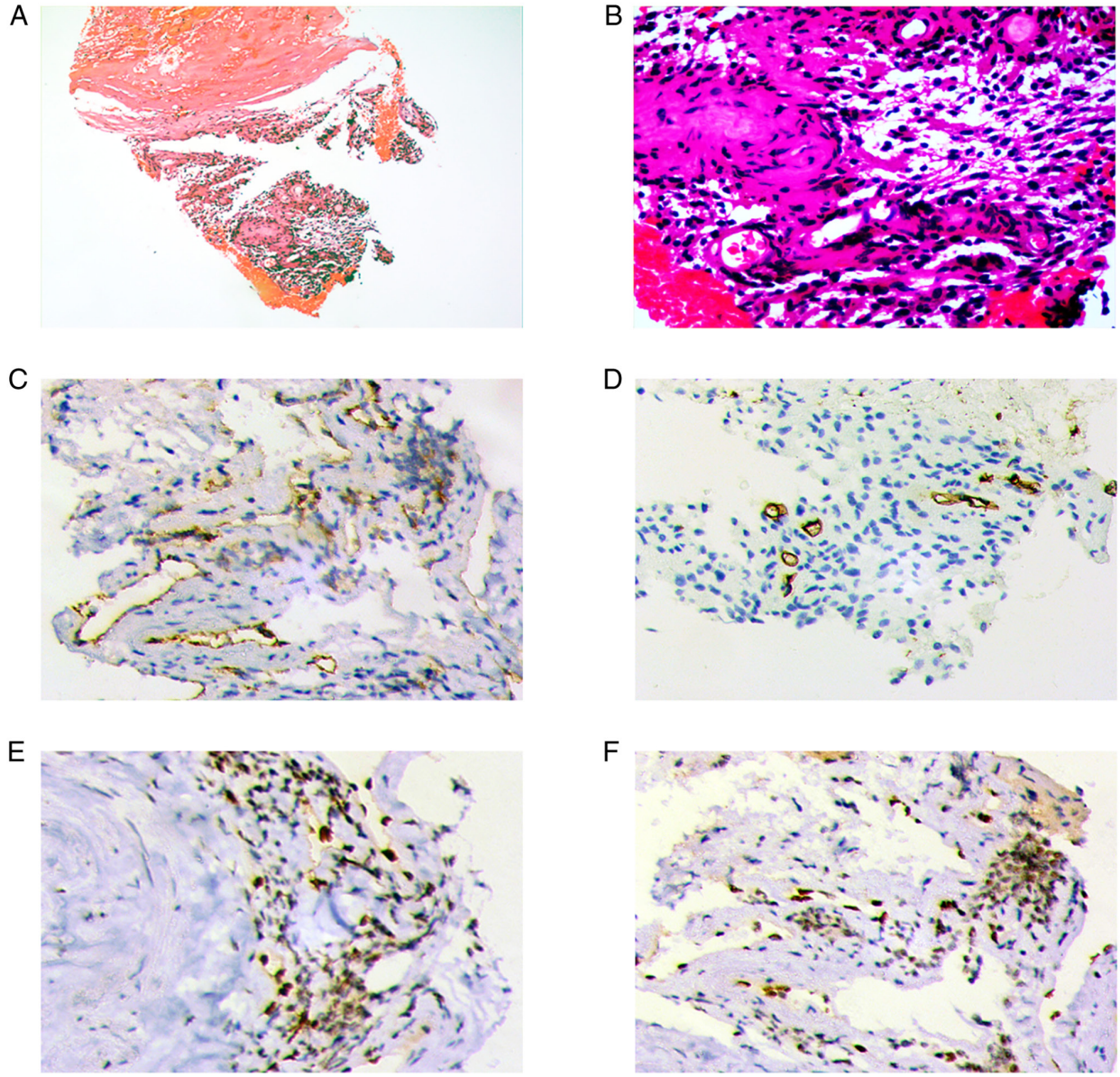

Figure 2. Pathological finding. (A and B) Hematoxylin and staining at different magnifications: (A) x100 magnification, and (B) x400 magnification. Immunohistochemical examination indicated malignant cells immunoreactive for (C) CD31, (D) negative for CD34, strongly positive for (E) ERG and (F) FLI-1 at a magnification of x200.

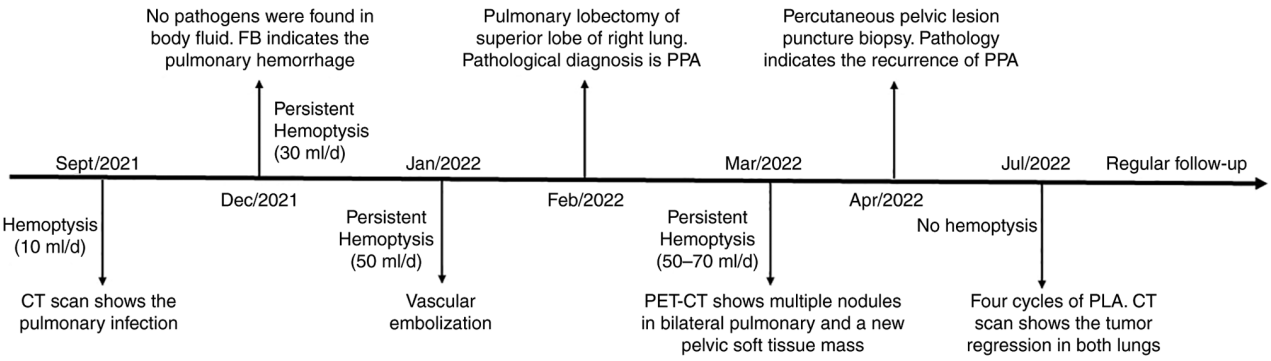

Figure 3. Timeline of the events of the patient from diagnosis to treatment.

are case reports. Therefore, it is difficult for us to determine which treatment is most suitable for patients.

The prognosis of angiosarcoma is extremely grave, the reported 5-year survival ranging from 16 to 56% (14). Most

patients die within one year of diagnosis regardless of the treatment mode.

In conclusion, we report a rare case of PPA misdiagnosed as diffuse pulmonary hemorrhage. The patient experienced intrapulmonary metastases and pelvic metastasis one month after surgery. Partial remission was achieved after 4 cycles of liposomal doxorubicin. The patient is doing well after 6 months of follow-up. Our experience with this case suggests that definitive diagnosis and timely treatment are essential for the successful management of this disease.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DZ conceptualized the study. YL, HY and CW acquired and analyzed the data, and wrote reviewed and edited the manuscript. YL, HY and CW confirm the authenticity of all the raw data. DZ acquired funding. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics and Scientific Committee of Hubei University of Medicine (approval no. XYY2021002).

Patient consent for publication

Informed consent was obtained from the patients and their families for the publication of this data.

Competing interests

The authors declare that they have no competing interests.

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