Primary pulmonary angiosarcoma: A case study with genetic insights and potential therapeutic targets

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Abstract. This case report describes a 71-year-old man who presented with hemoptysis, chest pain and shortness of breath. Computed tomography-guided biopsy and immunohistochemical analysis revealed positivity for markers CD34, CD31 and vimentin, confirming the diagnosis of primary pulmonary vascular sarcoma. Genetic testing revealed actionable mutations in *CD274* (programmed cell death ligand 1), kinase insert domain receptor, *KIT* and platelet-derived growth factor receptor α, which may provide targeted treatment options. Unfortunately, the patient's condition rapidly worsened, and he died before therapy was initiated. This case emphasizes the difficulties in diagnosing pulmonary angiosarcoma and highlights potential molecular targets for therapy. Swift disease progression emphasizes the critical need for early detection and accurate diagnosis. Furthermore, the identified genetic alterations offer a basis for personalized targeted therapies, underscoring the importance of further research and clinical trials to enhance patient outcomes.

Introduction

Angiosarcoma is a highly aggressive malignant tumor of endothelial cells that arises from blood or lymphatic vessels and accounts for ~2% of all soft tissue sarcomas (1). Primary pulmonary angiosarcoma is uncommon and is usually identified only after it has spread to other parts of the body (2). This report describes a case of primary pulmonary angiosarcoma and highlights the complexities of its diagnosis and treatment.

Primary pulmonary angiosarcoma is difficult to diagnose because its clinical symptoms are nonspecific (3,4). Patients with this condition frequently present with symptoms such as hemoptysis, chest pain and shortness of breath (5,6). However, these symptoms are often ascribed to other conditions, resulting in delayed diagnosis. Furthermore, the radiological features of pulmonary angiosarcoma are typically nonspecific and may resemble those of other pulmonary disorders (7,8).

This case report presents an uncommon manifestation of primary pulmonary angiosarcoma, delineates the typical diagnostic challenges and investigates potential therapeutic targets revealed through genetic analysis.

Materials and methods

Immunohistochemistry (IHC) and hematoxylin-eosin (HE) staining. IHC analysis of programmed cell death ligand 1 (PD-L1), vimentin, CD31, CD34, ETS-related gene (ERG) and factor VIII antibody (VIII-RA). Experiment was conducted using formalin-fixed, paraffin-embedded tumor tissue sections. Staining included routine dewaxing, antigen retrieval, inhibition of endogenous peroxidase activity, incubation with primary and secondary antibodies and counterstaining. The primary antibodies included anti-vimentin antibody (cat. no. AB5733; 1:1,000 dilution), rabbit anti-CD31 antibody (cat. no. SAB5700639; 1:100 dilution), rabbit anti-CD34 antibody (cat. no. HPA036722, 1:200 dilution) and anti-CD274 (cat. no SAB4301882; 1:100 dilution; all from Sigma-Aldrich; Merck KGaA), factor VIII-related antigen (cat. no. 36B11; 1:50 dilution; Novocastra) and rabbit monoclonal ERG antibody (cat. no. IPDX17045; 1:100 dilution; IPODIX). The secondary antibody was goat anti-rabbit IgG H&L (cat. no. ab150077; 1:2,000; Abcam). Subsequently, the samples were evaluated using a microscope (DMi3000 B; Leica Microsystems) to calculate the tumor proportion score and the comprehensive positive score.

HE staining was conducted to confirm the histopathological diagnosis. The tissue sections were first de-waxed using xylene to remove the paraffin. Subsequently, they were made transparent through a series of alcohol treatments. Next, hematoxylin (cat. no. H9627; Sigma-Aldrich; Merck KGaA) was used to stain the nuclei of the sections. Subsequently, distilled water was used to rinse off the excess hematoxylin. After that, eosin (cat. no. E4009; Sigma-Aldrich; Merck KGaA) was used for counter-staining to enhance cell differentiation. Finally, the sections were dehydrated through a series of alcohol treatments and covered with a coverslip

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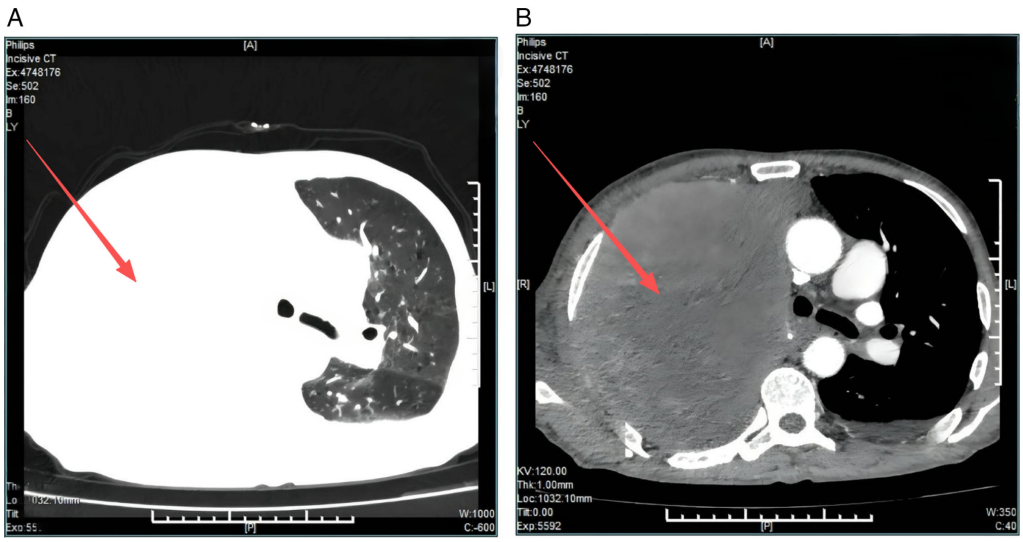

Figure 1. Computed tomography of the chest. (A) Lung window indicates a mass in the right lung (measuring ~147x113 mm). (B) Mediastinal window shows no evidence of calcification. The affected area has been marked with arrows.

for mounting. The sections were then observed using a light microscope (DMi3000 B; Leica Microsystems) to evaluate the tissue structure, cell morphology, and general pathological features.

Genetic testing. Genomic DNA was isolated from the patient's blood sample following established protocols (9), including proteinase K (cat. no. P2308-5MG; Sigma-Aldrich; Merck KGaA) digestion and phenol-chloroform extraction. Targeted next-generation sequencing was then conducted using a custom-designed panel encompassing 1,238 clinically relevant genes, including exons 2-22 of PD-L1. Next-generation sequencing library preparation involved genomic DNA fragmentation, end repair, A-tailing, adapter ligation and size selection (10). Sequencing was performed on an Illumina platform, achieving a minimum depth of 30-fold coverage within the targeted regions. The library was constructed using the Nextera XT kit (Illumina, Inc.), and sequencing was performed on the NextSeq™ 500 (Illumina, Inc.) platform using the 2x150 bp kit according to the manufacturer's instructions (11). Sequence reads were aligned using BWA-MEM (http://bio-bwa.sourceforge.net/bwa.shtml) and variant calling was performed with the Genome Analysis Toolkit (GATK) (https://gatk.broadinstitute.org/hc/en-us) (12). The identified mutations were annotated and classified based on data from the Human Genome Variation Database (ClinVar) (https://www.ncbi.nlm.nih.gov/clinvar/), Single Nucleotide Polymorphism Database (dbSNP) (https://www.ncbi.nlm.nih.gov/snp) and Catalogue of Somatic Mutations in Cancer (COSMIC) (https://cancer.sanger.ac.uk/cosmic/login). Filtering steps were subsequently applied to remove low-quality reads and false-positive variants. The final variant report provided comprehensive clinical information, including the identification and categorization of all clinically significant mutations, thereby facilitating informed therapeutic decision-making. These data have been uploaded to the SRA database, with the BioProject ID being PRJNA1344604. They are available for download (https://www.ncbi.nlm.nih.gov/Traces/study/?acc=SRP636518&o=acc_s%3Aa).

Case report. A 71-year-old man presented with a history of hypertension, cerebral infarction and coronary artery disease. The patient had a smoking history of >50 years, with an average daily consumption of 20 cigarettes. No significant family medical history was noted. The patient was admitted to the Department of Respiratory and Critical Care Medicine at the Banan Affiliated Hospital of Chongqing Medical University (Chongqing, China) in February 2023 after the onset of symptoms, including cough, sputum production and unexplained dyspnea.

On admission, the patient was conscious and cooperative. The patient exhibited a productive cough with expectoration of phlegm containing dark red blood clots, accompanied by fatigue and anorexia. The patient subsequently reported pain localized to the right hemithorax, accompanied by worsening cough. The pain radiated to the right shoulder and dorsal region.

Ultrasound examination of the thorax revealed pleural effusion on the right side. Physical assessment demonstrated diminished breath sounds in the right lung, but no significant wet or dry adventitious sounds were detected in the left lung. Thoracentesis yielded 350 ml of pleural fluid. Chest computed tomography (CT) imaging (Fig. 1, Videos S1 and S2) demonstrated the following findings: i) A mass located in the right lung measuring ~147x113 mm, highly suggestive of primary lung carcinoma with mediastinal invasion; associated right pulmonary bronchial obstruction with resultant atelectasis; involvement of the right pulmonary arterial trunk; suspected mediastinal lymphadenopathy; evidence of right pleural metastasis; and probable metastasis to the right ribs. ii) A small volume of bilateral pleural effusions. iii) A nodule in the left adrenal gland, with metastatic involvement excluded. iv) Mild dilation of the common bile duct. Additionally, chest radiography (Fig. 2) corroborated extensive pathological involvement of the right lung with possible tumor infiltration affecting the

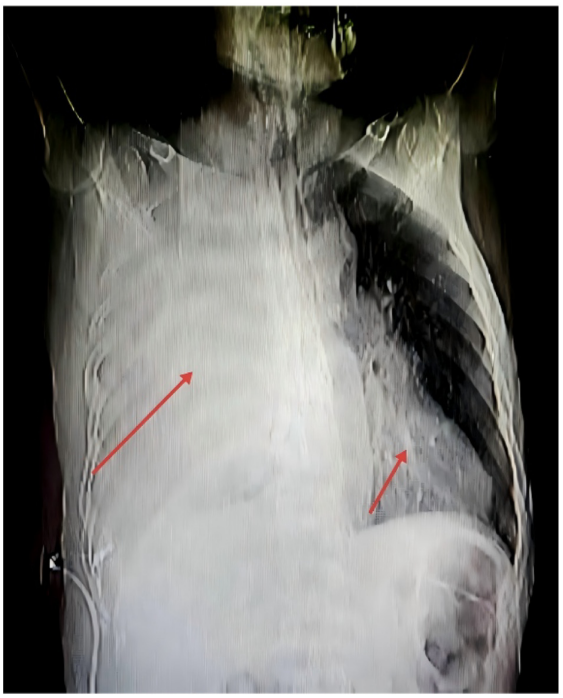

Figure 2. Patient's routine chest radiography examination. The right lung and right lower part of the left lung appear to be affected by the tumor. The affected areas have been marked with arrows.

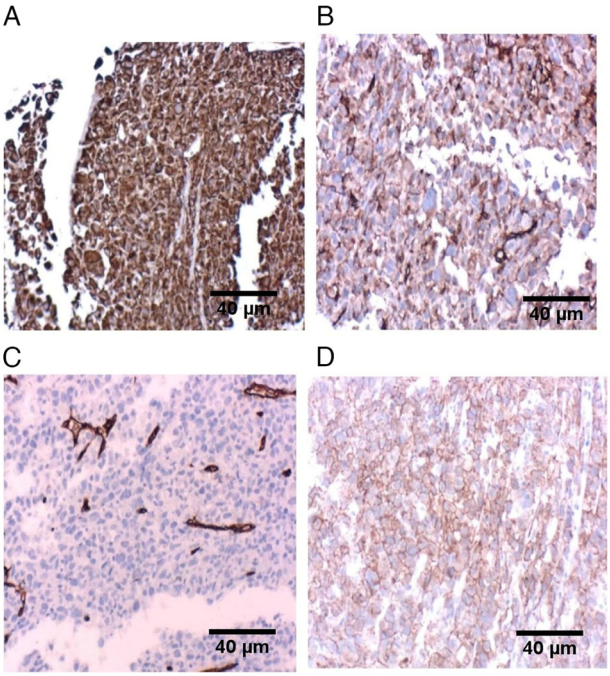

Figure 4. Immunohistochemical staining of lung biopsy specimen. (A) Positive vimentin staining; (B) positive CD31 staining; (C) positive CD34 staining; (D) positive ETS-related gene staining (scale bars, 40 μm).

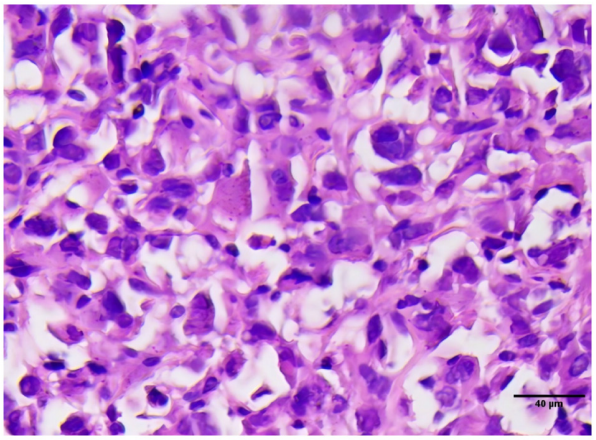

Figure 3. HE staining result. The cell nucleus is deeply stained, has an abnormal shape, and there are numerous instances of nuclear division (scale bars, 40 μm).

right lower lobe and extending into the left lung, collectively manifesting as a generalized 'white lung' appearance.

Cytological examination revealed a small number of atypical cells (data not shown) and the possibility of a malignant tumor could not be ruled out. To further evaluate the patient's condition, a thoracentesis was performed, which yielded 350 ml of pleural effusion. Subsequently, a CT-guided percutaneous lung biopsy was performed, resulting in the collection of three tissue specimens. Laboratory assessments revealed elevated levels of tumor markers, notably Carcinoembryonic antigen (CEA). The HE staining results showed that the cell nuclei were deeply stained, had abnormal shapes, and there were numerous instances of cell division (Fig. 3). IHC examination indicated positive expression of vimentin (Fig. 4A), CD31 (Fig. 4B), CD34 (Fig. 4C), and the ETS-related gene (Fig. 4D), collectively suggesting angiosarcoma. IHC analysis revealed positivity for both PD-L1 and VIII-RA (Fig. 5). Based on the ninth edition of the TNM classification system established by the International Union Against Cancer (13), the patient was diagnosed with pulmonary vascular sarcoma, staged as T2N1M1, corresponding to overall clinical stage IV. This stage is characterized by a primary tumor measuring between 5 and 10 cm in maximum diameter (T2), with involvement of regional lymph nodes (N1) and the presence of distant metastases (M1).

The patient's clinical condition progressively deteriorated, ultimately precluding systemic chemotherapy. Symptomatic treatment encompassed high-flow oxygen therapy, hemostatic interventions and analgesic management. At the family's request, genetic testing was performed to assess the feasibility of targeted therapeutic options. Owing to the limited tissue obtained from the initial lung puncture, a subsequent CT-guided percutaneous lung biopsy was performed, yielding six specimens for comprehensive multigene analysis pertinent to solid tumors. While awaiting multigene test results, the patient demonstrated gradual leukocytosis, suggestive of potential bone marrow involvement. Concurrently, the patient's level of consciousness declined and arterial blood gas analysis indicated hypercapnia. Nonsteroidal anti-inflammatory drugs were administered for pain control and local radiotherapy was provided. Regrettably, owing to the rapid disease progression, the patient died before targeted therapy could be initiated.

At three days after the patient's death, four potential therapeutic target genes were identified within the pan-cancer 1,238-gene panel, each of which exhibited an

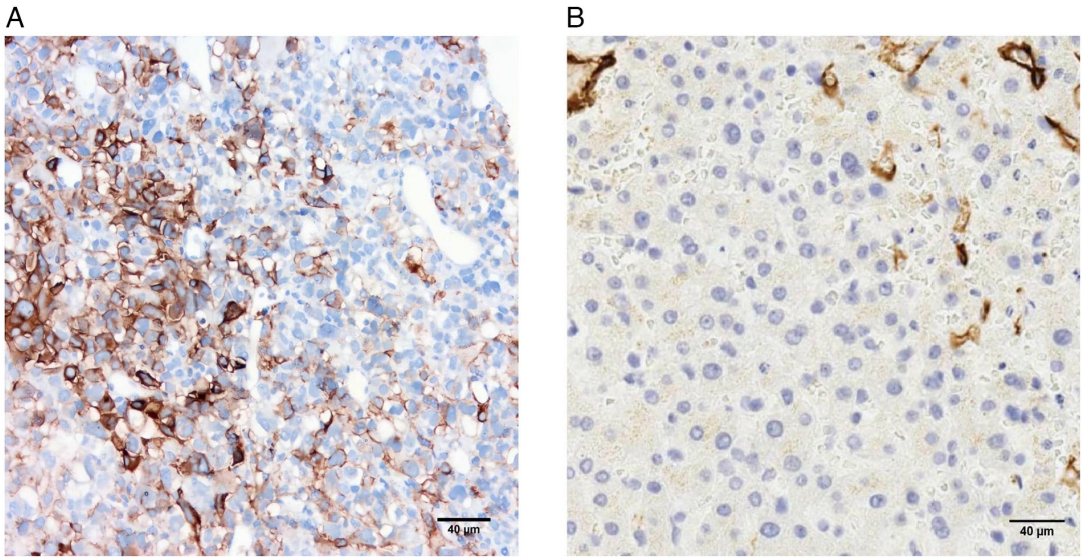

Figure 5. Immunohistochemical staining of PD-L1 and VIII-RA. (A) Positive PD-L1 staining; (B) Positive VIII-RA staining (scale bars, 40 μm). PD-L1, programmed death ligand 1; VIII-RA, factor VIII-related antigen.

amplification mutation. Specifically, *CD274* demonstrated a mutation abundance of 6.3-fold and atezolizumab was identified as a potentially effective therapeutic agent. Kinase insert domain receptor (*KDR*) showed a mutation abundance of 2.2-fold, with regorafenib, sunitinib and sorafenib being potentially beneficial drugs. Similarly, *KIT* exhibited a 2.2-fold mutation abundance, with pazopanib as a potential treatment option. Lastly, platelet-derived growth factor receptor α *(PDGFRA*) exhibited a 2.2-fold mutation abundance, with pazopanib and sunitinib considered potential therapeutic agents.

Discussion

The mechanisms underlying angiosarcoma have remained to be fully elucidated. Patients who have undergone breast cancer surgery and radiotherapy are prone to developing angiosarcoma of the skin and chest (14). Pulmonary angiosarcomas are even rarer, with most reports being case reports. In the present case, the patient had been smoking for a long time, similar to a previously reported case (15). However, the patient also had a history of hypertension, cerebral infarction and coronary artery disease. Currently, there is no direct evidence that pulmonary angiosarcoma is associated with these factors, to the best of our knowledge.

The clinical manifestations of pulmonary angiosarcomas are often nonspecific, making them difficult to detect. The most common clinical manifestation is hemoptysis, along with symptoms such as dyspnea, chest pain and cough (5,16). Patients often present with systemic manifestations such as weight loss, fatigue and fever. In the present case, the patient presented with a cough and hemoptysis. After examination, a mass was found in the right lung and the pathological diagnosis was pulmonary angiosarcoma. It can be seen that in clinical practice, common respiratory symptoms, such as hemoptysis, chest pain and shortness of breath, should be taken seriously and should not be readily dismissed, so as not to overlook the diagnosis of pulmonary angiosarcoma.

Currently, imaging examinations for pulmonary angiosarcoma are mainly based on chest radiography and CT. In the case reported by Yu *et al* (17), the main imaging manifestations were multiple nodules, ground-glass patches and diffuse infiltration. Imaging examination of this patient suggested a mass in the right lung, which is consistent with previous reports. However, the imaging features of pulmonary angiosarcoma lack specificity and are often similar to those of other lesions, such as metastatic tumors (including pulmonary tuberculosis), making differential diagnosis difficult. Therefore, imaging data may provide imited reference value for the diagnosis of this disease (5,17).

In the current clinical diagnosis of pulmonary angiosarcoma, immunomarkers, such as CD34, CD31, VIII-RA, Fli-1 proto-oncogene and vimentin, are commonly used (3-6,17), all of which are specific markers for endothelial cells of vascular origin. Certain studies have reported that VIII-RA and CD31 are the most specific marker antibodies for angiosarcoma, particularly in poorly differentiated tumors (18-23). In the present case, the IHC markers CD34, CD31 and vimentin were all positive, which may have helped confirm the diagnosis.

The Italian Sarcoma Organization and Japanese Sarcoma Association published consensus documents and guidelines for angiosarcoma treatment (24,25). The treatment plans typically include surgery, radiotherapy and chemotherapy. For localized angiosarcomas, extensive resection is the standard treatment method and a clean surgical margin is one of the factors affecting prognosis (26). Surgery is the primary treatment for localized disease; however, the postoperative recurrence rate is high. Bartakke and Saez de Ibarra Sanchez (27) reported a case of pulmonary angiosarcoma that was successfully treated surgically. Adjuvant radiotherapy after radical surgery has been proven to be an effective combination treatment for angiosarcoma; however, no formal observational trial has demonstrated that radiotherapy alone is effective. Chemotherapy is the primary treatment for patients who have lost the opportunity to undergo surgery. The main chemotherapeutic drugs include taxanes, doxorubicin, liposomal doxorubicin and ifosfamide.

Table I. Summary of reported cases of pulmonary angiosarcoma.

Patient details	Clinical presentation	Diagnostic basis	Treatment	Outcome	(Refs.)
71-year-old male	Recurrent cough, expectoration, hemoptysis, chest pain, dyspnea	Large right lung mass, pleural effusion, IHC ($CD34^+$, $CD31^+$, $vimentin^+$, Ki67 60%)	Symptomatic support, genetic testing identified actionable mutations (CD274, KDR, KIT, PDGF)	Died prior to targeted therapy initiation	Present case report
70-year-old male	Hemoptysis, weight loss, general weakness and mild recurrent epistaxis	Pulmonary nodules, hemorrhagic pleural effusion, pleural cavity masses, IHC ($CD31^+$, $vimentin^+$)	Discharged from the hospital and referred to the tumor center to consider any further treatment options	Died five days after discharge	(3)
11 cases	Chest pain, cough, breathing difficulties, hemoptysis	All patients were eventually diagnosed by pathology, and the positive rates of CD31 and CD34 were as high as 60%	Three cases received surgical treatment and the remaining eight patients received chemotherapy or immunotherapy	Surgical treatment OS: 23 months; Non-surgical treatment OS: 9.7 months	(4)
34-year-old woman	Cough, hemoptysis and breathing difficulties	Multiple small nodules and ground-glass patches in both lungs; Pleural bloody effusion; IHC ($CD34^+$, $CD31^+$, Ki67 70%, ERG^+, $FLI\text{-}1^+$)	Hypovolemic shock occurred after thoracoscopic lung biopsy and was transferred to the ICU for resuscitation	Died of respiratory failure 19 days later	(6)
72-year-old male	Shortness of breath worsens	Impaired right ventricular function, pulmonary artery mass	Endarterectomy for pulmonary thrombosis, paclitaxel chemotherapy	Died of acute pulmonary thrombosis after 4 months	(16)

OS, overall survival; ICU, intensive care unit; IHC, immunohistochemistry; KDR, kinase insert domain receptor; PDGFR, platelet-derived growth factor receptor; FLI-1, Fli-1 proto-oncogene; ERG, ETS-related gene.

Among these, taxanes are considered effective agents for the clinical treatment of angiosarcoma and are often used as first- or second-line treatments for metastatic disease (25,28,29). In addition, recombinant IL-2 may have a positive effect on angiosarcoma treatment (30). In recent years, new approaches have provided novel strategies for the treatment of angiosarcoma. Angiosarcoma cells with high VEGFR-2 expression are sensitive to anti-VEGFR antibody drugs, such as sorafenib and sunitinib (31). A similar drug, pazopanib, has entered clinical trials for cutaneous angiosarcoma as a second-line standard therapy, but its overall efficacy has not met the primary endpoint (32). Further trials are required before these drugs can be adopted clinically. As shown in Table I, there are various current treatment methods; however, most patients present with multiple metastases at diagnosis, resulting in a poor prognosis. In the present case, after diagnosis, the patient had multiple metastases to the mediastinum, right pulmonary artery trunk, mediastinal lymph nodes, right pleura and right third rib and eventually died. The patient therefore missed the opportunity to receive targeted therapy.

Most literature reports cases of pulmonary vascular sarcoma (4,5,33), as well as related studies (34,35). However, most of these articles focused on the clinical symptoms, diagnostic markers and conventional treatments of pulmonary vascular sarcoma, while in the present study, gene sequencing was conducted, thus paying more attention to gene mutations and related targeted therapies.

Regarding gene-targeted therapy, an angiosarcoma research project conducted by Painter *et al* (36) indicated that anti-PD-1 therapy may be an effective approach for head and neck, face and scalp angiosarcoma. Another study has shown that PD-L1 is positively expressed in 29% of angiosarcomas (37). PD-L1 is highly expressed in angiosarcoma (38-41). Research conducted by Kösemehmetoğlu *et al* (41) indicated that a higher tumor grade and a worse patient prognosis are associated with a higher expression of PD-L1 in soft tissue sarcomas. Atezolizumab can be used as an antibody targeting CD274 for cancer treatment (42). However, the therapeutic effects of anti-PD-1 drugs in primary pulmonary vascular sarcomas have not yet been confirmed. *KDR* mutations are present in pancreatic, cardiac, breast and renal angiosarcomas (43-46). In angiosarcoma, the incidence of KDR mutations is ~7-10% (47). Amplification of *KDR* is associated with activation of mTOR and p38, as well as infiltration of tumor cells caused by VEGF (48). The clinical trials NCT02693535, NCT03297606 and NCT02029001 have reported that regorafenib, sunitinib and sorafenib, respectively, can target and treat tumors caused by *KDR* amplification. Relatively few studies have reported significant mutation characteristics of *KIT* and *PDGFRA* in angiosarcoma (49-54). Research conducted by Xu *et al* (55) reported that *KIT* mutations are widespread in angiosarcoma, occurring in ~25% of cases. Because *PDGFRA* mutations are relatively rare in angiosarcoma, there are no published studies specifically reporting the incidence of these mutations, to the best of our knowledge. However, studies on the chromosome 4q11-q13.1 region (containing *KIT*, *PDGFRA* and *VEGFR2*) and the 4q12 amp region (containing *KIT*, *PDGFRA* and *KDR*) have shown that *PDGFRA* mutations are present in angiosarcomas (54,56), with 4q12 amp being detected in 4.8% of angiosarcomas (56). Since primary pulmonary angiosarcoma is relatively rare, *KIT* and *PDGFRA* mutations are more often found in other angiosarcomas, whereas pulmonary angiosarcoma cases are rarely reported. The clinical trial NCT02029001 demonstrated that pazopanib may be effective in treating advanced malignant solid tumors caused by *KIT* amplification. In addition, apatinib can be used to treat angiosarcomas caused by *KIT* and *KDR* gene amplification (50). Pazopanib may be applicable to gastrointestinal stromal tumors (57) and the US Food and Drug Administration has approved its use for soft tissue sarcomas. Sunitinib is used for the treatment of gastrointestinal stromal tumors and renal cell carcinomas (58,59). It may also inhibit the activity of various receptor tyrosine kinases, including PDGFR (38). The clinical trial NCT03297606 indicated that sunitinib may be applicable to various tumors caused by PDGFRA amplification.

Because of the rarity and nonspecific clinical symptoms of primary pulmonary angiosarcoma, early identification and treatment remain important challenges. This case highlights the diagnostic and therapeutic difficulties associated with primary pulmonary angiosarcoma and underscores the potential role of genomic findings in guiding future treatment strategies.

In conclusion, this study reports the case of primary pulmonary vascular sarcoma in a 71-year-old man with hemoptysis, chest pain and shortness of breath. Immunological marker testing confirmed the diagnosis of primary pulmonary vascular sarcoma. Genetic testing revealed mutations that may be targeted for therapy. However, the rapid progression of the tumor hindered treatment implementation, highlighting the need for early diagnosis and personalized treatment.

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Availability of data and materials

The raw sequence reads were uploaded to the SRA database, with the BioProject ID PRJNA1344604. They are available for download from the following URL: https://www.ncbi.nlm.nih.gov/Traces/study/?acc=SRP636518&o=acc_s%3Aa.

Authors' contributions

YZ conceived and designed the study, performed the experiments, analyzed the data and wrote the manuscript. CG collected clinical data, performed pathological analyses and contributed to manuscript preparation. YZ and CG confirm the authenticity of all the raw data. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present research followed the Declaration of Helsinki and was approved by the Banan Hospitals Ethics Committee

(Chongqing, China; approval no. BNLLKY2025074). As the patient's condition deteriorated and he lost consciousness, written informed consent was obtained from the patient's daughter for the patient to undergo imaging examinations, pathological examinations and genetic testing.

Patient consent for publication

Written informed consent was obtained from the patient's daughter for the publication of this manuscript and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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