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CASE REPORT

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A case of primary pulmonary angiosarcoma arising from tuberculous scar with fatal capillary bleeding

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Key Clinical Message

The etiology of primary pulmonary angiosarcoma is still unknown. Here we report a case of primary pulmonary angiosarcoma originated from a tuberculous scar and presented as aggressive deterioration with uncontrolled bleeding from capillaries with angiodysplasia.

KEYWORDS

anti-VEGF/VEGFR therapy, capillaries, hemangiosarcoma, hemorrhage, tuberculous scar

1 | INTRODUCTION

Angiosarcomas are rare and highly aggressive vascular malignancies defined in the 2002 World Health Organization (WHO) classification. Primary pulmonary angiosarcoma is extremely rare and usually reported case by case. Although the etiology of angiosarcomas is not well known, repair of damaged tissue seems to be one of the main factors in tumorigenesis. Angiosarcomas are associated with previous radiotherapies,[1] foreign body material,[2–5] and skin-burned scars.[6,7] Here we reported a case of primary pulmonary angiosarcoma arising from a scar of tuberculosis in an elderly patient who underwent continuous and slow capillary hemorrhage.

2 | CASE HISTORY

The patient was a 77-year-old male nonsmoker, with a scar of tuberculosis over 40 years. Two months before admission, the patient developed recurrent hemoptysis after a common cold and he had poor response to various antibiotics, hemostatics, and spasmolytics. One month before admission, the patient developed left-sided moderate to massive bloody pleural effusion. With continuous thoracic drainage and repeated blood transfusion in another hospital, the patient deteriorated dyspnea, low blood pressure and fever. During these 2 months, the patient underwent three chest computed tomography (CT) scans and one pulmonary artery contrast-enhanced CT (CE-CT) scan. The CT scans demonstrated: (1) A longstanding tuberculous scar with multi focuses calcification which was similar to the CT taken in 2004, while an irregular soft tissue mass arised from the boundary of this scar and rapidly and continuously grew from April 12, 2010 to July 6, 2010; (2) Multi subpleural nodules which gradually increased in number and size (less than 5 mm in diameter) during 2 months; (3) A large amount of left-sided pleural effusion; (4) A subsegmental pulmonary artery embolism in the left lower lobe. The patient was admitted to

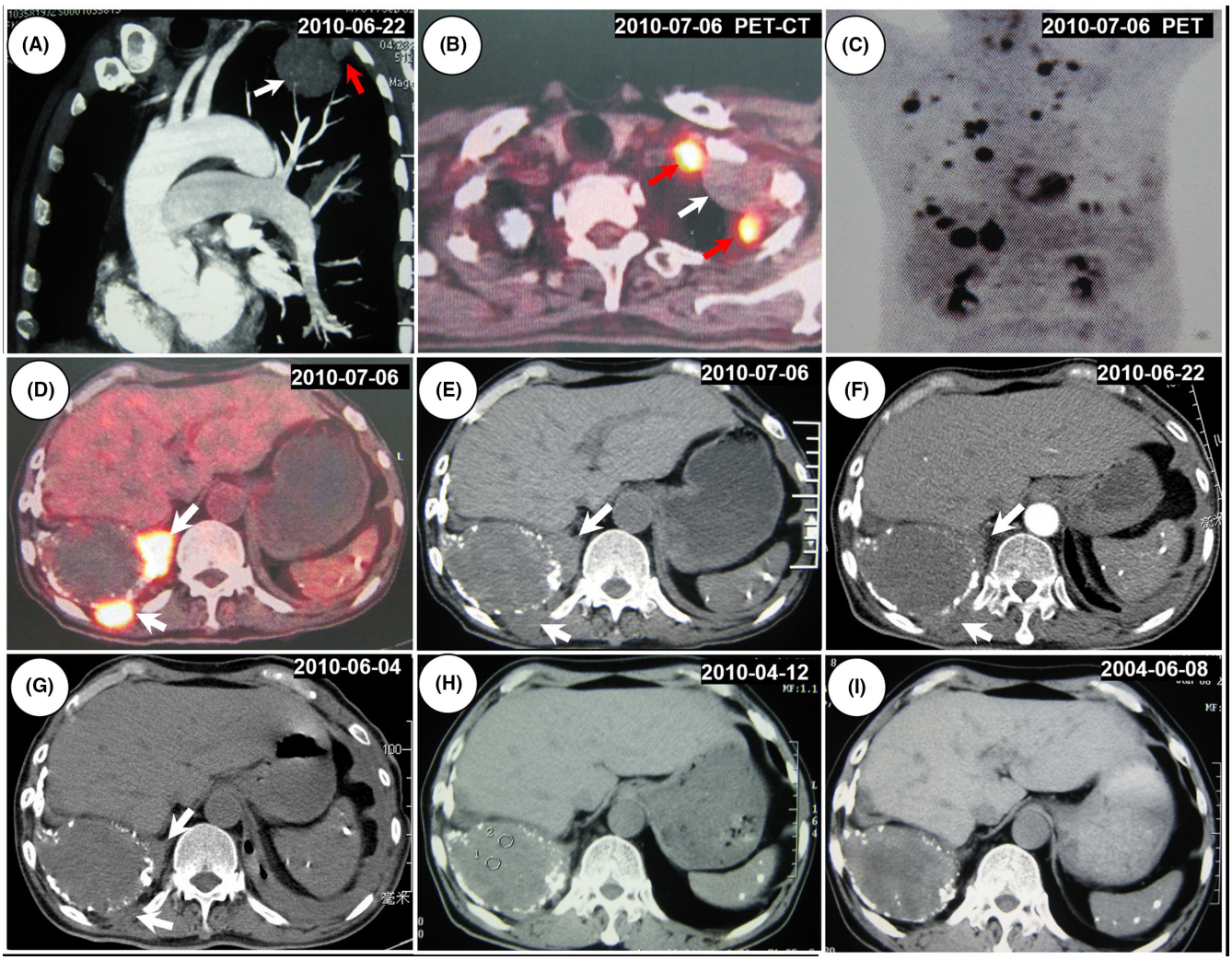

FIGURE 1 Image findings of primary pulmonary angiosarcoma. (A) Selected coronal image of computed tomography pulmonary angiography (CTPA) showed a new emerging low-density mass-like lesion (white arrow) adjacent to previously existing small nodules (red arrow) in the upper lobe of left lung after VATS operation. And all these lesions showed no enhancement to contrast agent. It was subsequently verified to be a localized thoracic hematoma by transthoracic biopsy. (B) The PET-CT scan showed the two nodules (red arrows) adjacent to the hematoma (white arrow) were larger than before and had high FDG uptake. (C) The PET-CT showed that all the lesions were located in the lung. (D–I) showed an irregular mass (white arrows) arising from the boundary of a long-lasting calcified tuberculous scar and kept enlarging during 3 months. The soft mass showed high FDG uptake in PET-CT (D), but no enhancement in CE-CT (F).

our hospital for further investigation on the unidentified hemorrhagic pleural effusion, severe anemia, paroxysmal atrial fibrillation, left lower pulmonary artery embolism. He had been well before and there was no history of tuberculosis relapse.

3 | METHODS

Suspected with active thoracic bleeding, the patient underwent an emergent video-assisted thoracoscopic surgery (VATS). There was about 2000 mL sanguineous fluid and blood clot in the left thoracic cavity. No visible bleeding site but a small area of errhysis on visceral pleura was found. After electrocoagulation on errhysis and removing blood clot and effusions, a 2×2 cm dust-color soft tissue mass with clear boundary and smooth envelope in costophrenic angle was found and resected completely. The histopathological examination showed that lesion area presented as blood clots, nested proliferated cells with atypia distributed focally in the fibrous capsule. The pathological diagnosis was made as a low-grade to intermediate-grade hemangioendothelioma.

After VATS operation, the patient kept having fever, hemoptysis, progressive anemia, and a gradual onset of thrombocytopenia. CT scans showed a new emerging round mass-like subpleural effusion in left anterior thorax (Figure 1A,B). It was verified to be a localized

thoracic hematoma by transthoracic biopsy. Adjacent to the hematoma, there were two nodules which were larger than before and showed no enhancement in CE-CT (Figure 1A), while high fluorodeoxyglucose (FDG) uptake in positron emission tomography (PET)/CT scan (Figure 1B). PET examinations strongly indicated that the lesions were highly malignant and distributed only in lung (Figure 1C). After reviewing the CT images overtime, the irregular soft tissue arising from the boundary of calcified tuberculous scar seemed to be the original site of the tumor. (Figure 1D–I) An intense violet color neoplasm was found rising from a skin scar about 1 month after VATS operation (Figure 2). With a suspect of malignancy, the previous histopathological diagnosis was reevaluated and extra sections were investigated. Nests of large, moderately pleomorphic, round to polygonal epithelioid cells, filled with abundant eosinophilic cytoplasm, and occasional cells with intracytoplasmic lumina containing erythrocytes were observed in H&E-stained sections (Figure 3A). Immunohistochemical stainings were positive for CD31 (Figure 3B), CD34 (Figure 3C) and Factor VIII (Figure 3D), P53 > 50(+), and negative for D2-40, cytokeratin (CK), CK7, epithelial membrane antigen (EMA), thyroid-transcription factor 1 (TTF-1). The renew diagnosis was epithelioid angiosarcoma.

The IHC staining showed positive for vascular endothelial growth factor receptor (VEGFR) and VEGFR-2 (Figure 3E,F), negative for epidermal growth factor receptor, estrogen receptor, progesterone receptor. Due to poor performance status, the patient underwent a single anti-VEGFR regimen with sorafenib (Nexavar) 0.4 g bid for 2 weeks. The situation of patient was not relieved. The treatment was changed to another anti-VEGFR agent, sunitinib (Sutent) at the dosage of 50 mg qd for the subsequent 2 weeks. However, the patient aggravated with persistent hemoptysis, hematochezia, and a capillary hemorrhage from the skin metastatic lesion and gums. CT showed more nodes bigger in size and characterized by interlobular septal thickening (arrows) (Figure 4). The hemoglobin fluctuated between 30 and 50 g/L, platelets decreased to about 30×10^9/L. The anti-VEGFR therapy was terminated and intermittent blood transfusion was administered.

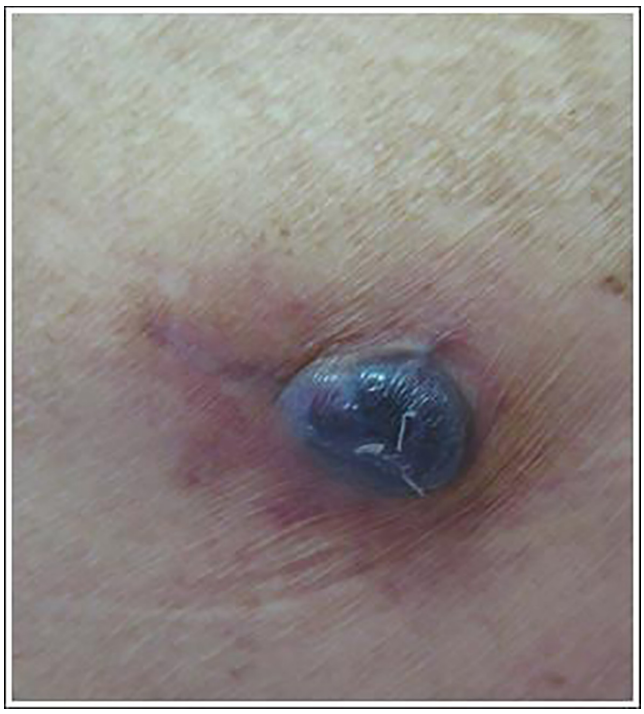

FIGURE 2 A dark-violet color neoplasm was found rising from a skin scar of chest incision caused by thoracoscopy surgery about 1 month ago.

4 | CONCLUSION AND RESULTS

The patient died 4 months after the onset of initial clinical symptoms.

5 | DISCUSSION

Patients with primary or secondary pulmonary angiosarcoma usually died of uncontrolled bleeding.[8] The common presentations showed prolonged hemoptysis, recurrent pleural hemorrhage. The speed of bleeding was slow and the hemoptysis can last several months and the total volume of hemothorax was about 2000 ~ 3600 mL.[9] A series of hemostatics including antifibrinolytic agents, hemocoagulase agents, anti-capillary permeability agents and vasopressin had been applied but none of them could stop bleeding. The patient in this case had undergone bronchial arteriography, and no extravasation of contrast agent or abnormal vessels were found during the whole process. The bronchial artery embolization was not suitable for this case. Even if bronchial angiography showed a tumor and bronchial artery embolization was performed in another case with hemoptysis, there was no amelioration in bloody sputum.[10] For the skin metastatic lesion and gum hemorrhages, the bleedings were slow in speed and continually occurring unless ligation of tumor pedicle or compression were administered. All evidences mentioned above implicated that the sites of bleeding in angiosarcoma patients mainly were micro-vessels or capillaries with angiodysplasia.

Except for complete resection of the lesions, none of the interventions such as radiation therapy and chemotherapy have been shown to be dramatically effective. The prognosis is still poor that the median overall survival was 7 months in patients with solitary lesions

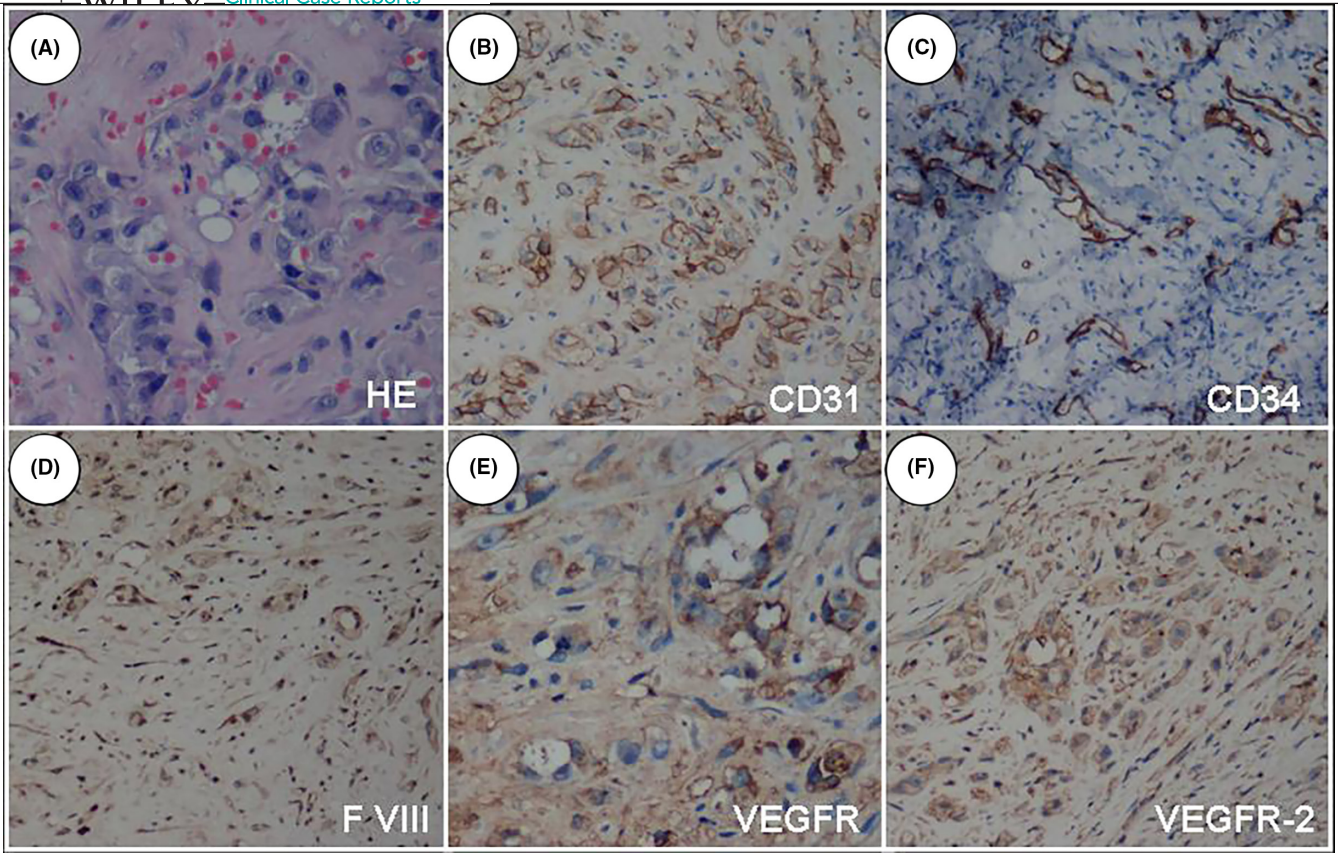

FIGURE 3 Pathology manifestations of primary pulmonary angiosarcoma. (A) H&E-stained sections showed nests of large, moderately pleomorphic, round to polygonal epithelioid cells, filled with abundant eosinophilic cytoplasm, and occasional cells with intracytoplasmic lumina containing erythrocytes (×200). (B–F) Immunohistochemical stainings (IHC) were positive for CD31 (B), CD34 (C) and Factor VIII (D), vascular endothelial growth factor receptor (VEGFR) and VEGFR-2 (E, F).

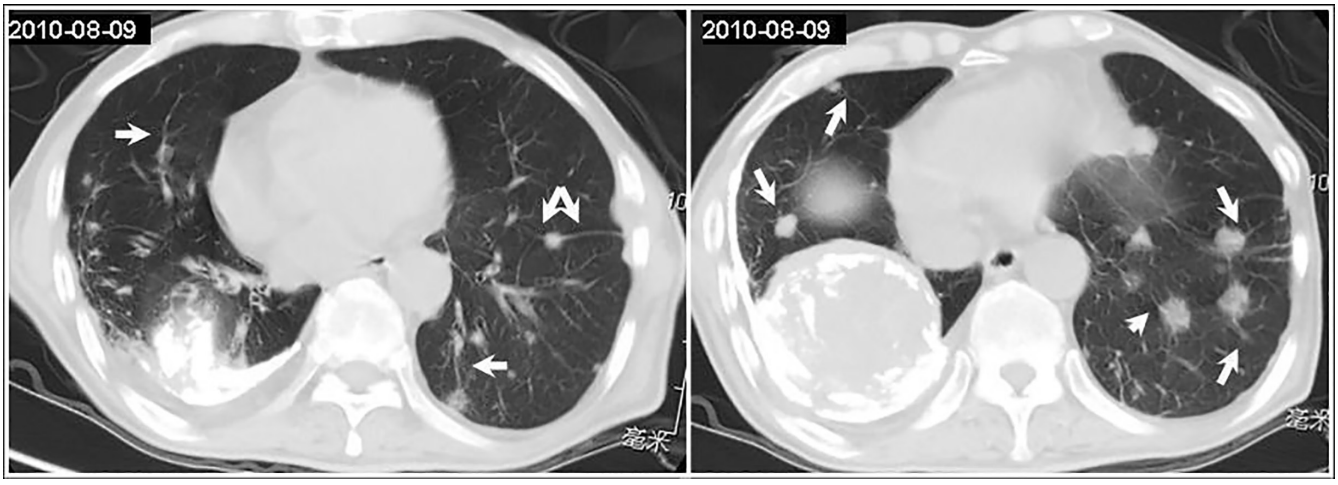

FIGURE 4 Axial computed tomography images of thorax showed the angiosarcoma metastasized along blood vessels, which characterized by thickening of interlobular septal (arrows).

while 2 months with multiple lesions.[8] The expression of VEGF (VEGF-A, VEGF-C) and their receptors (VEGFR-1, VEGFR-2, VEGFR-3) were both observed in a majority of angiosarcoma specimens.[11,12] Anti-VEGF/VEGFR pathway seems to be a promising therapy to angiosarcoma in theory but there is no stable positive response. A one-arm phase II study of bevacizumab in the treatment of angiosarcoma and epithelioid hemangioendotheliomas only showed 17% of patients in partial response, 50% in stable disease.[13] But in another two Randomized Phase II Trials, patient with advanced angiosarcoma did not show a better PFS or OS from bevacizumab therapy combined with

paclitaxel.[14,15] Sorafenib is a multitargeted tyrosine kinase inhibitor with activity against VEGFR2, VEGFR3, platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (KIT) as well as the Raf/Mek/Erk pathway, while sunitinib against VEGFR1, 2, 3, PDGFR, KIT, FMS-like tyrosine kinase-3 (FLT3), glial cell-line derived neurotrophic factor receptor (RET), and colony-stimulating factor (CSF-1).[16] In a phase II study of sorafenib, there was 1 complete response, 4 partial response and 21 stable disease in 37 angiosarcoma patients.[17] However, in a later research, Sorafenib only showed limited antitumor activity with short duration of tumor control[18] In our case, neither Sorafenib nor Sunitinib has clinical benefit for pulmonary angiosarcoma.

In summary, we report a rare case of primary pulmonary angiosarcoma arising from a tuberculous scar in an elderly patient. The clinical features presented as aggressive deterioration with uncontrolled hemorrhage. The sites of bleeding in angiosarcoma patients mainly are capillaries with angiodysplasia. There is no effective agents or interventions helpful to stop visceral bleeding, even though anti-VEGF/VEGFR targeted drugs.

AUTHOR CONTRIBUTIONS

Minghui Wang: Data curation; writing – original draft. **Xin Zhang:** Data curation; writing – review and editing. **Hongni Jiang:** Data curation; funding acquisition; project administration; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

No potential conflicts of interest were disclosed.

DATA AVAILABILITY STATEMENT

All data included in this report are accurate to the best of our knowledge. We will make available data (images and reports) upon request.

CONSENT

Written informed consent was obtained from the patients and their families for the publication of images or data included in this article.

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