Case report

A rare cause of hemoptysis

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A B S T R A C T

Angiosarcomas are rare, malignant, endothelial-cell tumors of vascular origin that can arise at any body site. They frequently metastasize to the lung, heralded by dyspnea, hemoptysis, chest pain, pneumothoraces, and diffuse pulmonary hemorrhage. However, in most cases lung metastases are discovered after the diagnosis of a primary angiosarcoma has already been established. Very rarely will an undiagnosed metastatic angiosarcoma present as diffuse pulmonary hemorrhage. We describe the case of a 59-year-old male who presented to hospital with dyspnea and hemoptysis. CT chest revealed rapidly progressing nodular changes and broncho-alveolar lavage returns were progressively bloody. Open lung wedge biopsy ultimately revealed metastatic angiosarcoma and extensive pulmonary hemorrhage. Our case highlights the key clinical, radiological, and pathological features of this rare malignancy that frequently metastasizes to the lung and reminds clinicians to consider it as a cause of hemoptysis and pulmonary hemorrhage.

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1. Introduction

We describe the case of a 59-year-old male who presented to hospital with diffuse pulmonary hemorrhage caused by an undiagnosed metastatic angiosarcoma. We highlight the key clinical, radiological, and pathological features of this rare malignancy that frequently metastasizes to the lung.

2. Case presentation

A 59-year-old non-smoking male of Chinese origin presented to hospital with a one-month history of worsening dyspnea and hemoptysis after recent travel to rural China. He denied fever or other constitutional symptoms. His symptoms had persisted despite completing two courses of antibiotics. His past medical history was significant for hypertension, type 2 diabetes mellitus, dyslipidemia, and thalassemia trait.

On presentation to hospital, the patient was hypoxic on room air and he had a low-grade fever. Physical examination was remarkable only for bilateral crackles on lung auscultation. No abnormal ocular, joint, or skin findings were noted. Blood work was remarkable only for microcytic anemia. Anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), and anti-glomerular basement membrane (anti-GBM) antibody testing were negative.

Chest CT revealed bilateral, multifocal, nodular changes with surrounding ground-glass attenuation and consolidation (Figure 1A).

Bronchoscopy with broncho-alveolar lavage (BAL) was performed and the BAL returns were progressively bloody. BAL cultures were negative for acid-fast bacilli, viral, bacterial, and fungal pathogens; cytology was negative for malignant cells and hemosiderin-laden macrophages.

The case was reviewed at the weekly Respirology-Radiology rounds, and it was decided to send the patient for an open lung biopsy via video-assisted thoracic surgery (VATS). Shortly after the biopsy was performed, the patient became more hypoxic and a repeat CT chest was performed. Compared to the CT chest just two weeks prior, there was significant interval worsening of the nodular changes and ground-glass opacities. There was no evidence of pulmonary embolus (Figure 1B).

The biopsies revealed multiple foci of highly mitotically active spindle cells with enlarged nuclei within the lumen of multiple pulmonary arteries. At multiple sites these cells invaded through the pulmonary artery and infiltrated the surrounding lung parenchyma. Extensive pulmonary hemorrhage, acute and organizing diffuse alveolar damage, and pulmonary infarcts were also noted. The spindle cells stained positive for CD31, CD34, and vimentin (Figure 2). The histological features, immunohistochemical staining pattern, intravascular nature, and multifocality of the tumor were consistent with a metastatic angiosarcoma.

The patient was seen by Medical Oncology, but was not a candidate for chemotherapy due to his poor clinical status and rapid deterioration. Further imaging to identify the primary

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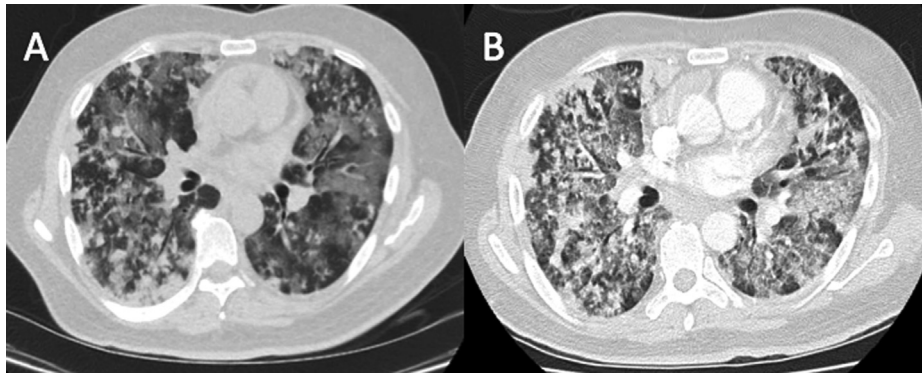
Fig. 1. CT chest showing bilateral, multifocal, nodulor changes with surrounding ground-glass attenuation and consolidation (A). CT chest obtained two weeks later showing interval worsening of the nodular changes, ground-glass attenuation, and consolidation bilaterally (B).
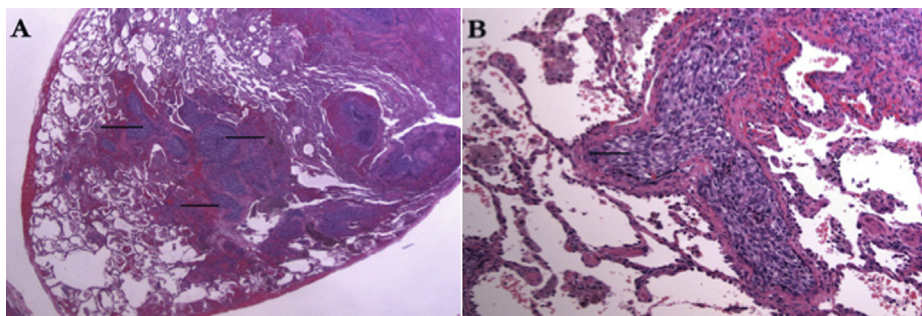
Fig. 2. A low-magnification photomicrograph illustrating several pulmonary vessels containing the highly mitotically active spindle cells with enlarged nuclei (A,arrows). A high-magnification view illustrating a single branching pulmonary vessels containing the spindle cell lesion (B,arrows).

angiosarcoma or other areas of metastasis prior to his death was also deferred. The patient expired twenty-two days after admission. The patient's family declined autopsy.

3. Discussion

Angiosarcomas are rare, malignant, endothelial-cell tumors of vascular origin that represent less than 2% of all sarcomas [1]. Although they most commonly arise in the skin, angiosarcomas can originate at any site, including the breast, liver, bone, spleen, heart, and lung. Patients with chronic lymphedema or a history of radiation exposure are at increased risk of developing angiosarcomas. Less common risk factors include exposure to vinyl chloride, thorium dioxide, arsenic, and immunosuppression (post liver and kidney transplantation) [2].

Pulmonary angiosarcomas represent metastases in the vast majority of cases. Angiosarcomas from all sites frequently metastasize via hematologic spread to the lung, heralded by dyspnea, hemoptysis, chest pain, pneumothoraces, or diffuse pulmonary hemorrhage [1]. However, in most cases lung metastases are discovered after the diagnosis of a primary angiosarcoma has already been established [3]. Very rarely will an undiagnosed metastatic angiosarcoma present as diffuse pulmonary hemorrhage, as in the case of our patient [3—10]. In these rare cases, the occult primary angiosarcoma is usually not identified ante-mortem but is most often found to be in the right atrium on autopsy [3]. There are no histological features of the pulmonary metastases that may portend the primary site [11].

As demonstrated in our patient's CT, key radiographic features of a metastatic angiosarcoma in the lung can include multiple bilateral, solid nodules, ground-glass opacities representing pulmonary hemorrhage, and interlobular septal thickening indicating lymphangitic spread. Metastases have also been reported as multiple thin-walled cysts, or as a mixed pattern of solid nodules and thin-walled cysts [12].

Exceedingly rare cases of primary pulmonary angiosarcomas have been reported. Not surprisingly, primary pulmonary angiosarcomas present very similarly to metastatic angiosarcomas in the lung, with dyspnea and hemoptysis being the most commonly cited symptoms [13]. On chest CT, a primary pulmonary angiosarcoma appears as either a solitary mass or multiple nodules in cases of multifocal growth [14]. If the tumor invades the pleural space, pleural effusions or pneumothoraces can be seen [13]. Differentiating a primary pulmonary angiosarcoma from metastases can be challenging, especially in cases of widespread organ involvement. As primary pulmonary angiosarcomas are typically characterized by more insidious growth [14], we felt that the extremely rapid progression of our patient's disease as captured with CT imaging was more in keeping with a metastatic angiosarcoma.

As demonstrated in this case, patients with metastatic angiosarcomas usually deteriorate quickly; the average survival from time of diagnosis is 9 months [1]. Palliative chemotherapy is the mainstay of treatment for metastatic angiosarcomas, although current recommendations are based on limited evidence from small retrospective or phase 2 studies [15]. Doxorubicin-based regimens have been shown to yield progression-free survival of 3.7—5.4 months in patients with unresectable angiosarcomas [16], and are considered first-line treatment [15]. Specifically, doxorubicin plus ifosfamide is often used as this combination was shown to increase progression-free survival by an average of 1.7 months compared to doxorubicin alone [16]. In 2008, a phase 2 study showed that weekly administration of paclitaxel achieved a

nonprogression rate of 74% at two months and 42% at four months in patients with metastatic or unresectable angiosarcomas [17]. Two retrospective case series have also indicated that gemcitabine, with or without the addition of docetaxel, may confer a clinical response in patients with metastatic angiosarcomas [18,19]. As such, the 2012 European Society for Medical Oncology Clinical Practice Guidelines recommend a doxorubicin-based regimen for metastatic angiosarcomas, but consider taxanes or gemcitabine (with or without docetaxel) to be acceptable alternatives [20].

Molecular targeted therapies have recently come into light as potentially promising treatment options for metastatic angiosarcomas. In two phase 2 studies, the tyrosine kinase inhibitors sorafenib and imatinib yielded progression-free survival of 3.8 and 2.76 months, respectively, in patients with metastatic angiosarcomas [21,22]. Very recently, a phase 2 study demonstrated that bevacizumab, a monoclonal antibody to circulating vascular endothelial growth factor (VEGF), achieves a median progression-free survival of 12 weeks in patients with metastatic or locally advanced angiosarcomas [23].

4. Conclusion

As our case illustrates, metastatic angiosarcomas in the lung can present with dyspnea, hemoptysis, chest pain, pneumothoraces, or diffuse pulmonary hemorrhage [1]. Angiosarcomas most commonly arise in the skin, breast, liver, bone, spleen, and heart. The lung is the most frequent site of metastatic spread but is rarely the site of the primary tumor [2]. Chest CT may reveal multiple bilateral, solid nodules with ground-glass opacities, multiple thin-walled cysts, or a mixed pattern of solid nodules and thin-walled cysts [12]. The prognosis of metastatic angiosarcoma averages 9 months [1]. Palliative chemotherapy using doxorubicin, taxanes, or gemcitabine (with or without docetaxel) is the treatment of choice [20]. Further phase 3 studies are needed to determine the role of molecular targeted therapies in the management of patients with metastatic angiosarcomas in the future.

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