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PRIMARY PLEURAL EPITHELIOID ANGIOSARCOMA PRESENTING WITH RECURRENT HAEMORRHAGIC PLEURAL EFFUSIONS

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ABSTRACT

Introduction: Primary pleural angiosarcoma is an extremely rare malignancy of the pleura arising from the vascular endothelial cells. The disease is highly aggressive and associated with a poor prognosis. Clinical and imaging features are non-specific often leading to delays in diagnosis.

Case description: We report a case of primary pleural epithelioid angiosarcoma in a 66-year-old man presenting with a 2-month history of progressive dyspnoea, anorexia and significant weight-loss. Chest imaging revealed a large pleural effusion which was haemorrhagic on sampling. Multiple haemorrhagic nodules on parietal pleura were biopsied at medical thoracoscopy. Tumour morphology and immunocytochemical analysis with positive staining for endothelial markers CD31 and ERG supported the diagnosis of pleural epithelioid angiosarcoma. He was treated with palliative chemotherapy with some initial response but developed rapid disease progression after 6 months resulting in his death.

Conclusion: Pleural angiosarcoma causes diagnostic uncertainty due to its rarity, non-specific presentation and inconclusive cytology. Histopathology and immunohistochemistry are crucial for prompt diagnosis of this aggressive disease.

KEYWORDS

Primary pleural angiosarcoma

LEARNING POINTS

- Primary pleural angiosarcoma is an incredibly rare disease.
- In the context of haemorrhagic effusions with non-diagnostic cytology, early consideration of thoracoscopic visually targeted pleural biopsy is important to improve diagnostic yield.
- Clinical presentation, imaging and cytology is often non-specific in these cases; histopathology and immunohistochemistry are crucial for diagnosis in primary pleural angiosarcoma.

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INTRODUCTION

Angiosarcomas are malignant neoplasms arising from vascular or lymphatic endothelial cells, accounting for approximately 1-2% of soft tissue sarcomas. They most frequently occur in skin, liver, breast, bone and spleen[1], with pleural involvement being extremely rare. These tumours are aggressive with rapid progression and poor prognosis[2].

The clinical presentation is heterogeneous and overlaps with common pleural diseases, such as mesothelioma or metastatic carcinoma. As a result, diagnosis is challenging and relies on histopathological confirmation supported by immunohistochemistry. Here we report a case of primary pleural angiosarcoma.

CASE DESCRIPTION

A 66-year-old man presented to the emergency department with a 2-month history of progressive cough and dyspnoea. He reported anorexia, fatigue and 20kg unintentional weight-loss. He denied any chest pain, haemoptysis, fevers, or sweats. His past medical history included a transient ischaemic attack and hypertension. His Eastern Cooperative Oncology Group performance status was 2. He had no smoking history and no known occupational or environmental exposures.

Clinical examination noted reduced breath sounds on the right. He was afebrile, haemodynamically stable with no oxygen requirement at rest.

Initial laboratory investigations demonstrated normocytic anaemia, with no other significant abnormalities.

A computed tomography scan of the chest *(Fig. 1)* revealed a large right pleural effusion with passive atelectasis, smaller left sided effusion, no pleural thickening, and a right renal cystic lesion which was considered likely benign.

Right thoracocentesis revealed haemorrhagic fluid. Cytological examination showed presence of atypical cells but was non-diagnostic.

The patient was further investigated with medical thoracoscopy under sedation. More than 3 litres of haemorrhagic fluid were drained. Multiple large exophytic haemorrhagic nodules *(Fig. 2)* were identified on the parietal pleura. Multiple biopsies of the nodules were taken. Talc slurry pleurodesis was performed the next day.

Histopathology revealed a highly cellular malignant neoplasm. The cells showed marked atypia with predominantly epithelioid appearance. High-power examination demonstrated poorly formed anastomosing vascular channels with extravasated red blood cells and frequent intracytoplasmic lumina, typical for angiosarcomas *(Fig. 3)*. Immunohistochemistry showed tumour cells positive for epithelial markers MNF116, CAM5.2, AE1/3. The vascular/endothelial markers CD31 and ERG also showed strong and diffuse positive expression *(Fig. 4)*.

As it lacked the spindle-cell appearance of sarcomas and mimicked metastatic carcinoma or mesothelioma, a precise immunohistochemistry panel was performed. Mesothelial markers (calretinin, WT1, D2-40 and Ck5/6), other carcinoma markers (BerEp4, P40, TTF1 and NapsinA) were negative.

The co-expression of robust endothelial markers (CD31 and nuclear ERG) paired the with absence of mesothelial

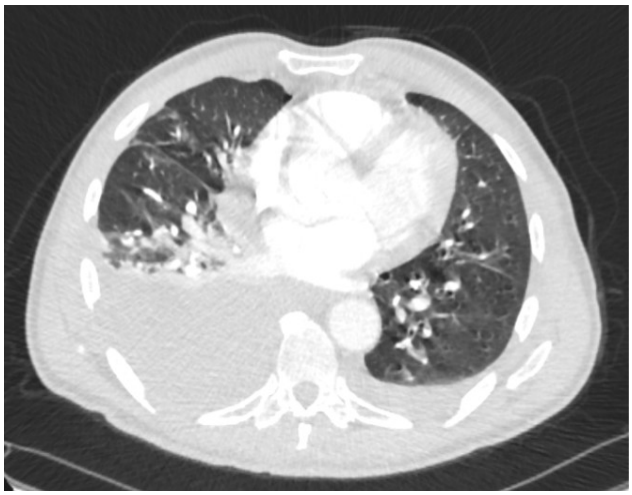


Figure 1. *Computed tomography scan of the chest demonstrating large right-sided pleural effusion.*

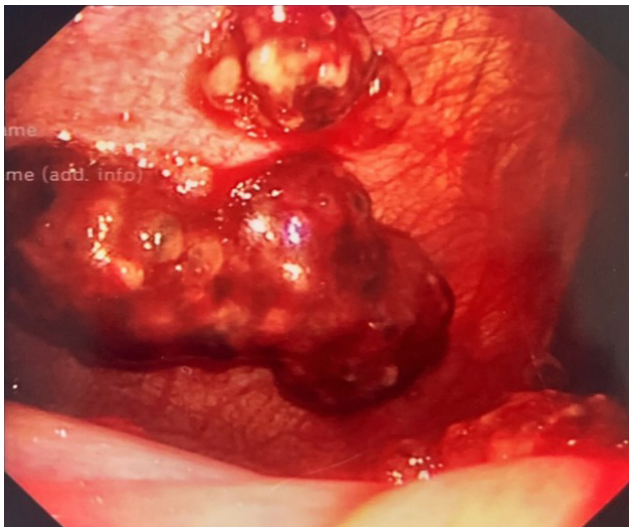


Figure 2. *Medical thoracoscopy showing multiple haemorrhagic nodules on the parietal pleura.*

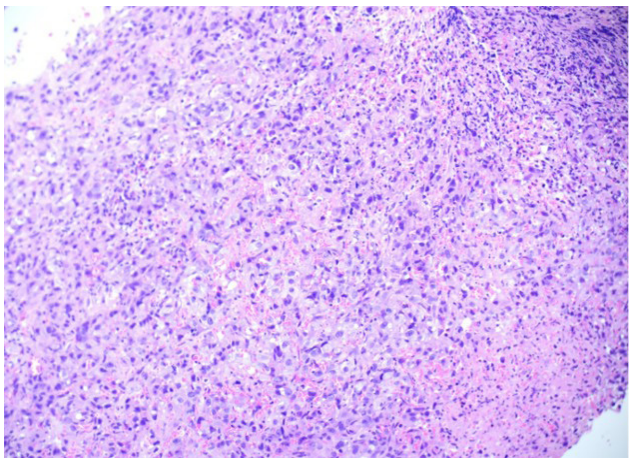


Figure 3. *Histopathology - Atypical epithelioid cells, intracytoplasmic lumina and red blood cell extravasation.*

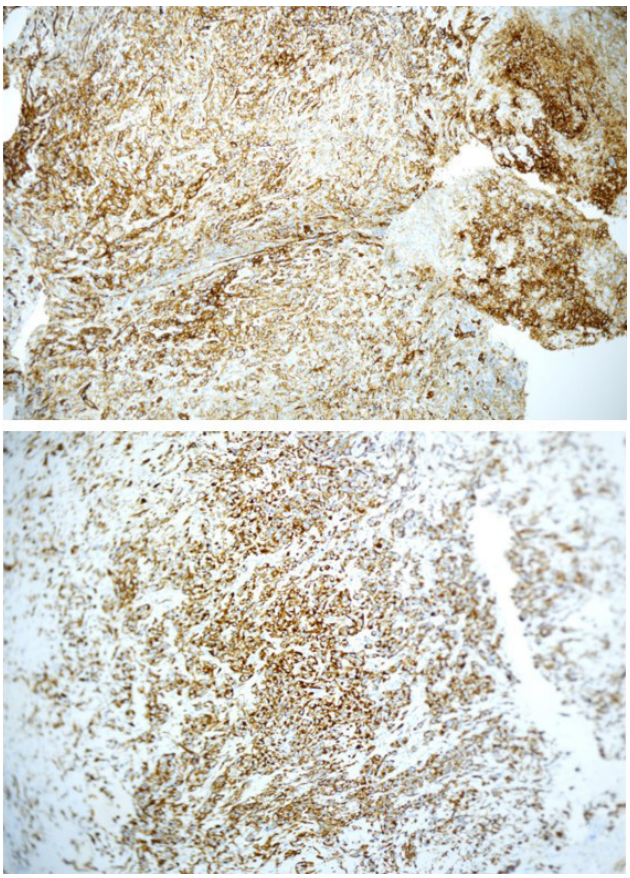


Figure 4. Immunohistochemistry analysis show tumour cells stained positive for CD31, a vascular endothelial marker (top) and AE1/3, an epithelial marker (bottom).

and some site-specific carcinoma markers confirmed the diagnosis of primary pleural epithelioid angiosarcoma.

The case was discussed at a specialist sarcoma multidisciplinary team meeting. Further staging investigations did not reveal any metastatic disease. Given the advanced nature of disease, no curative treatment options were available.

The patient received palliative anti-cancer therapy with 6 cycles of paclitaxel and low-dose dexamethasone for symptom control. He initially responded well to chemotherapy with control of his pleural disease but after 6 months developed rapid disease progression and died shortly afterwards.

DISCUSSION

Primary pleural angiosarcoma (PPA) is an exceedingly rare and aggressive malignancy associated with a very poor prognosis. The literature is limited to anecdotal case reports with approximately 45-50 cases of PPA described worldwide since the first reported case in 1943. Most recently Wang et al summarised 43 cases[3].

Aetiology and pathogenesis remain poorly understood. Exposure related risk factors include chronic tuberculous pyothorax, chronic inflammatory states, prior radiotherapy, or asbestos exposure[4]. Our patient was not exposed to any of these. Chronic pleural inflammation, and persistent tissue injury, has been postulated as potential mechanisms contributing to malignant endothelial transformation in susceptible individuals. The disease appears to occur more frequently in men, with mean age in the 60s[4].

Clinical presentation is non-specific. Reported symptoms include chest pain, dyspnoea, cough, haemoptysis, and constitutional symptoms (fatigue, anorexia and weight loss).

Radiological findings include unilateral/bilateral pleural effusions, focal/diffuse pleural thickening, and nodular/diffuse pleural masses[5]. These clinical and imaging features can mimic more prevalent pleural diseases such as malignant mesothelioma, metastatic carcinoma, empyema, or tuberculosis, leading to diagnostic uncertainty often delaying diagnosis.

Pleural fluid is usually haemorrhagic, and cytology is frequently non-diagnostic[5], as demonstrated in our case. Pathology is the gold standard for diagnosing PPA. Early consideration of thoracoscopic visually targeted pleural biopsy is therefore essential when clinical suspicion remains high, particularly in the context of haemorrhagic effusions.

Histopathological assessment combined with immunohistochemistry is crucial for diagnosis. The epithelioid morphology prompts pathologists to favour carcinoma or mesothelioma. The diagnostic pitfall in this case is the aberrant expression of cytokeratins (AE1/AE3), which occurs in up to 50% of epithelioid angiosarcomas. If a pathologist relies solely on pancytokeratin positivity in a pleural mass, misdiagnosis of poorly differentiated carcinoma or mesothelioma is likely. Expression of endothelial markers such as CD31 and ERG supports vascular origin, while exclusion of mesothelial and epithelial markers helps differentiate from other malignancies[6].

Management of PPA is challenging because no standardised treatment guidelines exist due to its rarity. Options include surgery, radiotherapy, and chemotherapy[3,4]. Surgical resection can be considered for localised tumour, however most patients will present with unresectable diffuse pleural involvement or disseminated disease. Preoperative vascular embolization has been used to reduce tumour size and vascularity thus reducing intra-operative bleeding. Radiotherapy may be beneficial as adjuvant therapy in post-operative cases or provide palliative benefit in selected cases. Palliative chemotherapy has been used with variable and generally limited success and only offered to patients with good performance status; regimes include paclitaxel, doxorubicin, ifosfamide, or gemcitabine-based combinations[7]. Emerging evidence suggests a potential role for immunotherapy[8], although data remain limited.

The prognosis remains poor, with most patients developing rapid disease progression despite treatment and survival measured in a few months following diagnosis. Factors contributing to poorer outcomes include diffuse pleural involvement, presence of haemothorax, and advanced disease at presentation[3].

This case contributes to the limited literature of PPA, highlighting the diagnostic challenges, and aggressive nature of this malignancy. Early recognition and accurate histopathological diagnosis with extended immunocytochemistry is therefore essential, especially in patients presenting with haemorrhagic pleural effusions and/or pleural masses.

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