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Case Report

Extremely late-onset pulmonary metastasis from uterine PEComa

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Summary

A 79-year-old woman underwent surgical resection of a peripheral, solitary, pulmonary lesion that was diagnosed as malignant PEComa. Her clinical history was positive for uterine leiomyosarcoma, excised 20 years before. Re-evaluation of the primary uterine lesion led to the final diagnosis of lung metastasis from uterine PEComa. While long latency between primary tumour and metastasis is a known and characteristic feature of PEComas, a 20-year interval is unprecedented in the literature.

Key words: PEComa, soft tissues, uterus, lung, metastases

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Introduction

Perivascular epithelioid tumours (PEComas) are a group of rare and relatively heterogeneous mesenchymal neoplasms with wide anatomical distribution. They are composed of perivascular epithelioid cells (PECs), tumoural cells whose normal counterpart is still unknown. PECs can show epithelioid or spindle morphology and are characterised by immunoreactivity for both melanocytic and smooth muscle markers. The family of PEComas comprises well recognized entities such as angiomyolipoma and lymphangioleiomyomatosis, and other tumours sharing morphological, immunohistochemical and genetic similarities and simply referred to as PEComas [1].

Histologically, PEComas are typically organised in nests or trabeculae around vascular structures. Perivascular cells are more often epithelioid in morphology and demonstrate strong expression of melanocytic markers, while peripheral cells appear usually spindle and tend to express smooth muscle markers [2]. Immunoreactivity for cathepsin K is a useful diagnostic marker of these tumours [1].

PEComas are more frequent in females than males. Most are sporadic, occasionally related to TFE3 gene rearrangements, while a subset is associated with tuberous sclerosis and harbours TSC1 and TSC2 mutations [2]. The biological behaviour varies from benign to malignant, but histologic criteria to assess malignancy are not well established. Retrospective studies suggested tumour size (> 5 cm), infiltrative growth pattern, high nuclear grade and cellularity, necrosis, vascular invasion, and mitotic activity (> 1/50 HPF) as features associated with malignant

behaviour. Presence of two or more of these elements was proposed as sign of malignancy [3]. Metastases can occur many years after the initial diagnosis of PEComa, a peculiar characteristic that increases the risk of misdiagnosis of the secondary lesion as a new primary tumour [4,5]. The most common metastatic sites are liver, lung, lymph nodes and bone.
Surgical treatment remains the gold standard approach when feasible, while mTOR inhibitors have been proposed for metastatic or advanced PEComas with TSC2 alterations. However, as previously demonstrated [4], salvage surgery in the form of repeated metastasectomy may represent an important therapeutic option, especially in patients with long survival.

Case report

We present the case of a 79-year-old woman seeking medical attention for chronic dry cough. Her anamnesis was positive for uterine leiomyosarcoma, treated with surgery and adjuvant chemo-radiotherapy 20 years before, in another institution. Chest X-ray showed a nodular opacity in the lower lobe of the left lung. The finding was confirmed by total body CT scan, which revealed a solitary, well-defined, peripheral, nodular lesion, suspicious for mesenchymal neoplasm (Fig. 1). No evidence of malignancy in other organs was noticed and wedge lung resection was performed.

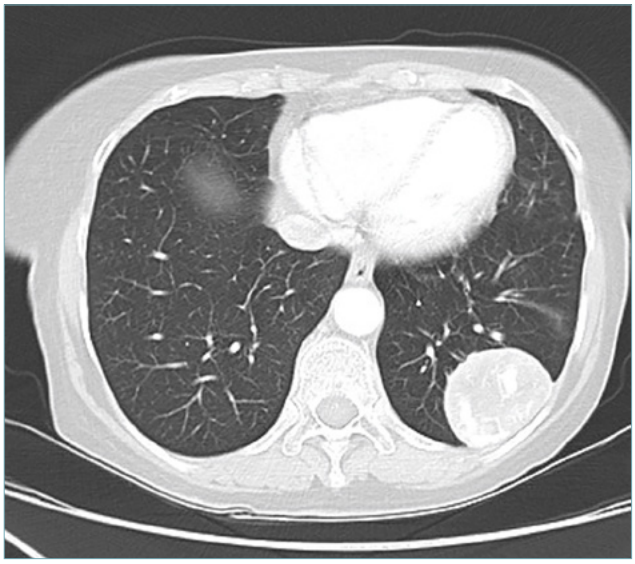

Figure 1. Axial, contrast-enhanced, high resolution CT scan image showing a large, round, peripheral lesion of the left lower lobe. The nodule shows pushing margins and appears heterogeneous in composition.

On gross examination, a round-shaped and cleavable lesion showing necrotic and haemorrhagic areas was demonstrated. On microscopic examination, neoplastic cells presented nested architecture and epithelioid morphology, with focal evidence of marked nuclear pleomorphism, multinucleation and eosinophilic nucleoli. Numerous mitoses, sometimes atypical, were observed, (Fig. 2A-B). The morphological findings were consistent with a malignant mesenchymal tumour and a diagnosis of PEComa was suggested. Considering the previous history of uterine leiomyosarcoma, extensive immunohistochemical profiling was carried out.
Neoplastic cells resulted immunoreactive for smooth muscle markers (smooth muscle actin, desmin, h-caldesmon), melanocytic markers (MITF, HMB-45 only in rare cells) and cathepsin K (Fig. 2C-F). Immunostains for cytokeratin, Melan-A, TTF-1, S100, SOX10, CD31, CD34, CD68, calretinin and TFE3 resulted negative.
The combination of morphological and immunohistochemical findings was consistent with malignant PEComa. This result prompted the review of the patient's uterine leiomyosarcoma diagnosed 20 years before, to determine a potential relationship between the two lesions.
Paraffin blocks from the uterine lesion were retrieved, and new slides obtained. Histological examination revealed a mesenchymal neoplasm with heterogeneous morphology, presenting both areas with spindle cells and fascicular architecture and areas with epithelioid cells and trabecular architecture (Fig. 3A and 3D).
Immunohistochemistry was performed and, similar to the pulmonary lesion, both spindle and epithelioid cells resulted immunoreactive for cathepsin K and smooth muscle actin (Fig. 3B-C and 3E-F). On the other hand, desmin, caldesmon, MITF and HMB-45, which tested positive in lung, were negative in the uterine neoplasm.
Even though no complete overlap between the two lesions' immunophenotypes could be found, the significant morphological analogies, the shared immunohistochemical positivity for cathepsin K and the well-known tendency for PEComas to give late metastases, formed a body of evidence significant enough to suggest a reformulation of the primary diagnosis of leiomyosarcoma as PEComa, favouring the pulmonary lesion as metastatic. The morphologic similarity was particularly striking between the epithelioid areas of the uterine lesion (Fig. 3A) and the more atypical areas of the pulmonary neoplasm (Fig. 2B), while no pulmonary counterpart of the spindle component of the uterine lesion (Fig. 3D) was found.

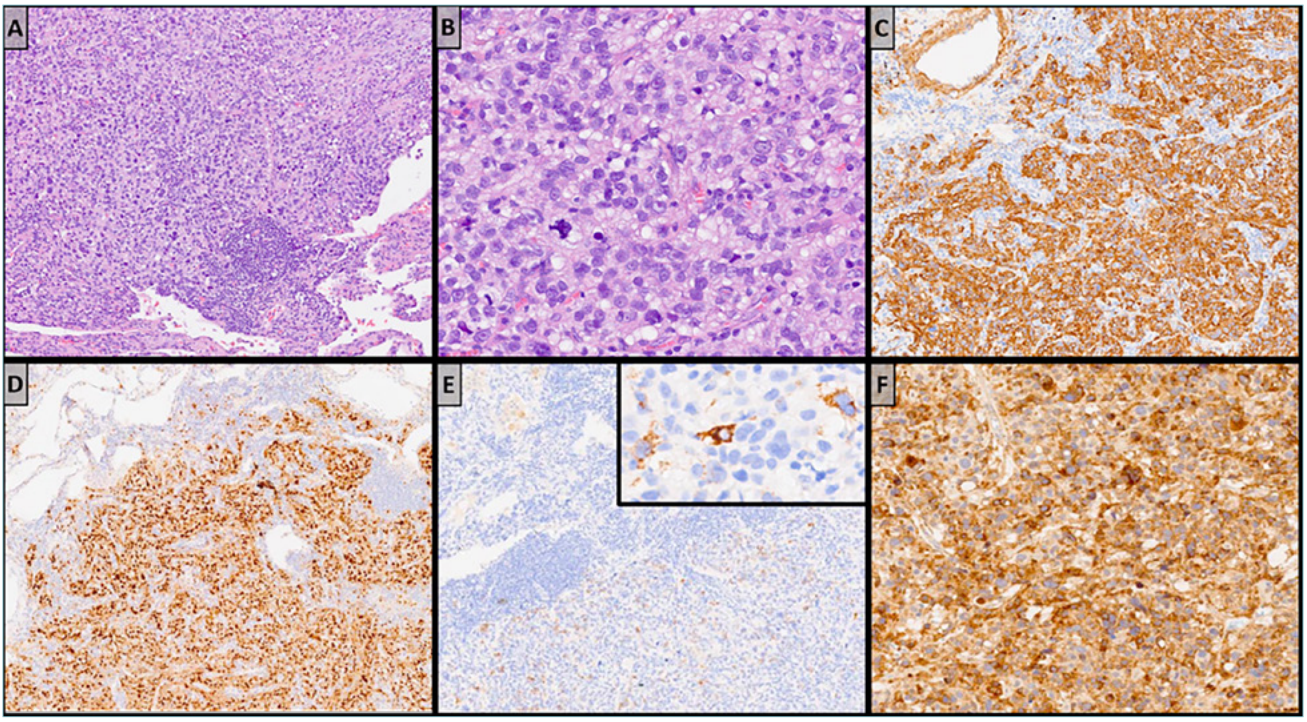

Figure 2. (A and B; H&E; 4x and 20x) The lesion reveals relatively high cellularity and nested and diffuse architecture. Large vessels can be appreciated. Neoplastic cells are epithelioid with eosinophilic and clear cytoplasm and moderate nuclear atypia. Mitotic figures, sometimes atypical, can be seen. (C-F; immunohistochemistry) Immunohistochemistry for SMA (C), MITF (D) and cathepsin K (F) resulted strongly positive, whereas HMB-45 (E) showed focal, granular reactivity (insert).

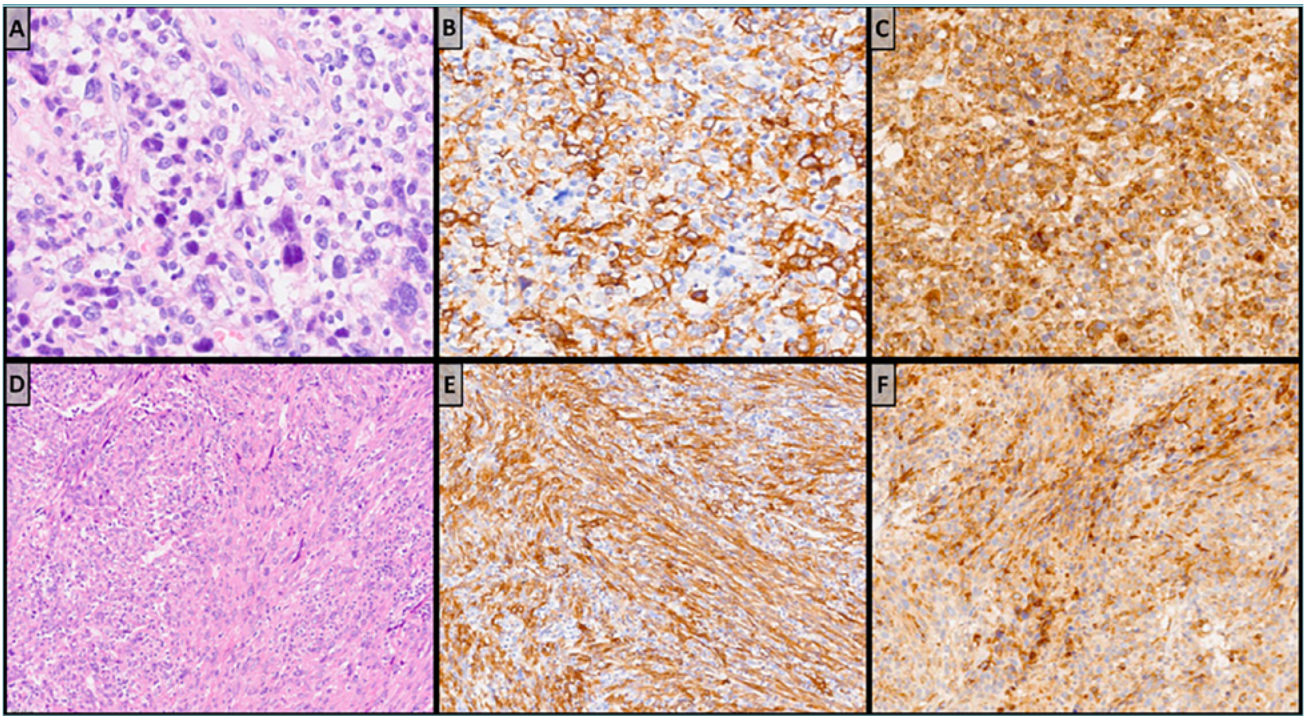

Figure 3. (A and D; H&E; 20x) The lesion is heterogeneous, with some areas (A) presenting trabecular architecture and epithelioid morphology and other areas (D) showing fascicular architecture and spindle morphology. Cytologic atypia is mostly evident in the epithelioid component. (B-C, E-F; immunohistochemistry) Immunohistochemistry for SMA and cathepsin K is diffusely positive in both spindle (respectively B and C) and epithelioid areas (respectively E and F).

Discussion

A few reports of PEComa discuss the reviewing of previous mesenchymal lesions to eventually achieve a diagnosis of late metastatic PEComa [4,5].

To our knowledge, this is the first case of a metastatic PEComa manifesting 20 years after the primary lesion. Moreover, the clinical manifestation as a single, peripheral, pulmonary nodule increased the diagnostic difficulty, as the picture was suggestive of a primary lung lesion. Because of its morphological heterogeneity, the diagnosis of PEComa can be challenging, with differential diagnoses including a wide host of tumours with clear cell, spindle and epithelioid morphology such as melanoma, clear cell sarcoma, smooth muscle tumours, myoepithelial tumours, alveolar soft part sarcoma and renal cell carcinoma. Consideration of this entity in daily practice and its recognition by an appropriate immunohistochemical panel should be strongly recommended.

This case highlights that a diagnosis of PEComa should prompt accurate anamnesis of the patient and reviewing of previous diagnoses of any neoplasm with overlapping morphological and immunohistochemical characteristics. The extremely long latency between primary and metastatic disease calls for extended follow-up of patients.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This is a case report, everything concerning it complied with the principles outlined in the declaration of Helsinki.

Author contributions

AA: investigation, project administration, visualization, writing; GM: review, supervision; Gd'A: conceptualization, review, supervision; CDR: review, supervision; PG: review, supervision; AP: conceptualization, investigation, project administration, review.

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