A rare case of malignant epithelioid angiomyolipoma in multiple locations: multifocal disease or metastases?

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BACKGROUND: *Perivascular epithelioid cell tumors (PEComas), make up a family of extremely rare mesenchymal neoplasms, with characteristic morphological, immunohistochemical and molecular findings. Malignant PEComas and gastrointestinal epithelioid angiomyolipoma (E-AML) are especially rare. To the best of our knowledge E-AML have not been found in the breast. The difficulty in determining what constitutes optimal therapy for PEComas, owing to the sparse literature available, led us to report this rare case.*
METHODS: *We report a case of a 44-year-old woman, with a family history of multiple endocrine neoplasia syndrome (MEN) (gastrinoma, medullary thyroid cancer and parathyroid hyperplasia), affected by PEComa located in the kidney, stomach, ileum, liver and breast.*
RESULTS: *The renal, gastric, ileal and mammarian tumors were completely resected, with no evidence of local disease. Liver lesions were biopsied. The morphological and immunohistochemical findings confirm the diagnosis of PEComa.*
CONCLUSION: *On this basis it is difficult to determine if some E-AML are multifocal tumors or metastatic disease.*

KEY WORDS: Breast Gastrointestinal, Malignant epithelioid angiomyolipoma, PEComas

Introduction

Angiomyelolipoma (AML) is a benign mesenchymal tumor with abnormal blood vessels, smooth muscle and adipose tissue as key histological features AML belongs to the family of perivascular epithelioid cell tumors (PEComas) [1,2]. These tumors are found most often in the kidney, are very difficult to interpret histologically, and are often associated with tuberous sclerosis [2,3]. AML of the gastrointestinal tract is very uncommon [4-6]. The epithelioid type (epithelioid angiomyolipoma;E-AML) is extremely rare and is characterized by a predominance of epithelioid smooth muscle cells [1-4]. Malignant E-AML is equally rare, and very aggressive [3,5]. In the case reported here, due to the presence of the tumor in the kidney and subsequently in the stomach, ileum and breast, and liver, we were faced with the question of whether the patient had multiple primary tumors or metastatic disease.

Case report

D.R:, a 48-year-old female, was admitted to our unit because of an episode of hematemesis and severe anemia (Hb:6g/dl). She had a family history of multiple

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endocrine neoplasia II (MEN II) (her father had gastrinoma, medullary thyroid cancer and parathyroid hyperplasia) She had undergone left nefrectomy due to an expanding lesion in the lower part of the middle third of her left kidney involving the renal pelvis and infiltrating the capsule. Definitive histology and immunohistochemical analysis, which excluded leiomyosarcoma and sarcomatoide renal cell carcinoma, identified E-AML (PEComa) without lymph node involvement. [Nese et al, Am J Surg Pathol, 2011]. The patient underwent esophagogastroduodenoscopy as an inpatient. The findings were a sessile, polypoid neoformation approximately 3cm in diameter, located just below the cardias, which bled upon contact with the scope. A computed tomography (CT) scan was therefore performed. The scan revealed a vascularized neoformation of the small curvature of the stomach, approximately 5cm in diameter, that protruded into the lumen and penetrated the full thickness of the gastric wall, emerging from the serosa (Fig. 1) as well as multiple vascularized lesions in the liver parenchyma (segments IV and VII) with signs of internal necrosis (Fig. 1-2). An richly vascularized expanding neoformation, approximately 20 cm in diameter was seen in the lumen of the ileum, at the level of the pelvic cavity (Fig. 3), and nodules (maximum diameter 6 mm) in the lungs (Fig. 4).

Due to the patient's severe anemia and the results of diagnostic imaging, an atypical gastric resection was performed (Fig. 5) liver lesions were biopsied, and the ileum

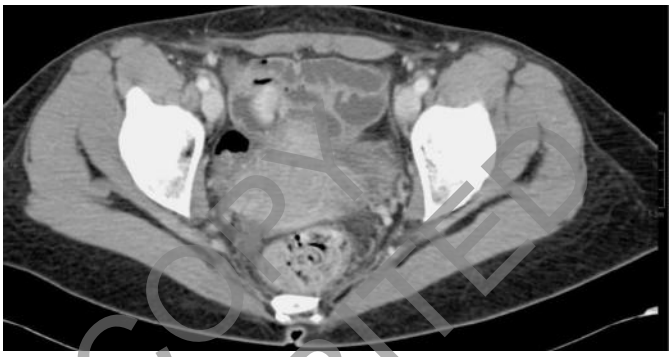

Fig. 3:Computed tomography scan showing an intraluminal ileal neoplasm.

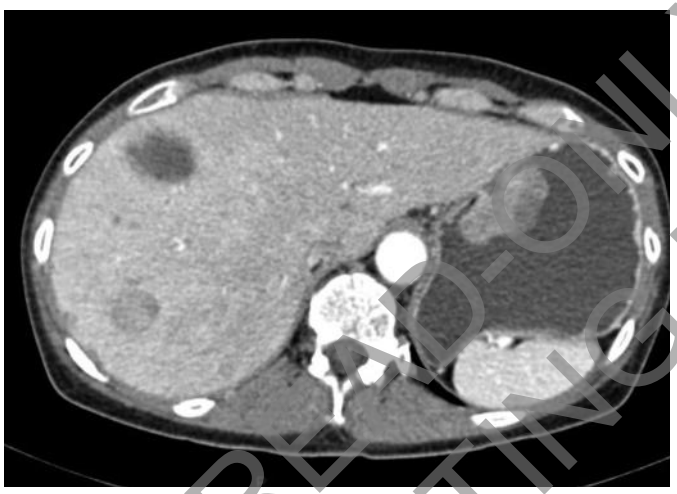

Fig. 1: Computed tomography scan showing gastric and hepatic neoplasms.

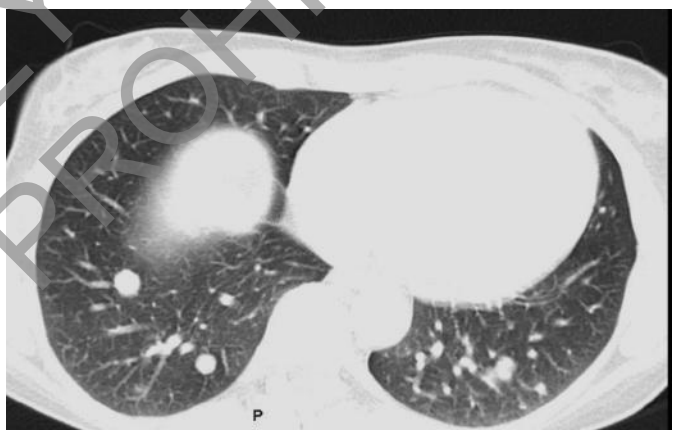

Fig. 4: Computed tomography scan showing lung lesions.

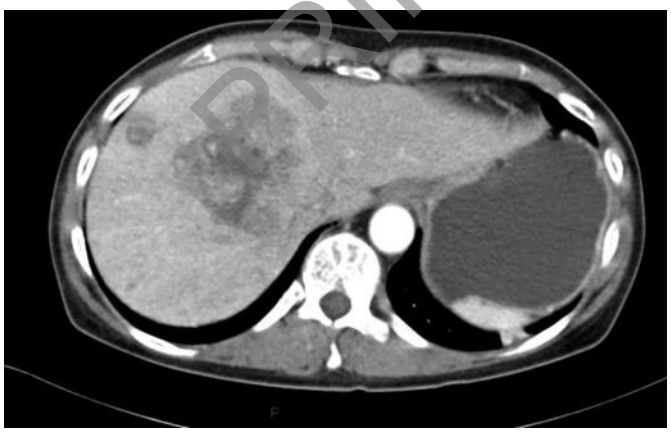

Fig. 2: Computed tomography scan showing liver lesions.

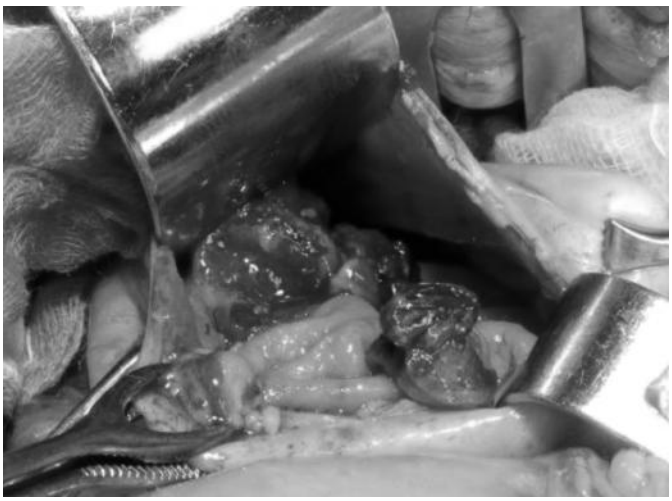

Fig. 5: Intraoperative image: gastric neoplasm extending into the lumen.

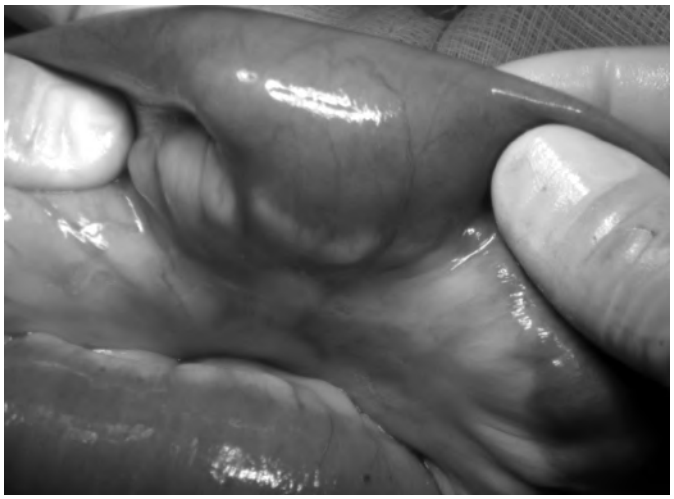

Fig. 6: Ileal neoplasm.

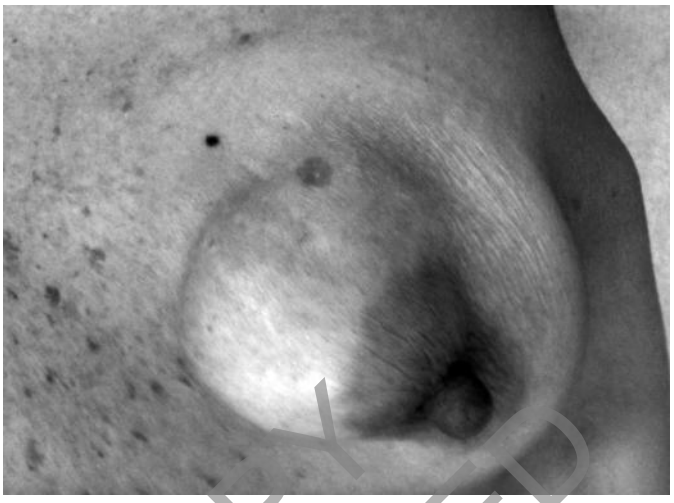

Fig. 9: Breast neoplasm.

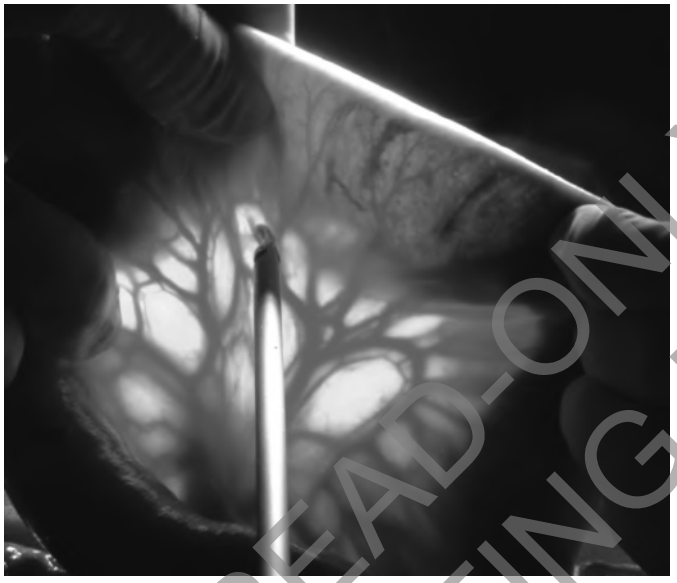

Fig. 7: Ileal neoplasm: vascularisation.

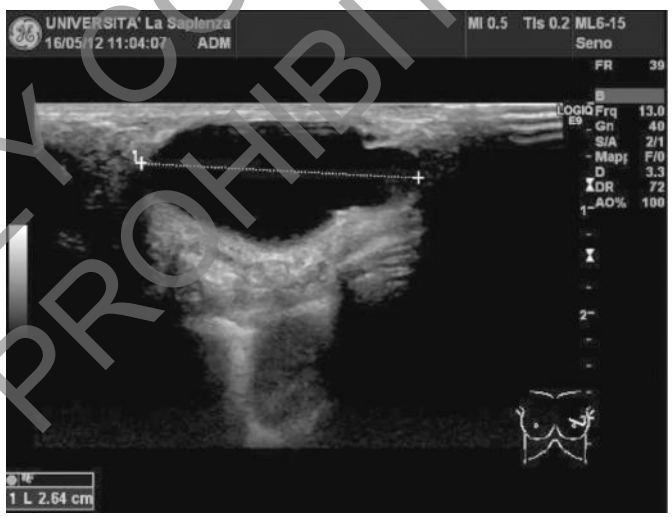

Fig. 10: Ultrasound image of the left breast.

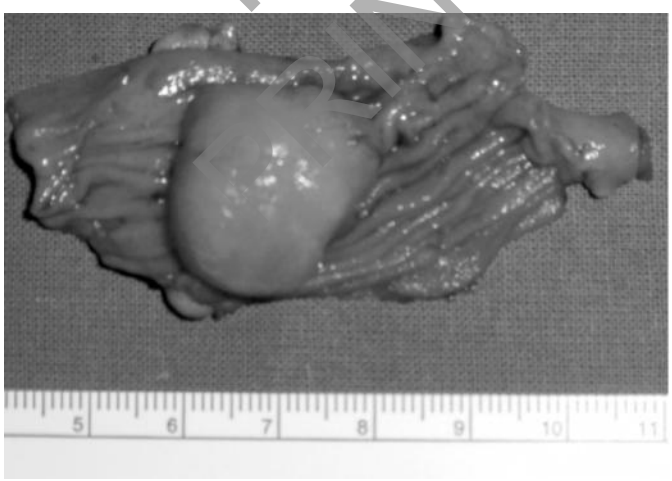

Fig. 8: Resected ileum with an intraluminal neoplasm.

was resected (Figg. 6-8). On definitive histology a rare form of malignant E-AML of the stomach and ileum with liver metastases was identified. Microscopic examination revealed cellular proliferation with some bands of spindle cells and some solid nests of epithelioid cells separated by thin-walled blood vessels. There was pronounced nuclear polymorphism with multinucleated cells and abundant eosinophilic, at times granular, cytoplasm. There were a few cells with vacuoles and a peripheral nucleus, morphologically much like adipocytes. In some areas there were numerous branching thick-walled blood vessels. Many mitotic figures, including atypical ones, were seen, as well as microfoci of necrosis. In one of the samples there was a small focus of neoplastic cells in the peritumoral tissue that was partly surrounded by smooth muscle tissue (but it was not possible to rule out blood vessel invasion). Immunohistochemical analysis of the

tumor cells showed intensely positive immunoreactivity for both smooth muscle actin and epithelial membrane antigen (EMA), and local immunoreactivity for CD 117 [Kit] and bcl2. Moreover, the tumor cells were positive for the melanocyte markers HMB-45 and A-103 (melA), as well as for desmin, S-100, and pan-cytokeratin..

The patient's postoperative course was uneventful, but approximately 2 months after discharge she returned to our institution because there was a nodule in her left breast (Fig. 9-10). Suspicion of a primary breast tumor led us to perform an excisional biopsy. However, on intraoperative histological assessment revealed the same morphological characteristics as those of the gastric, ileal, and hepatic tumors. Immunohistochemical analysis confirmed the diagnosis of E-AML of the breast.

Discussion

PEComas are defined by the World Health Organization (WHO) as mesenchymal tumors composed of perivascular epithelioid cells with special morphological and immunohistochemical characteristics. They belong to a family of heterogeneous tumors which have been genetically linked to the tuberous sclerosis complex (TSC) [1]. The differential diagnosis includes gastrointestinal stromal tumors (GIST), smooth muscle tumors, metastatic melanoma, and endocrine tumors. PEComa can mimic GIST when it has a spindle cell morphology or expresses CD117. Moreover, the morphology of leiomyomas or leiomyosarcomas can be very similar to that of PEComas. Only immunohistochemical analysis can provide a definitive diagnosis of PEComa, a metastatic melanoma must e ruled out especially when there is immunoreactivity for melanocytic markers. The ultrastructural characteristics such as the presence of glycogen in the cytoplasm, premalanosomes, thin filaments, occasional dense bodies, hemidesmosomes, and incomplete intracellular junctions, can help to determine the origin of these tumors. However ultrastructural analysis cannot be routinely performed [1,2]. Some authors state that E-AML with cellular atypia may be malignant. It has been shown that approximately one third of PEComas with these morphological characteristics produce local recurrence and/or distant metastases [2-5]. Recent metanalyses of 69 and 40 cases of E-AML, report that 38% and 26% of the tumors respectively were malignant [6,3]. The second study also reports a 10% mortality rate (n=4) and attempts to define tumor characteristics that predict the likelihood of malignancy: a high number of epithelioid cells, >70% nuclear atypia, a large number of mitoses (>2/10 high power field), and the presence of atypical mitotic figures, necrosis, and lymphovascular invasion [6,3]. According to the WHO guidelines PEComas should be considered malignant when their growth is characterized by local infiltration, marked hypercellularity, enlarged nuclei, hyperchromasia, extensive mitotic activity with atypical mitoses, and coagulative necrosis [1]. We reviewed the literature on PEComa and found 14 cases of disease in the gastrointestinal tract (n=14), the colon (n=5), the rectum (n=4), the small intestine (n=3), the stomach (n=1), the appendix (n=1). All the patients were female except for a 12-year-old boy suffering from cervical neuroblastoma, probably associated with TSC. The age of these patients ranged from 6-63 years, with an average age of 29 years. Tumor diameter ranged from 1.3 to 10 cm.

E-AML is a member of the PEComa family and most frequently found in the kidney and uncommon in other organs. Gastrointestinal E-AML is rare. PEComas of the gastrointestinal tract more often have histological characteristics of malignancy [1,2,7]. There are no reports in the literature of E-AML of the breast.

PEComas are extremely rare and before surgery it is often difficult to describe their biological behaviour. For these reasons as well as the difficulty in performing an adequate follow-up (due to the rarity of the disease and the absence of referral centers), there are no guidelines or evidence-based therapeutic protocols

A treatment approach proposed for these tumors is based on some characteristic findings on preoperative imaging that are thought to indicate malignancy [2]. Tumor diameter > 4cm is associated with a greater probability of malignancy and therefore with a worse prognosis, as shown in the literature [2]. Surgery is currently the treatment of choice for primary tumors, local recurrence, and metastases. Medical management with chemotherapy is used only for patients with advanced cancer who cannot benefit from surgery [8]. The literature demonstrates that traditional cytotoxic agents are ineffective. On the other hand, recent studies suggest that mTOR blockers are partially effective, but due to the rarity of the disease, no conclusive clinical trials are available [9,10].

Conclusion

Our case raises some questions that are difficult to answer. Had the patient developed multiple E-AML (in the kidney, stomach, ileum, breast and liver)? Was she suffering from malignant renal E-AML with metastases? Did she have multifocal (kidney stomach, ileum, breast) E-AML with liver metastases? If the theory of metastases is taken into consideration, what was the path of dissemination? The literature is of no assistance in providing a clear answer.

Riassunto

L'angiomiolipoma (AML) è un tumore mesenchimale benigno composto da vasi sanguigni anormali in un contesto di fibre muscolari lisce e tessuto adiposo.

Appartengono alla famiglia dei Perivascular Epithelioid Cells Tumors (PEComi). La variante epitelioide (E-AML)

è estremamente rara come quella maligna, soprattutto nel tratto gastrointestinale. Riportiamo un raro caso di E-AML maligno con localizzazione renale, gastrica, ileale, epatica e mammaria trattata con chirurgia resettiva. Risulta spesso complicato definire preoperatoriamente il comportamento biologico dei PEComi: attualmente la chirurgia è il trattamento di scelta per i tumori primitivi, per le recidive locali e per le metastasi.

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