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Case report

Multifocal retroperitoneal and pelvic PEComas mimicking liposarcoma: A case report and review of literature ☆☆☆

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ABSTRACT

Perivascular epithelioid cell neoplasms (PEComa) constitute a rare, but increasingly recognized family of seemingly distinct mesenchymal tumors which can occur in any part of the body. Due to their rarity, radiological descriptions of PEComas in the current literature are few and non-specific, making diagnosis difficult, though some common imaging features have been reported. We present an unusual case of multifocal retroperitoneal and pelvic PEComas, mimicking liposarcoma, subsequently treated with open surgery.

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Introduction

Perivascular epithelioid cell tumors (PEComas) are a group of rare neoplasms, defined in the World Health Organization Classification of Tumors in 2002 as “mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells” [1]. The PEComa family mainly includes angiomyolipomas (AML), clear cell “sugar” tumors (CCST) of the lung, lymphangioliomyomatosis (LAM),

as well as similar but less well-characterized tumors of other anatomic regions, for which the term “perivascular epithelioid cell tumors not otherwise specific” (PEComa-NOS) has been proposed. Such incidences of PEComa-NOS have been described in a variety of locations, including the retroperitoneum, uterus, pancreas, liver, bone, and multiple other visceral and soft-tissue sites [2]; of these, the retroperitoneum and uterus are consistently some of the most common sites of involvement [3,4].

Given their relatively new status and rarity, many open questions about PEComas remain, including their etiology and

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histogenesis; differentiation between benign and malignant PEComas on the basis of their imaging and histopathological features; and pre-operative characteristics that may help with risk stratification and treatment strategies. We report an unusual case of a patient with multiple PEComas presenting in the retroperitoneum and pelvis, mimicking the appearance of liposarcoma.

Case presentation

A 46-year-old Chinese woman with a background of end-stage renal failure, being treated with dialysis, was referred to the surgeons for a large retroperitoneal mass incidentally noted on a computed tomography (CT) study of the liver. The patient was asymptomatic, with no indication of weight loss or anorexia, and exhibited a soft and non-tender abdomen, with no palpable abdominal mass present. Of note, on previous examinations she was found to have cutaneous manifestations of tuberous sclerosis, including adenoma sebaceum, subungual fibromas, and a Shagreen patch on her back. Laboratory tests were non-contributory.

A contrast-enhanced CT study of the thorax, abdomen and pelvis revealed a large mass epicentered in the left retroperitoneum (Fig. 1). This was well-defined, heterogeneous with macroscopic fat and vessels within, and exhibiting intraleisional enhancement. It was closely related between the abdominal aorta and left kidney, but with no imaging evidence of encasement or involvement otherwise. In addition, a couple of smaller lesions were seen in the pelvis bilaterally, exhibiting similar imaging features; the larger one of these was closely related to the uterus, though not arising from it. No evidence of suspicious metastatic lesions or lymphadenopathy was seen. The initial radiological impression was that of a liposarcoma.

A CT-guided biopsy was performed for the left retroperitoneal and left iliac fossa masses. The resulting histological examination showed a mixture of mature adipocytes, blood vessels, and proliferation of spindle cells seen aggregating around the vessels. The spindle cells showed moderate amounts of clear, brightly eosinophilic to clear vacuolated cytoplasm, as well as ovoid- to spindle-shaped nuclei. No mitotic activity or significant cytological atypia was noted. On immunohistochemical staining, the spindle cells, as well as some of the adipocytes, were positive for SMA, HMB-45, and Melan-A. Some of the spindle cells also stained positively for desmin. S-100 was highlighted in the adipocytes. The histological diagnosis thus revealed a PEComa.

The patient subsequently underwent open surgery for resection of the left retroperitoneal tumor, with en bloc left nephrectomy; the pelvic masses were also removed. Complete resections with negative margins were achieved. Histological examination of the resected tissue specimens revealed similar findings to the above (Fig. 2). Scattered cells with degenerative atypia were also seen this time, but with no mitotic activity. A small portion of the left retroperitoneal tumor was closely related to the resected kidney, which contained a tubule lined by bland columnar epithelium, surrounded by a cambium-like layer of stromal cells, and bundles of myoid-like spindle cells.

These myoid cells stained strongly for SMA, some for Melan-A; the cambium-like layer stained for ER and CD10. Overall, no evidence for malignant transformation was seen.

Discussion

The perivascular epithelioid cell (PEC) was first described by Bonetti et al in 1992. Its pathological features, including strong immunoreactivity to the melanocyte marker, HMB-45, were deemed commonalities linking several rare neoplasms in unrelated locations [2,5]. In 1996, Zamboni et al coined the term “PEComa” to distinguish them [6].

Clinical features and epidemiology

PEComas may be encountered incidentally in imaging studies, as they can be asymptomatic. When symptomatic, they may present with pain or discomfort in the area affected, as well as loss of weight [7]. Site-specific presentations, for instance bloody discharges in uterine PEComas, may also be seen [8]. Patients most commonly present between 38.9 to 56 years of age, at a median of 43 years of age [2,7]. There is a strong female predilection; in previous reviews of reported cases, 54–86.9% of PEComas occurred in females, even after accounting for sex-specific locations (prostate, uterus) [7].

Tuberous sclerosis complex (TSC)

Autosomal dominant mutations of the TSC1 or TSC2 tumor suppressor genes lead to tuberous sclerosis, characterized by a multi-system development of benign tumors (such as subependymal giant cell tumors and cardiac rhabdomyomas), as well as seizures, cognitive delays, and cutaneous findings [9–11]. Some of these were observed in our patient, compatible with a presumptive clinical diagnosis of TSC.

Some entities within the PEComa family have a strong association with TSC; for example, 20% AMLs occur in association with TSC, while approximately 75% of TSC patients exhibit AMLs [12]. While the association is less tightly linked to the rest of the PEComa family, mutations of TSC genes have been observed in a significant number of PEComas, both sporadically and within the tuberous sclerosis complex; TSC has thus far been associated in up to 6.25% of affected patients [7,10].

Radiological characteristics

While radiological descriptions of PEComas in the current literature are non-specific, some commonalities exist. These include well-defined borders, and a regular shape, especially in those with non-aggressive histology [3,13,14]. Previous retrospective studies described masses with a mean tumor diameter of 5.1–11.0 cm. They were hypo- to isodense to skeletal muscle on non-contrast CT, some of which exhibited fat attenuation. Contrast-enhanced CT showed intense, heterogeneous enhancement in both arterial and venous phases; in the delayed phase, they were slightly hypodense. On magnetic resonance imaging (MRI) studies, they were hypo- to

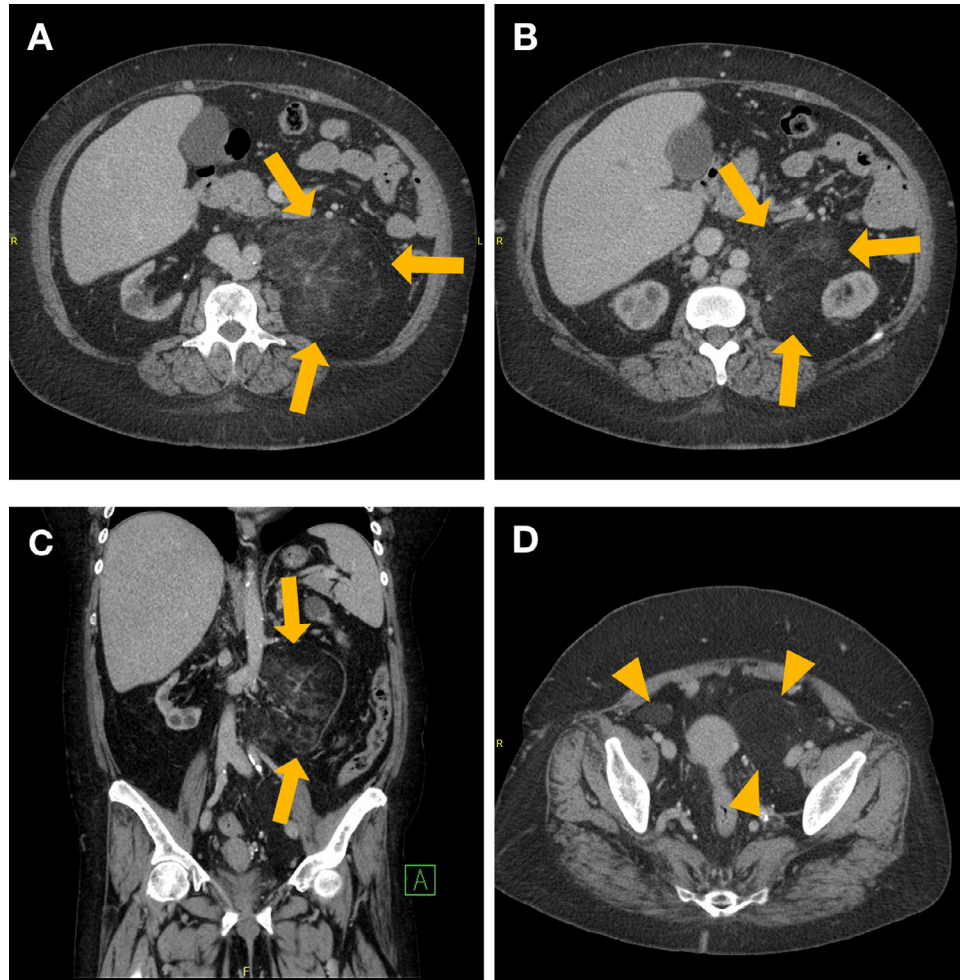


Fig. 1 – CT images revealed a large left retroperitoneal mass (arrows), measuring 7.4 × 8.5 × 10.4 cm (transverse × anteroposterior × craniocaudal dimensions). A) Left retroperitoneal mass enhancing heterogeneously, with macroscopic fat and vessels within. B) Left retroperitoneal mass closely related to the left kidney. C) Coronal view of the left retroperitoneal mass shows its craniocaudal extent. D) Similar and smaller lesions in the pelvis bilaterally, measuring 6.3 × 7.0 × 9.0 cm in the left iliac fossa and closely related to the uterus, and 2.6 × 1.5 × 2.7 cm in the right iliac fossa (arrowheads).

isointense on T1-weighted imaging, and heterogeneously hyperintense on T2-weighted imaging; a minority of the studied masses demonstrated fat density. Contrast sequences also showed heterogeneous enhancement in both arterial and venous phases, with slight hypointensity on delayed imaging. Some malignant tumors showed evidence of local invasion, for example in the renal vein and renal fascia. Larger tumors exhibited central necrosis, and a small proportion showed hemorrhage or dystrophic calcification [3,4].

Metastatic deposits are most commonly reported in the lungs, followed by liver and peritoneum [4,7]. Other sites have also been implicated, such as the central nervous system, ovary, adrenal glands, skin, bones, mesentery, and lymph nodes [7]. The site of origin may have an influence on the first site of metastasis; for example, 77.8% of tumors with the primary site as the kidneys or mesentery initially metastasize to the liver, while tumors involving the adrenal glands and

retroperitoneal soft tissues first spread to the peritoneum and lungs [4].

The differential diagnosis is broad, depending on the site of origin. In the retroperitoneum, the main differential is liposarcoma, which is the most common primary retroperitoneal sarcoma, accounting for 40% of cases [15]. Most are large at presentation, occurring in the 6th to 7th decades of life, with no gender predilection. They show macroscopic fat, varying in composition based on the subtype; for example, well-differentiated liposarcomas feature relatively smooth margins and >75% fat composition, whereas in the dedifferentiated subtype there may be increased proportions of poorly-defined non-lipomatous tissue, with no fat in up to 20% of cases [16]. Enhancing septa may be seen, tending to be nodular. Presence of calcification is considered a poor prognostic feature [15].

In the kidney, the main differential is AML, with varying amounts of angiogenic, myogenic, and fatty elements. A fat-rich appearance is most common, though the lesion may often

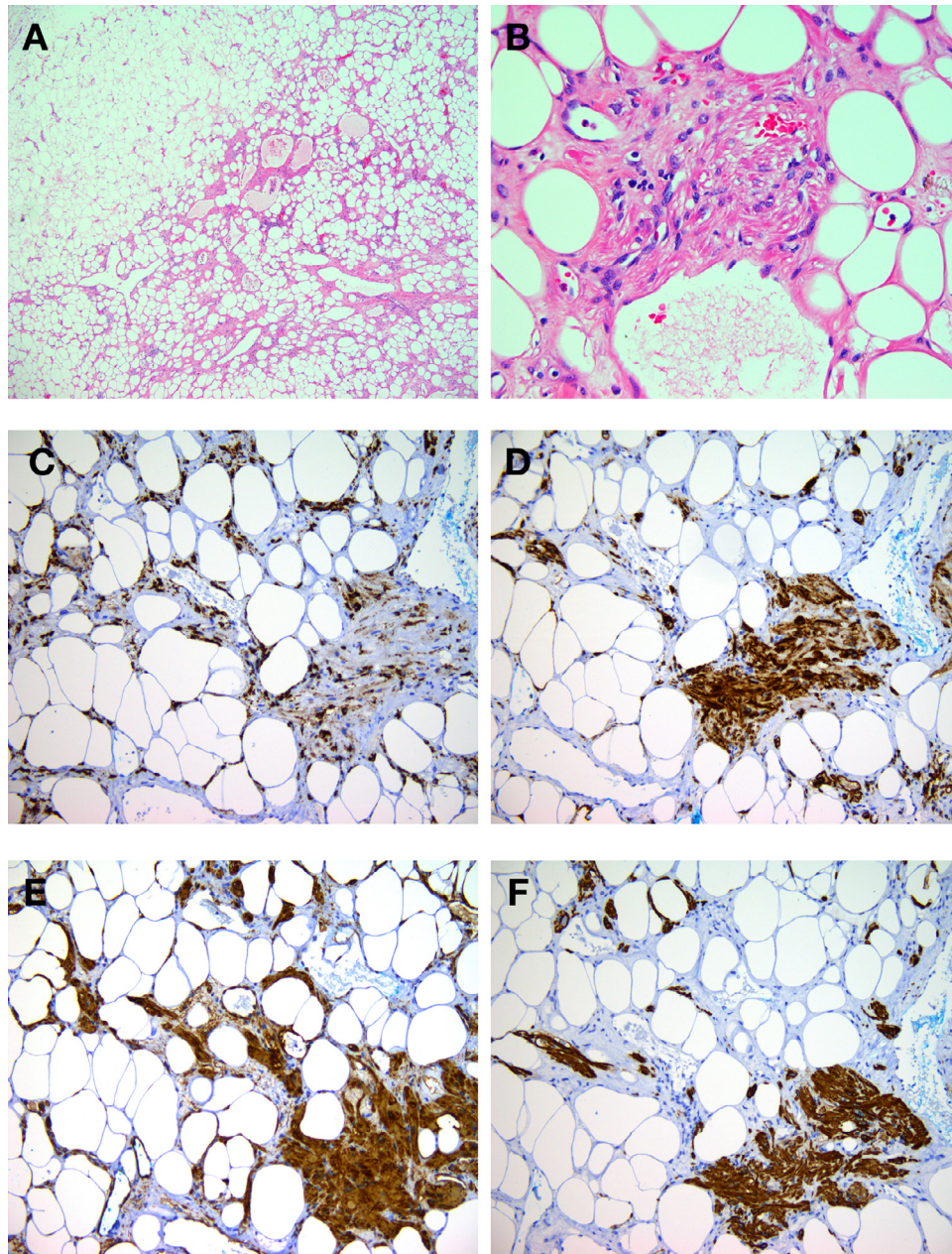


Fig. 2 – Pathological and immunohistochemical images from the biopsy/resection specimens. A) Lesional tissue comprising admixture of mature adipocytes, smooth muscle bundles, and dilated blood vessels (H&E stain, $\times 5$ magnification). B) Vacuolated smooth muscle bundles surrounding the abnormal blood vessels (H&E stain, $\times 40$ magnification). C) HMB-45 stain. D) Melan-A stain. E) SMA stain. F) Desmin stain.

appear with a hyperdense collection obscuring the fatty component due to presence of perirenal or intratumoral hemorrhage [9]. Calcification and necrosis have also been observed, raising the possibility of fat-containing renal cell carcinoma [17]. As AMLs most commonly originate in the kidney, radiological signs to that effect, including the “claw” sign, or “embedded organ sign”, should be appreciated. In our patient, while the mass was closely related to the kidney, there was no such imaging evidence of renal involvement. It may be speculated that the appearance of shrunken kidneys and relative

lack of renal parenchyma, due to the patient’s end-stage renal failure, would help to explain this absence. However, a CT-guided biopsy scan that was available from almost 10 years prior showed retrospectively that the mass was present at that time, much smaller and epicentered in the left retroperitoneum, showing a thin but clear fat plane between it and the left kidney, which was itself unremarkable in appearance (Fig. 3).

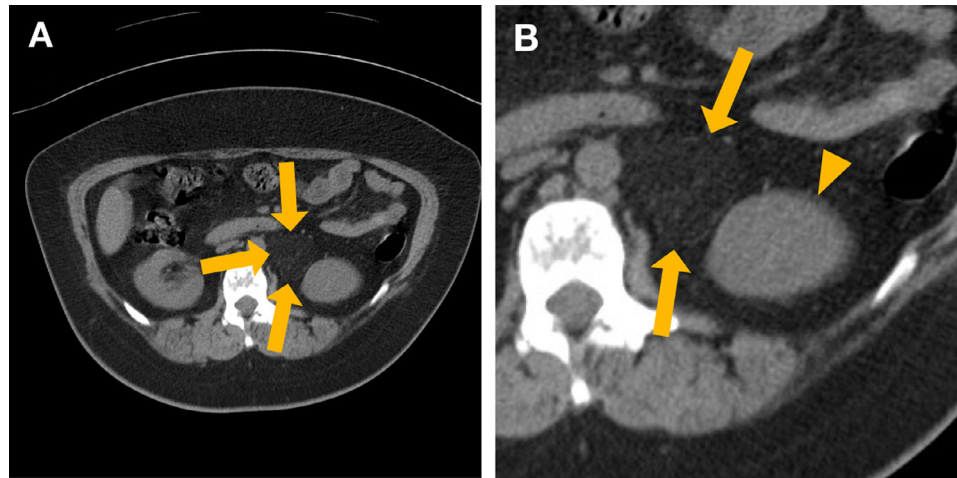


Fig. 3 – Non-contrast CT scan of the patient from an image-guided biopsy 9 years prior. A) Retrospectively, the left retroperitoneal mass was visible (arrows), much smaller and showing some degree of fat stranding; here it measures 3.4 × 3.8 cm in the axial dimensions. B) A very thin stripe of fat is visible between the left retroperitoneal mass (arrows) and left kidney (arrowhead); the kidney itself was unremarkable at the time. No evidence of renal origin or involvement is apparent, with no claw sign or embedded organ sign present.

Pathological characteristics

PEComas are characteristically composed of nests or bands of mainly epithelioid and occasionally spindle-shaped cells, seen surrounding blood vessels [7,9,10]. PECs exhibit clear to granular eosinophil cytoplasm, and round to oval, centrally-located nuclei and inconspicuous nucleoli. They can also become vacuolized, gaining the feature of an adipocyte [10]. Currently, no normal cell type counterpart is known [2,18].

Immunohistochemical staining plays an essential role in diagnosis, with co-expression of melanocytic markers in epithelioid cells and smooth muscle markers in spindle cells. Expression of melanocytic markers almost always includes HMB-45 (92-100%) and less commonly, Melan-A/Mart1 (23-88%); a minority stain for S-100 (8-33%). For smooth muscle makers, this includes smooth muscle actin (SMA) (59-93%), and desmin (36-100%) [7].

Management & Prognosis

Many PEComas follow a benign course, sufficiently curable with surgical resection alone; a minority have shown aggressive behavior, with local recurrence and/or distant metastases [3,4,19]. As their natural history is not well-characterized, periodic long-term clinical and radiological surveillance is strongly recommended after initial treatment.

There are no current established standards for determining malignancy and prognostication of PEComas, made difficult by their rarity. Folpe et al have proposed a set of criteria in order to help stratify them into “malignant”, “uncertain malignant potential”, and “benign” risk categories. A number of high-risk features have been identified, including: Size >5 cm, histologically infiltrative growth pattern, high nuclear grade and cellularity, mitotic rate >1/50 HPF, presence of necrosis, and vascular invasion. Of these, tumor size and high mitotic rate appear to be the best predictors for aggressive behavior [2]. In our case, the masses were sufficiently large to

warrant some concern, and would have been considered pre-operatively in the category of “uncertain malignant potential”.

Malignant PEComas lack a reliable curative therapy and are usually fatal, as chemotherapy and radiotherapy have thus far failed to show significant benefit [4,7,18]. However, activation of the mammalian target of rapamycin (mTOR) signaling pathway has been demonstrated in these tumors, and more recently, mTOR inhibitors have shown increasingly successful application for medical therapy [20]; they may thus have an emerging role in locally advanced, unresectable disease, or in metastases.

Conclusion

This case report demonstrates that the diagnosis of primary PEComa should be considered for large masses in the retroperitoneum and pelvis, as these are some of the most common sites of occurrence. The index of suspicion should be raised in the presence of TSC. Pathological features and immunohistochemical markers are essential for diagnosis, and along with the radiological findings, may help with risk stratification and management. Given the possibility of multifocality as demonstrated in this report, as well as malignant potential, a thorough search for synchronous PEComas as well as metastases is advised.

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