Abdominal Radiology

© Springer Science+Business Media New York 2015
Published online: 6 January 2016

Abdom Radiol (2016) 41:368–376
DOI: 10.1007/s00261-015-0568-8

Update on the imaging of malignant perivascular epithelioid cell tumors (PEComas)

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Abstract

Malignant perivascular epithelioid cell tumors (PEComas) are a histologic group of mesenchymal neoplasms that share a distinctive histological phenotype, the perivascular epithelioid cell. These tumors are known for their perivascular distribution. Malignant PEComas have a female predominance and are associated with aggressive disease and poor prognosis, making timely diagnosis critical to management. Imaging features of malignant PEComas are nonspecific and mimic other benign and malignant neoplasms. Surgery is the mainstay in the management of malignant PEComas. Promising novel molecular targeted therapies like m-TOR inhibitors have been shown to be effective in the metastatic setting. The aim of this review is to familiarize radiologists with the imaging appearances of and potential therapies for primary and metastatic malignant PEComa.

Key words: Malignant PEComa—CT—MRI—PET/CT

Neoplasms of the perivascular epithelioid cell (PEComas) are rare mesenchymal neoplasms that share specific histologic morphology of association with blood vessels, and hallmark co-expression of human melanocytic black (HMB-45) and smooth muscle cell markers. The PEComa family includes a wide spectrum of tumors including renal angiomyolipoma (AML), pulmonary lymphangioleiomyomatosis (LAM), clear cell sugar tumor of the lung (CCTL), clear cell myomelanocytic tumor of the ligamentum teres (CCMMT) as well as clear cell tumors of the rectum, retroperitoneum, thigh, heart, uterus, and pancreas [1]. Although the majority of PEComas are benign, small subsets of the so-called malignant PEComas exhibit aggressive behavior, which can resemble those of soft tissue sarcomas like leiomyosarcoma, gastrointestinal stromal tumor, and rhabdomyosarcoma.

Malignant PEComas are characterized at histopathology by any two of the following criteria: larger than 5 cm in size, high nuclear grade and cellularity, mitotic rate >1 per 50 high-power fields, and the presence of necrosis or vascular invasion [2]. The histogenesis of malignant PEComas is uncertain; however, some studies suggest that a benign PEComa can develop malignant potential several years after the primary diagnosis [3]. It is now known that *TFE3* gene rearrangement in some PEComas can be associated with malignant histological features [4]. Malignant PEComas have poor outcome with tendency toward local recurrence and distant metastasis. Recent advances in molecular genetics have shown that inhibitors of mammalian target of rapamycin (m-TOR) can be effective in some patients with malignant PEComa [5].

Literature on the imaging features of primary and metastatic malignant PEComa is scant. With increasing awareness of the clinical and pathologic features of this entity, it is important for radiologists to be familiar with the appearance of malignant PEComas across multiple imaging modalities and the potential therapies for primary and metastatic malignant PEComa. The goal of this review is to provide a primer to radiologists of the imaging features and management of primary and metastatic malignant PEComa. The more common type of PEComas like AML will not be discussed in the article.

Clinical and pathologic features

PEComas were first described in 1992 by Bonetti et al. [6] and established as a new category in the World Health Organization Classification of Tumors in 2002 [7]. Malignant PEComa is a recently described entity with

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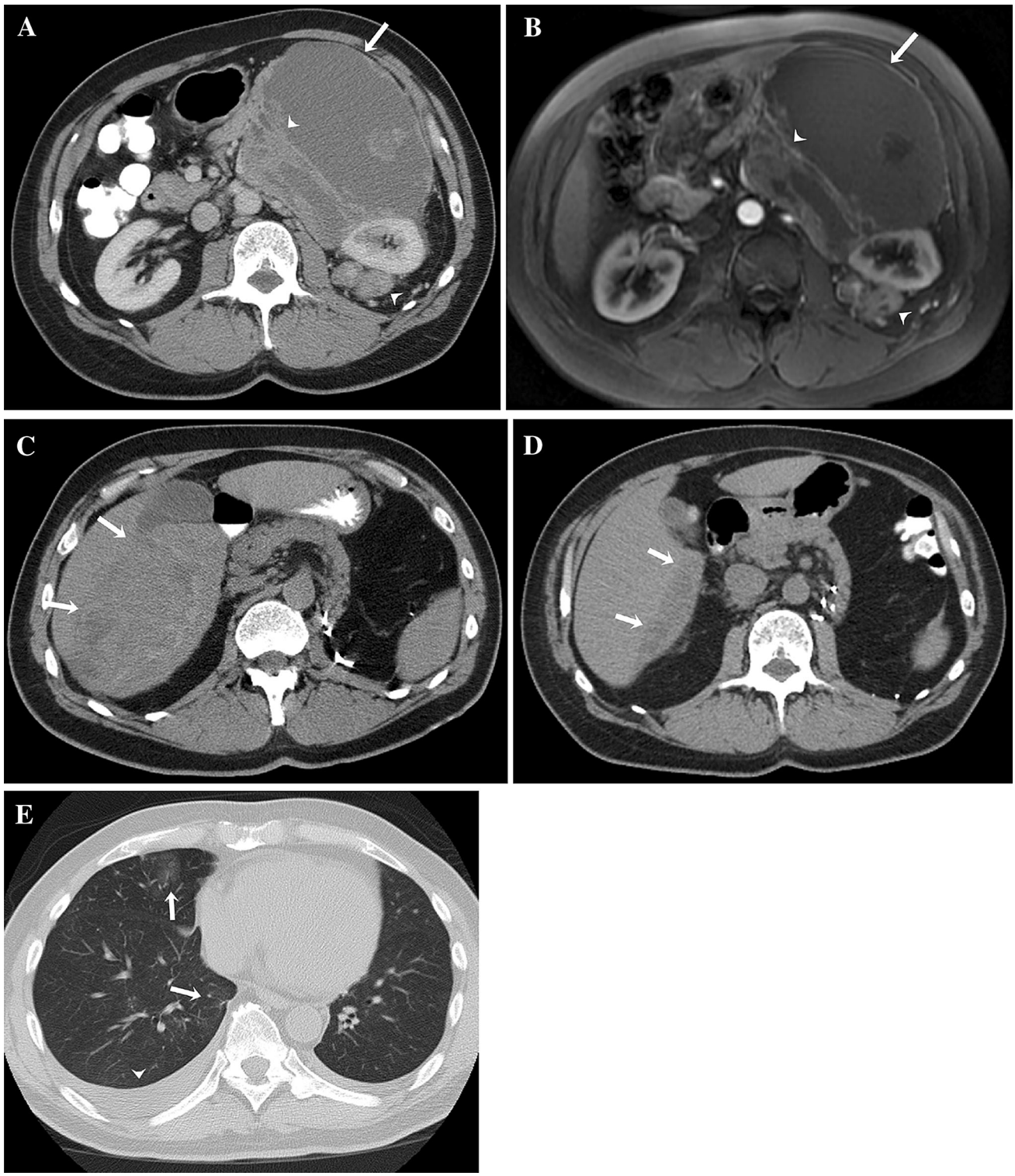

scant literature on demographic and clinical features exclusively reported for this entity. Given that malignant PEComas are a spectrum of their benign counterparts, many of the clinical features of benign PEComa are applicable to the malignant PEComa. PEComas in general are related to tuberous sclerosis complex (TSC) sharing mutations in the TSC genes [8, 9]. PEComas predominantly affect the female population and occur in a wide distribution of ages, with one article suggesting that as many as 78% of cases occur in women with an age range of 3–97 years; however, the most common age group is between 50 and 60 years [10]. PEComas have been reported in a wide variety of anatomic sites [11].

◀ **Fig. 1.** A 59-year-old man with malignant perivascular epithelioid cell tumor (PEComa) of the left kidney. **A** Axial contrast-enhanced CT image shows a large heterogeneous solid-cystic mass lesion arising from the left kidney (*arrow*) with enhancing components (*arrowheads*). **B** Axial fat-suppressed contrast-enhanced T1-weighted image shows a large necrotic mass (*arrow*) with heterogeneously enhancing components (*arrowheads*). There was no renal vein invasion or locoregional lymphadenopathy in spite of the large size. The patient underwent left radical nephrectomy and pathology was consistent with a PEComa. **C** Axial unenhanced CT performed 5 years later during surveillance showed a large subcapsular liver mass (*arrows*). Note the surgical clips in the left retroperitoneum related to prior nephrectomy. Biopsy of the mass confirmed metastatic PEComa. The patient was treated with the mammalian target of rapamycin (m-TOR) inhibitor, sirolimus. **D** Axial unenhanced CT image after 3 months of treatment shows a significant decrease in the subcapsular metastatic lesion (*arrows*). **E** Axial unenhanced lung window CT image at the same time shows patchy ground-glass opacities (*arrows*) in right lower lobe with right pleural effusion (*arrowhead*) suggestive of m-TOR pneumonitis.

Microscopically, similar to benign PEComa, malignant PEComa consists of perivascular epithelioid cells (PECs), which are identified by their perivascular location and frequent radial arrangement around a central vessel in nests or sheets. PECs have clear to lightly eosinophilic cytoplasm with small central normochromatic nuclei, which distinguish them from smooth muscle, which is densely eosinophilic. PECs are also characterized by positivity to melanocytic markers including HMB-45, tyrosinase, microphthalmia transcription factor, Melan-A, and NKI/C3 as well as smooth muscle markers including calponin, and smooth and pan muscle actin. However, for both benign and malignant PEComas, HMB-45, Melan-A, and microphthalmia transcription factor are the most sensitive melanocytic markers [12, 13]. Histological features unique to malignant PEComa include high nuclear grade and cellularity, mitotic rate >1 per 50 high-power fields, and the presence of necrosis or vascular invasion [2].

PEComas of the past and the present

In the past, the term PEComa was synonymous with AML. However, recent pathologic studies suggest reason to differentiate classic AMLs from epithelioid (or monomorphic) AMLs, which more closely resemble malignant PEComas. Classic AMLs are composed of adipose tissue and smooth muscle cells that can resemble benign PECs morphologically and behave in a nonaggressive manner [14, 15]. On imaging, classic AMLs demonstrate macroscopic fat attenuation and signal on CT and MRI, respectively. In contrast, epithelioid cell nests with relative paucity of fat and vessels mark the histology of epithelioid AMLs (EAMLs). These tumors are classified as potentially malignant lesions with potential for local invasion, post-operative recurrence, and metastatic spread. On imaging, EAMLs are typically large, extend beyond the renal capsule, and can invade the draining renal vein [16]. Heterogeneous enhancement is common as is necrosis and hemorrhage. Occasional near-absent intra-tumoral fat makes prospective CT and MRI diagnoses of EAML impossible [16]. In practice, EAMLs should be considered in the differential of an invasive mass with macroscopic fat.

Imaging features of primary malignant PEComa

The imaging features of malignant PEComa are nonspecific and indistinguishable for their benign counterparts in the absence of adjacent organ invasion or locoregional metastasis. Imaging studies such as CT, MRI, US, and PET can however help in the detection of tumor location, size, and relationship with surrounding tissues. Common sites of origin of malignant PEComas include the kidneys (Fig. 1) and retroperitoneal soft tissues, as well as the uterus and cervix of the female genital urinary tract (Fig. 2). Other less common sites of origin include the liver (Fig. 3), gallbladder (Fig. 4), small bowel mesentery, pancreas, and soft tissues (Figs. 5, 6) [11].

Computed tomography

The most common CT findings of malignant PEComas are of a well-circumscribed visceral or retroperitoneal mass that is hypodense to isodense to the surrounding musculature on non-contrast studies and avidly enhancing on contrast-enhanced CT (Fig. 4). Enhancement patterns are variable, with heterogeneous enhancement being more common than homogenous enhancement (Fig. 6) [11]. The presence of macroscopic fat within the tumor may mimic much common retroperitoneal tumor, e.g., liposarcoma, and the distinction between these entities on imaging is usually impossible [17]. Punctate calcifications are less frequently present, although the significance of calcification is uncertain in the current literature. Hepatic PEComa generally has well-defined margins and shows heterogeneous enhancement on arterial phase of contrast-enhanced CT and become iso- to hypodense to adjacent hepatic parenchyma on portal venous phase and delayed phase [18]. The imaging features of hepatic PEComas can mimic focal nodular hyperplasia (FNH), hemangioma, adenoma, and malignant tumors like hepatocellular carcinoma and metastases. Some studies suggest hypervascularity and arteriovenous connections as distinguishing features, particularity in hepatic PEComas (Fig. 3) [19]. Areas of non-enhancement and low attenuation are likely to represent necrosis, which is frequent (Fig. 1).

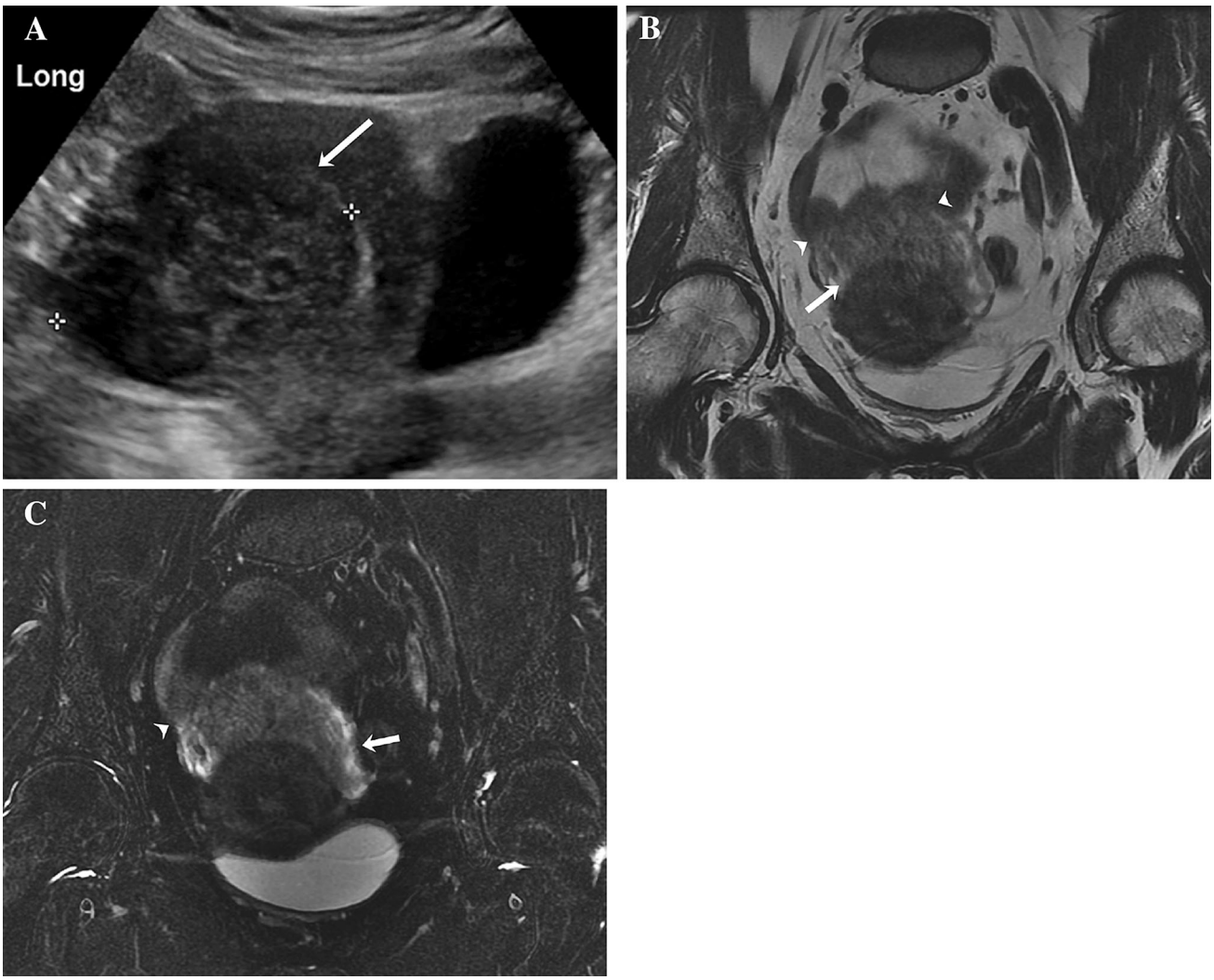

Fig. 2. A 48-year-old woman with malignant PEComa of the uterus. **A** Transabdominal gray-scale ultrasound image shows heterogeneous mass lesion arising from anterior wall of uterus (*arrows*). This was thought to most likely represent an exophytic fibroid arising from the uterine fundus. On diagnostic laparoscopy, the mass was arising from the uterus but adherent to the small bowel. **B** and **C** Coronal T2-weighted (**B**) and STIR (short-tau inversion-recovery) MR images show loss of fat planes between the mass (*arrows*) and adjacent small bowel loops (*arrowheads*). The mass was resected en bloc with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial small bowel resection. Pathology of the mass was consistent with malignant PEComa.

Magnetic resonance imaging

On MRI, most tumors are isointense to slightly hypointense to skeletal muscle on T1-weighted images. Notable exceptions are PEComas associated with renal AML as detailed previously, which demonstrate T1 shortening secondary to the presence of macroscopic fat, and hemorrhagic PEComas, which can be seen as hyperintense foci on fat-suppressed T1-weighted images. Heterogeneous hyperintense signal on T2-weighted images is characteristic (Fig. 2); however, smaller lesions usually show more homogenous hyperintensity on T2-weighted images (Fig. 5). Occasionally, areas of T2 shortening can be seen due to hemorrhage or proteinaceous content. After gadolinium administration, malignant PEComas enhance avidly (Fig. 5). Non-enhancing areas representing necrosis are frequently seen due to their large size. Occasionally, they can have the appearance of multi-septated cystic mass (Fig. 1). The majority of the hepatic PEComas are solitary [19]. On MRI, they demonstrate heterogeneous hypointensity on T1-weighted images and hyperintensity on T2-weighted images usually with well-demarcated tumor margins [18]. On dynamic contrast-enhanced MRI, they show variable and heterogeneous enhancement, including persistent enhancement in delayed phase, which can potentially confuse them with benign lesions like hemangioma and FNH [19].

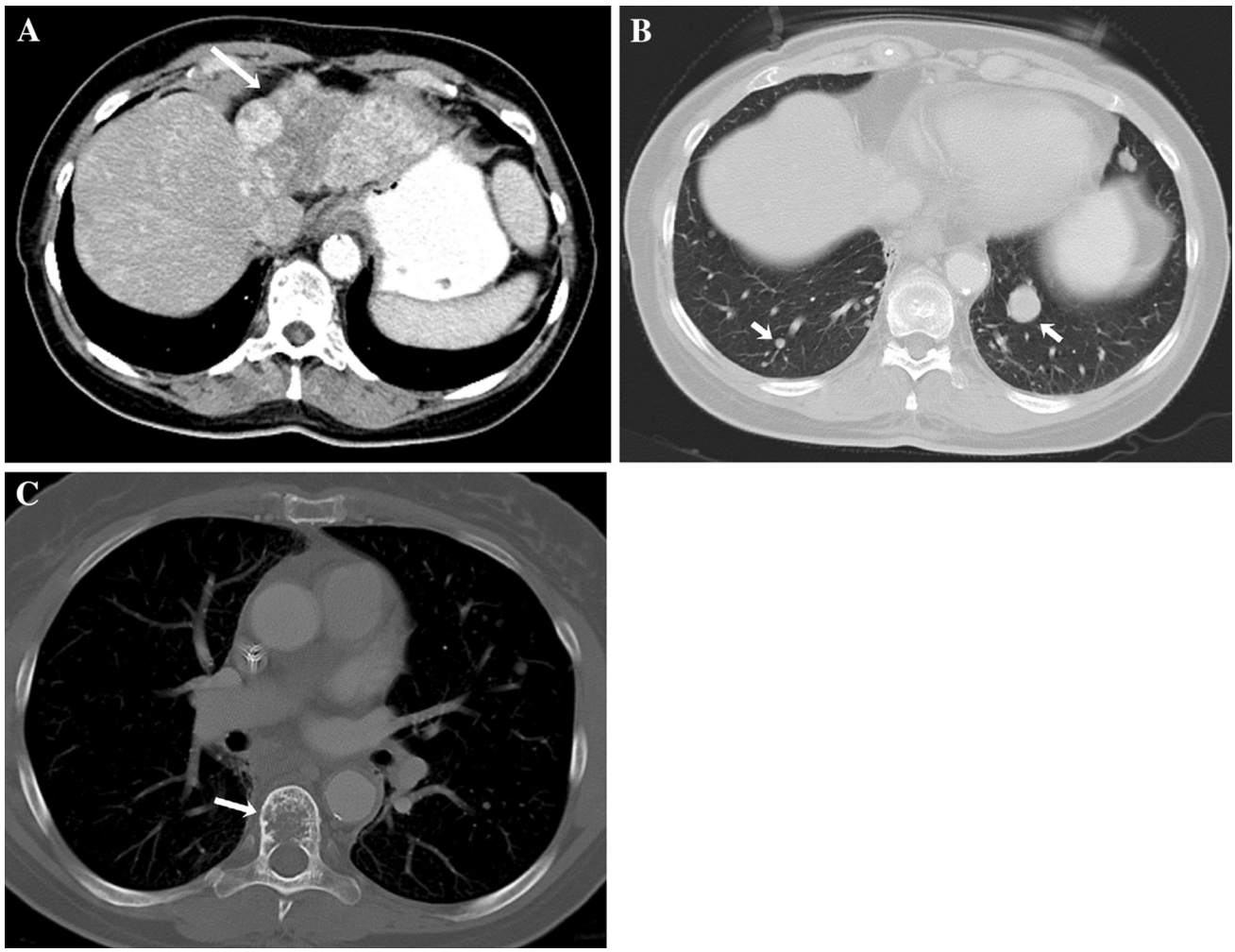

Fig. 3. A 64-year-old woman with malignant PEComa of liver with pulmonary and osseous metastases. **A** Axial contrast-enhanced CT image shows a large heterogeneously hypervascular lesions with ill-defined margins in the left lobe of the liver. **B** and **C** Axial contrast-enhanced CT images of the chest in lung (**B**) and bone (**C**) window settings show multiple bilateral pulmonary metastases (*arrows* in **B**) and an irregular lytic lesion involving the T8 vertebra (*arrow* in **C**) suggestive of osseous metastasis.

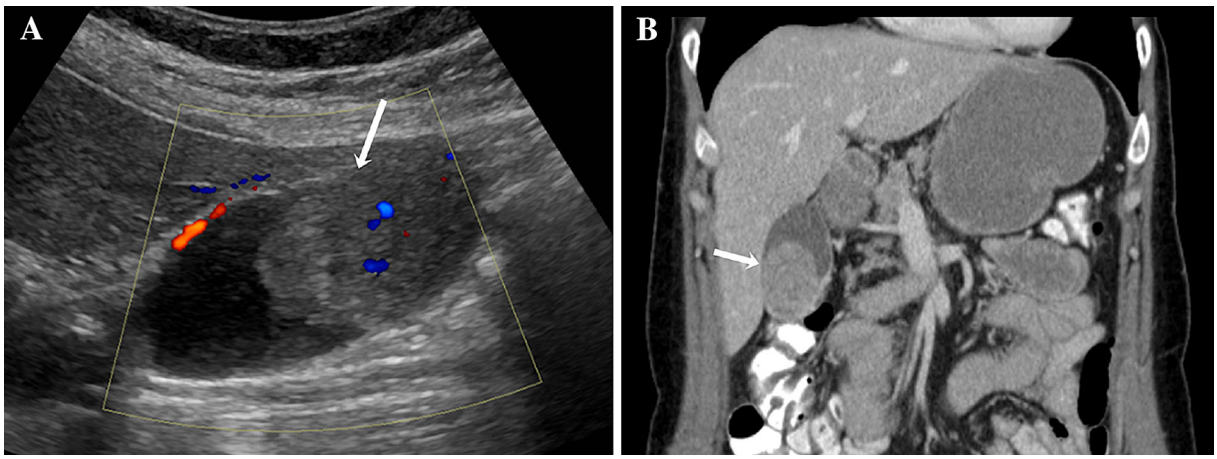

Fig. 4. A 46-year-old woman with malignant PEComa arising from the gallbladder. **A** Gray-scale ultrasound with Color Doppler image of the gallbladder shows a well-circumscribed intraluminal mass with mild internal vascularity (*arrow*). **B** Axial contrast-enhanced CT image shows a polypoidal intra-luminal enhancing lesion arising from the gallbladder fundus (*arrow*).

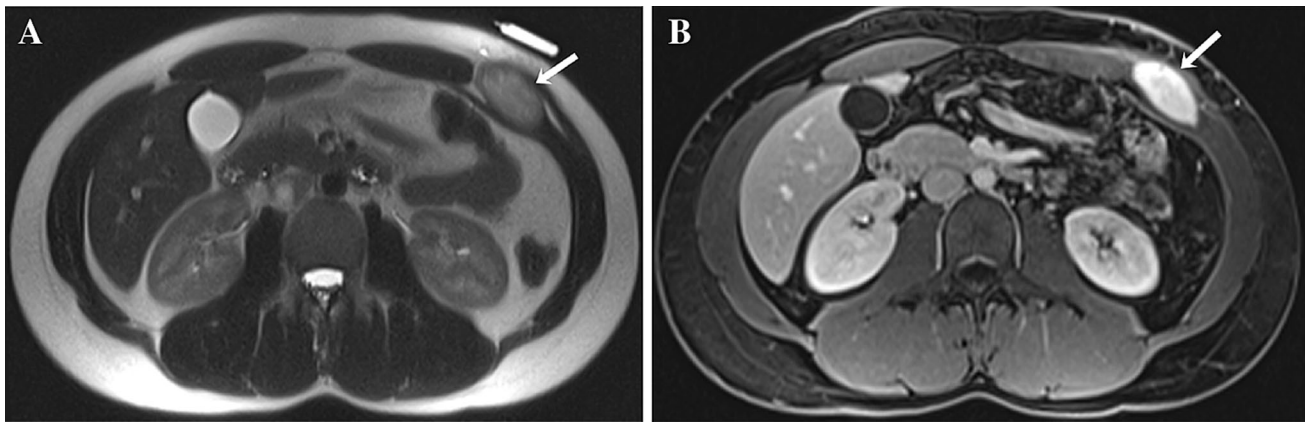

Fig. 5. A 30-year-old man with malignant PEComa in the left lower abdominal wall. **A** Axial fat-suppressed T2-weighted MR image shows a well-defined T2 hyperintense lesion in the intermuscular plane lateral to the left rectus abdominis muscle (*arrow*). **B** Axial contrast-enhanced fat-suppressed T1-weighted MR image shows homogenous enhancement of the lesion (*arrow*).

Ultrasonography and positron emission tomography/computed tomography

Although ultrasound is not commonly performed, malignant PEComas are well-circumscribed heterogeneously echogenic masses that can be seen displacing adjacent vasculature (Fig. 2). Hypoechoic areas representing necrosis and cystic changes are commonly seen in large tumors. Although avid arterial enhancement is a key cross-sectional imaging feature, color Doppler flow is mild to absent in renal, gallbladder, and uterine PEComas (Fig. 4) [11, 19].

18F-fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) can be useful in the work-up of primary PEComa as well as the detection of metastasis as these tumors tend to be moderate-intensely FDG avid (Fig. 7). Recent studies have also demonstrated the role of 18F-FDG PET/CT in differentiating malignant and benign PEComas. Malignant PEComas and their metastatic foci usually show intense FDG uptake, while benign PEComas exhibit low or negative FDG uptake [20, 21]. FDG PET/CT is also a valuable tool for detecting unsuspected metastatic disease and defining the reassessment of the patient after chemotherapy [20–23]. The role of advanced modalities like combined PET/MRI is unclear due to lack of established literature.

Imaging features of recurrent and metastatic malignant PEComa

Local recurrences after surgical resection of malignant PEComa can be seen as heterogeneous masses in the surgical bed. Metastatic lesions are typically found in the lungs (Fig 3), liver (Figs. 1, 7), and peritoneum and less likely in the lymph nodes, bones (Fig. 3), brain (Fig. 6), and muscles [11]. Metastatic lesions in malignant PEComa have nonspecific imaging features with variable heterogeneous enhancement on arterial phase imaging, and less so on portal venous and delayed phases. Pulmonary metastases manifest as multiple bilateral pulmonary nodules of varying size (Fig. 3). Peritoneal metastasis is seen as discrete peritoneal nodules and serosal implants.

Imaging approach to malignant PEComa

The diagnosis of a malignant PEComa is based on histopathology. Diagnosing malignant PEComas on imaging alone is a challenging task as there are no pathognomonic imaging features to distinguish them. However, there are specific scenarios where malignant PEComa can be considered. For example, the differential for a large heterogeneously enhancing exophytic renal mass should include renal cell carcinoma (RCC). Non-RCC tumors also in the differential include transitional cell carcinoma, lymphoma, and sarcoma. All of these except sarcomas are typically associated with enlarged regional lymph nodes. Since PEComas are derived from the same mesenchymal line as sarcomas, PEComas are also characterized by the relative absence of lymphadenopathy. This principal was recently investigated in a study of 41 patients with renal epithelioid PEComas, which found that the liver (63%) and lung (25%) were the most common sites of disease spread, while lymphadenopathy was present in less than a quarter of patients [24]. Thus, if a large renal mass is identified without enlarged nodes, PEComa is a viable addition to the differential (Fig. 1).

The same applies for uterine enhancing masses with growing solid nodules on CT or hypovascular heteroechoic masses on ultrasound. On imaging, uterine PEComas mimic more common uterine pathologies like fibroids and leiomyosarcomas. First considerations tend toward fibroids and leiomyosarcoma [3]. However,

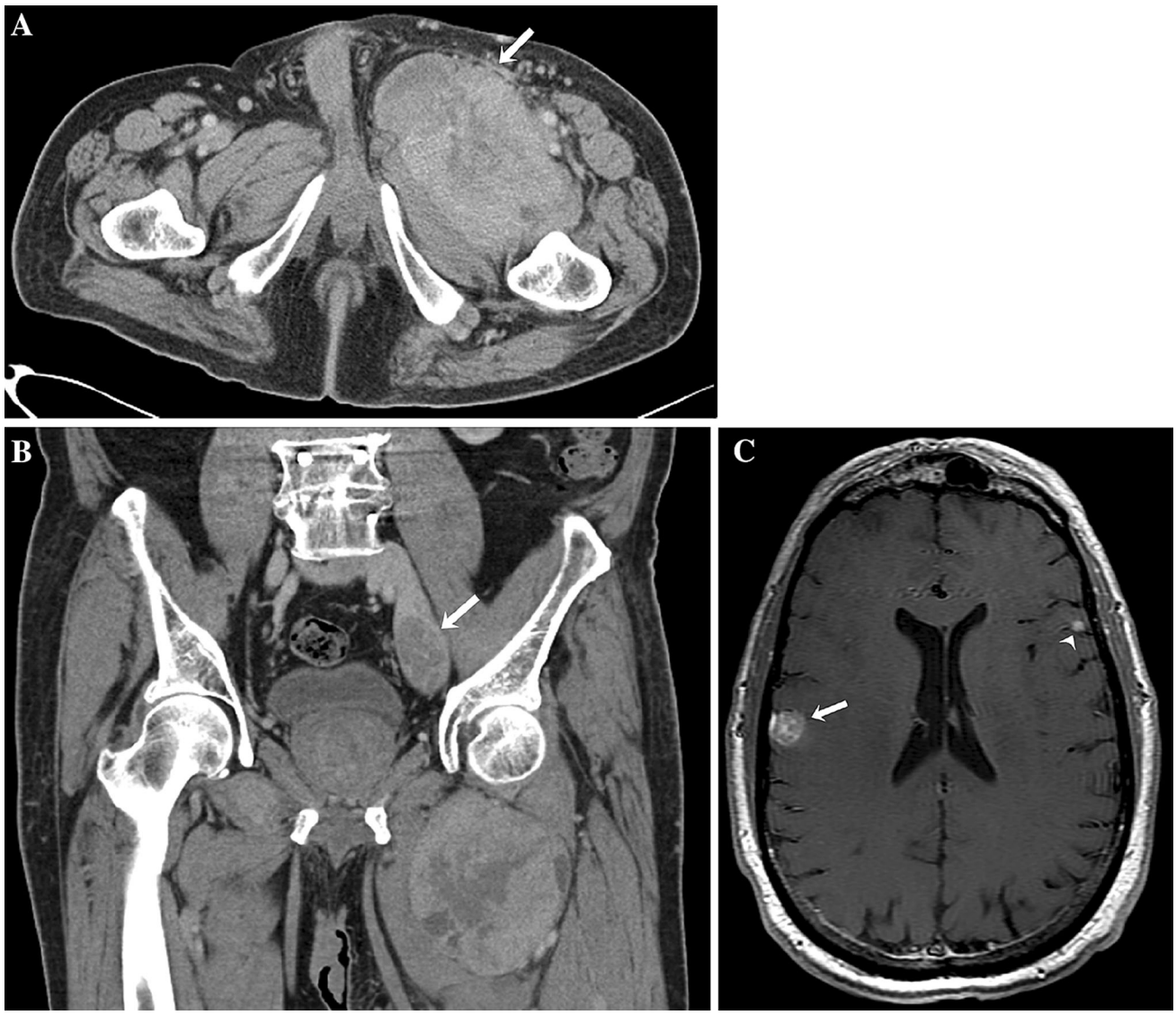

Fig. 6. A 77-year-old man with malignant PEComa in the left thigh with brain metastases. **A** and **B** Axial (**A**) and coronal (**B**) contrast-enhanced CT images show a large heterogeneously enhancing mass involving the adductor compartment of the left upper thigh (*arrow* in **A**) with tumor thrombus in the left external iliac vein (*arrow* in **B**). **C** Axial contrast-enhanced T1-weighted MR image of the brain shows enhancing parenchymal metastatic lesions in right temporal (*arrow*) and left frontal (*arrowhead*) lobes.

malignant PEComa is included in the differential where appropriate. A distinguishing feature of malignant PEComas is T2 prolongation, which is not found in typical uterine fibroids that are T2 hypointense (Fig. 2). Hepatic PEComa can resemble other benign lesions on imaging, and due to the rarity of these tumors, PEComas are usually not considered in the differential diagnosis of hepatic lesions. Hepatic PEComas are typically right sided and associated with the ligamentum teres/falciform ligament [5], and thus should also be considered in well-circumscribed enhancing masses in this location. In contrast to non-encapsulated acinar and hypervascular endocrine tumors, pancreatic PEComas often present as well-defined, encapsulated, hypovascular masses without signs of local invasion and should be included in the differential of such masses [25].

Management

Surgical resection is the mainstay in the management of malignant PEComa, and chemotherapy and radiotherapy are usually not effective. In patients with metastasis, studies suggest the possibility of molecular targeted therapies as a viable therapeutic option. A high number of PEComas have aberrant m-TOR signaling secondary to the loss of negative regulation of m-TOR complex 1 (m-TORC1) due to mutations in *TSC1*/*TSC2* genes. Wagner et al. demonstrated that the use of sirolimus, an

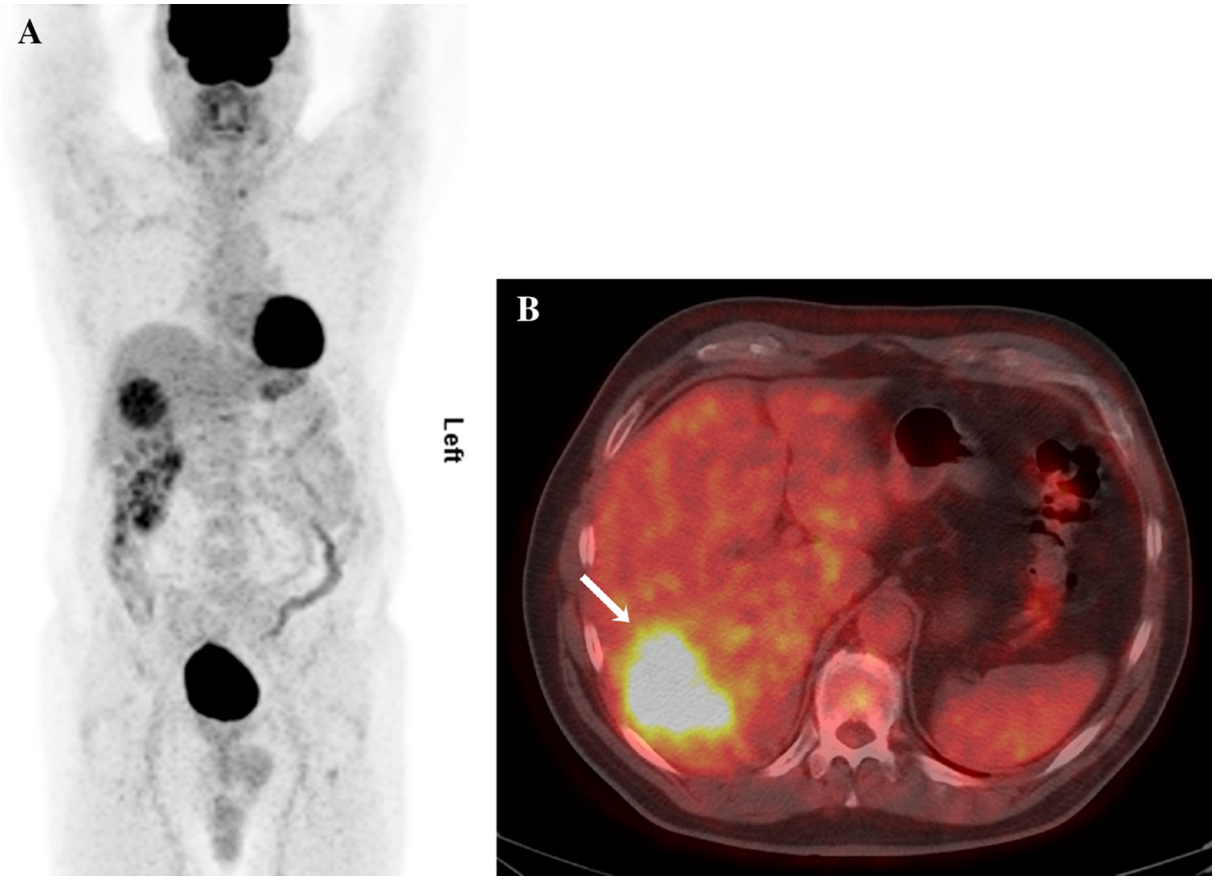

Fig. 7. A 70-year-old man with malignant PEComa of the left kidney, which was previously resected, now presenting metastasis to the liver. **A** and **B** Coronal maximum intensity projection (MIP) (**A**) and axial fused (**B**) ^{18}F-FDG PET images show an FDG-avid lesion in right lobe of the liver. Note the absence of the left kidney related to prior nephrectomy.

m-TORC1 inhibitor, was associated with significant clinical responses and ongoing near-complete response for greater than 14 months in one patient [26] (Fig. 1). Further analysis by Benson et al. confirmed that the use of m-TOR inhibitors in a larger population was well tolerated and with good radiologic response, although response was short-lived [27]. Restaging scans in patients with metastatic PEComa treated with m-TOR inhibitors can demonstrate, in addition to treatment response, drug toxicities including cholecystitis, enterocolitis, and pneumonitis. The most common of these is dose-dependent non-infectious pneumonitis seen in up to 30% of patients [28]. Imaging features of m-TOR inhibitors associated pneumonitis include ground-glass opacities, reticular opacities, and multifocal consolidation with marked subpleural predilection. (Fig. 1). The radiological pattern of pneumonitis is usually seen as interstitial pneumonia or cryptogenic organizing pneumonia-like pattern with bilateral although asymmetric involvement. Radiological findings suggestive of drug-associated pneumonitis can precede clinical symptoms, and up to 50% of patients can be asymptomatic [28]. Management of m-TOR-associated pneumonitis depends on severity and includes dose reduction, drug withdrawal, and steroids [29].

Conclusion

Malignant PEComas are rare tumors, which can be associated with poor outcomes. Although imaging features are nonspecific and the diagnosis of a malignant PEComa is based on histopathology, malignant PEComas can be considered in the differential diagnosis of large soft tissue masses arising in the GU tract, liver, or lung. Various imaging modalities including CT, MRI, US, and PET/CT are useful in the evaluation of primary and metastatic malignant PEComa. Early detection of metastatic spread can facilitate the detection of malignant PEComa and expedite early treatment.

Financial Disclosures None pertaining to the content in the manuscript.

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