Chapter 25
Mostly Benign/Rarely Metastasizing

25.1 Ossifying Fibromyxoid Tumor

Ossifying fibromyxoid tumor (OFMT) is a very uncommon soft tissue lesion that can occur anywhere in the body, but most commonly in the lower extremity. While most tumors are benign, malignant examples may metastasize in more than half of cases [1]. The largest series to date included only typical cases, excluding tumors with other morphologies, and in that series there were no patients who developed metastatic disease. In the few patients that we have observed recurrences, metastases are observed, typically to lung, and local–regional recurrence can be observed in a multifocal "shotgun" pattern around the area of the tumor, as has been observed in patients with epithelioid sarcoma.

The cell of origin of these tumors is unknown, but after the finding of an unbalanced translocation in one tumor by cytogenetics in 2001 [2], perhaps it is not surprising that these sarcomas were found to have recurrent gene fusions, mostly involving *PHF1* gene [3]. The most common translocation in a series of 39 OFMTs is *EP400-PHF1*, while other fusion variants such as *ZC3H7B-BCOR* and *MEAF6-PHF1* were more common in the S100 negative proportion of tumors, or in the malignant subset of OFMT [4]. These findings suggested a genetic overlap between OFMT and low grade endometrial stromal sarcomas (LGESS), since *EPC1-PHF1* translocations are found in both OFMT and LGESS [4].

Radiographically, scattered calcifications can be found throughout the lesion. Primary treatment of these tumors mirrors that of other soft tissue tumors, surgery and radiation for larger tumors, but adjuvant chemotherapy is difficult to recommend as the response rate to standard agents is very low. Given the relatively slow growth rate of the tumor, sustained exposure with lower doses of an agent continuously would appear a better means to treat these tumors than high dose therapy over the short term. The few patients we have treated have not responded durably to standard doxorubicin or ifosfamide, so new options for care are needed (Fig. 25.1)

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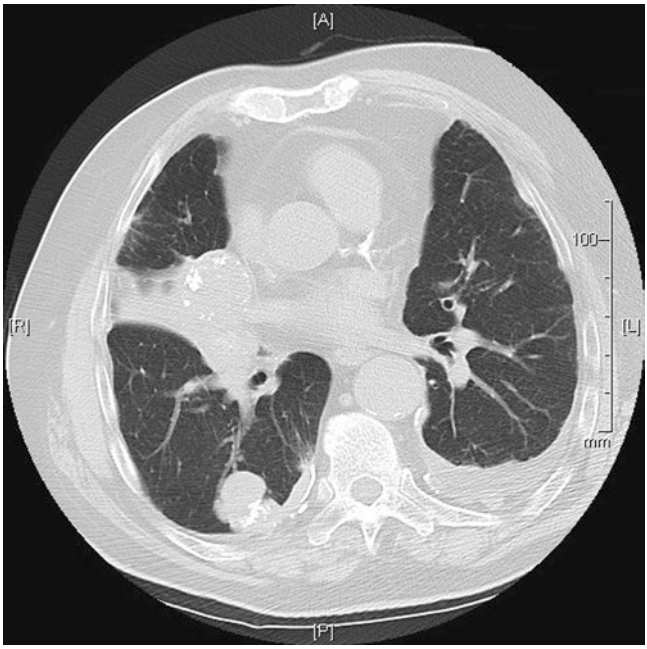

Fig. 25.1 Non-contrast CT image of metastatic ossifying fibromyxoid tumor featuring pleural effusions, lung- and pleural-based metastases, and speckled calcification of the metastatic deposits

Table 25.1 Systemic therapeutic recommendations for ossifying fibromyxoid tumor

Clinical scenario		Comments
Adjuvant chemotherapy		Not administered outside the setting of a clinical trial, given the poor response rate in the metastatic setting
Metastatic disease	First line	Clinical trial; topoisomerase I inhibitor-based therapy, e.g., temozolomide-irinotecan or cyclophosphamide-topotecan, has activity in anecdotal experience. Immune checkpoint inhibitors are untested as of 2016. Doxorubicin + olaratumab is approved in this situation but there are no prospective data as of 2016

(Table 25.1). At least two patients we have treated had durable responses from irinotecan-based therapy, e.g., temozolomide-irinotecan, suggesting a biological relationship to small round blue cell tumors more common in children.

25.2 Perivascular Epithelioid Cell Tumor (PEComa) and Related Entities, Lymphangioleiomyomatosis, Angiomyolipoma, Sugar Cell Tumor

The PEComa family of tumors includes a variety of tumors that express markers of both smooth muscle and melanocytes [5]. Thus, they are positive for SMA (smooth muscle actin), as well as for melanocytes markers such as HMB45 and Melan-A.

A variety of names for these tumors has been developed before the concept of PEComa was recognized as a distinct biological entity, on the basis of all lesions containing perivascular epithelioid cells, an unusual cell with no recognized normal counterpart. As a result, the PEComa family of tumors encompasses a variety of diagnoses such as angiomyolipoma, clear cell "sugar" tumors of the lung and other sites, lymphangioleiomyomatosis, and tumors with a similar morphology at a variety of other sites, such as Xp11 translocation renal cancers [6]. At least a subset of PEComas show inactivating mutations or deletion of *TSC2* (tuberin), causing its loss of expression. Coexistent *TP53* mutations were identified in 63 % of *TSC2*-mutated PEComas [7]. *TSC2*-deleted mouse muscle cells can develop into PEComas, showing a possible lineage for these unusual tumors [8]. Tuberin is one of the genes associated with tuberous sclerosis, as is *TSC1*, also called hamartin [9, 10]. Another subset of PEComas (23 %) harbor *TFE3*-related fusions, which are mutually exclusive to *TSC2* gene abnormalities [7, 11]. The most common fusion was *PSF-TFE3* with one case of *DVL2-TFE3* [7]. In addition, novel RAD51B gene rearrangements were identified in 8 % of uterine PEComas [7]. *TSC2*-deficient PEComas show activation of the mammalian target of rapamycin (mTOR) and activate a program of transcription and translation with the cell as a result [12, 13]. mTOR exists with other proteins in two complexes, mTORC1 and mTORC2. First-generation TOR inhibitors such as sirolimus only block mTORC1 but do not affect mTORC2 signaling, providing a bypass pathway for signaling when mTORC1 is blocked. As *TFE3* translocation PEComas lack *TSC2* mutations [11], it provides a mechanistic rationale that some PEComas would not respond to mTOR inhibitors.

An example is shown in Fig. 25.2 with a well-demarcated lesion in the vastus lateralis with edema in the soft tissue and central necrosis. These lesions, when metastatic, sometimes arise from the uterus, which is one of the more common sites for PEComas. Key pathological identification is the HMP45 which occurs but in patchy distribution. A recent review [14] of 234 cases reported from the literature suggests that size greater than 5 cm and high (1/50 HPF) mitotic rate were the only factors associated with recurrence following resection. Chemotherapy and radiation therapy seem to have little benefit..

25.3 Therapy

Primary treatment is surgical, when feasible; radiation plays little role in the primary treatment of these tumors since they tend to be visceral (Fig. 25.3). For patients with unresectable or recurrent disease, mTORC1 inhibitors, such as sirolimus, have been proved clinically useful in patients with recurrent angiomyolipoma [15], lymphangioleiomyomatosis [15], and recently in recurrent/metastatic PEComas [16–18]. Responses to mTORC1 inhibitors are not as robust as that of imatinib in GIST, with median duration of response on the order of 6–12 months [18]. It is not clear if mTOR inhibitors beyond sirolimus are useful for this diagnosis, but it is the opinion of the authors that the near equivalence of most of the first-generation

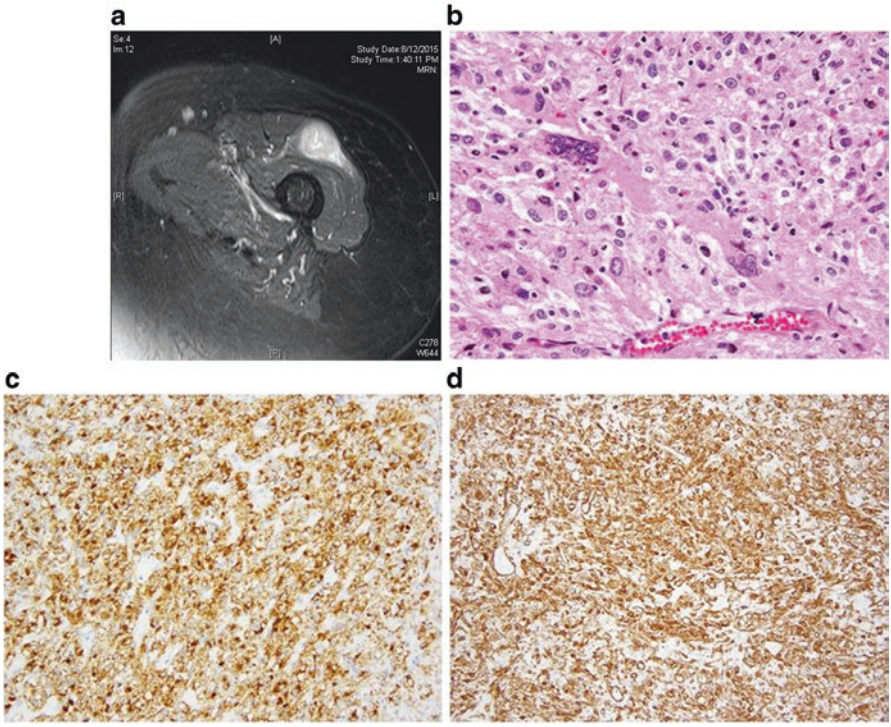

Fig. 25.2 (**a**) PEComa with a well-demarcated lesion in the vastus lateralis with edema in the soft tissue and central necrosis. (**b**) PEComa morphology is characterized by spindle and pleomorphic cells with abundant clear or granular cytoplasm; (**c**, **d**) immunoprofile typically includes reactivity for both melanocytic (HMB45, **b**) and smooth muscle (SMA, **b**) markers

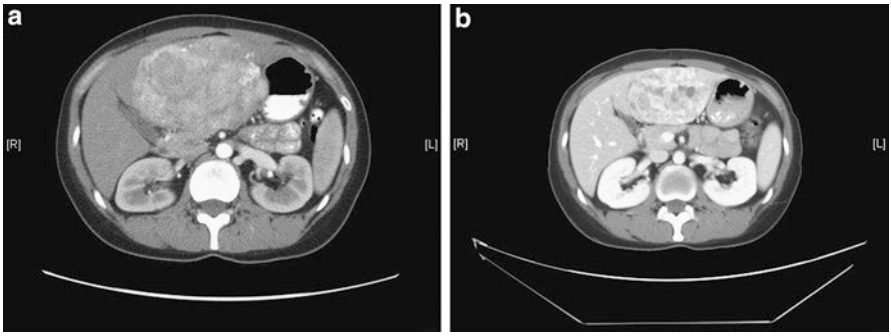

Fig. 25.3 CT response of a recurrent angiomyolipoma (PEComa family of tumors) to sirolimus 4 mg oral daily. (**a**) Pretreatment, 12.6 × 7.6 cm mass; (**b**) after 3 months, mass size 9.1 × 5.6 cm

mTOR inhibitors speaks to their interchangeability and lack of activity of the others if one of them fails. We have not observed activity of anthracyclines or of ifosfamide in the small number of patients we have treated with standard agents, arguing that such patients are appropriate for clinical trials. Less investigated are other

Table 25.2 Systemic therapeutic recommendations for perivascular epithelial cell tumor (PEComa) and related entities, lymphangioleiomyomatosis, angiomyolipoma, sugar cell tumor of the pancreas

Clinical scenario		Comments
Adjuvant chemotherapy		Not administered due to low risk of relapse and lack of long-term efficacy of systemic agents in the recurrent setting; this tumor subtype appears to be one in which genomic analysis would be worth pursuing
Metastatic disease	First line	Sirolimus or other mTOR inhibitor for *TSC2* mutant PEComas
	Second line	It is unclear if other kinase inhibitors, e.g., pazopanib, have any activity, for example in *TFE3*-related sarcomas such as alveolar soft part sarcomas. Clinical trials of agents blocking downstream targets of mTOR and VEGFR, e.g., S6 kinase, or metabolic-directed therapy, may be worth examination as well. Immune checkpoint inhibitors are untested as of 2016

small molecule inhibitors yielding greater "area under the curve," which may be worth examining as well (Table 25.2); in particular, since VEGFR inhibitors have some activity in alveolar soft part sarcomas, it stands to reason that renal PEComas with *TFE3* translocations could be targeted with VEGFR inhibitors such as pazopanib or sunitinib.

25.4 Giant Cell Tumor of Tendon Sheath/Pigmented Villonodular Synovitis

Giant cell tumor of tendon sheath (TGCT), also termed pigmented villonodular synovitis (PVNS), is an uncommon neoplasm of the synovium of joints that can occur in any joint. Unlike synovial sarcoma, which does not appear to be related nor resemble synovium microscopically, TGCT/PVNS is a true tumor of the synovium. The tumor comes in several forms: a localized variety most common in small joints, a diffuse type more common in large joints like the knee, and an extra-articular variety.

The key finding that has changed treatment for TGCT/PVNS is the consistent translocation t(1;2)(p11;q36-37) (*COL6A3-CSF1*) found in a minority of the cells of the lesion, which leads to the production of CSF-1 and presumed activation of FMS (the M-CSF receptor), and local cytokine production that leads to the characteristic inflammatory changes in the lesion [19].

The tumor presents as an inflammatory mass and/or effusion. Primary therapy consists of primary resection, but recurrence is common within several years of primary diagnosis, typically with the diffuse variety of the tumor (Fig. 25.4). Rare cases of metastatic disease to lung are reported. In the past postoperative intra-articular radioactive phosphate (labeled with ^{32}P) or ^{90}Y (yttrium) has been used as

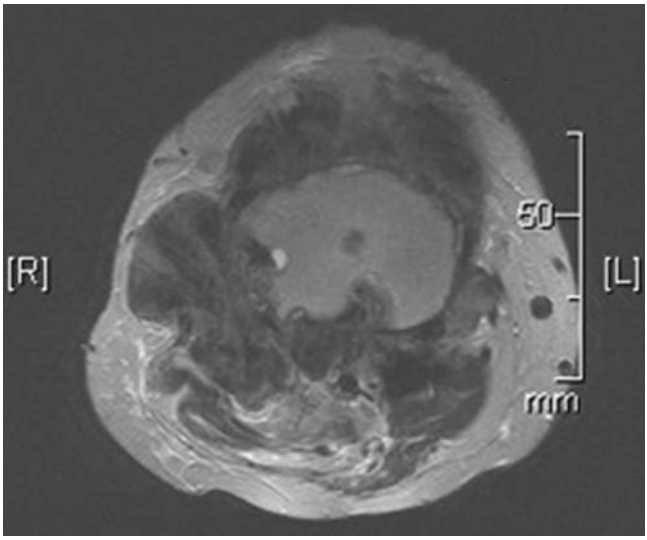

Fig. 25.4 T1-weighted axial MRI image of a multiply recurrent tenosynovial giant cell tumor of the knee

Table 25.3 Systemic therapeutic recommendations for giant cell tumor of tendon sheath/pigmented villonodular synovitis

Clinical scenario		Comments
Adjuvant chemotherapy		Not administered due to low risk of relapse
Recurrent/metastatic disease	First line	Reoperation; imatinib or improved CSF1 inhibitor, e.g., pexidartinib, if available
	Second line	Alternative tyrosine kinase inhibitor; surgery and external beam radiation; clinical trial. Immune checkpoint inhibitors are untested as of 2016

an antiproliferative measure for recurrence of disease, though there is significant toxicity in treating at least certain anatomic sites with intra-articular radionuclides. Postoperative external beam radiation (~35 Gy) has been used successfully in some patients with recurrence of disease [20, 21]. The long-term effects of moderate dose radiation in terms of joint function and secondary cancers are unknown.

As a coincidence, imatinib blocks FMS (as well as BCR-ABL, KIT, PDGFRs, and other targets) owing to their structural similarity, and there are anecdotes of patient responses to imatinib. In the index case study, a responding patient stopped therapy, and the lesion recurred rapidly, but then responded again to another course of imatinib [22]. A group of anecdotes from several centers demonstrated that there was significant activity of imatinib in TGCT/PVNS, but given the concern of recall bias, these data may represent an upper estimate of activity [23] (Table 25.3).

Strikingly, a more specific attack against CSF1R has yielded more potent activity against the tumor. Both monoclonal antibodies and small molecule inhibitors with greater specificity against the CSF1R compared to imatinib have been significantly more effective in TGCT than has been imatinib in its anecdotal experience [24, 25].

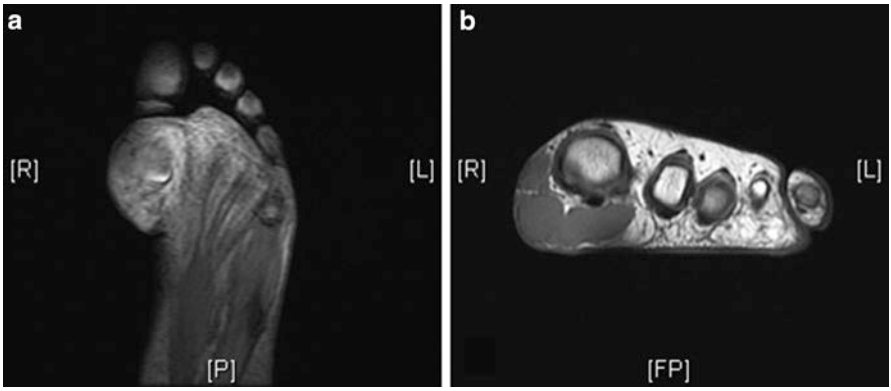

Fig. 25.5 Coronal (**a**) and axial (**b**) T1-weighted MRI images of a left foot low grade myoepithelioma involving flexor hallucis longus and subcutaneous tissue

A randomized trial of the small molecule inhibitor pexidartinib (PLX3397) is underway and may lead to approval of the agent in the near future.

Giant cell tumors of soft tissue can rarely be seen in other sites. They usually occur subcutaneously but can be seen in deep muscle tissue. The cytological characteristics are often clear and can be identified by aspiration cytology. The majority behave in a benign fashion although rare malignant counterparts occur. Surgical excision is usually curative.

25.5 Myoepithelial Tumors of Soft Tissue

Soft tissue myoepithelial tumor is a distinct entity from the pleomorphic adenoma arising in salivary glands, from which a myoepithelial carcinoma ex-pleomorphic adenoma can develop. Myoepithelial tumor of soft tissue is an extremely rare neoplasm which typically occurs in the superficial or deep soft tissue of the limbs or head and neck of both children and adults (Fig. 25.5). Both benign and malignant forms exist, separated by increased mitotic activity, nuclear pleomorphism, and necrosis. Half of myoepithelial tumors (including benign and malignant) have EWSR1 gene rearrangements; the most common fusions being *EWSR1-POU5F1* and *EWSR1-PBX1* [26]. Other less common fusion variants have been reported including *EWSR1-ZNF444* [26, 27], *EWSR1-PBX3*, and *FUS-KLF17* [28, 29]. Soft tissue myoepithelial tumors are defined by the co-expression of cytokeratin +/− EMA and S100 protein +/− smooth muscle actin. In a recent review [30], treatment is standard surgical resection and the majority of the lesions behave in a benign or indolent fashion such that surgery is curative. Malignant examples can occur, often with a virulent course. A good example is illustrated in Fig. 25.6, with a large lesion of the foot with a discontiguous bone lesion and pulmonary metastases in a 25-year-old male.

Chemotherapy is not well defined for patients with such recurrences. It is difficult to more than speculate on treatment given the few cases of this family of tumors treated in the literature; in our own hands no radiological responses have been observed with any specific agent, making clinical trial enrollment paramount for the rare patient with metastatic disease [31].

25.6 Glomus Tumor

Glomus tumors must not be confused with paragangliomas (e.g., glomus faciale, glomus jugulare, glomus tympanicum, glomus vagale, or carotid body tumors) as pertains to anatomy and terminology [32]. While paragangliomas can occur associated with the carotid body, for example, glomus tumors are tumors of the cells that give rise to glomus bodies, the specialized smooth muscle that controls blood flow to the periphery/skin. Glomus tumors have histology that can be classified by their predominant components, e.g., glomangioma, glomangiomyoma, and rare malignant counterparts called malignant glomus tumor or glomangiosarcoma, amongst other varieties.

Benign glomus tumors, which have a broad age distribution among adults, classically present as painful lesions in a subungual location on the fingers or on the skin of the distal extremities. Treatment is surgical for what are typically small tumors [33–35]. They are also occasionally found in the wall of the stomach, and less commonly in other visceral locations, and again surgery is typically curative (Fig. 25.7). These lesions are positive for smooth muscle actin, like leiomyomas and leiomyosarcomas.

Glomus tumors are found in the spectrum of neurofibromatosis type I-related neoplasms. Furthermore, remarkably, there is a familial condition involving familial glomus tumors, which are called glomangiomas or glomangiovenous malformations, mimicking arteriovenous malformations [36–40]. Multiple discolored lesions are found in the skin in this condition, in which there germ line mutations are found in the glomulin gene on chromosome 1p.

More recently recurrent *NOTCH* gene rearrangements have been reported in about half of glomus tumors, including most malignant variants [41]. The most common NOTCH family member involved was *NOTCH2* which was fused to *MIR143*, resulting in significant NOTCH2 upregulation. Less commonly fusions involving NOTCH1 and NOTCH3 were present fused to MIR143 [41].

For the rare person with a malignant glomus tumor (in which there is evidence of mitotic activity or atypical mitotic figures), metastatic spread to lungs is common (similar to leiomyosarcomas) or to peritoneum or bowel (Fig 25.8). Chemotherapy

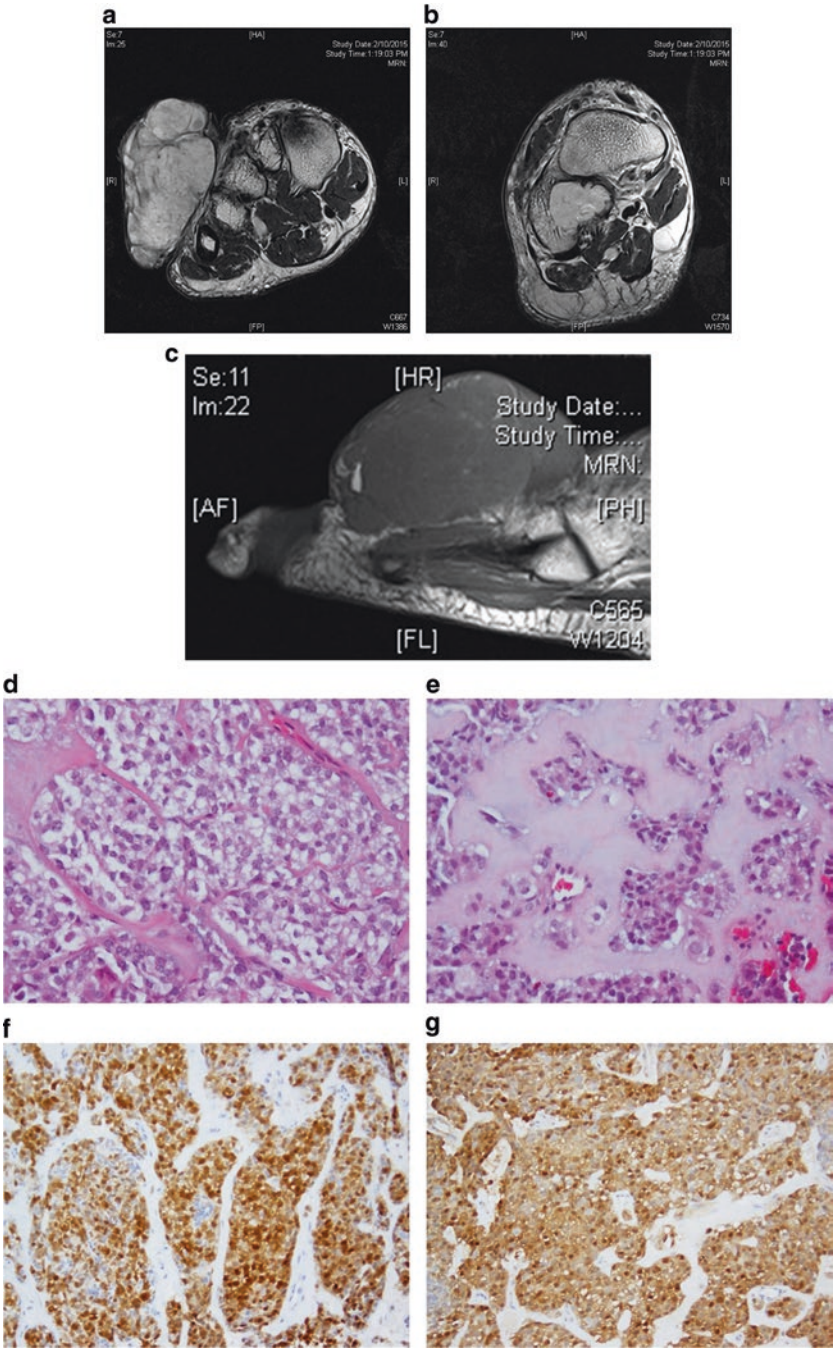

Fig. 25.6 (**a**–**c**) Myoepithelial right foot—large lesion of the foot with a discontiguous bone lesion and pulmonary metastases in a 25-year-old male. (**d**) EWSR1-POU5F1 fusion positive soft tissue myoepithelial tumor showing a nested growth with epithelioid cells with clear cell cytoplasm or (**e**) reticular pattern in a dense chondromyxoid stroma. (**f**) Immunostaining shows strong reactivity for both cytokeratin and (**g**) S100 protein

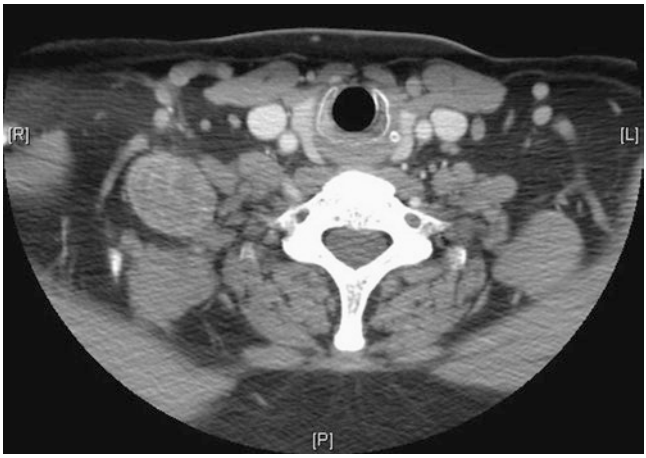

Fig. 25.7 Axial contrast-enhanced CT image of a malignant glomus tumor of the right neck

Table 25.4 Treatment recommendations for malignant glomus tumor

Primary disease	Surgical resection; no adjuvant chemotherapy or radiation is employed
Recurrent/metastatic disease	Clinical trials; we speculate that doxorubicin, dacarbazine, or gemcitabine-based therapy is reasonable if there are no clinical trial options. Notch inhibition is a theoretically interesting approach to consider given the biology of these tumors. Immune checkpoint inhibitors are untested as of 2016. Doxorubicin and olaratumab are approved for this situation but there are no prospective data as of 2016

is undefined for such rare lesions, but agents typically used for leiomyosarcoma for the rare patient requiring chemotherapy can be suggested based on histology alone (Table 25.4), although there are no reports of therapy in the literature (Table 6.1). The new genetic information emerging with recurrent NOTCH-related fusions that result in oncogenic activation of the protein, especially seen in most malignant glomus tumors (glomangiosarcomas), suggests treatment with NOTCH inhibitors might be effective.

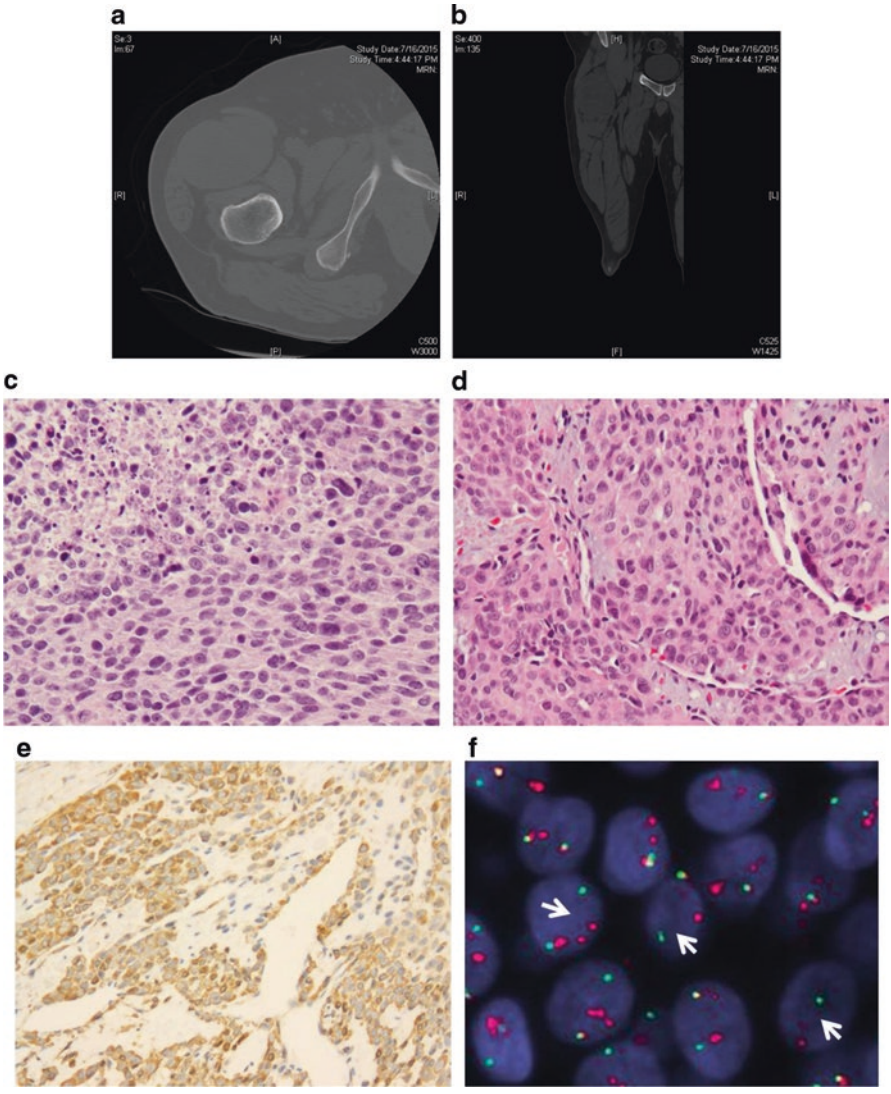

Fig. 25.8 (**a**, **b**) CTs of malignant glomus (**c**) malignant glomus tumor (glomangiosarcoma) shows a high grade morphology with necrosis, indistinguishable from other spindle cell sarcomas; (**d**) areas of classic glomus tumor can be found by extensive sampling, that can lead to the correct diagnosis, (**e**) with reactivity for SMA; and (**f**) NCOA2 gene rearrangement by FISH (*arrows* show break-apart signal, *red*, *green*)

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