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SCIENTIFIC ARTICLE

Plexiform fibrohistiocytic tumor: imaging features and clinical findings

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Abstract

Objective To describe the imaging features of plexiform fibrohistiocytic tumor and its associated clinical findings.

Materials and methods An institutional database was searched to identify all patients with a pathological diagnosis of plexiform fibrohistiocytic tumor. The electronic medical record was reviewed for relevant clinical data. Radiologic images of the primary tumor site were reviewed by two radiologists to assess primary, residual, or recurrent tumor with respect to tumor location, size, morphology, MR signal characteristics and enhancement, and involvement of adjacent structures.

Results Thirteen patients with imaging of the primary tumor site were identified [eight female, five male; mean age, 15.9 years (range, 3–41 years)]. Plexiform fibrohistiocytic tumor typically manifested as a solitary, painless, firm, slow-growing lesion centered in the subcutaneous tissues, with a predilection for the upper extremity or head and neck region. Most tumors had a purely plaque-like or infiltrative morphology at MRI; some demonstrated no round or oval mass. Tumors were predominantly isointense to muscle on T1-weighted imaging and hyperintense on fluid-sensitive imaging, and enhanced after gadolinium contrast administration. Five patients (38%) had residual tumor after initial surgery, resembling postoperative changes. No patient had recurrent tumor. One patient (8%) developed metastases to local lymph nodes and to the lung. No patient died from plexiform fibrohistiocytic tumor.

Conclusions Plexiform fibrohistiocytic tumor often manifests as a plaque-like or infiltrative process, sometimes without a round or oval mass, most commonly in the subcutaneous tissues of the upper extremity or head and neck region. Residual tumor is often present after initial surgery, and may be indistinguishable from postoperative changes.

Keywords Plexiform fibrohistiocytic tumor · Imaging · MRI · Soft tissue tumor

Introduction

Plexiform fibrohistiocytic tumor (PFHT) was first described in 1988 [1], with over 100 cases having been reported to date in the pathology and surgical literature [2]. PFHT is a rarely metastasizing dermal and subcutaneous neoplasm, which was classified as a soft tissue tumor with intermediate malignant potential in the latest WHO classification of soft tissue tumors [3]. PFHT grows slowly and is usually asymptomatic, manifesting as a soft tissue nodule or indurated plaque in the subcutaneous adipose tissue; the most common site is the upper extremity [1, 4, 5]. The tumor uncommonly metastasizes to the lymph nodes and lungs [4].

PFHT occurs in three morphological patterns at histopathologic examination, all with a relatively benign appearance: fibroblastic, histiocytic, and mixed [1]. To our knowledge, the imaging features of this tumor have not been described, other than for one case that was illustrated in a review article about benign fibrous soft tissue tumors in adults [6]. This study therefore was undertaken to describe the imaging features of PFHT and its associated clinical findings in a series of patients.

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Materials and methods

Patient selection and clinical data

This retrospective study, performed at a tertiary referral cancer center, was approved by the Institutional Review Board with a waiver of informed consent. The institutional

pathology database was searched for the keywords "plexiform" and "fibrohistiocytic" in pathology reports dated between January 1989 and September 2017. The resultant list was searched for all cases with a confirmed final pathological diagnosis of PFHT. The pathology findings were reviewed by an experienced pathologist who subspecializes in soft tissue tumors. Relevant clinical data from the hospital electronic medical record, including patient demographics, clinical course, and treatment, were recorded for these patients.

Imaging studies and image interpretation

For each confirmed case of PFHT, all available radiologic examinations (including submitted studies performed elsewhere) of the primary tumor site were reviewed on a picture archiving and communication system (PACS). The imaging studies were reviewed in consensus by two musculoskeletal fellowship-trained radiologists (with 1 and 14 years of experience, respectively), who were not blinded to the diagnosis of PFHT. Tumors were analyzed for location, maximum dimension (in any plane), morphology (infiltrative, plaque-like, mass-like), multifocality, MR signal and enhancement characteristics, and involvement of adjacent structures.

Results

The search revealed 13 patients with a final pathologic diagnosis of PFHT and who also had imaging of the primary tumor site available. Review of the pathologic findings revealed typical microscopic features in all cases, showing an ill-defined, often infiltrative growth within subcutaneous fat. The lesions were composed of ovoid to epithelioid cells arranged in nests, ball-like nodules, or sheets, separated by a collagenous stroma (Fig. 1a, b). The neoplastic cells resembled histiocytoid cells, with pale-eosinophilic cytoplasm, round nuclei with open chromatin, and inconspicuous nucleoli. Tumors typically lacked significant cytologic atypia, hyperchromasia, increased mitotic activity, or necrosis (Fig. 1c). A variable number of multinucleated giant cells were often present (Fig. 1d). Immunohistochemical stains included diffuse reactivity for histiocytic markers, such as NKI-C3 (Fig. 1e) and CD68 (Fig. 1f), while being negative for cytokeratin, EMA, S100, SMA, and desmin.

Clinical data

The 13 patients (eight female, five male) had a mean age of 15.9 years (range, 3–41 years). Their tumors presented as slow-growing [six of six (100%) patients for whom this data

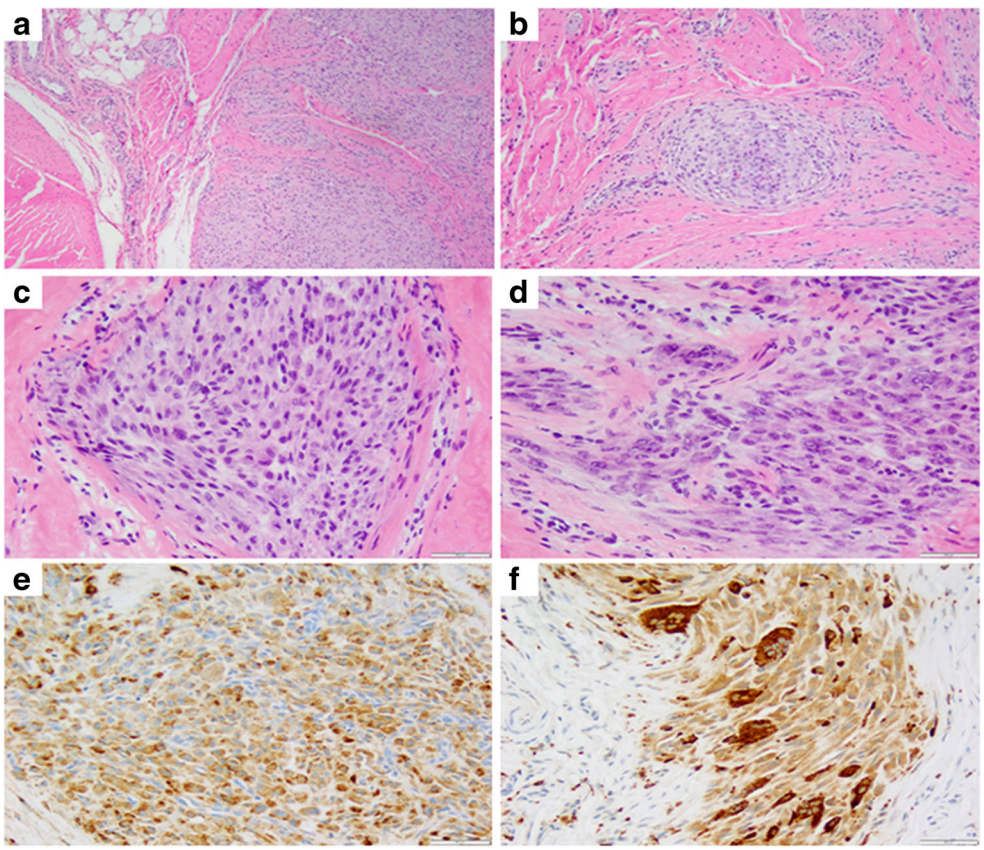

Fig. 1 Pathologic findings of PFHT. **a** Multinodular growth within adipose tissue (H&E, 40×). **b** Higher power reveals tight nodules of epithelioid cells, separated by a densely collagenized stroma (H&E, 100×). **c** The lesional cells show bland cytologic features with light eosinophilic cytoplasm and round nuclei with fine chromatin (H&E, 200×). **d** Higher-power view of one of the nodules shows histiocytoid cells with scattered multinucleated giant cells. Immunohistochemically, the lesional cells show diffuse reactivity for histiocytic markers, including **e** NKI-C3 (200×) and **f** CD68 (400×)

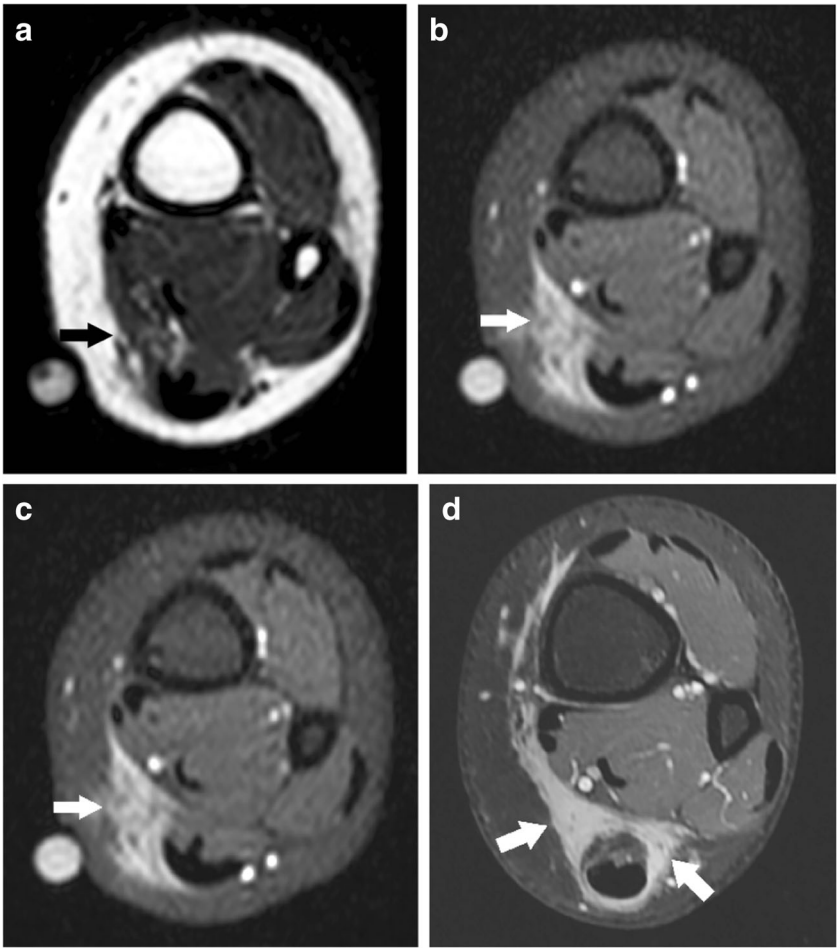

Fig. 2 A 9-year-old girl with PFHT of left lower extremity. Preoperative MR images of the initial tumor show plaque-like tissue (*arrow*) with signal isointense to muscle on **a** T1-weighted image; moderately hyperintense signal on **b** fat-suppressed T2-weighted image; and avid enhancement on **c** post-contrast fat-suppressed T1-weighted image. The tumor is located in the posterior compartment of the lower leg, abutting the Achilles tendon and deep posterior compartment musculature. **d** Post-contrast fat-suppressed T1-weighted MR image obtained 3.5 years after surgery shows extensive, plaque-like recurrent tumor (*arrows*), encasing Achilles tendon, and extending near the tibia

was available], firm (6/6, 100%), painless (12/13, 92%) lesions that were visible to inspection (13/13, 100%). None of the patients reported a history of preceding trauma or radiotherapy to the area, and none had another known malignancy.

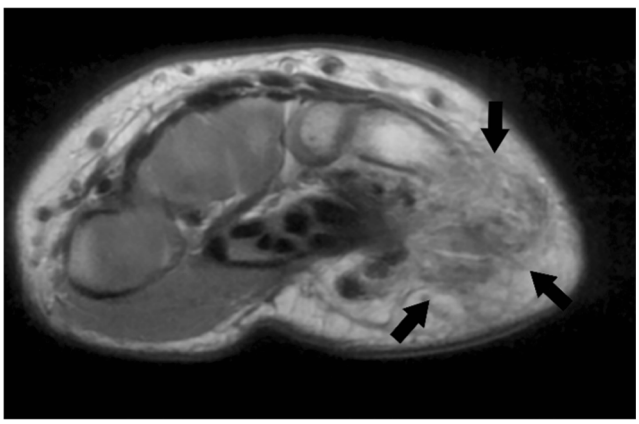

Fig. 3 A 3-year-old boy with PFHT of hypothenar eminence of the right hand. Axial proton density MR image of the original tumor shows poorly defined, infiltrative tumor (*arrows*) in the subcutaneous tissues, similar in intensity to muscle

All patients underwent surgery for their primary and/or residual PFHT. Two (15%) of these patients underwent surgery after a period of clinical observation. None were treated with chemotherapy or radiotherapy.

After initial surgery that yielded positive resection margins, five patients (38%) had histopathologic confirmation of residual disease at re-resection of the tumor bed, one of whom underwent re-resection without additional imaging. After resection with negative margins (defined as > 0.1 cm from the specimen margin as measured on the glass slide), none of the other patients developed recurrent PFHT within the period of clinical and MRI follow-up [mean follow-up, 57 months (range, 9–124 months)]. One patient (8%), who was 6 years old and had a superficial PFHT in the oral cavity and left submandibular region, developed pathologically proven metastases to an ipsilateral submandibular lymph node and to lung. No patient died from PFHT.

Imaging findings

The MRI studies had been performed on 1.5-T (12 patients) and 3.0-T (one patient) scanners. The available sequences for

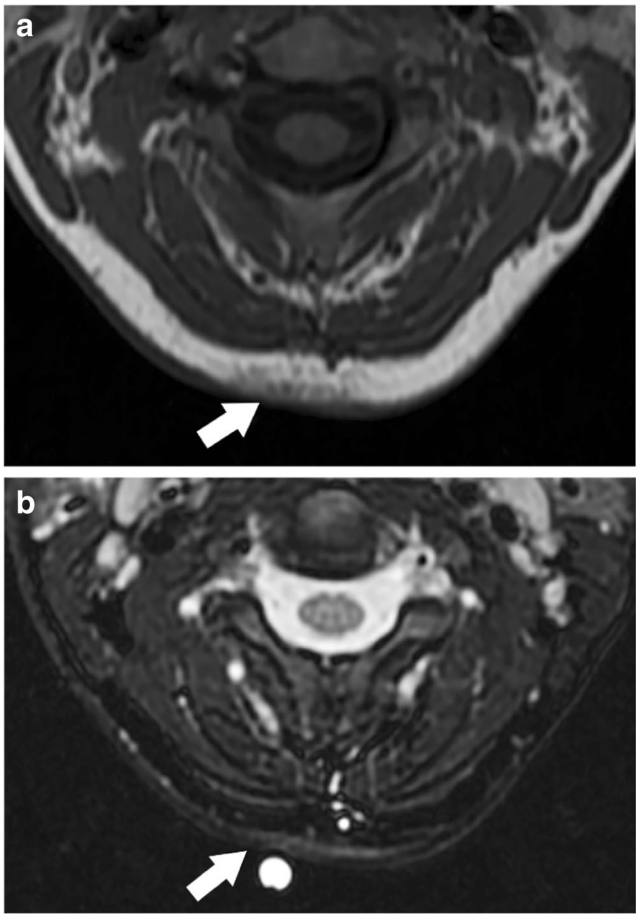

Fig. 4 A 34-year-old woman with PFHT of posterior midline neck. **a** Axial T1-weighted and **b** fat-suppressed T2-weighted MR images show subtle, infiltrative tumor (*arrow*) localized to the subcutaneous tissues

each study included at least two of the following: T1-weighted, proton density (with or without fat suppression), T2-weighted (with or without fat suppression), short-tau inversion recovery (STIR), and post gadolinium-enhanced fat-suppressed T1-weighted.

Each of the 13 patients had a solitary lesion, located in the upper extremity (six patients; 46%), head and neck region (five patients; 38%), lower extremity (one patient; 8%) and subcutaneous tissues of abdominal wall (one patient; 8%).

Six (46%) of the 13 patients had preoperative imaging available of the primary tumor (one of whom also had imaging of subsequent residual PFHT after initial resection). Three (23%) of the 13 patients had only postoperative imaging available of residual tumor, with no imaging available of the primary tumor (one of whom had residual superficial oral cavity and left submandibular tumor palpable on clinical examination, but occult on imaging). Four (31%) of the 13 patients had only postoperative imaging of the primary tumor site, with no residual or recurrent tumor demonstrated at time of imaging (one of these patients had residual PFHT resected without preoperative imaging; imaging was performed only after definitive re-resection).

Of the eight patients with tumor visible at imaging, six (75%) had tumors with purely plaque-like (Fig. 2) or infiltrative morphology (Figs. 3 and 4) without a solid or round mass, and two (25%) had tumors with solid morphology (Figs. 5 and 6). The plaque-like or infiltrative morphology was sometimes indistinguishable from postoperative changes at imaging performed after the initial resection. All tumors were located in subcutaneous tissues, and contacted tendon or bone in six patients (75%), extended to skin in four (50%), invaded muscle in one (13%), and contacted nerve in one (13%). No major vessel was encased by PFHT. The mean lesion size (either primary or residual tumor) at first available imaging study was 2.2 cm (range, 1.3–3.3 cm).

PFHT lesions were isointense to muscle on T1-weighted imaging in four of six patients (67%) for whom that sequence was available, and hyperintense in 2/6 (33%); hyperintense on proton density imaging (with or without fat suppression) in 3/3 (100%); hyperintense on T2-weighted imaging without fat suppression in 4/5 (80%); hyperintense on T2-weighted imaging with fat suppression in 5/5 (100%); and hyperintense on STIR in 3/4 (75%). Moderate or avid enhancement was demonstrated in 4 of 4 (100%) tumors after intravenous administration of gadolinium contrast material.

Radiographs were available in three patients. In one patient, radiographs demonstrated soft tissue swelling in the region of the tumor, without calcification, discrete mass, or subjacent osseous changes (Fig. 5). The tumor was radiographically occult in the other two patients. Ultrasound was available in one other patient, in whom the tumor manifested as a discrete hypoechoic mass (Fig. 6).

CT of the chest performed for follow-up tumor staging demonstrated a small, solitary pulmonary metastasis in one patient (Fig. 7), who also had a metastasis in a submandibular lymph node.

Discussion

The demographic and clinical characteristics of our study population were similar to those in prior reports in the pathological and surgical literature. PFHT is more common in females and typically presents in children and young adults [1, 4] as a small, slow-growing, asymptomatic soft tissue nodule or flattened, indurated plaque of firm consistency [4]. The most common site is the upper extremity [1], with all but one previously reported PFHT being located in the subcutaneous adipose tissue with extension into the dermis, skeletal muscle, or both [4]; a single case of an osseous PFHT, within the left fibula, has been reported [7]. Unlike the single case of PHFT illustrated in the article by Ng et al. [6], in which the patient had paraneoplastic hypophosphatemia, none of our patients exhibited a paraneoplastic syndrome.

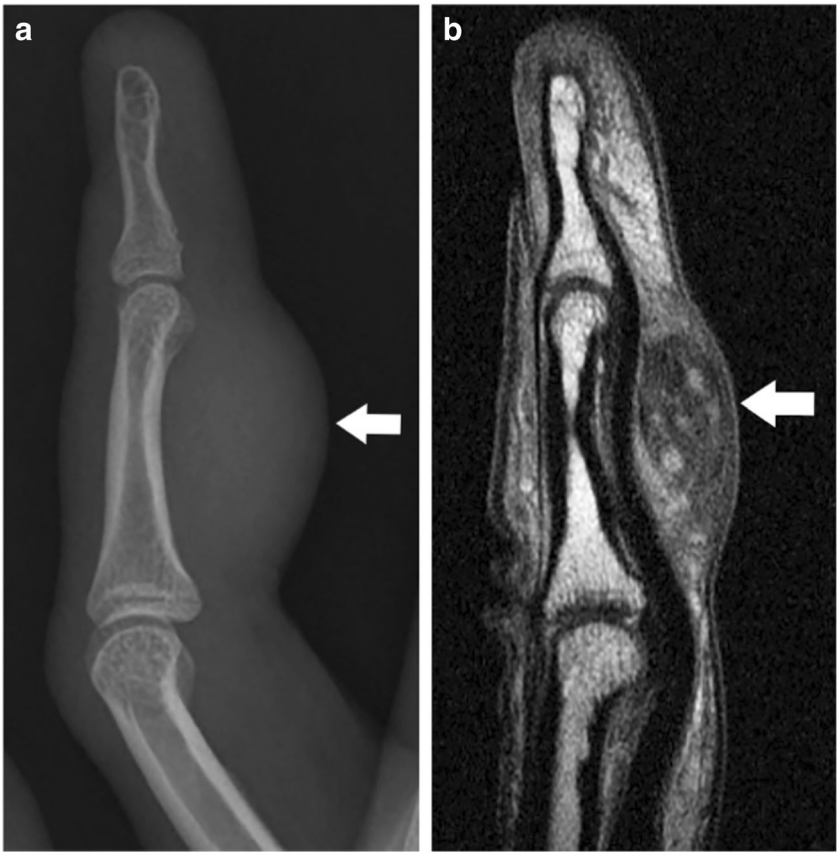

Fig. 5 A 20-year-old man with PFHT of palmar soft tissues of left ring finger. **a** Pre-operative radiograph shows non-specific soft tissue mass (*arrow*), without calcification or subjacent osseous change. **b** Sagittal proton density MR image shows the mass (*arrow*) in the subcutaneous tissues, superficial to the flexor tendon

In our series, the MRI appearance of PFHT was similar for both primary and residual tumor, most commonly manifesting as a plaque-like or infiltrative lesion centered in the subcutaneous tissues, sometimes without a round or oval mass. The observed MRI signal characteristics are not unique to this lesion, most often being isointense on T1-weighted images, hyperintense on fluid-sensitive images, and enhancing after gadolinium contrast material administration. In contrast to the PHFT reported by Ng et al. [6], none of the PHFT in our series showed low signal intensity on fluid-sensitive MR images.

The radiological differential diagnosis of PFHT is broad, including benign and malignant entities. Benign entities that can present with an infiltrative growth pattern in locations similar to PFHT include angiolipoma, hemangioma, diffuse infiltrative/superficial plexiform neurofibroma, and phosphatase and tensin homolog (PTEN) hamartoma. Angiolipoma is a benign soft tissue tumor with two subtypes—the more common, non-infiltrating type that usually presents as multinodular painful lumps, and the rarer, infiltrating type that can be nonencapsulated and infiltrative within soft tissues and bone. The most common location of angiolipoma is the forearm, followed by the trunk and upper extremity. Angiolipoma is often a painful lesion [8], in contrast to PFHT, which is almost always painless. Hemangiomas also can mimic PFHT at imaging, although they often exhibit rounded and tubular structures surrounded by fatty septa, and may contain phleboliths [9].

Diffuse neurofibroma (referred to as superficial plexiform neurofibroma by Lim et al. [10]) is a rare neurofibroma variant, which occurs as a reticular or plaque-like lesion in subcutaneous tissues [9]. Diffuse neurofibroma has an infiltrative morphology on MRI and lacks the typical target-like or bag-of-worms appearance of localized or plexiform neurofibromas involving larger nerves [10]. Given that only 10% of diffuse neurofibromas occur in patients with neurofibromatosis type 1 [9], lack of a history of that disease does not assist in distinguishing between these entities.

The rare and relatively recently described PTEN hamartoma also has a predilection for soft tissues of extremities, but more commonly manifests as a mass, and less commonly as a purely subcutaneous lesion. It may also violate fascial planes and invade bone [11], features not seen in our series or other reports of PFHT.

Malignant mimics of PFHT at imaging include other superficial infiltrative lesions, such as myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), and T cell lymphoma. Both myxofibrosarcoma and UPS are frequently associated with a "tail sign," consisting of infiltrative bands of enhancing tumor extending along fascial planes from the tumor margin

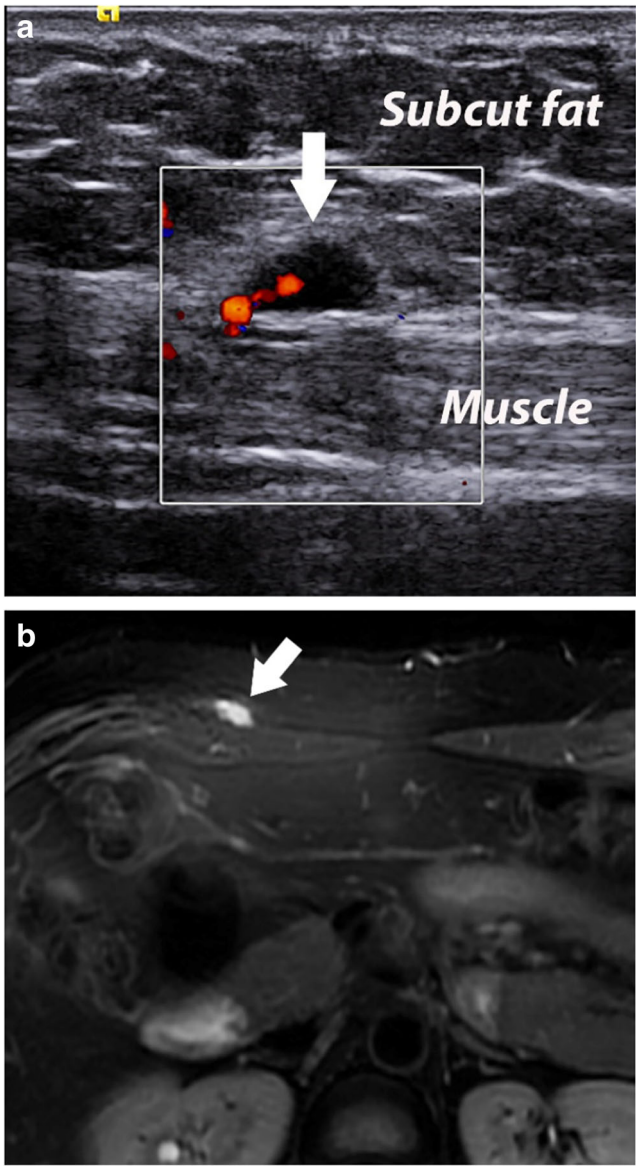

Fig. 6 A 41-year-old woman with PFHT in subcutaneous tissues of anterior abdominal wall. **a** Pre-operative Doppler ultrasound demonstrates a small, hypoechoic nodule (*arrow*) containing some vascular flow. **b** Axial T2-weighted fat-suppressed MR image shows a small, hyperintense nodule (*arrow*) in the subcutaneous tissues, abutting the anterior abdominal wall musculature

[12, 13]. Although such tails of tumor may resemble PFHT at imaging, myxofibrosarcoma and UPS generally have an associated mass, unlike PFHT. Peripheral T cell lymphoma can occur as infiltrative changes in subcutaneous tissues, but usually has a multinodular morphology [14], unlike PFHT.

Hemosiderotic fibrolipomatous tumor (HFLT) and myxoinflammatory fibroblastic sarcoma (MIFS) are, respectively, the benign and malignant ends of a tumor spectrum. HFLT has a predilection for the subcutaneous tissues of the ankle in middle-aged females [15]. Whereas HFLT commonly has an infiltrative morphology and similar location and signal characteristics to PFHT, most HFLT demonstrate regions of low-signal "blooming" (susceptibility) artifact at gradient-echo imaging, due to hemosiderin content [16]. MIFS has a predilection for the subcutaneous tissues of distal extremities. Low-grade MIFS may resemble PFHT, with similar locations and homogeneous enhancement characteristics, although MIFS is more commonly multinodular and grows along a tendon, which is not typical for PFHT. Distinguishing high-grade or dedifferentiated MIFS from PFHT would be expected to be less problematic, given the heterogeneously enhancing mass and faster growth of the former entity [17].

Treatment for PFHT is complete surgical resection. Although PFHT has low-grade malignant potential, the local recurrence rate is reportedly high—between 35 and 40%—which reflects the infiltrative nature of PFHT and the difficulty in obtaining a complete resection [1, 18]. The infiltrative nature of the tumor also poses challenges in diagnosing residual or recurrent PFHT after tumor resection, as both tumor and postoperative changes appear infiltrative at MRI. Adjuvant radiotherapy has been used by some authors [4]. Previous studies have not distinguished between rates of residual versus recurrent PFHT. In our series, 38% of patients had a positive resection margin after initial surgery, and subsequent histopathologically confirmed residual disease. No patient in our study with negative margins after initial surgery developed recurrent PFHT.

Metastases of PFHT are uncommon, with a low incidence of nodal and pulmonary metastases [4, 18]. Pulmonary metastases have been reported to occur both at initial diagnosis and up to 2 years after initial surgery [4]. One patient in our series developed both nodal and pulmonary metastases.

Limitations of this study include the small number of patients, all from a single institution, potentially limiting the generalizability of the results. However, the demographics, clinical presentation, and lesion locations in our cohort were similar to those in previous reports. The study was necessarily retrospective, due to the rarity of PFHT. The MRI studies available for review included studies performed at outside facilities; MRI protocols were not standardized, potentially limiting assessment of PFHT signal characteristics. Consensus readings were performed, as the number of cases was insufficient to allow meaningful assessment of inter-reader variability. The number of imaging studies other than MRI examinations is too small to allow meaningful conclusions about the imaging appearances of PFHT on those other imaging modalities; however, MRI is the dominant imaging modality for evaluation of soft tissue tumors, and MRI examinations were available for all patients in the study. The spectrum of imaging manifestations of PFHT may increase as more cases are reported.

In summary, PFHT often manifests with non-mass-like, plaque-like, infiltrative morphology on imaging, reflecting the typical growth pattern of this tumor in subcutaneous

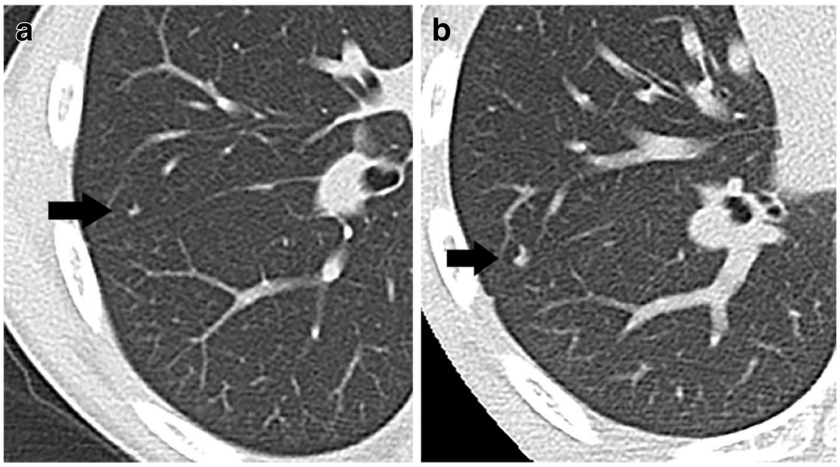

Fig. 7 A 6-year-old boy with PFHT of oral cavity and left submandibular region. The primary and subsequent residual tumor both were evident only on clinical examination, being occult on imaging. **a** Axial CT image of chest performed 1 year after initial diagnosis revealed a minute pulmonary nodule (*arrow*) in the right middle lobe, anterior to the major fissure. **b** A follow-up CT image obtained 15 months later shows slight interval growth of the nodule (*arrow*). The nodule was resected, and histopathologic analysis demonstrated metastatic PFHT

tissues. As a result of such growth and the fact that MRI only demonstrates macroscopic infiltration, residual PFHT is often present after initial surgical resection. The radiologist needs to maintain a high index of suspicion for residual PFHT on postoperative MRI, as the findings of residual tumor may be indistinguishable from those of postoperative changes—a point that should be made explicit in the imaging report.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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