Modern Pathology (2020) 33:1889–1895
https://doi.org/10.1038/s41379-020-0562-8

ARTICLE

Xanthogranulomatous epithelial tumor: report of 6 cases of a novel, potentially deceptive lesion with a predilection for young women

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Received: 17 March 2020 / Revised: 23 April 2020 / Accepted: 24 April 2020 / Published online: 15 May 2020

Abstract

Epithelial marker expression and/or epithelial differentiation, as well as "anomalous" expression of keratins, are features of some soft tissue tumors. Recently, we have encountered an unusual mesenchymal tumor composed of bland, distinctly eosinophilic, keratin-positive epithelial cells, which were almost entirely obscured by xanthogranulomatous inflammation. Six cases were identified (5 F, 1 M; 16–62 years (median 21 years)) arising in soft tissue ($n = 4$) and bone ($n = 2$) and ranging in size from 2 to 7 cm. The tumors were generally circumscribed, with a fibrous capsule containing lymphoid aggregates, and consisted in large part of a sheet-like proliferation of foamy histiocytes, Touton-type and osteoclast-type giant cells, and chronic inflammatory cells. Closer inspection, however, disclosed a distinct population of uniform, cytologically bland mononuclear cells with brightly eosinophilic cytoplasm arranged singly and in small nests and cords. Overt squamous and/or glandular differentiation was absent. By immunohistochemistry, these cells were diffusely positive with the OSCAR and AE1/AE3 keratin antibodies, and focally positive for high-molecular weight keratins; endothelial and myoid markers were negative and SMARCB1 was retained. RNA-seq identified a *PLEKHM1* variant of undetermined significance in one case, likely related to this patient's underlying osteopetrosis. Follow-up to date has been benign. In summary, we have identified a novel tumor of soft tissue and bone with a predilection for young females, provisionally termed "xanthogranulomatous epithelial tumor". These unusual lesions do not appear to arise from adnexa, or represent known keratin-positive soft tissue tumors, and the origin of their constituent epithelial cells is obscure. The natural history of this distinctive lesion appears indolent, although study of additional cases and longer term follow-up are needed.

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Introduction

Epithelial marker expression and/or overt epithelial differentiation are nearly constant features of selected soft tissue and bone neoplasms (e.g., epithelioid sarcoma, adamantinoma), while "aberrant" expression of keratins is relatively common in certain other mesenchymal tumors, in particular epithelioid endothelial tumors[1, 2], smooth muscle neoplasms[3–5] and subsets of rhabdomyosarcoma [6, 7]. In contrast, keratin expression and the presence of keratin-positive cells are not features of "fibrohistiocytic" tumors (e.g., fibrous histiocytoma), true histiocytic lesions (e.g., solitary/juvenile xanthogranuloma) or mesenchymal tumors typified by the presence of large numbers of histiocytes, multinucleated giant cells and/or osteoclasts, such as tenosynovial giant cell tumor and giant cell tumors of bone or soft tissue.

Recently, we have encountered a cohort of unusual masses of soft tissue and bone, initially thought to represent xanthogranulomatous inflammation or solitary xanthogranuloma, where close inspection and immunohistochemical study identified a very distinctive subpopulation of cytologically bland, keratin-positive epithelial cells. We sought to better characterize the clinicopathologic features of these "xanthogranulomatous epithelial tumors".

Materials and methods

Case selection

Approval for this study was granted by the Mayo Clinic Institutional Review Board. The 1st of these cases was identified during routine workup of a calf mass from an internal Mayo Clinic patient (Case 1). Subsequently, three identical cases were identified in our consultation archives. Following publication of our abstract in Modern Pathology [8], two identical cases were found in the consultation archives of two of the other authors of this study (KT, SV). Clinical information and including radiologic studies were obtained from existing institutional medical records and referring pathologists.

Immunohistochemistry

Immunohistochemistry was performed on deparaffinized, rehydrated sections obtained from a representative formalin-fixed, paraffin-embedded block from each case using antibody-specific epitope retrieval techniques with the Dako Envision (Dako, Carpinteria, CA, USA) automated system for detection of the following primary antigens: keratins (Covance, clone OSCAR, ≥ 1:40; Dako, AE1/3, 1:50; Dako, 34betaE12, 1:100; Dako, CK7, 1:50; Dako, CK20, 1:25; Leica, CK5/6, 1:100), p63 (Biocare, clone 4A4, 1:100), p40 (Biocare, clone BC28; 1:100), CD68 (Dako, KP1, 1:50-1:00), CD163 (Leica, 10D6, 1:200), CD11c (Leica, clone 5D11, 1:100), S100 protein (Dako, polyclonal rabbit S100, 1:400), CD31 (Dako, JC70A, 1:20-1:40), CD34 (Leica, QBEnd/10, 1:100), ERG (Ventana, EPR3864), FLI1 (BD Pharmigen, G146-254, 1:50), smooth muscle actins (Nordic Biosite, BS66, 1:100-1:400), desmin (Leica, DE-R-11, 1:50–1:100), BRAF V600E (Spring Biosciences, Clone VE1, mouse anti-human BRAF V600E monoclonal IgG2a antibody, 1:100), Langerin (Leica, 12D6, 1:50), anti-histone H3.3 G34W (RevMab Biosciences USA, RM263, rabbit monoclonal antibody, 1:100–1:200), GATA3 (Biocare, clone L50-823, 1:100), SMARCB1 (BD Biosciences, clone 25, 1:100) and SMARCA4 (Abcam, clone EPR3912, 1:100).

RNA sequencing (RNA-seq)

RNA-seq was performed as described previously [9]. mRNA isolation, cDNA synthesis, and library preparation were performed using TruSeq Stranded Total RNA Sample Preaation (Illumina, CA) for the fresh frozen sample according to the manufacturer's protocol; for FFPE samples, SureSelect^{XT} Human All Exon V7 exome (Agilent, CA). The sequencing was performed on Illumina HiSeq 2500 instrument using 101 PE reads. A customized bioinformatics pipeline for RNA-Seq analysis known as MAP-RSeq was used to assess specimens for fusions and RVBoost was used for calling eSNVs in PLEKHM1 [10, 11].

Results

Clinical features

The 6 tumors occurred in five women and one man, ranging from 16 to 62 years of age (median 21 years) and involved both soft tissue locations ($n = 4$; calf, thigh, back, leg) as well as bone ($n = 2$; T1-2 posterior elements, pubic ramus) (Table 1). The majority of the soft tissue cases arose in the subcutis ($n = 3$), while the depth of the fourth case was unknown; tumor sizes ranged from 2 to 7 cm (median 3.7 cm). The 20-year-old female who presented with a calf mass (Case 1) had a medical history consistent with Guibaud-Vainsel syndrome including mixed type III renal tubular acidosis secondary to carbonic anhydrase deficiency, osteopetrosis, and cerebral calcifications. No significant past medical histories or comorbidities were identified in the other five patients.

Radiologic findings

There were four patients with imaging studies available for review, two with bone (Cases 3 and 6) and two with soft

Table 1 Clinicopathologic features.

Case	Age/ Sex	Site (depth)	Size (cm)	Keratins					Vascular markers				S100	Desmin	SMARCB1	Original pathologist dx/ddx	Follow-up (months)
				AE1/3	OSCAR	34BE12	CK5/6	CK7	CD31	CD34	FLI1	ERG					
1	20/F	Calf (SQ)	3.7	P (D)	P (D)	P (R)	NP	NP	N	N	N	N	N	N	Ret	Not applicable	AWOD (15)
2	16/F	Back (N/A)	3.0	P (F)	NP	NP	NP	NP	N	N	N	N	N	NP	Ret	JXG, reticulohistiocytoma	AWOD (10)
3	20/F	T1-2	N/A	P (D)	P (R)	N	N	P (F)	NP	N	N	N	N	N	Ret	JXG, GCTB	AWD (3)
4	22/F	Thigh (SQ)	6.5	P (D)	P (F)	P (R)	N	P(F)	N	N	N	N	N	N	Ret	Giant cell containing neoplasm	AWOD (6)
5	23/M	Thigh (SQ)	2.0	P (D)	P (R)	P (F)	P(D)	P(F)	N	N	N	N	N	N	Ret	Giant cell rich neoplasm	AWOD (3)
6	62/F	Pubic ramus	7.0	P(D)	P (D)	N	N	P(D)	N	N	N	N	N	N	Ret	Fibrohistiocytic proliferation	AWD (3)

N/A not available, *SQ* subcutaneous, *P* positive, *N* negative, *D* diffuse, *WD* weak diffuse, *F* focal, *R* rare, *NP* not performed, *Ret* retained, *Dx* diagnosis, *Ddx* differential diagnosis, *JXG* juvenile xanthogranuloma, *GCTB* giant cell tumor of bone, *AWOD* alive without disease, *AWD* alive with disease.

tissue lesions (Cases 1 and 5). The imaging studies included MRI for all four, CT for two and radiographs for one patient. Both of the soft tissue masses were located in the subcutaneous tissues, one in the calf and one in the thigh. The soft tissue masses had nonspecific imaging features presenting as solid heterogeneous masses, with soft tissue attenuation on CT and intermediate T1 signal, hyperintense T2 signal and avid enhancement on MRI (Fig. 1). The osseous lesion in the thoracic spine was located in the posterior elements of T1 and T2, where it presented as a lytic lesion with a peripheral rim of sclerosis on CT (Fig. 2). The latter mass had intermediate signal intensity on T1, heterogeneous but predominantly intermediate to low signal intensity on T2 and showed avid enhancement with gadolinium. The second osseous lesion involved the left superior pubic ramus and anterior column of the acetabulum and presented as an expansile lytic lesion with a peripheral rim of sclerosis around portions of the lesions, but with loss of definition of the cortex in other areas on the radiographs. The MRI of the latter lesion showed a large mass with nonspecific T1 intermediate and T2 hyperintense signal intensity with either marked expansion or an associated soft tissue mass anteriorly.

Morphologic features

The soft tissue-based tumors were circumscribed, surrounded by a fibrous capsule containing lymphoid aggregates, and consisted in large part of a sheet-like proliferation of foamy histiocytes, Touton-type giant cells, osteoclast-type giant cells and mixed chronic inflammatory cells (Fig. 3a, b). The fragmented nature of the bone specimens made evaluation of the low power architecture difficult, although these lesions also consisted for the most part of a xanthogranulomatous infiltrate. Closer inspection of both soft tissue and bone lesions disclosed a distinctive population of small, uniform, mononuclear cells with brightly eosinophilic cytoplasm, and normochromatic, round to reniform nuclei with pinpoint nucleoli, arranged singly and in small nests and cords (Fig. 3c, d). In some cases this mononuclear population was easily recognizable, while in other cases identification of these cells required close study of multiple high-powered microscopic fields (Fig. 3e). Overt squamous and/or glandular differentiation was absent in all cases. Necrosis was present in only one case (Fig. 3f), and mitotic activity was very low (less than 1 mitotic figure per 20 high power fields). Atypical mitotic figures were absent.

Immunohistochemistry

By immunohistochemistry, the mononuclear cell population was generally diffusely positive with the AE1/AE3 keratin antibodies, and more variably positive with the OSCAR antibody, CK7, and high-molecular weight keratins (Fig. 4;

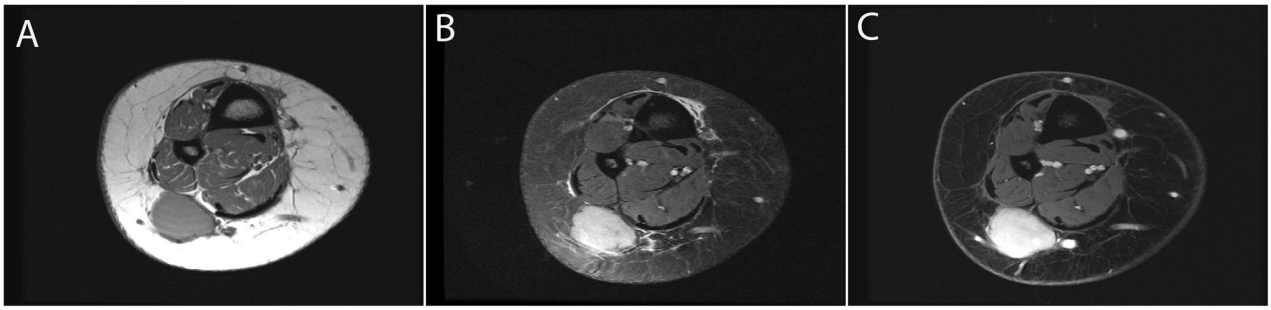

Fig. 1 Radiologic images of the soft tissue masses. Axial T1 (**a**), fat suppressed T2 (**b**) and gadolinium-enhanced SPGR (**c**) MR images show a well-circumscribed solid heterogeneous enhancing mass in the subcutaneous tissues with predominantly intermediate signal on T1 and increased signal on T2. The imaging features are nonspecific and therefore, the mass is indeterminate and suspicious for a soft tissue sarcoma.

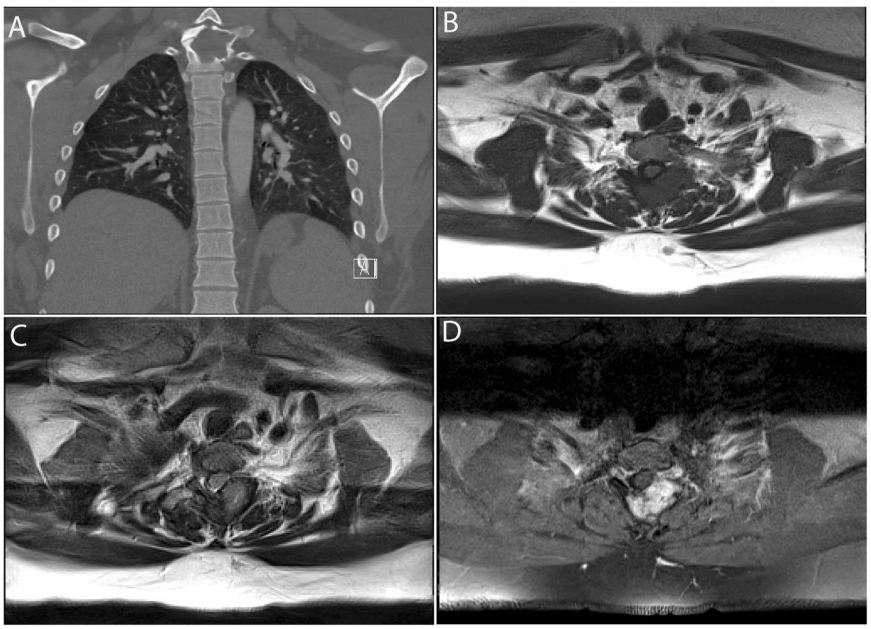

Fig. 2 Radiologic features of the osseous lesions. Coronal CT (**a**), axial T1 (**b**), axial T2 (**c**) and axial gadolinium-enhanced (**d**) MR images show a lytic expansile lesion involving the posterior elements of T1 and T2 with a peripheral rim of sclerosis. The lesion shows intermediate signal on T1, intermediate to low signal of T2, and enhances avidly with gadolinium. The mass has indolent imaging features with differential diagnosis including entities such as fibrous dysplasia, tenosynovial giant cell tumor, and low grade central osteosarcoma.

Table 1). All other tested markers, including CK20 (0/4), p63 (0/3), p40 (0/3) and GATA3 (0/3), were negative on these cells; SMARCB1 (5/5) and SMARCA4 (3/3) expression was retained. As would be expected, the histiocytic component expressed CD68, CD11c, and CD163. BRAF V600E ($n = 4$) and Langerin ($n = 2$) were evaluated in subsets of cases, and were negative. Histone H3G34W, performed on the 2 bone tumors to exclude an unusual manifestation of giant cell tumor of bone, was negative.

RNA-seq

RNA-seq was performed on two cases. A *PLEKHM1* variant of undetermined significance was identified in Case 1 involving a histidine to proline change at codon 98, while Case 2 was negative for genetic alterations. Mutations of *PLEKHM1* have been reported in osteopetrosis, which this patient had.

Clinical follow-up

Follow-up was available on all cases ranging from 3 to 15 months (median 4.5 months). Three of the 4 patients with soft tissue lesions were treated with complete surgical excision, while the fourth patient underwent only excisional biopsy; these patients remain recurrence-free (range 3 to 15 months, median 8 months). Resection of the pubic ramus lesion is forthcoming, while the T1-2 mass appears stable after biopsy.

Discussion

Keratin expression was once thought to be unique feature of epithelial neoplasms, and one that would allow their discrimination from tumors of other lineages [12, 13]. However,

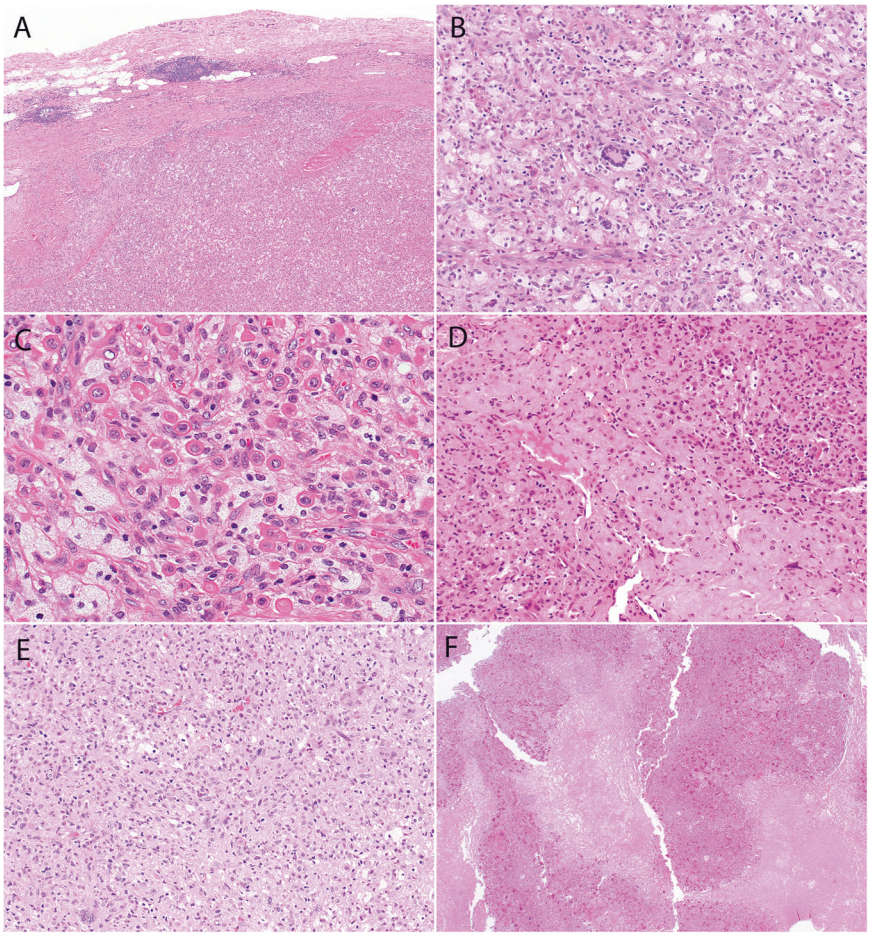

Fig. 3 Histologic features of xanthogranulomatous epithelial tumor. Low power histologic examination of xanthogranulomatous epithelial tumor reveals a circumscribed lesion with a fibrous capsule and surrounding lymphoid aggregates (**a**). The predominant feature of these tumors is often a prominent xanthogranulomatous proliferation composed of histiocytes, osteoclast-type giant cells, Touton-type giant cells (**b**). However, closer inspection reveals a distinct population of plump epithelioid cells with prominent eosinophilic cytoplasm (**c**) which occasionally form cords or small clusters in a densely collagenous stroma (**d**). Occasionally, these eosinophilic mononuclear cells are sparse and difficult to appreciate (**e**). A single case in our series showed geographic necrosis (**f**).

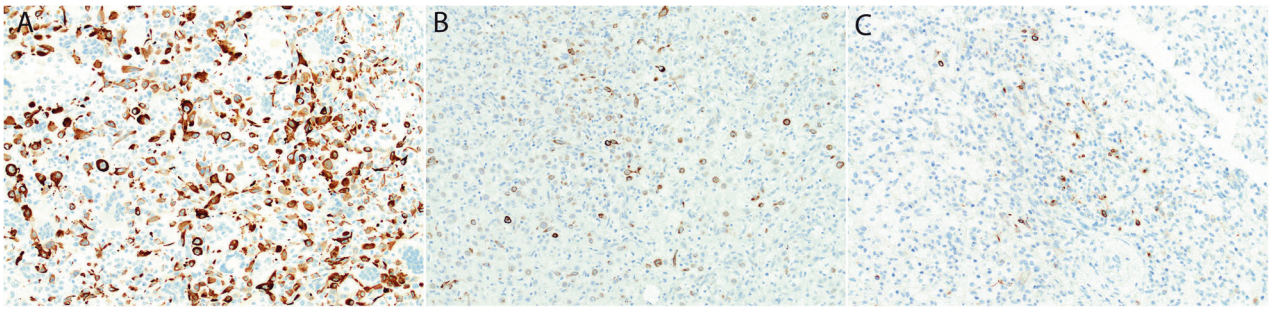

Fig. 4 Immunoprofile of xanthogranulomatous epithelial tumor. By immunohistochemistry, the eosinophilic mononuclear cells typically show diffuse expression of keratin AE1/3 (**a**) with more variable keratin OSCAR (**b**) and high-molecular weight cytokeratin staining (**c**).

over the past 50 years it has become abundantly clear that keratin expression can be seen in a variety of mesenchymal tumors. Keratin expression in mesenchymal tumors falls roughly into three categories: (1) mesenchymal tumors in which keratin expression or the presence of keratin-positive cells is characteristic or even definitional (e.g. synovial sarcoma, epithelioid sarcoma, adamantinoma), (2) "anomalous" or "aberrant" keratin expression in tumors derived from mesenchymal cells which may normally express keratins (e.g., endothelial cells and angiosarcomas, smooth muscle cells and leiomyosarcomas), and (3) aberrant (and often confusing) keratin expression in tumors typically thought of as keratin negative, such as Ewing sarcoma and osteosarcoma [14–19]. In general, mesenchymal tumors showing aberrant keratin expression demonstrate expression only of low-molecular weight isoforms, whereas those sarcomas *characterized* by the presence of keratin-positive cells often express both low and high-molecular weight isoforms. In tumors having "small cell" morphology, aberrant keratin expression often displays a "dot-like" pattern.

Although the list of potentially keratin-positive mesenchymal tumors is by now fairly long, aberrant keratin expression is not a feature of so-called fibrohistiocytic tumors, such as fibrous histiocytoma or dermatofibrosarcoma protuberans, or of lesions of apparent histiocytic origin, such as solitary/juvenile xanthogranuloma and xanthoma. Furthermore, keratin expression in the tumors reported herein is confined to a morphologically distinctive subset of lesional cells, and does not represent simply aberrant keratin immunoreactivity (or nonspecific immunolabeling) in solitary xanthogranuloma or a xanthogranulomatous inflammatory process. Furthermore, the subcutaneous and osseous origins of these lesions would be quite unusual in solitary xanthogranuloma, a tumor that most often occurs in the skin. In addition, the keratin-positive cells of these lesions show an immunophenotype characteristic of complex or stratified epithelia, with expression of high-molecular weight keratins (identified by the 34betaE12 antibody and to a lesser degree by AE1/AE3) and low-molecular weight keratins (identified by the OSCAR clone and AE1/AE3).

Although we have little doubt that these novel tumors of soft tissue and bone contain a cell population showing epithelial differentiation, the exact nature of this epithelium is obscure. Although the distinctly eosinophilic cytoplasm of these cells suggests squamous differentiation, intercellular bridges and squamous pearls were not present. Similarly, although the nested or cord-like growth pattern observed focally in some cases raised the possibility of a glandular lesion, glands and/or papillary structures were absent. It also seems highly unlikely that these epithelial cells represent entrapped or proliferating non-neoplastic elements, as the soft tissue masses grew in a generally circumscribed fashion within the subcutis, without involvement of overlying dermal adnexa, and 2 cases arose in bone (and not in the tibia or fibula). We speculate that the presence of these epithelial cells in soft tissue and bone locations reflects a yet-to-be discovered genetic event in a multipotential stromal cell capable of limited epithelial differentiation or perhaps some form of remnant of embryonic development. Possibly the striking xanthogranulomatous reaction to these cells represents a "landscape effect" induced by cytokine production by the neoplastic cells themselves, as seen in tenosynovial giant cell tumor and giant cell tumor of bone [20, 21].

The identification of a pleckstrin homology domain containing, family M [with RUN domain] member 1 (*PLEKHM1)* mutation in a single case is intriguing. Mutations in the *PLEKHM1* gene were first implicated in osteopetrosis in incisor-absent rats by Van Wesenbeeck and colleagues and later found to be involved in an intermediate type of osteopetrosis in humans [22]. Aberrations in the PLEKHM1 protein lead to decreased interaction with Rab7, a small molecular GTPase, ultimately resulting in disturbances in endocytosis and autophagy [23]. Interestingly, Almarzooqi et al. reported a newborn with infantile osteopetrosis secondary to *PLEKHM1* mutation and coexistent juvenile xanthogranuloma of the liver [24]. While it is tempting to speculate that *PLEKHM1* alterations may play a role in the histiocytic/giant cell-rich background of xanthogranulomatous epithelial tumor, the second case evaluated by RNA seq in our study was wild-type for this gene, and no other patients in our study had evidence of osteopetrosis. To the best of our knowledge, there are no other known reports of xanthogranulomatous lesions presenting in patients with altered *PLEKHM1*.

When these tumors arise in soft tissue, the differential diagnosis includes tumors with prominent xanthogranulomatous inflammation as well as epithelioid vascular neoplasms, myogenic tumors and epithelioid sarcoma. The closest morphologic mimics, solitary (juvenile) xanthogranuloma and tenosynovial giant cell tumor, may be differentiated by their lack of keratin-positive mononuclear cells, while the immunoprofile of the tumors in our cohort also helps to exclude vascular and myogenic neoplasms with anomalous keratin expression, in particular pseudomyogenic hemangioendothelioma. Pseudomyogenic hemangioendotheliomas, characterized by *SERPINE1-FOSB* fusions, are composed of plump epithelioid cells with glassy cytoplasm. Furthermore, myogenic neoplasms such as leiomyosarcoma are distinguished by cytologically atypical spindle cells with blunt ended nuclei, features lacking in this tumor. Epithelioid sarcoma may also be a diagnostic consideration, especially when necrosis is present, but the very bland cytologic features of xanthogranulomatous epithelial tumor and retained expression of SMARCB1 should allow this distinction without great difficulty.

Xanthogranulomatous epithelial tumors presenting as osseous masses may mimic a variety of giant cell-rich bone lesions. The presence of mononuclear cells with reniform/grooved nuclei admixed with giant cells could lead to the consideration of Langerhans cell histiocytosis; however, the absence of Langerin and S100 protein expression would argue against this possibility. Giant cell tumors of bone show a sheet-like proliferation of osteoclast-like giant cells, usually lack xanthogranulomatous features, and are keratin-negative, H3G34W-positive. The morphologic features of xanthogranulomatous epithelial tumor are obviously quite different from other keratin-positive tumors of bone, such as osteofibrous dysplasia, adamantinoma, or adamantinoma-like Ewing sarcoma. Finally, any keratin-positive bone lesion raises the possibility of metastatic disease. Fortunately, xanthogranulomatous epithelial tumors seem to exhibit a predilection for young adults, and careful inspection of the keratin-positive population fails to demonstrate

the degree of atypia and/or mitotic activity expected in metastatic carcinoma. Clearly, it would be prudent to exclude metastatic carcinoma on clinical grounds.

In summary, we have reported the clinicopathological features of a distinctive tumor of soft tissue and bone, characterized by the presence of small numbers of cytologically bland epithelial cells and a striking xanthogranulomatous reaction, provisionally termed "xanthogranulomatous epithelial tumor". These lesions preferentially occur in young females and may arise at both bone and soft tissue sites. The natural history of this unusual lesion appears to be favorable, although study of additional examples and longer clinical follow-up are needed. Awareness of this entity and application of a limited panel of immunohistochemical markers should allow its ready distinction from other tumors of soft tissue and bone containing epithelial or xanthogranulomatous elements.

Compliance with ethical standards

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

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