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Review Article

Skin and superficial soft tissue neoplasms with multinucleated giant cells: Clinical, histologic, phenotypic, and molecular differentiating features

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ABSTRACT

Multinucleated giant cells (MGC) are commonly seen in an array of neoplastic and non-neoplastic conditions, to include: granulomatous dermatitis, fibrohistiocytic lesions such as xanthogranulomas, and soft tissue tumors such as giant cell tumors of soft tissue. In addition, multinucleated giant cells are infrequently seen in melanoma, squamous cell carcinoma, and atypical fibroxanthoma. There are many different types of MGCs and their presence, cytologic, and immunohistochemical features within these pathologic entities vary. Thus, correct identification of the different types of MGCs can aid the practicing pathologist in making the correct diagnosis of the overall pathologic disease. The biologic diversity and variation of MGCs is currently best exemplified in cytologic appearance and immunohistochemical profiles. However, much remains unknown about the origination and evolution. In this review, we i) reflect on the various types of MGCs and the current understanding of their divergent development, ii) describe the histologic, immunohistochemical, and molecular (if previously reported) differentiating features of common skin and superficial soft tissue neoplasms that may present with multinucleated giant cells.

1. Introduction

Multinucleated giant cells (MGC) are a group of cells that may be identified in a variety of biologically diverse processes, to include benign and malignant neoplastic entities, as well as infectious and non-infectious chronic inflammatory conditions. MGC are vital to tissue remodeling/repair and they are uniquely derived from the fusion of cells of the monocyte/macrophage lineage. In the process of giant cell formation, monocytes, macrophages and epithelioid cells cluster together in response to a diverse array of stimuli which are produced because of the surrounding tissue pathology [1].

MGC display a considerable amount of phenotypic variation, supported by differences in the immunohistochemical expression between various types of MGC. This variation is widely believed to be due to the influence of a variety of different chemical and physical stimuli which can be present in the local environment during MGC formation, adhesion, maturation, and survival. Even though theories exist to explain the development and differentiation of MGC, much remains to be discovered about their development, including the chemical composition and cell to cell interactions of the local environment [2].

Various types of multinucleated giant cells are commonly seen in skin and soft tissue diseases, including Touton-like giant cells in juvenile xanthogranuloma (JXG), necrobiotic xanthogranuloma, xanthoma, and dermatofibroma (DF); floret-like giant cells in giant cell fibroblastoma and multinucleated cell angiohistiocytoma; and foreign body type giant cells in reticulohistiocytoma and DF; osteoclast-like giant cells in soft tissue giant cell tumor, DF, and atypical fibroxanthoma (AFX) and glassy giant cells in multicentric reticulohistiocytosis and xanthogranuloma (in adults) [3].

One theory to explain the variation in phenotype between MGC suggests that monocyte/macrophage fusion is induced by several cytokines; however, different combinations of cytokine exposure can lead to morphologic variants of MGC. For example, bone marrow-derived macrophages have the capacity to differentiate into osteoclasts in response to macrophage colony-stimulating factor (M-CSF) and receptor activator for nuclear factor (NF)-κB ligand (RANKL). In contrast, interleukin (IL)-4 or IL-13, or a combination of IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) induce the formation of foreign body-type giant cells from human monocyte-derived macrophages. On the other hand, interferon gamma (IFN-γ) and IL-3 are

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responsible for the development of Langhans giant cells. It has been suggested that cytokines such as (IFN)-γ, IL-3, and M-CSF may also play essential roles in the production of Touton giant cells [4].

The variation among MGC phenotypes can be exemplified by the differences in cytologic and immunohistochemical profiles. Touton-like giant cells are characterized by a central ring of nuclei with central, homogeneous eosinophilic cytoplasm and outer peripheral cytoplasm with a foamy appearance due to high lipid content. This type of MGC shows immunoreactivity for lysozyme, alpha 1-anti-trypsin, and alpha 1-anti-chymotrypsin [5,6]. Osteoclast-like giant cells have abundant eosinophilic, finely granular, or homogeneous cytoplasm containing up to 100 uniform oval nuclei, with small nucleoli and peripheral chromatin. These cells exhibit immunoreactivity for osteoclast biomarkers such as CD45, CD51, and CD68 and lack of reactivity for CD163 [7]. It is proposed that Osteoclast-like giant cells develop their phenotypic profile when precursor macrophage/monocytes are induced by RANKL to express several different integrins and receptors, such as $\alpha_v\beta_3$, $\alpha_2\beta_1$, collagen-laminin receptor, $\alpha_v\beta_1$, and vitronectin receptor, of which $\alpha_v\beta_3$ is the predominant osteoclast integrin [2].

Floret-like giant cells have hyperchromatic, wreath-like nuclei with surrounding eosinophilic cytoplasm. These cells express vimentin and CD34 but are negative for S100 and CD68 [8]. Glassy giant cells are histiocytes with abundant dense, pink, glassy cytoplasm and either randomly distributed nuclei (as in the foreign body type giant cells) or nuclei located at the periphery of the cells (as in Langhans giant cells). This type of MGC is positive for TRAP, CD68, lysozyme, and HAM-56 [9].

The origination, evolution, and exact functions of the many types of MGC seen in skin and soft tissue tumors is currently not completely understood, but their identification and correct classification within and among these lesions can aid in making a correct overall diagnosis. Here we describe the clinical, histologic, phenotypic, and molecular features (if available) of clinically encountered skin and superficial subcutaneous tumors with multinucleated giant cells: squamous cell carcinoma (SCC) with giant cells, melanoma with giant cells, atypical fibroxanthoma (AFX), dermatofibroma (DF), reticulohistiocytosis, juvenile xanthogranuloma (JXG), plexiform fibrohistiocytic tumor (PFHT), and giant cell tumor of the soft tissue (GCTST). The features we described may be useful for differentiating these tumors from one another.

2. Squamous cell carcinoma with giant cells

Squamous cell carcinoma with giant cells is a rare variant of SCC. Most cases have been described in elderly patients with increased sun exposure [10]. Studies suggest that SCC with giant cells may be associated with high-risk features such as moderate to poor differentiation, greater tumor size, more aggressive behavior and worse outcome compared to conventional SCC [11]. Additionally, SCC with giant cells is more common in recipients of solid organ transplants than in the general population, when compared to conventional SCC [12]. SCC with giant cells usually presents as an exophytic, ulcerated lesion and is often associated with spontaneous bleeding. The most common location is the head and neck region; lesions on the trunk and upper extremities are less commonly reported [10,11]. In a review by Chung et al., it is reported that patients with SCC with giant cells have rates of recurrence and nodal metastasis after excision of 33% and 17%, respectively [10]. Osteoclast-like giant cells (OGCs) are the predominate type of MGC in cases of SCC with giant cells in the previous reports and are thought to be a reactive process [13].

Histologically, tumors are composed of moderate-to-poorly differentiated (round to spindle shape) epithelioid cells with hyperchromatic nuclei that infiltrate the dermis in a whorl-like pattern (Fig. 1A and B) (Table 1) [11,14]. Most of the previously reported cases show presence of a sarcomatoid component of SCC [13]. Tumors may or may not be connected to the basal layer of the epidermis (Fig. 1A). Deep penetration into the dermis, subcutaneous fat, and underlying fascia may be seen. Typical or atypical *mitotic* figures are common and osteoclast-like multinucleated giant cells may feature prominently. The giant cells are composed of abundant eosinophilic cytoplasm with multiple nuclei (Fig. 1B). Multinucleated cells are generally evenly distributed throughout the dermis and are occasionally aggregated. The nuclei may be haphazardly arranged or peripherally organized [10-14].

Immunohistochemically, the infiltrating malignant cells are positive for high-molecular-weight cytokeratin, epithelial membrane antigen (EMA), 34 beta E12 (Fig. 1C), p63 (Fig. 1D), and AE1/AE3 and often negative for CAM5.2. The giant cells exhibit diffuse and strong expression of CD68 (Fig. 1E) but are negative for cytokeratins [13].

Various well-known cancer-associated gene mutations, including *TP53*, *CDKN2A*, *NOTCH1*, *AJUBA*, *HRAS*, *CASP8*, *FAT1*, and KMT2C (MLL3) and three tumor suppressor gene mutations including NOTCH2, PARD3, and RASA1 were found in cutaneous SCC. KMT2C mutations have been reported to predict increased risk of invasion and worse disease-outcome in patients with SCC. However, no molecular profiles have been established to distinguish SCC with MGC from conventional SCC [15].

The differential diagnosis of SCC with MGC, includes AFX (negative for cytokeratins and commonly negative for p63), spindle cell melanoma (negative for cytokeratins and positive for melanocytic markers such as MART1, SOX10, and HMB45 antigen), and leiomyosarcoma (positive for smooth muscle actin and desmin and negative for cytokeratins). Morphologically, distinguishing SCC from these other conditions can be difficult in the absence of keratin pearls or connection to the overlying epidermis [13].

In most cases, the preferred treatment option for SCC with giant cells is removal of the entire tumor by wide surgical excision. This may be followed by radiation therapy and/or chemotherapy. In cases with metastasis, a combination of chemotherapy and radiation therapy, and/or targeted therapy or immunotherapies may be used [16].

3. Melanoma with giant cells

The presence of multinucleated giant cells in melanoma is rare; these cells are more frequently associated with melanocytic nevi [17]. However, multinucleated giant cells have been reported in desmoplastic melanomas, balloon cell melanomas, clear cell sarcomas, lentigo malignas, and some regressing melanomas [18-21]. Different types of giant cells have been reported to be associated with melanoma, including osteoclast-like giant cells [22], Touton-like giant cells [23], and foreign body type giant cells [24].

To our knowledge, only seven cases of melanoma with osteoclast-like giant cells have been reported in the literature [24]. The origination of giant cells in melanoma remains unknown. One theory suggests that melanocytes can differentiate into osteoclast-like giant cells, while another theory favors the idea that osteoclast-like giant cells are reactive macrophages [22].

Interestingly, only three patients with melanoma with Touton-like MGCs have been reported. All three patients were older than 70 years of age and presented with amelanotic melanoma [24]. One patient had atypical fibroxanthoma-like melanoma, and the other two had xanthogranuloma-like melanoma [24]. Medina et al. reported a case of a Spitzoid Melanoma with Touton-like, osteoclast-like and foreign body giant cells in a 15-Year-old girl [24].

Histologically, melanoma with giant cells is composed of atypical cells with hyperchromatic nuclei admixed with large scattered multinucleated giant cells (Fig. 2A and B) of different types, including osteoclast-like, and Touton-like. Melanoma with giant cells may present with different morphological features, including spindle cell (Fig. 2A), nodular, desmoplastic, and pleomorphic. Melanocytic tumor cells may or may not contain melanin pigment [17-24].

On immunohistochemical study, tumor cells are positive for melanocytic markers, including S100 (Fig. 2C), SOX10 (Fig. 2D), MART1/

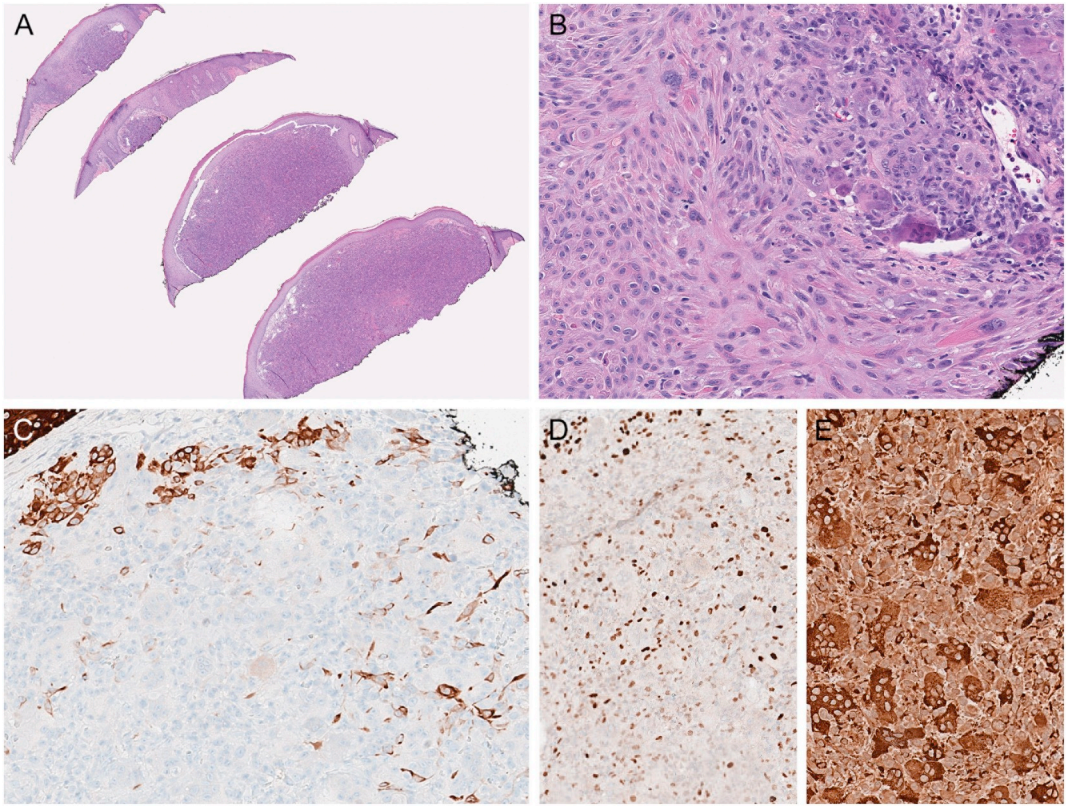

Fig. 1. Microscopic findings in SCC with giant cells.
(A) Representative section of specimen from shave biopsy of the skin showing (A) diffuse basophilic cellular proliferation in at least the dermis and focal epidermis (hematoxylin-eosin [H&E], ×20).
(B) Representative section showing atypical spindle to epithelioid cells with eosinophilic cytoplasm and pleomorphic and hyperchromatic nuclei that infiltrate the dermis in a whorl-like pattern. Admixed multinucleated giant cells are seen at right (H&E, ×400).
(C–E) Representative immunohistochemically stained sections showing expression of (C) high-molecular-weight keratin (34 beta E12, patchy) and (D) p63 by tumor cells and (E) CD68 by associated multinucleated giant cells (×400).

Melan-A (Fig. 2E), and HMB45 (Fig. 2F). The multinucleated giant cells are negative for melanocytic markers and in most cases positive for CD68, vimentin, p16, and microphthalmia transcription factor-1 (MITF1) [17-24].

Several molecular pathways are altered in melanocytic tumors. The three most frequently altered pathways are RAS-RAF-MEK-ERK (through mutation of *BRAF*, *NRAS*, or *KIT*), p16 INK4A-CDK4-RB (through mutation of *CDKN2A* or *CDK4*), and ARF-p53 (through mutation of *ARF* or *TP53*). Less frequently altered pathways include PI3K-AKT (through mutation of *NRAS*, *PTEN*, or *PIK3CA*) and the canonical Wnt signaling pathway (through mutation of *CTNNB1* or *APC*) [25]. *BRAF* mutations are common in superficial spreading melanoma, and *NRAS* mutations are common in nodular melanoma. *BRAF* mutations are also present in spindle cell melanoma, albeit at a much lower frequency than in superficial spreading melanoma, and *NRAS* and *KIT* mutations are exceptionally rare in spindle cell melanoma and desmoplastic melanoma [26-28].

The differential diagnosis of melanoma with giant cells includes AFX, fibrous histiocytoma, necrobiotic xanthogranuloma, xanthelasma, foreign body reaction, Langerhans cell histiocytosis, and metastatic visceral carcinoma with giant cells [17-24]. All these tumors can be differentiated from melanocytic lesions by the lack of expression of melanocytic markers.

We are aware of no published long-term prospective study on the outcome of melanoma with giant cells. However, studies have shown that melanomas with multinucleated giant cells had a similar rate of recurrence and metastasis, compared to melanomas without multinucleated giant cells and multinucleated giant cells phenotype is not associated with shorter survival [29].

4. Atypical fibroxanthoma

AFX is a rare primary mesenchymal neoplastic skin disease that usually presents as a nodular and/or ulcerative lesion. AFX was first described by Helwig in 1963 as a nodule with characteristically marked cellularity lacking any distinctive pattern of growth and exhibiting significant nuclear pleomorphism [30].

AFX commonly occurs in sun-exposed areas of the head or neck, although it can also occur in other sun-exposed areas, and commonly occurs in elderly individuals—predominantly non-Hispanic white males, although it can occur in individuals of any racial or ethnic background. The average age at diagnosis is 72 to 80 years [31]. However, it may also be seen in children with xeroderma pigmentosum and, rarely, in children without this condition [32,33]. Though the pathogenesis of AFX is unclear, exposure to ultraviolet radiation is a major contributing factor [34]. The origin of AFX has been a topic of debate since the 1960s; however, immunohistochemical analysis suggests that AFX most likely originates from myofibroblasts or fibroblast-like cells [35]. AFX is associated with a favorable prognosis [35].

Histologically, AFX usually shows a well-circumscribed, nonencapsulated, highly cellular dermal nodule (Fig. 3A) that is contiguous with the epidermis or separated from the epidermis by a grenz zone of uninvolved dermis. AFX is composed predominantly of atypical spindle-shaped tumor cells (~72% of tumor cells) with frequent mitotic figures (including many atypical mitotic figures) and bizarre multinucleated cells in various proportions arranged in haphazard, fascicular, or

Table 1
Summary of histologic, immunohistochemical, and molecular differentiating features and differential diagnosis of neoplasms with multinucleated giant cells.

Tumor type	Histologic features	Immunohistochemical features	Type(s) of giant cells	Molecular features	Other diseases to be considered in the differential diagnosis
SCC with giant cells	- Moderate-to-poorly differentiated (round to spindle shape) epithelioid cells with hyperchromatic nuclei that infiltrate the dermis - Most cases show sarcomatoid component - Frequent typical or atypical mitotic figures, deep penetration to the dermis, subcutaneous fat, and underlying fascia - Giant cells are generally evenly distributed throughout the dermis and are occasionally aggregated	SCC: Positive for high-molecular weight cytokeratin, EMA, 34 beta E12, p63, and AE1/AE3 Giant cells: positive for CD68	Osteoclastic	Gene mutations: TP53, CDKN2A, NOTCH1, AJUBA, HRAS, CASP8, FAT1, and KMT2C (MLL3) Tumor suppressor gene mutations: NOTCH2, PARD3, and RASA1	- AFX - Spindle cell melanoma - Spindle cell sarcoma - Leiomyosarcoma
Melanoma with giant cells	- Composed of atypical cells with hyperchromatic nuclei; may or may not contain melanin pigments - Melanoma may present with different morphological features, including, spindle cell, nodular, desmoplastic, and undifferentiated type - Large scattered multinucleated giant cells of different types - Deep infiltration into the dermis and subcutaneous adipose tissue may be seen	Tumor cells: positive for HMB45, Melan-A, SOX10, and S100 Multinucleated giant cells: negative for melanocytic markers and in most cases positive for CD68, vimentin, P16, and microphthalmia transcription factor (MITF1)	Touton-like Osteoclastic Foreign body type giant cells	- RAS-RAF-MEK-ERK pathway (through mutation of *BRAF*, *NRAS*, or *KIT*) - p16 INK4A-CDK4-RB pathway (through mutation of *CDKN2A* or *CDK4*) - ARF-p53 pathway (through mutation of *ARF* or TP53) - PI3K-AKT pathway (through mutation of *NRAS*, *PTEN*, or *PIK3CA*) - WNT signaling pathway (through mutation of *CTNNB1* or *APC*)	- Benign melanocytic lesion - AFX - Fibrous histiocytoma - Necrobiotic xanthogranuloma - Xanthelasma - Foreign body reaction - Langerhans cell histiocytosis - Metastatic visceral carcinomas with giant cell features
AFX	- Spindle to round or epithelioid tumor cells arranged in haphazard or fascicular pattern - Bizarre multinucleated pleomorphic cells present - Frequent mitotic figures; many atypical mitotic figures - Grenz zone - Background solar elastosis	Positive for procollagen type 1, CD10, S100A6, vimentin, alpha 1-antitrypsin, alpha 1-antichymotrypsin HAM56, and CD68	Osteoclastic	- Mutation in *COL11A1*, *ERBB4*, *CSMD3*, and *FAT1* - Deletion of segments of chromosome arms 9p and 13q - No gene fusions	- Spindle cell SCC - Melanoma - Pleomorphic sarcoma - Dermatofibrosarcoma protuberans
DF	- Dermal proliferation of bland, spindle to histiocytoid cells - Characteristic collagen trapping at periphery - Overlying epithelial basilar induction with hyperpigmentation - Grenz zone - Numerous morphologic variants: Fibrocollagenous, aneurysmal, clear cell, hemosiderotic, lipidized, atypical, cellular, epithelioid, angiomatous, granular cell, halo, osteoclastic, myofibroblastic, myxoid, keloidal, palisading, and atrophic	- Positive for factor XIIIA, CD10, CD163, HMGA1/HMGA2 - CD68 highlights histiocytic-appearing cells - Epithelioid DF: often positive for ALK-1	Touton-like Foreign body-like Osteoclast-like Floret-like	Epithelioid-type DF: clonal *ALK* gene rearrangement resulting in *VCL–ALK* and *SQSTM1–ALK* gene fusions	- Dermatofibrosarcoma protuberans - AFX - Amelanotic spindle cell melanocytic tumor - Angiosarcoma - Kaposi sarcoma
Reticulo-histiocytoma	- Diffuse infiltration of numerous large, mononucleated or multinucleated histiocytes in the dermis - Lymphocytes and dermal fibrosis - Cells have a dense pink cytoplasm, variously referred to as “oncocytic” or “ground glass”	- Positive for CD163, CD68, lysozyme (variably), vimentin, and microphthalmia transcription factor (MITF1) - Focal reactivity for factor XIIIa and S100 protein - Variable positivity for CD31, CD43, and CD45	Glassy Touton-like	None yet reported	- Rosai-Dorfman disease - JXG - Epithelioid fibrous histiocytoma - Melanocytic lesion - Epithelioid sarcoma - Histiocytic sarcoma - Langerhans cell histiocytosis - Infectious granuloma
JXG	- Predominantly histiocytes - Varying morphologies: vacuolated, xanthomatized, scalloped, oncocytic, spindle-shaped	- Positive for factor XIIIa, CD68, CD163, CD14, and fascin - Negative for S100 and CD1a	Touton-like	- Mutations in several MAPK pathway genes, including *ARAF*, *KRAS*,	- Langerhans cell histiocytosis - Dermatofibroma - Spitz nevus

(*continued on next page*)

Table 1 (*continued*)

Tumor type	Histologic features	Immunohistochemical features	Type(s) of giant cells	Molecular features	Other diseases to be considered in the differential diagnosis
	- Admixed lymphocytes, eosinophils, occasional neutrophils and plasma cells, and giant cells - Touton-like giant cells are characteristic			*MAP2K1*, and *NRAS*, in cases with systemic involvement - Rarely mutations in *PIK3CA*, *NF1*, and *BRAF V600E*	- Papular xanthoma
Plexiform fibrohistiocytic tumor	- Poorly circumscribed - Three morphologic types: fibroblastic, histiocytic, mixed - Fascicles of spindle fibroblastic cells - Aggregates of epithelioid histiocytoid cells - Osteoclast-like giant cells common - Low mitotic rate; usually no cellular pleomorphism	Fibroblastic cells: positive for vimentin and HHF35; focally positive for smooth muscle actin and calponin Histiocytic cells: positive for CD68 Osteoclast-like giant cells: positive for CD68	Osteoclast-like	- All analyzed cases diploid - Simpler karyotype of 46,XY,t(4;15)(q21; q15) - Complex karyotype with numerous deletions	- Cellular neurothekeoma - Plexiform neurofibroma - Fibrous hamartoma of infancy - Giant cell tumor of soft tissue - Fibromatosis - DF - Nodular fasciitis - Ossifying fibromyxoid tumor of soft parts
Giant cell tumor of soft tissue	- Multinodular with fibrous septa - Peripheral rim of metaplastic ossification - Mononuclear stromal cells (oval to spindle-shaped nuclei without significant cytological atypia) - Osteoclast-like giant cells (evenly distributed throughout tumor) - Mitotic rate 2–5 mitoses per 10 high-power fields; rare tumors with > 30 mitoses per 10 high-power fields	Mononuclear stromal cells: positive for vimentin, HAM56, smooth muscle actin, and TRAP; focally positive for CD68 and Ki-67 Osteoclastic giant cells: positive for CD68 and TRAP	Osteoclast-like	None yet reported	- Tenosynovial giant cell tumor - Malignant fibrous histiocytoma-giant cell type - Plexiform fibrohistiocytic tumor - Undifferentiated pleomorphic sarcoma with giant cells - Extraskeletal recurrence of giant cell tumor of bone

AFX, atypical fibroxanthoma; DF, dermatofibroma; JXG, juvenile xanthogranuloma.

storiform patterns [35]. The spindled cells are typically pleomorphic, with a prominent nucleus, which is often vesicular [36]. Some tumors even contain vacuolated, lipid-containing cytoplasm, like xanthoma [36]. Solar elastosis, associated with ultraviolet radiation, is regularly encountered adjacent to the tumor. Tumors do not extensively involve the subcutaneous tissue but frequently involve undamaged adnexal structures within the dermis. In addition to exhibiting these classic features, AFX may exhibit other rare histologic variants, including clear cells; osteoclast-like giant cells; or pigmented, osteoid, chondroid, or granular plaque-like cells [35,37]. Osteoclast-like giant cell proliferation is infrequent in AFX [37,38].

In 2010, a study of 171 cases of AFX reported only two cases with Osteoclast-like giant cells [37].

Use of a panel of immunohistochemical markers is essential to accurately distinguish AFX from other conditions that are histologically similar. The diagnosis of AFX is largely based on lack of expression of markers characteristic of other lesions (i.e., keratins for carcinoma, MART1, SOX, or HMB45 antigen in melanoma, smooth muscle actin or desmin in leiomyosarcoma). Procollagen 1, CD10 (Fig. 3B), and S100A6 are typically positive in AFX. Procollagen-1 is expressed strongly in 87% of AFX lesions. However, procollagen type 1 has also been observed in some cases of desmoplastic SCC and desmoplastic melanoma [39]. CD10, also known as CALLA (common acute lymphocytic leukemia antigen), has been reported to be a useful marker for AFX because of its high positivity rate [40,41]. However, CD10 is also positive in most cases of malignant fibrous histiocytoma and DF and in some cases of leiomyosarcoma, SCC, and melanoma [40,41]. The combination of procollagen type 1 and CD10 may be more useful than either marker alone for the diagnosis of AFX [42]. S100A6 is a member of the S100 family of proteins, which contains two EF-hand calcium-binding motifs. S100A6 is expressed in many cases of AFX. However, this marker is also positive in other spindle cell neoplasms such as desmoplastic melanoma, leiomyosarcoma, and spindle cell SCC [43]. Cytokeratins, S100, and HMB45 antigen are typically negative in AFX and thus are helpful for distinguishing AFX from SCC and melanoma. However, S100-positive dendritic cells (possibly Langerhans cells) can colonize with AFX. In addition, focal expression of HMB45, MART1, and Melan-A in giant cells associated with AFX have been reported [44,45]. AFX tumor cells are also positive for vimentin, alpha 1-antitrypsin, alpha 1-antichymotrypsin, HAM56, and CD68 (Fig. 3C) but are characteristically negative for desmin and h-caldesmon [45]. Osteoclast-like giant cells present in AFX cases are positive for histiocytic markers including CD68, actin, MAC387 and [alpha]-1-antichymotrypsin, confirming the histiocytic nature of these multinucleated cells [37,46].

In general, we suggest that when encountered with a suspected AFX composed of the atypical spindle cells with mitotic figures predominantly involving dermis, a panel of immunohistochemical stains should be performed to make the correct diagnosis. It includes SOX10 and pan-melanoma cocktail to exclude the possibility of melanoma, p63 or high molecular weight keratin to rule out the possibility of spindled cell SCC and desmin for exclusion of leiomyosarcoma. If all those makers are negative, CD10 and/or procollagen type 1 may be performed to confirm the diagnosis of AFX.

AFX is considered a diagnosis of exclusion. The differential diagnosis of AFX includes malignant spindle cell neoplasms of skin, specifically, spindle cell SCC, melanoma, pleomorphic sarcoma, and dermatofibrosarcoma protuberans [46]. Extensive invasion of subcutaneous fat, a high atypical mitotic index, and perineural and lymphovascular invasion are thought to be associated with adverse outcome. AFX lesions with any of these features have been designated “malignant fibrous histiocytomas” or “pleomorphic dermal sarcomas” [47].

AFX is characterized by recurrent mutations in several genes, including *COL11A1*, *ERBB4*, *CSMD3*, and *FAT1*. Most mutations in AFX are due to ultraviolet radiation damage, which predominantly results in

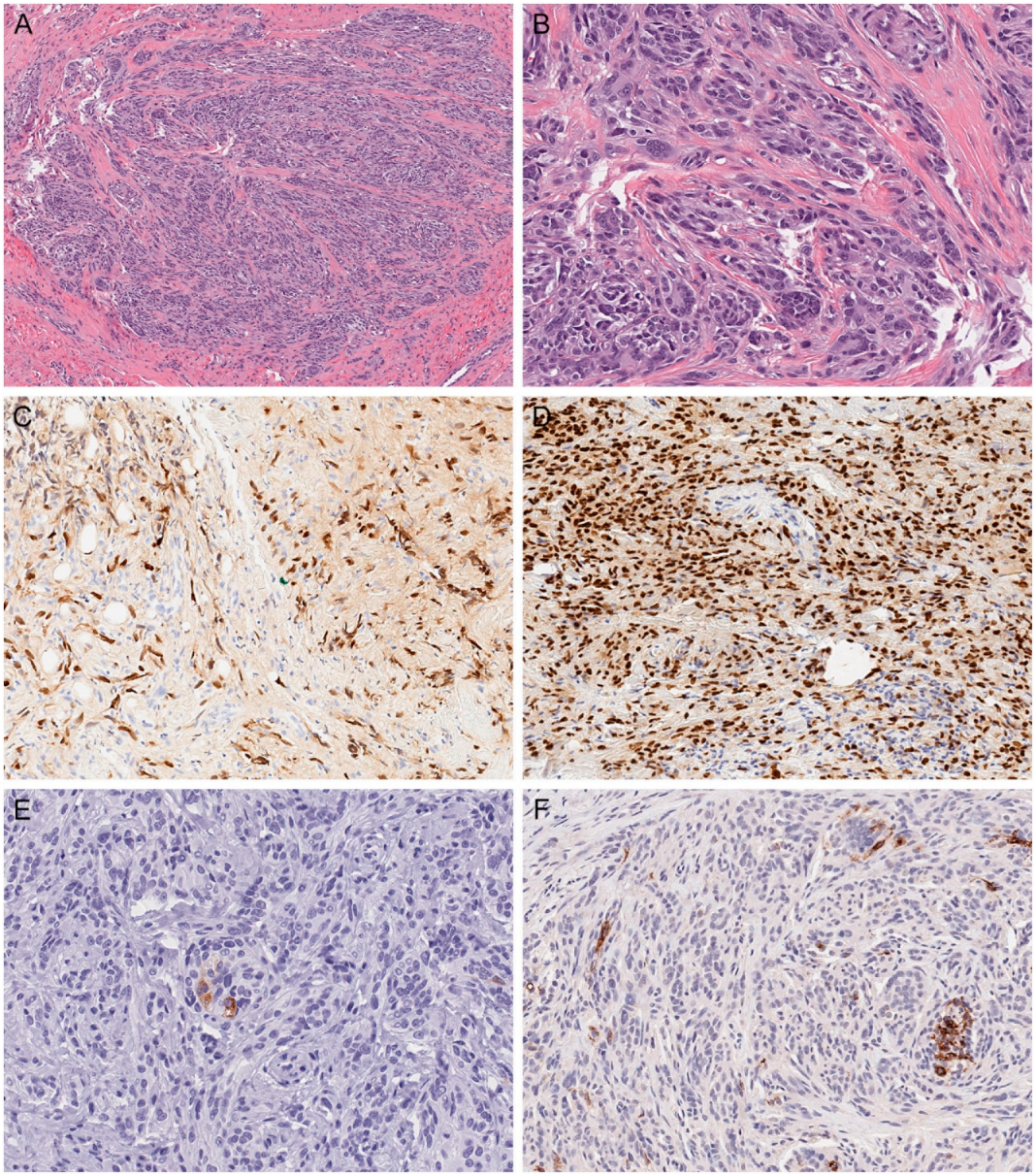

Fig. 2. Microscopic findings in melanoma with giant cells.
(A) Representative section showing diffuse atypical spindle to epithelioid cellular proliferation (hematoxylin-eosin [H&E], ×100).
(B) Representative section showing atypical spindle to epithelioid cells with eosinophilic cytoplasm and pleomorphic and hyperchromatic nuclei, admixed multinucleated giant cells, and focal perineural invasion (H&E, ×400).
(C–F) Representative immunohistochemically stained sections showing tumor cell expression of (C) S100 (patchy), (D) SOX10 (diffuse and strong), (E) MART1 (focal), and (F) HMB45 (patchy) (×400).

cytosine to thymine changes in dipyrimidines. There may be deletions of segments on chromosome arms 9p and 13q, including deletions involving tumor suppressor genes such as *KANK1* and *CDKN2A*, but so far, no characteristic gene fusions have been identified [48].

Surgical excision including wide local excision and Mohs micrographic surgery are the treatment of choice for AFX. The long-term prognosis associated with AFX is excellent. However, there may be recurrence and even metastasis, especially among immunocompromised patients [49,50].

5. Dermatofibroma/benign fibrous histiocytoma (DF/BFH)

DFs are common fibrohistiocytic lesions that exhibit remarkable variation in histologic features, and controversy continues regarding its histogenesis. DF has also been termed histiocytoma, fibrous histiocytoma, sclerosing hemangioma, and nodular sub-epidermal fibrosis [51-54].

DF typically occurs on distal extremities but may also occur at other cutaneous sites, such as fingers, palms, soles, scalp, face, vaccination scars, and tattoo sites [52,55,56]. DF typically occurs in younger people and are more common in females than in males. Lesions are firm, flesh-colored cutaneous or subcutaneous papules or nodules, usually smaller than 1 cm in diameter [57]. DFs can present as polypoid, flat, atrophic, or depressed lesions [58,59]. The majority of DFs occur as solitary lesions; however, 10% of patients have two to five simultaneous lesions [60], and most cases of DF with simultaneous lesions occur in patients with immunosuppression [61]. A characteristic finding in DF is the “dimple sign,” in which lateral pressure on the skin produces a depression. Lesions are white to yellow on the cut surface. Focal cystic changes or hemorrhage may be seen [62].

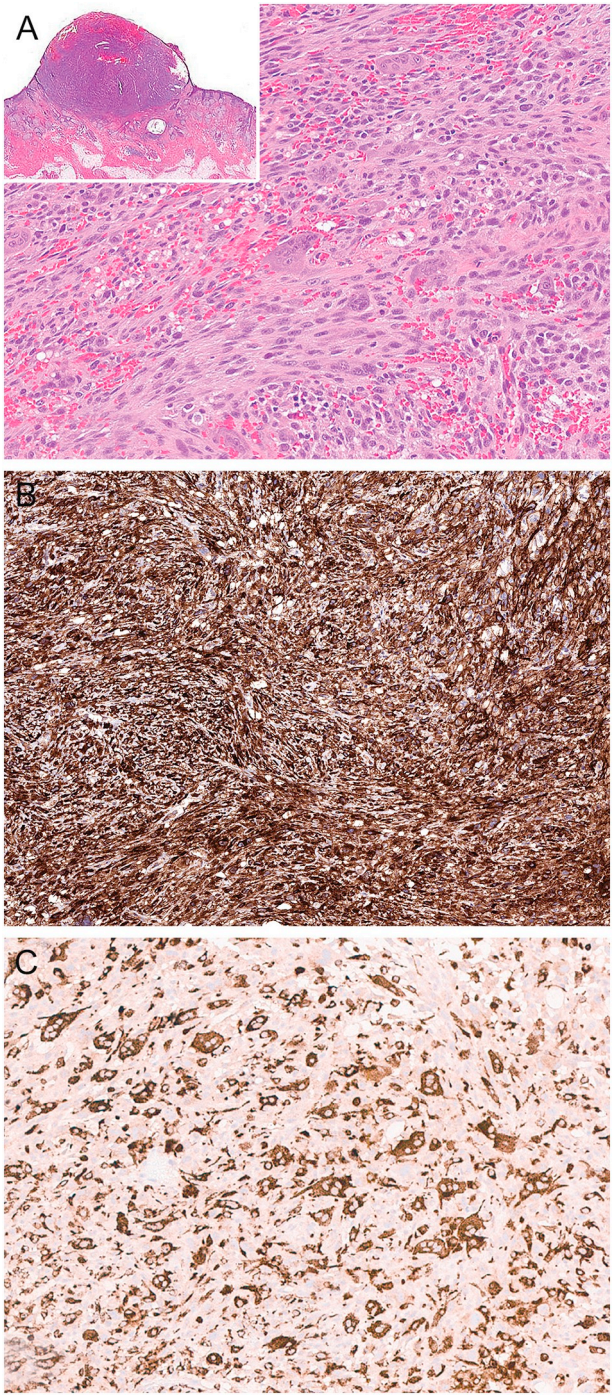

Fig. 3. Microscopic findings in AFX.
(A) Representative section showing diffuse cellular atypical spindle cell proliferation with admixed hemorrhage (hematoxylin-eosin, x200; inset, ×20).
(B–C) Representative immunohistochemically stained sections showing expression of (B) CD10 (diffuse) by the tumor and multinucleated cells (×400) and (C) CD68 predominantly by the multinucleated cells (×400).

The etiology of DF is unclear. Evidence supports both neoplastic and reactive pathogeneses. It is believed that many DFs result from an inflammatory response to local trauma, such as an insect bite or a superficial puncture wound from thorns or wood splinters [63].

Histologically, DFs are composed of dermal-based proliferations of typically bland, spindled to epithelioid cells associated with scattered multinucleated giant cells of different types, including Touton-like, foreign body-type, osteoclast-like, and floret-like giant cells (Fig. 4A and B) [64-66]. Classic DF usually involves the papillary and reticular dermis and is composed of thick, brightly eosinophilic collagen bundles ("keloidal collagen"); especially at the periphery of the lesion, collagen fibers are surrounded by the tumor cells ("collagen trapping") (Fig. 4A and B). Approximately 70% of cases of classical DF have a thin rim of uninvolved dermis (grenz zone) of variable thickness. Overlying epidermal hyperplasia with basilar hyperpigmentation ("dirty fingers") and occasional melanocytic hyperplasia is common. DF is composed of a heterogeneous population of oval to fusiform fibroblasts, histiocytes (some of which may be xanthomatous or multinucleated, Fig. 4B), hemosiderin-laden macrophages, and blood vessels. Early lesions typically show lymphocytic proliferation. Mitotic figures can be seen. Established lesions show greater cellularity and spindled cells [67,68]. Numerous histologic variants of DF have been described, including fibrocollagenous, aneurysmal, hemosiderotic, clear cell, lipidized, cellular, epithelioid, pseudosarcomatous FH/DF with monster cells, cellular, atypical DF/indeterminate FH, angiomatous, granular cell, halo, osteoclast-like, myofibroblastic, myxoid, keloidal, palisading, and atrophic [57,69,70].

Fibrocollagenous DF has a predominance of collagen and fibroblast-like cells in a prominent storiform or swirled pattern [70]. The *aneurysmal DF* variant is distinct, with cleft-like hemorrhagic spaces that mimic a vascular tumor but lack endothelial lining. The vascular channels are surrounded by histiocytes; hemosiderin deposition may be an additional feature [71]. *Hemosiderotic DF* probably represents an early stage in the development of the aneurysmal variant. The lesion is composed of numerous small vessels, extravasated erythrocytes, and extensive hemosiderin deposits [57]. *Clear cell DF* is a rare variant with sheets of cells with vesicular nuclei and clears to reticulated cytoplasm that occupy the reticular dermis and occasionally extend into the subcutis [72,73].

Lipidized DF, also known as *ankle type DF*, is characterized by foamy histiocytes surrounded by sclerotic collagen resembling amyloid [74]. *Pseudosarcomatous fibrous histiocytoma or DF with monster cells*, is a rare variant with a low recurrence rate and a very low rate of development of distant metastasis [75].

Cellular DF accounts for fewer than 5% of cutaneous DFs and is slightly more common in males than females. Lesions are highly cellular with a more prominent fascicular growth pattern than is seen in classical DF with or without focal extension to superficial subcutaneous tissue. Up to 12% of cases show focal central necrosis, and 30% of cases recur locally after incomplete surgical resection [57,70]. *Epithelioid DF* is predominantly composed of large, angulated epithelioid cells with round to oval, vesicular nuclei that mimic intradermal Spitz nevus clinically, histologically, and molecularly. Many epithelioid DFs show *ALK* rearrangements resulting in *VCL–ALK and SQSTM1–ALK* gene fusions, and epithelioid DF may exhibit ALK overexpression by immunohistochemistry, a finding that may distinguish this lesion from classical DF [76,77].

Most DFs are positive for factor XIIIa (Fig. 4C), CD10, CD163, D2-40, and HMGA1/HMGA2. The aneurysmal variant is usually negative for factor XIIIa. The strength and distribution of CD68 staining varies (Fig. 4D), but typically highlights histiocytic-appearing cells. Vimentin and α-smooth muscle actin may be positive in some DF indicating possible myofibroblastic differentiation. DFs are typically negative for CD34 but may show focal staining, especially at the periphery of the lesion. DFs are negative for nestin, S100, MART1/Melan-A, HMB45, muscle specific actin, and desmin. Epithelioid DF is often positive for ALK-1 [77-80].

The most important entity in the differential diagnosis of DF is dermatofibrosarcoma protuberans (DFSP). This entity typically extends deeply along septa of subcutaneous fat and produces honeycombing fat entrapment. DFSP is usually positive for CD34 and nestin and negative for CD10, CD163, HMGA1/HMGA2, and factor XIIIa; however, a small proportion of cases are negative for CD34 and positive for factor XIIIa. Factor XIIIa is expressed much more commonly in DF than in DFSP

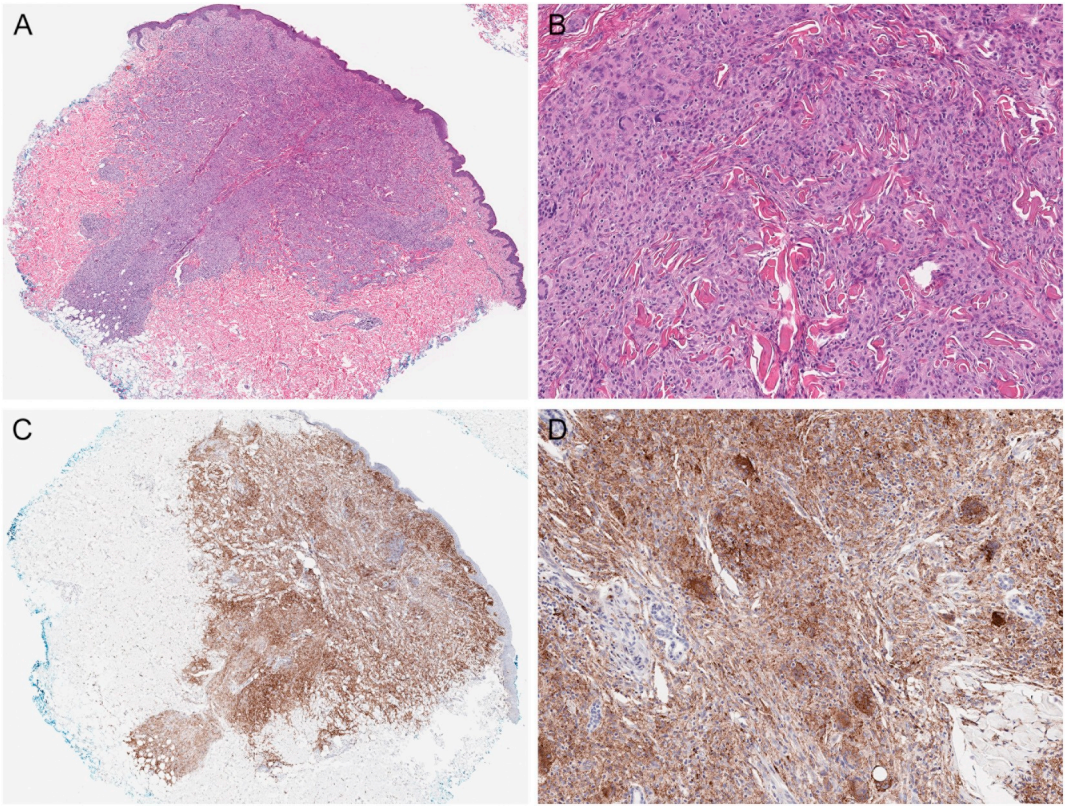

Fig. 4. Microscopic findings in DF.
(A) Representative section showing wedge-shaped eosinophilic cellular proliferation involving dermis and focal superficial subcutaneous tissue (hematoxylin-eosin [H&E], ×40).
(B) Representative section showing spindle to epithelioid cells with eosinophilic cytoplasm and admixed multinucleated giant cells and entrapped eosinophilic (keloidal) collagen bundles (H&E, ×200).
(C–E) Representative immunohistochemically stained sections showing expression of (C) factor XIIIa (diffuse, ×40) by the spindle cells and (D) CD68 (diffuse, ×200) by the spindle and multinucleated giant cells.

[70]. Phosphohistone-H3 and Ki67 indicate higher proliferation index and mitotic counts in DFSP than in DF. In challenging cases, especially cellular DF or DF with extension into the superficial subcutis, molecular studies may be useful. A reciprocal translocation, t(17;22) (q22;q13), and a supernumerary ring chromosome resulting in fusion of collagen type I alpha 1 (*COL1A1*) and platelet-derived growth factor B-chain (*PDGFB*) are characteristic findings of dermatofibrosarcoma protuberans. Many alternative markers have been explored for distinguishing DF from dermatofibrosarcoma protuberans, including apoD, tenascin, S100A6, MMP2, MMP11, IGFBP7, cathepsin K, and D2-40 [45,78-81].

Other entities to be considered in the differential diagnosis of DF include amelanotic spindle cell melanocytic tumor (positive for melanocytic markers, including S100, Melan-A, and SOX10) [82], angiosarcoma (positive for endothelial markers, including CD34 and ERG), and Kaposi sarcoma (positive for HHV-8, CD31, CD34, and D2-40) [57]. AFX must also be considered in some cases. AFX, like DF, is typically positive for CD10, CD68, and vimentin; however, AFX typically occurs in sun-damaged skin of elderly patients [45,50].

Atypical DF or indeterminate fibrohistiocytic lesion shows combining clinical, histologic, and immunohistochemical features of both DF and DFSP. Horenstein and colleagues reported that this lesion occurs predominantly in the trunk (6/10, 60%) followed by extremities (30%) and face (10%) with an average size of 1.2 cm (range, 0.4–2.7 cm), and slight female predominance (M:F = 2:3). Average age of the patients is 30.6 yrs. (range, 15–50 yrs.) Histologically, there are acanthosis, densely cellular fascicles with focal storiform areas, keloidal collagen, infiltration into the subcutis in a honeycomb pattern, and low mitotic counts (0 to 4 mitoses per square millimeter). Immunohistochemical study also shows overlapping features of DF and DFSP demonstrating diffuse immunoreactivity for factor XIIIa (30%–60% of the neoplastic cells) as well as CD34 (20%–70%). A recurrence was identified in one case (1/6 = ~17%) after an average follow up of 22.3 months (range, 10–46 mos.) [83].

Classic DF and its variants are benign tumors with an excellent prognosis and are usually cured through surgical excision. The cellular or atypical variants may require re-excision to ensure clear margins because of the increased risk of local recurrence [84]. Metastasis are extremely rare but have been reported to occur most notably to the lungs; metastatic lesions appear to behave in an indolent fashion [85,86].

6. Reticulohistiocytoma

Reticulohistiocytoma is a rare histiocytic lesion that was originally reported and named by Zak when it was first reported in 1950 [87]. In a study of 44 cases from the Armed Forces Institute of Pathology, reticulohistiocytoma was designated a “solitary epithelioid histiocytoma” [88]. The etiology of reticulohistiocytoma remains unclear; however, the presence of a high number of neutrophils in some lesions has raised the possibility of infectious etiologies [88].

Reticulohistiocytoma can affect the skin and other organs. It may present as a solitary nodule or may occur as multiple superficial papules. Clinically, the color of the lesions may vary from tan to light brown. Lesions may appear yellowish if they contain abundant, lipidized macrophages [88].

Reticulohistiocytoma is more common in young adults but can

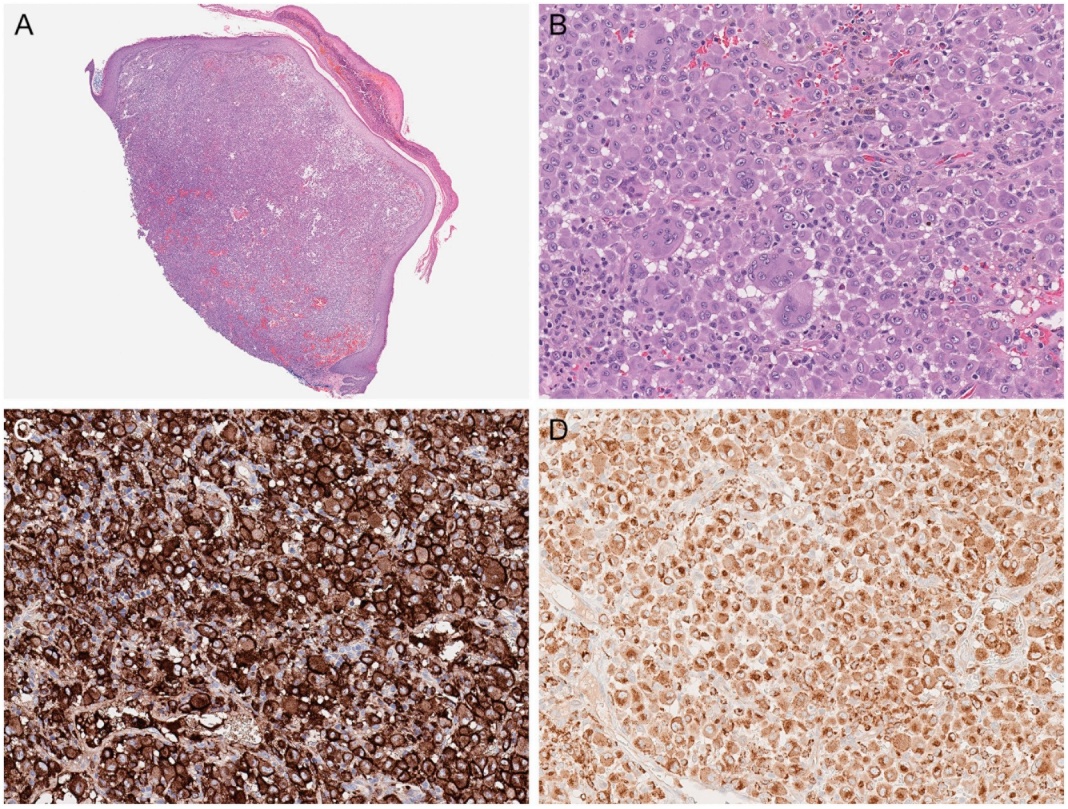

Fig. 5. Microscopic findings in reticulohistiocytoma.
(A) Representative section showing diffuse eosinophilic cellular proliferation with clear cell changes and admixed hemorrhage involving at least the dermis and overlying hemorrhagic scale crust (hematoxylin-eosin [H&E], ×20).
(B) Representative section showing atypical epithelioid cells with eosinophilic cytoplasm and pleomorphic and hyperchromatic nuclei and admixed multinucleated giant cells, focal extravasated erythrocytes, hemosiderin deposition, and inflammatory infiltrate (H&E, ×400).
(C–D) Representative immunohistochemically stained sections showing expression of (C) CD163 and (D) CD68 by the lesional cells as well as associated multinucleated giant cells (×400).

occur at any age from early childhood to late adolescence; the disease is slightly more common in males than in females [89,90]. Lesions vary in size from 0.5 cm to 2 cm. Lesions can arise anywhere on the skin but arise in the head and neck area (especially ear and nose) more commonly than in other areas [91]. Multicentric reticulohistiocytosis is characterized by cutaneous or mucosal nodular lesions often associated with severe arthritis, systemic lesions, and paraproteinemia. In 10% of cases, an internal malignancy, such as carcinoma of the lung, breast, or stomach, is present when multicentric reticulohistiocytosis is diagnosed [92,93]. Multiple reticulohistiocytosis usually occurs in young females and presents as multiple small, periungual papules ("coral beads"). Some patients develop multiple lesions without having systemic involvement [94].

Histologically, lesions typically exhibit a nodular infiltration composed of numerous large, mononucleated or multinucleated epithelioid histiocytes involving the upper and mid dermis (Fig. 5A). The lesions also include varying proportions of lymphocytes, eosinophils, and neutrophils and dermal fibrosis. The histiocytes have abundant dense pink cytoplasm with "oncocytic" or "ground glass" appearance and minimal to mild nuclear atypia. Nuclei are vesicular with distinct nucleoli, variable nuclear grooves, and multinucleation (Fig. 5B). Mitotic figures (0–4 mitoses per 10 high-power fields) are occasionally observed. A few multinucleated giant cells with high lipid content (Touton-like or glassy giant cells) may be present [95].

The histiocytes in reticulohistiocytomas are positive for CD163 (Fig. 5C), CD68 (Fig. 5D), lysozyme (variably), and vimentin. They often show positive nuclear staining for microphthalmia transcription factor, and they sometimes show focal reactivity for factor XIIIa and S100 protein. Immune reactivity for CD31, CD43, and CD45 is variable. The histiocytes are negative for CD3, CD20, CD30, HMB45, and keratins [88].

The differential diagnosis of reticulohistiocytoma includes Rosai-Dorfman disease (strongly S100 positive), Langerhans cell histiocytosis (positive for CD1a and langerin), JXG (classically contains scattered Touton-like histiocytic giant cells), infectious granuloma (well-formed spherical granuloma with or without central necrosis), epithelioid fibrous histiocytoma (usually lacks giant cells), melanocytic lesions (positive for melanocytic markers), epithelioid sarcoma (shows deep invasion and contains numerous atypical cells with areas of necrosis), and histiocytic sarcoma (exhibits significant nuclear atypia and mitotic activity) [88,96].

To date, no associated molecular findings have been described in reticulohistiocytoma.

7. Juvenile xanthogranuloma

JXG is a benign non-Langerhans-cell histiocytosis that was originally thought to be derived from dermal dendrocytes [97]. However, a subsequent study suggested that JXG is derived from precursor plasmacytoid dendritic cells [97,98]. JXG is typically a disorder of early childhood and presents as a solitary or multiple reddish or yellowish skin papulo-nodules. Approximately two-thirds of all cases occur within the first 6–9 months of life; 5% to 35% of JXG cases present at birth [99-101]. JXG also rarely occurs in adults, for which reason some authors recommend dropping the word "juvenile" from the name and referring to the disease as simply "xanthogranuloma". JXG is more common in

males than females (1.4:1), and cases with multiple lesions have a particularly strong tendency to occur in males [102]. Lesions are 1–10 mm in diameter or larger and most commonly located on the head and neck, upper part of the trunk, and proximal parts of the limbs [103-106]. Lesions have also rarely been reported on the sole of the foot, vulva, anogenital region, finger, and proximal nail fold [107-111]. Occasionally, fine telangiectasia can be seen overlying the lesion. Lichenoid lesions, clustered lesions, and linear distribution have been reported [112-114]. Intraocular complications are detected in small percentage of young patients with JXG [115]. Systemic involvement of JXG, including oral lesions, is exceedingly rare [116,117]. JXG has been reported in approximately 5% to 10% of patients with neurofibromatosis type 1 [118,119]. The triad of JXG, neurofibromatosis type 1, and juvenile myelomonocytic leukemia has been well documented [120]. There are limited reports about correlations of JXG with Niemann–Pick disease, contralateral lymphadenopathy with a histiocytic infiltrate, adult T cell leukemia/lymphoma, follicular lymphoma, urticaria pigmentosa, and cytomegalovirus infection [121-123].

Histologically, JXG contains a diffuse infiltrate of histiocytes, multinucleated giant cells (Touton-like or Langhans-like), and spindle cells admixed with lymphocytes and granulocytes, notably eosinophils (Fig. 6A and B). The lesion most commonly involves the dermis but sometimes involves the superficial subcutis as well. The epidermis can be thin with elongated rete ridges; in rare cases, it may be ulcerated. Mitoses are rare [97]. The microscopic appearance varies depending on the age of the lesion. In early JXG, non-lipidized histiocytes predominate. Mature JXG contains xanthomatous histiocytes and Touton-like giant cells. Late JXG contains prominent foamy or spindle cells with fibrosis [98].

Immunohistochemistry plays an important role in establishing the diagnosis of atypical cases of JXG. JXG expresses factor XIIIa, CD68 (Fig. 6C), CD163, CD14, and fascin. S100 is rarely positive, while CD1a is only expressed in interspersed Langerhans cells [106,124-127].

The differential diagnosis of JXG includes Langerhans cell histiocytosis (positive for S100 and CD1a), papular xanthoma (very uncommon lesion, factor XIIIa negative, most cases located on the trunk in older individuals), dermatofibroma (dense collagenous stroma, storiform growth pattern, overlying pseudo-epitheliomatous hyperplasia), and Spitz nevus (positive for melanocytic markers such as S100, Melan-A, and tyrosinase) [128].

Genomic alterations appear to be more common in more advanced cases (i.e., systemic and diffuse cutaneous JXG). Mutations in several MAPK pathway genes, including *ARAF*, *KRAS*, *MAP2K1*, and *NRAS*, were detected in 7 of 12 JXG cases with systemic involvement [129]. In addition, some lesions have *PIK3CD* and *NF1* mutations. In rare intracranial lesions, JXG may have *BRAF V600E* mutation, which is also seen in Erdheim-Chester disease and Langerhans cell histiocytosis [130].

The management of JXG depends on the site of involvement. Solitary cutaneous lesions may spontaneously regress in approximately 1 to 5 years. Multiple lesions that involve internal organs (e.g., liver or lungs) may be associated with a poor prognosis and may require aggressive treatment, but deaths from JXG are exceedingly rare [98,131].

8. Plexiform fibrohistiocytic tumor

Plexiform fibrohistiocytic tumor is a rare mesenchymal neoplasm first described in 1988 by Enzinger and Zhang in a report of 65 cases [132]. More than 200 cases have now been reported in the literature, confirming the original description [133]. Plexiform fibrohistiocytic tumor is a slowly growing and painless tumor that predominantly involves the upper extremities (fingers, hands, and wrists); the trunk is also a common location. The disease is most often diagnosed in infants and children (median age at diagnosis, 14.5 years) and is more common in females than in males (female:male ratio; 6:1). It is believed to be a malignancy of intermediate aggressiveness. Lesions usually present as poorly demarcated, lobulated or micronodular subcutaneous or dermal masses without ulceration [132,134,135]. They are white-gray and rarely exceed 3 cm in greatest diameter. The largest plexiform fibrohistiocytic tumor reported to date measured 8.5 cm in diameter and involved the anterior left thigh in a 13-year-old girl [136]. The etiology of plexiform fibrohistiocytic tumor is unclear. Previous trauma has been reported in a few cases [132].

Histologically, the tumor is composed of three major components in variable proportion: (i) an infiltrative, plexiform, or multinodular proliferation of histiocytes, (ii) with or without osteoclast-like giant cells in the center, and (iii) interconnected spindle-shaped fibroblast-like or myofibroblast-like cells arranged in short fascicles (Fig. 7A and B). Plexiform fibrohistiocytic tumors are well established as having three main histologic patterns: fibroblastic, histiocytic (with or without osteoclast-like giant cells), and mixed [135]. Osteoclast-like giant cells have 3 to 10 nuclei (Fig. 7C). Because of the absence of cellular pleomorphism and the presence of low mitotic activity, dense hyalinization, chronic inflammation, microhemorrhages (Fig. 7A and B), and hemosiderin (Fig. 7B and C), plexiform fibrohistiocytic tumor may mimic a chronic granulomatous inflammatory process [132-135]. Overlying epidermis and dermis are usually unremarkable. Myxoid change, bone formation, and focal marked cytologic atypia have been noted in a few cases [134,137,138].

Immunohistochemically, the fibroblastic cells express vimentin, focal smooth muscle actin, and occasionally calponin but not factor XIIIa, CD34, or S100. The fibroblastic cells also display HHF35 labeling [134,135]. The histiocytic cells express CD68 and lack CD45 or Mac387 antigens [132,139]. The osteoclast-like giant cells are positive for CD68 [140].

To our knowledge, there are only two reports in the literature on clonal genetic analysis of plexiform fibrohistiocytic tumors. One case had a complex karyotype with numerous deletions, and the other case had a simpler karyotype [46, XY, t(4;15)(q21;q15)] [141,142]. DNA diploidy has been confirmed by flow cytometry in all analyzed cases [135].

The differential diagnoses of plexiform fibrohistiocytic tumor includes plexiform neurofibroma (no distinct nodules, positive for S100), cellular neurothekeoma (uniform population of epithelioid cells, no distinct nodules of histiocytoid cells or osteoclast-like giant cells, usually diffusely positive for microphthalmia transcription factor and S100A6), fibrous hamartoma of infancy (affects infants, proximal sites, contains foci of immature myxoid mesenchymal tissue), nodular fasciitis (small, rapidly growing, often well-circumscribed, abundant myxoid stroma in early lesions; lacks multinodular or plexiform growth; contains an *MYH9-USP6* gene fusion), DF (storiform pattern and keloidal collagen), benign and malignant soft tissue giant cell tumors (mainly occur in adults, prominent nodularity with abundant osteoclast-like giant cells, lack an infiltrative spindle cell component), ossifying fibromyxoid tumor of soft parts (varying components of fibrous and myxoid stroma, peripheral shell of woven bone), and fibromatosis (lacks nodules of histiocytoid or osteoclast-like giant cells, shows elongated stromal vasculature, nuclear expression of β-catenin) [135,139].

The treatment of choice is wide surgical excision of the primary lesion or re-excision with negative margins. The rate of local recurrence after incomplete excision ranges from 12.5% to 40% [134,135,139]. Examination of regional lymph nodes may be warranted since lymph node metastasis was reported in 6% of the cases in two series of plexiform fibrohistiocytic tumor [132,140,143].

9. Giant cell tumor of soft tissue

Primary giant cell tumor of soft tissue is a rare neoplasm with low malignant potential that was first described in 1972 by Salm and Sissons [144]. Giant cell tumors of soft tissue are the soft tissue analog of giant cell tumors of the bone and have histologic and

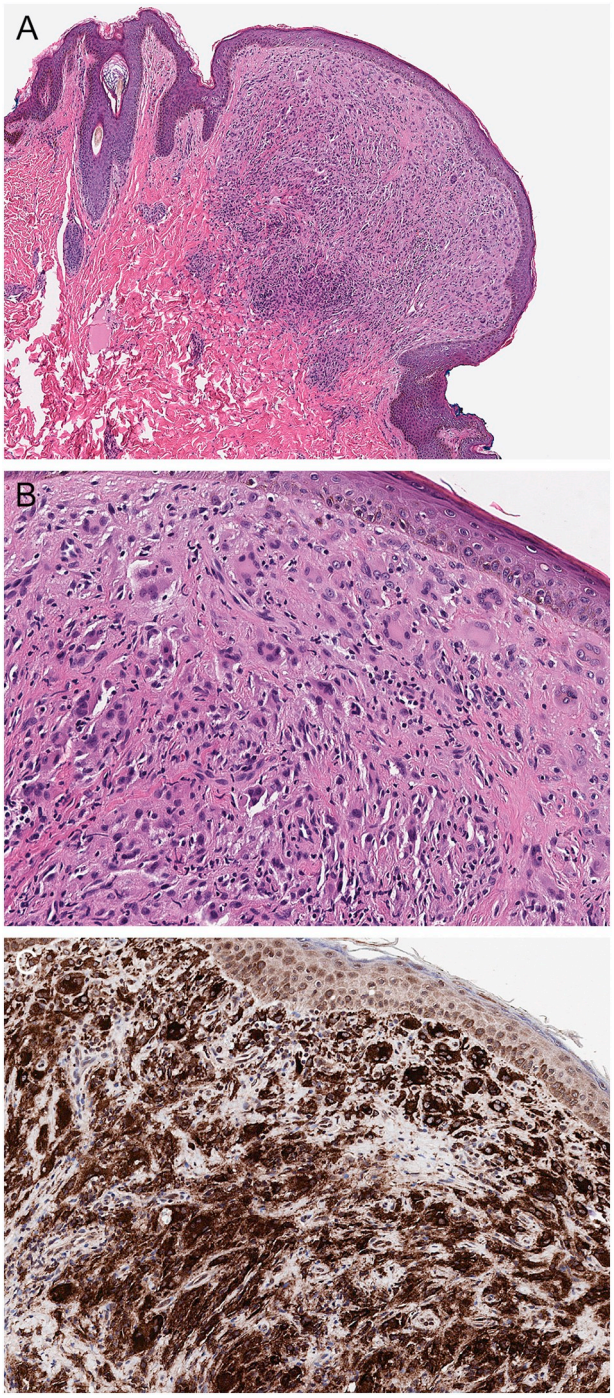

Fig. 6. Microscopic findings in JXG.
(A) Representative section showing a polypoidal growth of eosinophilic cellular proliferation involving superficial dermis (hematoxylin-eosin [H&E], ×20).
(B) Representative section showing the hallmark of this lesion, Touton-like giant cells with a peripheral ring of nuclei and focal vacuolization of the cytoplasm and other giant cells with a crescent or horseshoe arrangement of nuclei (Langhans cells). The intervening cells have spindle to epithelioid morphology and usually have round nuclei and associated scattered inflammatory cells (H&E, ×400).
(C) Representative immunohistochemically stained section showing expression of CD68 (diffuse and strong) by the tumor and multinucleated cells (×400).

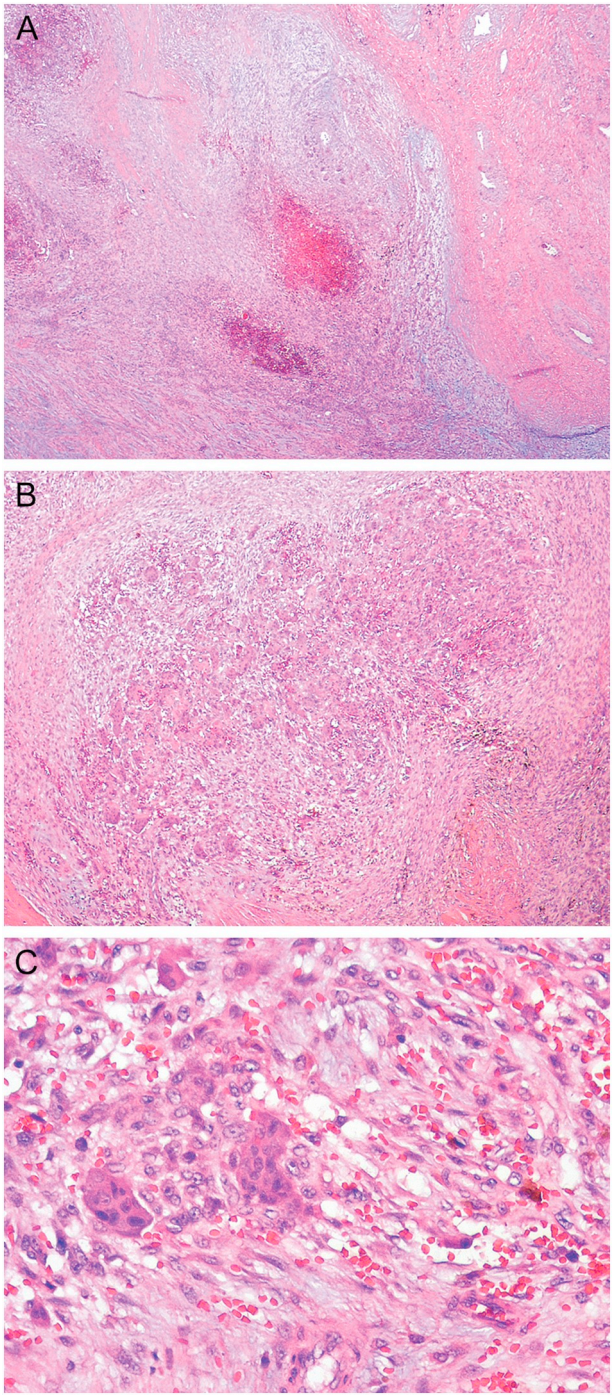

Fig. 7. Microscopic findings in plexiform fibrohistiocytic tumor.
(A) Representative section showing infiltrative, plexiform proliferation of histiocytes with hemorrhage (hematoxylin-eosin [H&E], ×100).
(B–C) Nodular proliferation of osteoclast-like giant cells in the center and interconnected spindle-shaped fibroblast/myofibroblast-like cells arranged in short fascicles with extravasated erythrocytes and hemosiderin deposition (panel B: H&E, ×200; panel C: H&E, ×400).

immunohistochemical features identical to those of giant cell tumors of the bone [145]. Giant cell tumors of soft tissue are most commonly found in superficial or deep soft tissue of the thighs, trunk, and upper extremities [146]. Lesions may also arise in other locations, such as the breast, mediastinum, groin, and surgical scars [147-149]. Giant cell tumor of soft tissue is mainly seen in adults and the elderly but affects individuals across a broad range of ages and there is no sex predilection [145]. Lesions are well-circumscribed, multinodular tumors involving skin and subcutis that range in size from 0.7 cm to 10 cm (median, 3.0 cm) [146]. Most patients present with a painless skin-colored mass or *red* to *brown* lesion [147]. Subcutaneous fat involvement has been

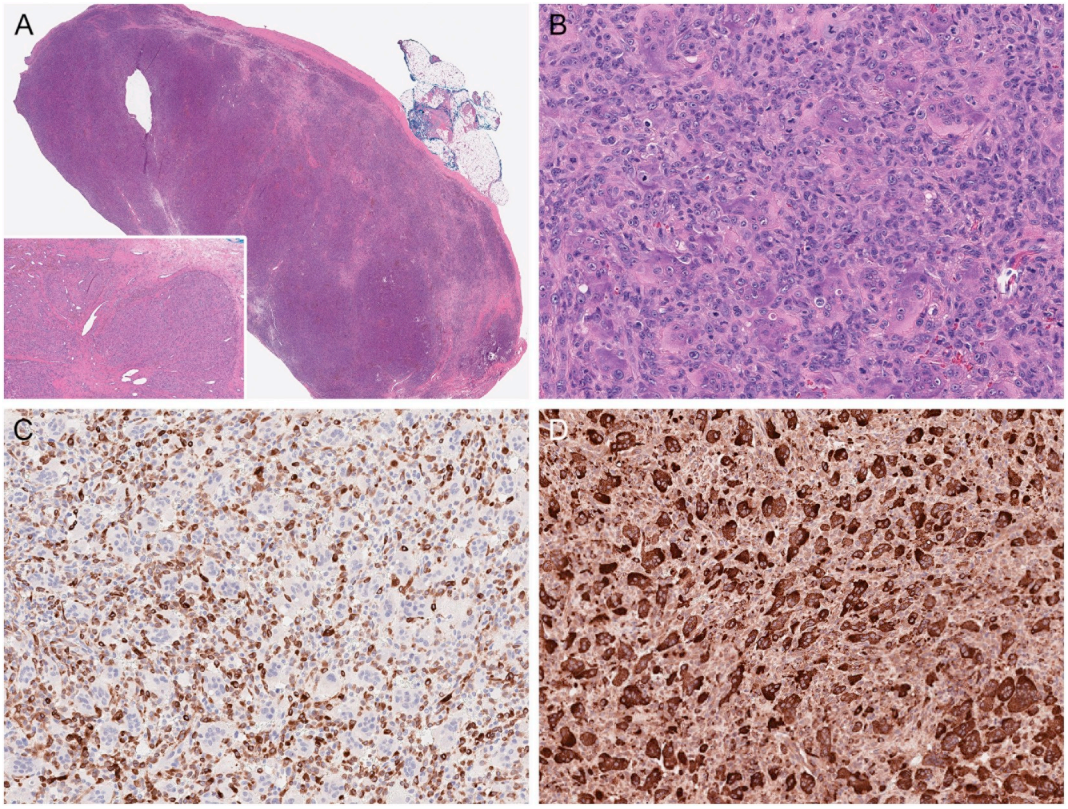

Fig. 8. Microscopic findings in giant cell tumor of soft tissue.
(A) Representative section showing multinodular lesion with fibrous tissue separating nodules in the background of vascular stroma (hematoxylin-eosin [H&E], ×20; inset, ×40).
(B) Representative section showing nodules composed of round to spindle-shaped mononuclear cells with eosinophilic cytoplasm and centrally located nuclei and uniformly scattered, osteoclast-like multinucleated giant cells and admixed pigmented macrophages (H&E, ×200).
(C–D) Representative immunohistochemically stained sections showing expression of (C) RANKL by the tumor cells and (D) CD68 by the associated multinucleated giant cells (×200).

reported [150].

Histologically, the tumor is multinodular with fibrous tissue containing siderophages separating nodules (Fig. 8A and inset). Nodules are composed of round to spindle-shaped mononuclear cells with uniformly scattered, osteoclast-like multinucleated giant cells (Fig. 8B). Mononuclear cells have eosinophilic cytoplasm with centrally located nuclei (Fig. 8B) and occasional mitotic figures (mean 2–3 per 10 high-power fields). The stroma is vascularized without significant cytological atypia of tumor cells. Rare tumors with up to 30 mitotic figures per 10 high-power fields have been reported. Reported cases did not show atypical mitosis or necrosis. Foci of hemorrhage, hemosiderin deposition, vascular invasion, telangiectatic spaces, and foamy macrophages are usually present [146,150-153].

Immunohistochemically, the stromal cells are positive for HAM56 and smooth muscle actin. The mononucleated cells exhibit focal p63 and CD68 expression (Fig. 8D) [153-156]. The multinucleated giant cells are strongly positive for CD68. Tumors show expression of alkaline phosphatase, osteoprotegerin, RANKL (Fig. 8C), TRAIL, and TRAP in both mononuclear cells and multinucleated giant cells. This similarity in expression may underlie the similar phenotypic features of mononuclear cells and multinucleated cells in giant cell tumor of soft tissue [157].

The differential diagnosis of giant cell tumor of soft tissue includes tenosynovial giant cell tumor (located near tendons, composed of hyalinized stroma, foam cells, and hemosiderin-laden macrophages; metaplastic bone is uncommon), malignant fibrous histiocytoma (also known as undifferentiated pleomorphic sarcoma of giant cell type) (infiltrative, moderate to severe atypia of non-giant cells; necrosis; atypical mitotic figures), plexiform fibrohistiocytic tumor (childhood tumor with plexiform growth pattern, complex tentacle-like extensions), and extraskeletal recurrence of giant cell tumor of bone (grossly and microscopically indistinguishable from giant cell tumor of soft tissue) [146,150-152,158].

Most cases of giant cell tumor of soft tissue have benign behavior, but tumors can be locally aggressive and recur locally after excision; thus, complete excision with clear surgical margins is considered the best treatment approach [152]. The reported rate of recurrence is 6.2% [159]. Whereas metastasis of giant cell tumors of soft tissue is extremely rare, but cases with metastases to the lungs and parotid glands have been reported [147,155,156].

10. Summary

In summary, a relatively large group of soft tissue tumors can present with multinucleated giant cells. Careful attention to the clinical and histologic features, along with immunohistochemical and/or molecular analysis, will permit the correct diagnosis to be established in most cases.

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Declaration of Competing Interest

Nothing to declare.

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