Phosphaturic mesenchymal tumor (PMT) is an uncommon tumor causing oncogenic osteomalacia (OO) by virtue of overexpressing fibroblast growth factor-23 (FGF-23), a recently described protein capable of inhibiting renal tubular phosphate transport, probably corresponding to the previously hypothesized phosphaturic serum factor “phosphatonin.” Although the first description reporting a case of osteomalacia in a patient affected by a (bone) tumor had been already described in the late forties and the causal role for a tumor in this clinicopathologic syndrome was hypothesized in the late fifties and subsequently confirmed in the seventies, the term phosphaturic mesenchymal tumor (PMT) was first coined in 1987 by Weidner and Santa Cruz. According to a recently published paper comprehensively reviewing the literature and adding 32 new cases, a total of 141 cases of PMT have been published so far.

**Clinical findings**

Usually patients complain of a long history of bone pain and muscle weakness dating back to many years (up to 20), often being so severely affected to be unable to walk and wheelchair bound. The typical laboratory findings secondary to renal phosphate reabsorption and consequent phosphate loss are hypophosphatemia and hyperphosphaturia, which finally result in an inadequate mineralization of osteoid in mature bone, the metabolic disorder known as osteomalacia/riekets. Almost always patients have also low serum levels of 1,25-dihydroxyvitamin-D3, probably due to the inhibiting effect by the phosphaturic factor on the renal 25-hydroxyvitamin D-1-alpha-hydroxylase, the enzyme converting 25-hydroxyvitamin-D3 to the active metabolite 1,25-dihydroxyvitamin-D3. However OO is vitamin-D resistant. Serum alkaline phosphatase is elevated. Other serum chemical analyses usually show normal serum calcium, normal parathormone and calcitonin levels, normocalciuria and normal kidney function. Hypophosphatemic rickets and osteomalacia are respectively detected by skeletal radiographs and bone scintigraphy. By conventional imaging techniques (CT and MRI scans) usually but not always a tumor is discovered if accurately searched for. Somatostatin receptor imaging has been recently proved to improve the detection of such tumors, based on the postulate that such tumors do express somatostatin receptors.

Phosphaturic mesenchymal tumor is usually located in soft tissue, but intraosseus as well as sinonasal locations are also on record. In Folpe et al.’s own series of PMT 18 out of 32 total cases occurred in soft tissue, 9 in bone and 2 in paranasal sinuses, while from the 109 reviewed cases by the same authors as many 41 were soft tissue lesions, 59 bone lesions and 9 nasal/sinusal. Patients are usually in their adulthood, but pediatric cases are also on record (age range: 5 to 63
years in the series of 17 cases reviewed by Weidner and Santa Cruz, and 9 to 77 years in the original series of Folpe et al. Any site can be affected with the lower extremities as the most common (40-50% of cases), followed by the head and neck area (15-20%), trunk (15-20%) and upper extremities (around 10%). Unusual locations (e.g., big toe) are not uncommon. Tumor size is variable, ranging from 1 cm to 15 cm. The median size for soft tissue locations was of 5.6 cm in Folpe et al.’s series.

**Pathological features**

In soft tissue grossly the tumor is quite circumscribed, of firm consistency and not infrequently endowed with a partial shell of metaplastic bone. On sectioning microcysts or hemorrhagic foci can also be seen. At histology the most common morphological pattern of PMT is the so-called mixed connective tissue type, which was seen in 20 out of 21 of soft tissue cases in Folpe et al.’s original series and in 36 cases revised by Folpe et al. from the available literature out of 41 PMT of soft tissue previously published with sufficient histological illustrations.

Thus the mixed connective tissue pattern is to be intended as the prototype of the morphology of PMT, being characterized by a distinctive oval to bland spindle cell proliferation, embedded in a myxoid or myxochondroid matrix, with smudgy appearance and peppered by distinctive flocculent calcifications (Fig. III-1i→III-1ii). A prominent fibrohistiocytic reaction, hemorrhages and osteoclast-like giant cells are usually seen (Fig. III-1iii). Giant cells may appear in groups, so vaguely recalling a giant cell tumor (Fig. III-1iii). A well-developed and variously sized vasculature is a constant feature. Microcysts, osteoid-like matrix, woven metaplastic bone, adipocytic differentiation and sometimes some perivascular myoid changes are all in the spectrum of this same pattern.

Some cases of PMT of the mixed connective tissue variant have histological features of malignancy, of which probably 9 total cases have been published so far (both of soft tissue and bone locations), partly reported under different names. Conventional hemangiopericytoma has also been reported by Folpe et al. as the causal tumor of oncogenic osteomalacia in one case. In bone, the mixed connective tissue variant is also the most frequent histological pattern of PMT, having been recognized by Folpe et al. in 25 out of 39 cases which had appeared in the literature with sufficient illustrations/data. Other histological variants/patterns occurring in bone (but not in soft tissue) are the osteoblastoma-like tumor, the non-ossifying fibroma-like tumor and the ossifying fibroma-like tumor, which on aggregate have been diagnosed by Weidner and Santa Cruz in 7 of 8 cases of bone PMT of their revised series and in 14 of 39 cases of bone PMT revised from the literature by Folpe et al. Other occasional different tumor types seen in bone cases of PMT are enchondroma, hemangioma and osteosarcoma.

In sinonasal locations PMT usually exhibits a morphological pattern recalling the sinonasal-type hemangiopericytoma.

**Immunohistochemistry and special studies**

Tumor cells are negative for neural, epithelial, vascular, neuroendocrine and hematolymphoid markers, including CD34. Muscle markers, including desmin are negative, except alpha-smooth muscle actin, which occasionally has been found focally positive. Tumor cells are positive for vimentin, a feature which is common to any mesenchymal tumor, but are specifically immunoreactive with FGF-23 antibody (Fig. III-1iv). Expression of FGF-23 was also confirmed by RT-PCR in 2 of 2 cases in which frozen tissue was available. By electron microscopy tumor cells show an organelle-poor cytoplasm, devoid of any specific fine structure, thus appearing as primitive mesenchymal cells.

**Differential diagnosis and commentary**

The differential diagnosis concerning with the clinicopathologic entity of oncogenic osteomalacia has many folds; the laboratory findings, the clinical discovery of a tumor, the histopathological diagnosis. Serum and urinary laboratory findings should suggest in differential both X-linked hypophosphatemic rickets and autosomal dominant hypophosphatemic rickets, two conditions apparently due to deranged genetic mechanisms likely causing ineffective degradation of FGF-23 and overexpression of FGF-23, respectively. However, these two latter syndromes have an inheritance pattern and clinical onset in early childhood, characteristic enough to be distinguished from oncogenic osteomalacia. If a tumor is discovered in a patient presenting with OO, PMT must be proved on histological basis, since there are several other mesenchymal lesions and clinical conditions such as fibrous dysplasia and neurofibromatosis, as well as other non-mesenchymal tumors, such as breast, prostate and lung carcinomas, which may be associated with OO. Histopathologically and especially in soft tissue, the differential diagnosis involves the mixed connective tissue variant and in this context includes special variants of benign fibrous histiocytoma, soft tissue hemangiopericytoma, soft tissue chondroma, soft tissue giant cell tumor, mesenchymal chondrosarcoma, extraskeletal osteosarcoma, but the awareness of this histological polymorphous entity is essential for the correct diagnosis.

**Biological behaviour**

PMT is usually a benign tumor, but some cases of malignant transformation – even with metastatic disease – are also on record both in soft tissue and bone locations (malignant connective tissue variant). OO – the clinical effect of tumor – is vitamin D resistant, while it is dramatically cured by tumor removal.
References


III-2. Chondroid lipoma

Chondroid lipoma is a rare benign adipose tumor recognized by Meis and Enzinger in 1993, although Chan et al. seem to describe it first in 1986 as extraskeletal chondroma with lipoblast-like cells.

Clinical findings

Chondroid lipoma predominantly occurs in adults, mostly females. Most commonly, it presents itself clinically as an asymptomatic, deep-seated mass in the proximal extremities or limb girdles. Rare locations include the trunk, head and neck area and upper limbs. The lesion is asymptomatic and its duration is variable, some patients report a recent history of enlargement. Studies of the appearance of chondroid lipoma on magnetic resonance imaging are scarce; at present the lesion seems to have no distinctive features.

Pathological features

Grossly, the neoplasm is well-demarcated, often encapsulated and shows a homogeneous yellow, white or pink-tan cut surface. Histopathologically, chondroid lipoma is a well-circumscribed, often encapsulated lesion composed of 3 elements, namely: 1. lipoblast-like cells, 2. mature adipose tissue and 3. chondroid matrix, in varying proportions. The lipoblast-like cells, which are relatively small and uniform and may be uni- or multivacuolated, are arranged in cords, strands and small nests. In some cells eosinophilic cytoplasm and intranuclear inclusions are seen. The chondroid matrix varies in the appearance from myxoid to hyalinized and small nests (Fig. III-2i). In some cells eosinophilic cytoplasm and intranuclear inclusions are seen. The chondroid matrix varies in the appearance from myxoid to hyalinized and small nests (Fig. III-2ii). In some cells eosinophilic cytoplasm and intranuclear inclusions are seen. The chondroid matrix varies in the appearance from myxoid to hyalinized and small nests (Fig. III-2iii) to mature adipocytes was detected. The common ultrastructural feature seems to be the presence of knob-like...
protrusions of the cell membrane, which contains granular, amorphous, and fibrillar material that appears to be extruded into the adjacent matrix. The myxohyaline matrix has ultrastructural features of cartilage.

**SPECIAL STUDIES**

Although not numerous in chondroid lipoma, cytogenetic studies revealed a balanced translocation t(11;16)(q13;p12-13). Interestingly, the 11q13 breakpoint was also noted in hibernomas, raising the possibility of a histogenetic link between these two lesions. Of further interest is the fact that a similarity between these 2 neoplasms was also noted at the ultrastructural level.

**DIFFERENTIAL DIAGNOSIS**

Due to the presence of lipoblast-like cells the principal differential diagnosis of chondroid lipoma is a liposarcoma, chiefly myxoid liposarcoma. Another important differential diagnostic consideration is extraskeletal myxoid chondrosarcoma. These 2 entities also have a predilection for the deep soft tissue of the extremities. A clue to myxoid liposarcoma is the presence of a plexiform capillary network and primitive non-lipogenic mesenchymal cells with round to oval nuclei. Although small vessels are prominent in chondroid lipoma, they never have the appearance of "chicken-wire" vasculature. Extraskeletal myxoid chondrosarcoma is excluded by the absence of mature adipocytes and lipoblasts. This tumor often has a multilobular architecture, which is a rare finding in chondroid lipoma. Immunohistochemistry may also be helpful: in contrast to the diffuse positivity with S-100 protein in chondroid lipoma, this marker is expressed in a minority of extraskeletal myxoid chondrosarcomas and only focally.

**BIOLOGICAL BEHAVIOUR**

Chondroid lipoma is a benign neoplasm.

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**III-3. Dendritic fibromyxolipoma**

Dendritic fibromyxolipoma is a recently recognized entity fist reported by Suster et al. The tumors generally present in superficial soft tissues involving the subcutis and muscular fascia, although a case has been recently reported in intramuscular location. The tumors are usually well-circumscribed but unencapsulated, and can generally attain a large size (> 10 cm in diameter). Because of their large size and histologic features, they are frequently mistaken for a malignancy. Some authors have contended that dendritic fibromyxolipoma may represent a myxoid variant of spindle cell lipoma. The distinctive morphologic features of this lesion, however, warrant separating it into a unique and distinctive category.

**CLINICAL FEATURES**

In the study by Suster et al., of 12 cases, the tumors occurred predominantly in men (11:1) with a broad age range of 33 to 81 years (mean: 64 years). The lesions presented as superficial soft tissue masses located in the subcutis or muscular fascia of the head and neck region, chest and back. All cases were treated by simple local excision. Clinical follow-up in five patients showed no evidence of recurrence or metastasis over a follow-up period of 5 to 12 years (mean follow-up: 8 years). In one case, the lesion had been present for 4 years without change prior to surgical excision. It is of note that three of the cases were initially interpreted as myxoid liposarcoma by the original pathologists and one case was diagnosed as a myxoid malignant fibrous histiocytoma.
**Pathological features**

Grossly the lesions can vary in size from 2 to 11 cm (mean: 6 cm). They are well-circumscribed but unencapsulated and display a soft, yellow-gray, gelatinous cut surface. Cystic changes can also occasionally be observed grossly on the cut surface in some lesions. Microscopically dendritic fibromyxolipoma is characterized by a proliferation of spindle or stellate fibroblastic cells variably admixed with mature adipose tissue embedded in an abundant myxoid or collagenized stroma (Fig. III-3i–III-3ii). The spindle and/or stellate cells are characterized by slender dendritic cytoplasmic prolongations that extend for short distances along connective tissue planes touching each other (Fig. III-3iii). The tumors can display a prominent plexiform, branching vascular pattern, which when combined with the myxoid stroma can closely resemble myxoid liposarcoma. The collagenuous areas can display linear strands of rope-like collagen reminiscent of solitary fibrous tumors. The proportion of collagenuous and myxoid matrix can vary in different areas within the same tumor, with some areas showing a predominantly myxoid or a predominantly collagenized stroma, and other areas showing an even admixture of the two. The spindle cells contain small, hyperchromatic nuclei with very little nuclear detail and a scant rim of cytoplasm. Nuclear pleomorphism, cytologic atypia or mitotic activity is not seen. The stroma contains abundant mast cells and may harbor other inflammatory cells. Foci of chondroid metaplasia have been described in one case 2.

**Immunohistochemical findings**

The spindle and stellate cells in these tumors stain strongly positive for vimentin, CD34 and bcl-2 14. Vimentin and CD34 stains, in particular, highlight the dendritic nature of the spindle and stellate tumor cells, and demonstrate the slender dendritic cytoplasmic prolongations which resemble in areas a network of synaptic axons (Fig. III-3iv). Stains for smooth muscle actin, muscle-specific actin, desmin, S-100 protein, keratin and EMA were uniformly negative in the tumor cells.

**Ultrastructural findings**

Only two cases have been studied under the electron microscope so far 1. The tumor cells displayed fibroblastic features, including rough endoplasmic reticulum, occasional mitochondria, Golgi apparatus, and scattered cytoplasmic intermediate filaments. The cells were separated by abundant amorphous intercellular matrix with occasional scattered collagen fibrils. Many of the spindle cells also showed elongated cytoplasmic processes devoid of basal lamina material with foci of pinocytotic activity.

**Differential diagnosis**

The most important differential diagnosis is with myxoid liposarcoma, which this lesion can closely resemble. The combination of a prominent myxoid stroma admixed with spindle or stellate cells and branching, plexiform capillary vessels can be easily mistaken for this condition. Absence of signet-ring lobules or of a monotonous small round cell population in the background is the most important feature for distinguishing myxoid liposarcoma from dendritic fibromyxolipoma. Fibromyxolipoma should also be distinguished from spindle cell lipoma, with which it shares many features in common, including the predilection for the head and neck region, the spindle cell proliferation admixed with mature adipose and fibrous tissue, and strong CD34 and bcl-2 positivity 5. Cases of spindle cell lipoma displaying a myxoid stroma have been cited in the literature 6. However, the spindle cells in spindle cell lipoma tend to group into tight fascicles rather than be scattered singly and at a distance from each other as in dendritic fibromyxolipoma. Additionally, the spindle cells in spindle cell lipoma tend to be fusiform and elongated resembling normal fibroblasts, similar to the cells in solitary fibrous tumors, unlike the short, often teardrop-shaped and stellate cells in dendritic fibromyxolipoma. Another feature that distinguishes dendritic fibromyxolipoma from spindle cell lipoma is the striking dendritic nature of the spindle and stellate cells, which display long cytoplasmic processes emanating from the cytoplasm, unlike the spindle cells in spindle cell lipoma which generally display short blunt edges. The possibility that these three conditions (dendritic fibromyxolipoma, spindle cell lipoma and solitary fibrous tumor) are closely related entities that represent different morphologic aspects in the same spectrum of lesions has been acknowledged 1. However, dendritic fibromyxolipoma is sufficiently distinctive morphologically to merit separation as a distinct and separate entity from spindle cell lipoma and solitary fibrous tumor of soft tissue 7.

**References**

Epithelioid liposarcoma is a distinctive variant of pleomorphic liposarcoma showing an epithelial-like solid pattern of growth that may be confused with carcinoma, especially primary or metastatic renal or adrenal cortical carcinoma.

**CLINICAL FINDINGS**
The only series of 12 cases published to date had nine men and three women. Five tumors were present in the thigh, two in the axilla, two in the chest wall, and one each in the calf, groin and retroperitoneum.

**PATHOLOGICAL FEATURES**
Grossly the tumors were large (> 10 cm), firm, and multinodular with a yellow cut surface. Variegated zones of necrosis were present in large tumors. The striking histologic feature is the presence of solid, cohesive sheets of epithelioid-appearing cells separated by fine fibrovascular septa. The absence of an extracellular matrix reaffirms the resemblance to carcinoma, especially renal cell or adrenocortical carcinoma. Large areas of coagulative necrosis appear to be a consistent feature. Other areas of these tumors show adipocytic differentiation comprising single or multiple vacuoles. This feature may also sometimes be present adjacent to the well-demarcated epithelioid areas. The adipocytic differentiation range from a few scattered lipoblasts in some tumors to more extensive adipocytic differentiation in others. The cells of the epithelioid-like areas demonstrate distinct cell borders with clear to mildly eosinophilic “hypernephroid” cytoplasm. The nuclei are round to oval with a prominent nucleolus. These cells typically demonstrate a high mitotic rate (> 20 per 10 high power fields).

**IMMUNOHISTOCHEMISTRY**
Not surprisingly, focal S-100 protein immunoreactivity, confined to scattered lipoblasts, was present in approximately half of the cases. Compounding the confusion with carcinoma, approximately half of epithelioid liposarcomas were also keratin immunopositive with both AE1/AE3 and CAM 5.2. However, all cases were negative with epithelial membrane antigen, muscle actins, desmin, and CD34. A 30 to 70% proliferative activity was demonstrated with MIB-1 immunostaining.

**DIFFERENTIAL DIAGNOSIS**
The epithelioid variant of pleomorphic liposarcoma is a distinctive high-grade tumor that may be confused with carcinomas with a solid growth pattern viz renal cell and adrenal cortical carcinomas. Further, the demonstration of keratin immunopositivity in epithelioid liposarcomas underscores the need to distinguish these tumors from primary or metastatic carcinomas. The presence of true adipocytic differentiation comprising lipoblasts with large lipid vacuoles (as opposed to the fine cytoplasmic lipid droplets seen in renal carcinoma) is a useful distinguishing feature. Further, renal cell carcinomas are both keratin and EMA immunopositive, whilst epithelioid liposarcomas may be keratin positive but are EMA negative. Conversely, many adrenal cortical carcinomas are keratin and EMA negative. In this context, caution should be exercised with small biopsy specimens and it is recommended that relevant imaging studies be applied in this distinction.

Metastatic balloon-cell melanomas may also be confused with the epithelioid variant of pleomorphic liposarcoma. However, melanomas are diffusely S-100 positive and are often positive for HMB-45. Epithelioid leiomyosarcoma in the retroperitoneum or gastrointestinal tract commonly comprises trabeculae of uniform epithelioid cells with a lobular pattern and variably eosinophilic cytoplasm. Whilst fine vacuolization may be present, the large vacuoles of lipoblasts are not present. In addition, muscle markers (actins and desmin) are often expressed along with CD34.

**BIOLOGICAL BEHAVIOR**
Five of the ten patients in whom follow-up information was available died within one year, confirming the potential for highly aggressive behavior of these tumors. Two patients died of unrelated causes ten or more years after diagnosis. The remaining patients were alive at the time of publication, including one patient who survived 24 years following an above the knee amputation for recurrent tumor in the distal thigh.

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**References**

TUMORAL, QUASITUMORAL AND PSEUDOTUMORAL LESIONS OF SOFT TISSUE

III-5. Lipoleiomyosarcoma (Well-differentiated Liposarcoma with Leiomyosarcomatous Differentiation)

The presence of mature smooth muscle in “atypical lipomatous tumors” (i.e., well-differentiated liposarcoma) was first described by Evans in 1990, in a report of three cases located in the spermatic cord, mediastinum and retroperitoneum. The foci of smooth muscle did not exhibit any significant evidence of cytologic atypia and were not felt to influence the prognosis of these tumors, despite the fact that one of the lesions later recurred as a “dedifferentiated” liposarcoma with a high-grade spindle cell sarcomatous component of undetermined lineage. Suster et al. in 1993 reported two cases of well-differentiated liposarcoma that contained smooth muscle elements with features of well-differentiated leiomyosarcoma. An additional case was subsequently reported by Gomez-Roman and Val-Bernal in a patient with a mediastinal tumor containing well-differentiated liposarcoma and areas of well to moderately-differentiated leiomyosarcoma. More recently, Folpe & Weiss presented a study of 9 cases displaying well-differentiated leiomyosarcoma. An additional case was subsequently reported by Folpe and Weiss in five of their cases consisted of areas in which the smooth muscle elements appeared to blend or arise from the smooth muscle wall of vessels within the tumor, suggesting that these foci may represent an early or “in-situ” change. One case reported by Folpe and Weiss contained a focus of high-grade “dedifferentiated” liposarcoma in addition to the low-grade, well-differentiated smooth muscle component.

IMMUNOHISTOCHEMISTRY

Immunohistochemical stains performed in the study by Suster et al. showed strong positivity of the spindle cell component for actin, desmin and vimentin, and negative staining for low-molecular weight cytokeratin (CAM 5.2), S-100 protein, and factor VIII-related antigen. Two of five referred cases in the Folpe & Weiss study had immunoperoxidase stains done at the referring institutions; both cases showed positivity of the atypical spindle cells for smooth muscle actin but not for desmin (Fig. III-5iv).

DIFFERENTIAL DIAGNOSIS

Lipoleiomyosarcoma must be distinguished from well-differentiated liposarcomas harboring a benign, well-differentiated smooth muscle component (i.e., a combined liposarcoma with leiomyoma), as described by Evans. Another important distinction is with the so-called “dedifferentiated” liposarcoma with leiomyosarcomatous components. As per Evans’s original definition, “dedifferentiated” liposarcoma refers to a tumor in which distinct areas of well-differentiated liposarcoma and of a cellular spindle cell or pleomorphic sarcoma without recognizable lipogenesis are present within the same neoplasm. By definition, the high degree of differentiation of the smooth muscle component precludes inclusion of these tumors under the category of “dedifferentiated” liposarcoma. A few cases of “dedifferentiated” liposarcoma with smooth muscle components have been reported in the literature. Unlike lipoleiomyosarcoma, such tumors are generally high-grade sarcomas with frequent local recurrences and death from disease in a high proportion of patients. The clinical behavior of lipoleiomyosarcoma, on the other hand, appears to be essentially similar to that of well-differentiated liposarcoma without a smooth muscle component. Progression to a high-grade sarcoma from the spindle cell component, however, can occur in some cases, thus indicating a need for close follow-up of these patients.


** Biological behaviour**

All cases so far described were treated by surgical excision and in the majority of instances displayed positive

**Pathological features**

The recorded size of the epithelioid leiomyosarcoma of soft tissue varies from 1.2 to 2.5 cm in greatest diameter. They are usually well-circumscribed but unencapsulated, and grow in an expansile fashion. The tumors often occupy the deep dermis and subcutis (Fig. III-6i). Epithelioid leiomyosarcoma is characterized by a neoplastic proliferation of round to oval cells with abundant eosinophilic cytoplasm. Areas of transitions with foci displaying a more conventional (non-epithelioid) spindle cell appearance are frequently encountered. An interesting feature of these tumors is the intimate relationship of the tumor cells with the walls of large and mid-caliber vessels, whereby large, epithelioid tumor cells appear to be originating from the media of the vessel wall (Fig. III-6iv).

The majority of the tumors show extensive infiltration along tissue planes at the edges of the lesions. In the majority of the tumors, discrete areas can usually be identified displaying the conventional features of leiomyosarcoma, with intersecting fascicles of spindle cells with “cigar-shaped” nuclei and finely fibrillar cytoplasm; however, the predominant cell population in all tumors is composed of the round, epithelioid cells.

**Immunohistochemistry**

The tumor cells in all cases in the study by Suster were immunoreactive for actin and vimentin antibodies, and were negative for cytokeratin, EMA, S-100 protein, desmin, FVIII-RA, alpha-1-antichymotrypsin and HMB45 antibodies. An additional, subsequently reported case of cutaneous epithelioid leiomyosarcoma was also positive for actin and vimentin but negative for desmin.

The absence of desmin immunoreactivity has been explained as a site-specific phenomenon or as an attribute of smooth muscle tumors originating from vessel walls, which are known not to express desmin intermediate filaments. The cases described by Lopez-Barea et al. arising in bone, and by Yamamoto et al. originating within the muscle in the thigh, likewise stained positively only for smooth muscle actin and pan-actin antibodies but were negative for desmin.

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**References**


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**III-6. Epithelioid leiomyosarcoma**

Epithelioid leiomyosarcoma has been well-recognized for many years in the female genital tract; it is, however, quite rare in other locations. In 1994, Suster published a study of 5 cases of epithelioid leiomyosarcoma of the skin and superficial soft tissue and called attention to this unusual variant of smooth muscle tumor outside of the female genital tract. Since then, multiple additional cases have been reported involving the skin and somatic soft tissues, including retroperitoneum (2), liver (3), larynx (4), bone (5), heart (6), thigh (7), para-testicular region (8), and skin of nose (9). The recorded size of the epithelioid leiomyosarcoma of the back of the neck.
Electron microscopy
Ultrastuctural examination was performed in three cases in the study by Suster from fresh tissue fixed in glutaraldehyde. All three cases showed similar features, namely the presence of abundant cytoplasmic microfilaments with focal condensations, surface pinocytotic activity, focal subplasmalemmal densities, and an incomplete basal lamina surrounding the cells. Similar ultrastructural findings were identified in the cases studied by Lopez-Barea et al., Pins et al. and Yamamoto et al. 1.

Differential diagnosis
The three main conditions that can closely resemble epithelioid leiomyosarcoma are malignant melanoma, malignant sarcoma, and metastatic carcinoma. Malignant melanoma can also show an atypical neoplastic proliferation of spindle and epithelioid cells that can closely simulate these tumors; however, the cells show a tendency to form nests rather than to grow forming fascicles. Immunohistochemical studies can easily resolve the problem by demonstrating melanoma-associated markers in the latter (including S-100 protein, Melan-A, HMB45, and tyrosinase) as opposed to muscle markers in epithelioid leiomyosarcoma. Epithelioid sarcoma can also present with a similar histologic picture and anatomic distribution as cutaneous epithelioid leiomyosarcoma; they will be distinguished by their multinodular growth pattern, more bland appearing cytology, prominent areas of stromal collagenization, and at the chemical level by the expression of epithelial-associated markers such as EMA and cytokeratin. Metastatic carcinoma should also be ruled out when dealing with these tumors; this can be done by a combination of clinical history and immunohistochemistry.

Biological behaviour
All patients in Suster’s series were treated by surgical excision and two received postoperative radiation therapy. Two cases recurred after 1 year requiring wide excision. A second recurrence from one of those cases showed the emergence of a highly anaplastic, pleomorphic spindle cell sarcoma. In the latter case, the patient died of unrelated causes 2 years after re-excision, with extensive residual disease. In the remainder of cases, the patients were alive and well with no evidence of recurrence or metastases from 2 to 6 years. The reason for the relatively indolent behavior of these lesions is most likely related to their small size and superficial location. Epithelioid leiomyosarcomas in somatic organs and deep soft tissues, on the other hand, can follow a very aggressive behavior similar to their non-epithelioid counterparts 6.

References

III-7. Granular cell leiomyosarcoma
Granular cell leiomyosarcoma is a rare variant of smooth muscle tumor first described by Suster et al. in 1988. Since then, several other examples have been reported in the literature. The tumors tend to most frequently involve the skin, although granular cell changes in smooth muscle neoplasms have now also been recognized in lesions located in deep soft tissue such as the retroperitoneum.

Clinical features
The tumors more often affect children and young adults, with no particular sex predilection. In the original case described by Suster et al., the tumor arose in the head and neck region following radiation therapy for cerebellar medulloblastoma. In one of the cases reported by LeBoit et al., the tumor was said to arise at the site of a previous scar following excision of a “fibrous cyst”. No other specific association or precondition was described for the other reported cases. The tumors show a wide distribution, including head and neck, back, thumb, ankle and vulva (labium majus).
**Pathological features**

Grossly the tumors measure from 2 to 5 cm in greatest diameter. Some tumors were characterized by a polypoid, multinodular appearance with an exophytic configuration involving the dermis and extending into the subcutaneous tissue. Other lesions have been described as mainly involving the subcutis as a plaque-like area of induration or as a well-circumscribed tumor mass. The tumor described by Suster et al. was multifocal and presented with multiple subcutaneous nodules in the back and lower neck.

Histologically the tumors are characterized by a fascicular growth pattern, primarily occupying the deep dermis and occasionally invading the subcutis (Fig. III-7i). The neoplastic proliferation is composed of large, oval to spindle cells with abundant granular eosinophilic cytoplasm (Fig. III-7ii). Some of the cells display mitotic figures (Fig. III-7iii). The neoplastic cells are remarkable for the abundance of periodic acid-Schiff (PAS)-positive, diastase-resistant intracytoplasmic granules (Fig. III-7iv). Areas of hemorrhage and tumor necrosis are rare. Nuclear pleomorphism has been noted in the majority of cases. Transitions with foci showing more conventional features of leiomyosarcoma are also apparent.

**Immunohistochemistry**

Immunohistochemical studies have been performed in the majority of the published cases to establish the smooth muscle nature of the lesion. In the study by Suster et al., the tumor cells stained strongly positive for desmin, vimentin and smooth muscle myosin, and were negative for cytokeratin, S-100 protein and myoglobin. In the study by LeBoit et al. there was strong positivity of the tumor cells for muscle-specific actin and the cells were surrounded by collagen type IV, but they were negative for S-100 protein. In the study by Sommerhausen and Fletcher, all tumors stained for desmin or smooth muscle actin and were negative for S-100 protein.

**Electron microscopy**

Three cases have been studied by electron microscopy showing similar results, namely, widely dilated cytoplasm containing abundant phagolysosomes and focal cytoplasmic microfilaments with dense bodies. The presence of numerous autophagic vacuoles in the cytoplasm of the tumor cells accounts for the cytoplasmic granularity observed on routine microscopy, and indicates that the granular cell change in these tumors may be a secondary, albeit non-specific degenerative phenomenon without any specific clinical biologic significance.

**Differential diagnosis**

These tumors need to be separated from granular cell peripheral nerve sheath tumors (“granular cell tumor” of Abrikossoff, granular cell schwannoma). The latter do not normally display the well-developed fascicular architecture of granular cell leiomyosarcoma, which tends to form fascicles that intersect at right angles, and the cells are usually round or ovoid as opposed to the frequent presence of spindle cells in granular cell leiomyosarcoma. When in doubt, application of immunohistochemical stains should help resolve the problem. Ultrastructural study may also be helpful by identifying features of smooth muscle differentiation in the latter. Another unusual type of skin tumor that may show a similar morphology is the so-called “primitive polypoid granular cell tumor of nonneural origin” described by Leboit et al., which is distinguished from granular cell leiomyosarcoma by the absence of immunoreactivity for a wide panel of immunohistochemical stains, including muscle markers.

**Biological behaviour**

Most cases so far described were treated by complete surgical excision with clear margins. Clinical follow-up so far has shown no evidence of recurrence from 3.5 to 5 years after excision in 3 patients, and multiple metastases to the lungs and pleura 1 year after initial diagnosis in one. The latter patient, a 65 year old woman, had a large, deeply infiltrative tumor in the vagina.

**References**

III-1. Phosphaturic mesenchymal tumor

Fig. III-1i. A circumscribed soft tissue mesenchymal tumor involving the subcutis of the thigh in a 56-year-old man is seen (on the left). At higher power, tumor cell composition with small, bland cells embedded in a smudgy matrix (on the right).

Fig. III-1ii. In other fields of the tumor distinctive flocculent calcifications ("grungy" pattern) could be noted.

Fig. III-1iii. Fibrohistiocytic proliferation (on the left) and giant cell reaction (on the right) are usual aspects of this composite tumor ("mixed connective tissue pattern").

Fig. III-1iv. Immunohistochemical expression of FGF-23 in a spindle cell area.

III-2. Chondroid lipoma

Fig. III-2i. Relatively small, uniform, uni- or multivacuolated lipoblast-like cells admixed with mature lipocytes are seen.

Fig. III-2ii. A case of chondroid lipoma with a high number of lipoblast-like cells.
III-3. Dendritic fibromyxolipoma

Fig. III-3i. Scanning magnification showing adipocytes embedded in abundant myxoid stroma containing scattered small, stellate to spindle cells.

Fig. III-3ii. Higher magnification showing admixture of three cellular elements that characterize this lesion: mature fat, strands of collagenous tissue, and sparse population of small spindle and stellate cells embedded in a myxoid stroma.

Fig. III-3iii. Higher magnification of spindle and stellate cells showing slender, elongated dendritic cytoplasmic processes.

Fig. III-3iv. Immunoperoxidase for CD34 showing elaborate, branching dendritic prolongations of the tumor cells resembling a network of synaptic axons.
III-4. Epithelioid liposarcoma – a variant of pleomorphic liposarcoma

Fig. III-4i. Solid, cohesive sheets of epithelioid-appearing cells separated by fibrovascular septa are demonstrated in this epithelioid liposarcoma.

Fig. III-4ii. Low power view to demonstrate the transition between the adipocytic differentiation and well-demarcated epithelioid areas.

Fig. III-4iii. The tumor cells of the epithelioid-like areas demonstrate distinct cell borders with clear to mildly eosinophilic cytoplasm.

Fig. III-4iv. The nuclei are round to oval with a prominent nucleolus in this high power image.

III-5. Lipoleiomyosarcoma (Well-differentiated Liposarcoma with Leiomyosarcomatous Differentiation)

Fig. III-5i. Scanning magnification. Soft tissue tumor showing admixtures of two distinct cellular areas, one composed of fascicles of spindle cells, and another predominantly composed of adipocytic elements.

Fig. III-5ii. Higher magnification from adipocytic component showing scattered large, atypical adipocytes and floret-type cells admixed with mature adipocytes.
III-5. Higher magnification from solid spindle cell area showing fascicles cut at 90 degree angles composed of atypical cells with enlarged nuclei and abundant fibrillary eosinophilic cytoplasm.

Fig. III-5iv. Immunohistochemical stain for smooth muscle actin showing strong positivity of the spindle cell component (lower right) with this antigen, and negative staining of the adipocytic component on the left.

III-6. Epithelioid leiomyosarcoma

Fig. III-6i. Scanning magnification of epithelioid leiomyosarcoma involving the deep dermis and subcutaneous tissue.

Fig. III-6ii. Higher magnification showing solid proliferation of round, epithelioid tumor cells with abundant eosinophilic cytoplasm.

Fig. III-6iii. Notice round to polygonal shape of the tumor cells with abundant eosinophilic cytoplasm and sharp cell borders. A mitosis is present at the center of the field.

Fig. III-6iv. Area of the tumor showing transition between the wall of a large caliber vessel and the epithelioid neoplastic proliferation.
III-7. Granular cell leiomyosarcoma

Fig. III-7i. Scanning magnification of skin lesion showing a spared epidermis and upper dermis and solid cellular proliferation occupying the deep dermis and subcutaneous tissue.

Fig. III-7ii. The cellular proliferation in the deep dermis is composed of large, oval to spindle cells with abundant eosinophilic cytoplasm.

Fig. III-7iii. Higher magnification demonstrates occasional mitotic figures.

Fig. III-7iv. High power highlights the finely granular cytoplasm of the tumor cells.