Primary cutaneous sarcomas
Sarcomas cutâneos primários

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Abstract: Soft tissue tumors represent a heterogeneous group of mesenchymal and neural lesions. The cutaneous presentation of these tumours is rare. With the evolution of dermatologic surgery and cutaneous oncology, dermatologists have emerged as specialists for skin cancer management. This article reviews primary cutaneous sarcomas with particular emphasis on the epidemiologic, clinical, and histological features of diagnosis, as well as treatment modalities and prognosis. The most frequent cutaneous sarcomas were reviewed, including angiosarcoma, dermatofibrosarcoma protuberans, atypical fibroxanthoma, leiomyosarcoma, liposarcoma, malignant nerve sheath tumor, and epithelioid sarcoma. Kaposi's sarcoma, due to specific characteristics, was omitted from this review.
Keywords: Angiosarcoma; Dermatofibrosarcoma; Leiomyosarcoma; Liposarcoma; Sarcoma/diagnosis; Skin neoplasm

Resumo: *Os sarcomas com apresentação cutânea primária são tumores raros e de grande heterogeneidade histológica. Com a evolução da oncologia cutânea e da cirurgia dermatológica, os dermatologistas têm sido cada vez mais requisitados para o diagnóstico e orientação terapêutica de tumores menos freqüentes. Este artigo de revisão analisa os sarcomas cutâneos primários observando suas características clínicas, etiopatogênicas e histológicas, bem como aspectos do tratamento e evolução. Enfatiza os sarcomas de maior relevância para o dermatologista, como angiossarcoma, dermatofibrossarcoma protuberans, fibroxantoma atípico, leiomiossarcoma, lipossarcoma, tumor maligno de bainha de nervo periférico e sarcoma epitelióide. O sarcoma de Kaposi não é abordado devido a suas características individuais específicas.*
Palavras-chave: Dermatofibrossarcoma; Hemangiossarcoma; Leiomiossarcoma; Lipossarcoma; Neoplasias cutâneas; Sarcoma/diagnóstico

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INTRODUCTION

According to data from the National Cancer Institute [Instituto Nacional do Câncer] (INCA), skin neoplasms are responsible for 25% of malignant tumors reported in Brazil.[1] There are about 30 different types of skin cancer,[2] 70% of them basal cell carcinomas (BCC), 25% squamous cell carcinomas (SCC), 4% cutaneous melanomas (CM), and 1% related to less common types not specified in epidemiologic data.[1] Because of the greater prevalence of BCC, SCC, and CM cases, dermatologists are more familiar with the diagnosis, prognosis, and treatment of these neoplasms. However, with the progress of cutaneous oncology, dermatological surgery, and Mohs micrographic surgery, dermatologists are being consulted more often on diagnosis and treatment management of infrequent tumors.[3]

Among the neoplasms that are a part of a nonhabitual group in the dermatologist's daily practice are the sarcomas. Sarcomas are malignant tumors of soft tissues[4] that constitute a highly heterogeneous group of neoplasms histologically classified according to the mature tissue they resemble. Among the histological categories, soft tissue tumors are typically divided into benign and malignant. The first, which most resemble normal tissue, are 100 times more frequent. They have a limited capacity for growth, a small tendency for local invasion, and a low rate of local recurrence after conservative treatment. Malignant tumors or sarcomas, on the other hand, are locally aggressive and capable of invasive and destructive growth, local recurrence, and metastases.[4,5]

Sarcomas are usually manifested by deep lesions, but they may affect the skin and subcutaneous tissue, presenting to the dermatologist as a superficial lesion or subcutaneous nodule. These tumors may cause cutaneous lesions in three distinct ways: 1- originating primarily in the skin and subcutaneous tissue; 2- as a direct extension of deep lesions; 3- by metastatic involvement of the skin, an extremely rare phenomenon.[6]

For classification purposes, superficial sarcomas are all those originated above the fascia, although there is no classification in literature that defines cutaneous sarcomas. Chart 1 summarized the main sarcomas capable of primary cutaneous manifestation. In this article, primary sarcomas of the skin and subcutaneous tissue are addressed, since they are of greatest interest to the dermatologist. Kaposi's sarcoma was excluded because of its specific and well-defined characteristics.

ANGIOSARCOMA

This is a malignant tumor whose cells recapture the morphological and function characteristics of normal endothelium. It can vary from highly differentiated tumors that resemble hemangiomas to those in which the high degree of anaplasia complicate its differentiation from carcinomas or melanomas.[7] Angiosarcoma is one of the rare sarcomas that develop, in most cases, as a primary cutaneous tumor. About 50% of cutaneous angiosarcomas occur on the head and neck, especially on the scalp of elderly men. They are aggressive tumors, with difficult delineation of surgical margins, a high tendency toward local recurrence, and distant metastases.[7-10]

Epidemiology and Pathogeny

This tumor can affect the skin in three distinct ways: cutaneous angiosarcoma associated with chronic lymphedema (also called lymphangiosarcoma), cutaneous angiosarcoma induced by radiation, and cutaneous angiosarcoma per se (not associated with lymphedema or radiotherapy).[7]

Angiosarcomas originating from chronic lymphedema occur predominantly on arms of women submitted to radical mastectomy with axillary clearance. This syndrome was described by Stewart and Treves in 1948, and is commonly referred to by this eponym (Figure 1). Some cases are described in patients with congenital, traumatic, or infectious lymphedema.[9]

Post-radiotherapy angiosarcoma is also found more often in women submitted to radiotherapy for treatment of mammary carcinoma. However, it seems to be a rare phenomenon, as there are about 58 cases reported in literature.[11] Usually, it is a high-grade sarcoma with extremely aggressive behavior.

The cases of primary cutaneous angiosarcoma that originate in the absence of prior radiation or lymphedema generally affect elderly men, and favor the head and neck areas, especially the scalp and frontal region[12] (Figure 2). Excessive exposure to ultraviolet rays has been considered a risk factor for tumor development, although there are arguments contrary to this position.[10,12,13]

Clinical Presentation

Clinically, it presents as poorly defined erythematous macules, papules, plaques, or nodules, with rapid expansive growth, in some cases resembling hematomas. Lesions are habitually echymotic and edematous, and during progression may ulcerate. Most patients have a history of a few months' evolution with pain and bleeding.[7,12] Cases associated with lymphedema generally are manifested as single or multiple erythematous-violaceous nodules on the affected limb, in average around 10 years

CHART 1: Histological classification of soft tissue cutaneous sarcomas

- **Fibrous tumors**
  - **Intermediate**
    - Adult fibromatosis
      - Superficial (including palmar, plantar, penile, and knuckle pads)
    - Juvenile fibrosarcoma
  - **Malignant**
    - Adult fibrosarcoma
- **Fibrohistiocytic tumors**
  - **Intermediate**
    - Atypical fibroxanthoma
    - Dermatofibrosarcoma protuberans (including Bednar's pigmented form)
    - Giant cell fibroblastoma
    - Angiomatoid fibrohistiocytoma
    - Plexiform fibrohistiocytic tumors
    - Giant cell tumor with low malignancy potential
  - **Malignant**
    - Malignant fibrohistiocytoma
- **Lipomatous tumors**
  - **Intermediate**
    - Atypical lipoma (well-differentiated superficial liposarcoma / atypical lipomatous tumor)
  - **Malignant**
    - Well-differentiated liposarcoma
    - Myxoid – round cell liposarcoma
    - Pleomorphic liposarcoma
    - Dedifferentiated liposarcoma
- **Smooth muscle tumors**
  - **Malignant**
    - Leiomyosarcoma
- **Skeletal muscle Tumor**
  - **Malignant**
    - Rhabdomyosarcoma
- **Blood and lymphoid vessel tumors**
  - **Intermediate**
    - Hemangioendothelioma
  - **Malignant**
    - Angiosarcoma
    - Kaposi's sarcoma
- **Perivascular Tumors**
  - **Malignant**
    - Malignant glomic tumor
    - Malignant hemangiopericytoma / malignant solitary fibrous tumor
- **Peripheral Nerve Sheath Tumors**
  - **Malignant**
    - Malignant perineural sheath tumor (MPNST)
- **Primitive neuroectodermal tumor (PNET) and related lesions**
  - **Malignant**
    - Neuroblastoma
    - Ganglioneuroblastoma
    - Extra-osseous Ewing Sarcoma / primitive neuroectodermal tumor
- **Paraganglionar Tumors**
  - **Malignant**
    - Malignant paraganglioma
- **Extra-skeletal Osseous and Cartilaginous Tumors**
  - **Malignant**
    - Chondrosarcoma
    - Extra-skeletal osteosarcoma
- **Miscellaneous Tumors**
  - **Malignant**
    - Synovial sarcoma
    - Soft tissue alveolar sarcoma
    - Epithelioid sarcoma
    - Small round cells desmoplastic tumor
    - Malignant extra-renal rhabdoid tumor

Adapted from: Enzinger FM, Weiss SW. Soft tissue tumors. 4th ed. St Louis: Mosby; 2001, p. 7-8.

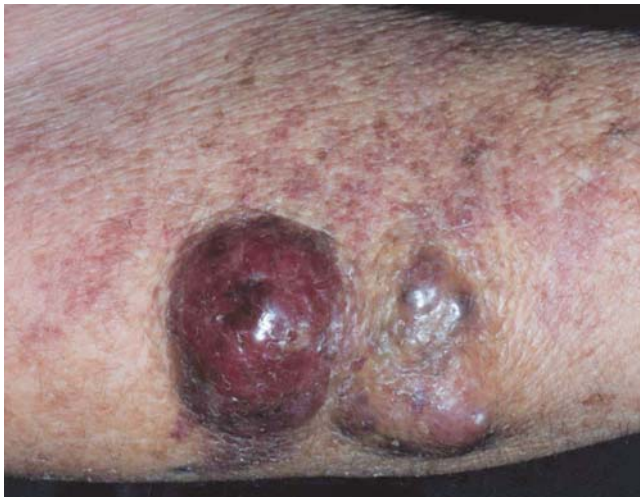

Figure 1: Angiosarcoma on chronic lymphedema (Stewart-Treves syndrome). Violaceous nodule on upper limb

after the mastectomy. Lesions may coalesce and form a polypoid tumor. Ulceration accompanied by serous-sanguineous secretion is common in older lesions. Cutaneous angiosarcoma associate with radiotherapy habitually appears at the irradiated site, in average five years after radiation therapy, mostly after conservative surgery for mammary carcinoma.[7,9,11,12]

Diagnosis

Histologically, the three groups of lesions are undistinguishable, and consist of a network of dermal vascular canals varying in size from small capillaries to sinusoid spaces interspersed by normal endothelium. The endothelium shows a variable degree of pleomorphism and atypia (Figure 3). In general, mitoses are rare or focal. The tumor may also take on a solid epithelial spindle cell pattern with islets or blocks of epithelioid or spindle cells without forming sinusoid or vascular spaces; they may also present a mixed pattern. The histological differential diagnosis of angiosarcoma should be made primarily with Kaposi's sarcoma, benign hemangiomas, hemangiopericytoma, and in some cases, even with squamous cell carcinoma and melanoma.[7]

Although immunohistochemistry may be useful in establishing the diagnosis of a vascular neoplasm, it does not distinguish angiosarcoma from other vascular tumors.[11] Despite being amply utilized as a vascular marker, the anti-factor VIII antibody has shown poor sensitivity in the diagnosis of angiosarcoma.[7,11] The antibody against CD31 ("platelet-endothelial cell" adhesion molecule) is highly sensitive and specific for endothelial differentiation. Practically all vascular tumors express this membrane protein. The CD34 (human hematopoietic cell antigen), in spite of being present in a great number of angiosarcomas, is also positive in several other soft tissue tumors.[7]

Treatment

Treatment should be led by a multidisciplinary team and should be individualized according the extension of the lesion, anatomical location, and patient consent. Surgery alone or combined with radiotherapy is used for initial lesions, although a surgical removal with adequate margins is not always possible.

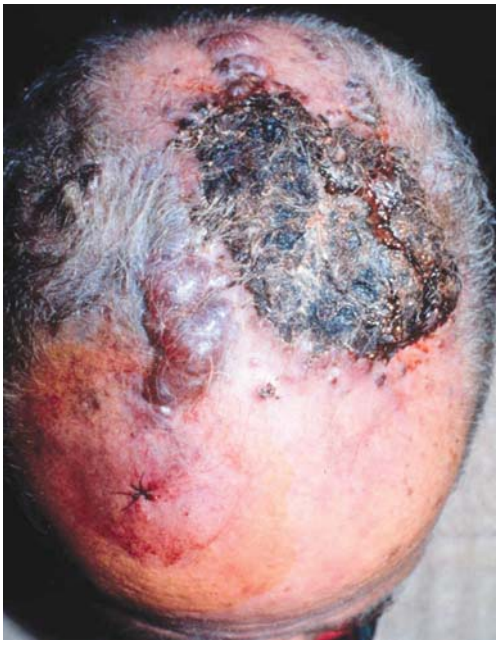

Figure 2: Cutaneous angiosarcoma. Ulcerated erythematous-violaceous plaque on scalp

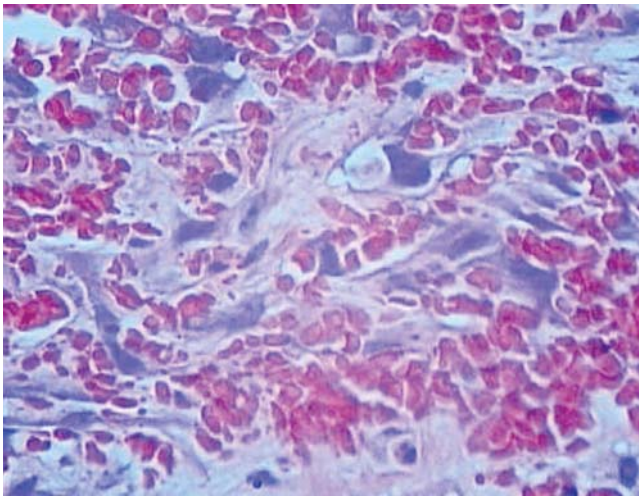

Figure 3: Cutaneous angiosarcoma. Fusiform cells involving vascular fissures and atypical epithelioid cells with intracellular lumen containing red blood cells (HE 400X)

Chemotherapy is indicated for disseminated tumors, associated with radiotherapy for loco-regional treatment of extensive lesions or as neoadjuvant therapy. The chemotherapy agents used most frequently are doxorubicin, cyclophosphamide, methotrexate, and vincristine.[12] The combination use of interferon alpha and 13-cis-retinoid acid, in advanced disease, has been reported as effective.[14]

The treatment of lesions originated in areas previously irradiated should be aggressive, and frequently total mastectomy is indicated. Ressection of even the chest wall may be necessary in some cases. Axillary lymphadenectomy is not indicated, since lymph node metastases are rare. Even with aggressive treatment, relapses are frequent and prognosis is guarded.[11] The angiosarcoma that originates in chronic lymphedema also shows an aggressive behavior, with the greatest survival reported after radical amputation of the affected limb.[7]

Prognosis

Despite clinical remissions attained with the proposed treatments, the prognosis in angiosarcoma is poor, with a high rate of local relapses, 84% in five years, and a tendency towards systemic dissemination. Most patients die because of the disease, with metastases to the lungs, heart, or brain. Five-year survival rates are between 10 and 35%.[7,12]

DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans (DFSP) is a fibrohistiocytic tumor of intermediate malignancy, and represents most cutaneous sarcomas. It shows aggressive local growth, a high recurrence rate, but low metastatic potential.[15]

Epidemiology and Pathogeny

The estimated incidence of this tumor varies from 0,8 to 5 cases per million each year.[16] It is more common in the 20 to 50 years-of-age bracket, although there are cases reported from birth up to 80 years of age. Distribution is equal for both genders, with some studies showing a slight male predominance.[17]

Trauma antecedents as triggering factors are described in 10 to 20% of cases. Several reports, however, describe tumor development in scars from a previous operation, burn wound, varicella or BGC immunization,[18-20] as well as rapid growth during pregnancy, a fact attributed to progesterone receptors in the tumor.[21] Associations with prolonged exposure to arsenic,[22] acanthosis nigricans, and enteropathic acrodermatitis[23] have also been reported.

One characteristic of DFSP is the presence of a specific cytogenetic alteration involving chromosomes 17 and 22, t(17;22)(q22;q13), habitually resulting in chromosomal anomalies with fusion of the collagen type-1 alpha-1 (COL1A1) gene of chromosome 17 with the gene from the platelet-derived chromosome 22 β-chain growth factor (PDGFβ).[24-26]

Clinical Presentation

The trunk is the area most affected by DFSP, encompassing 50 to 60% of tumors (Figure 4), followed by proximal limbs (20%), and head and neck (10 to 15%).[27] Acral and genital dermatofibrosarcomas are infrequent.[27,28]

Initially, it presents as a hardened plaque, asymptomatic, violaceous, reddish-brown, or slightly hyperchromic, similar to a cheloid. The indolent behavior of DFSP and its imprecise characteristics frequently lead to a delay in its being perceived by patients, and hence, a late diagnosis. Nevertheless, when the lesion has progressed, dermatofibrosarcoma is not difficult to diagnose because of its distinctive clinical appearance (Figure 5). Atypical variations such as pigmented DFSP (Bednar's tumor) and the atrophic form are rare. Differential diagnosis is made with lymphomas, sarcoidosis, melanoma, cutaneous metastases, cheloids, desmoid tumor, fibrosarcoma, appendage tumors, and dermatofibroma.[15,28]

Diagnosis

DFSP originates in the dermis as a dense arrangement of cells with spindle cell.[29] Tumor cells are organized in irregular interwoven fasciculi, resulting in a storiform pattern.[30] In some areas they seem to originate in a central core of acellular collagen with a "cartwheel or whirlwind" pattern[31]

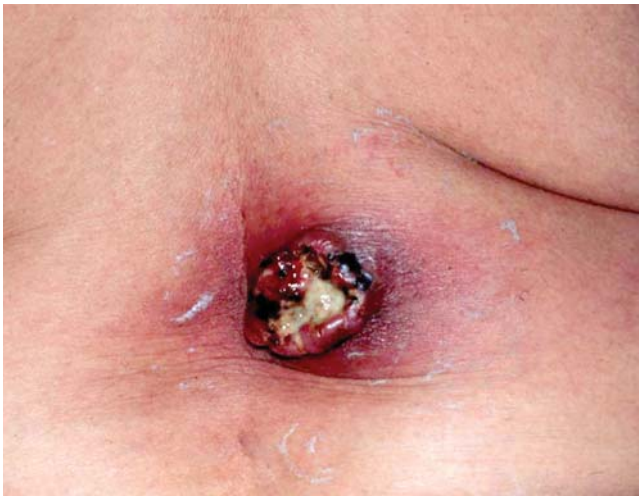

Figure 4: Dermatofibrosarcoma protuberans. Ulcerated erythematous nodule on dorsum

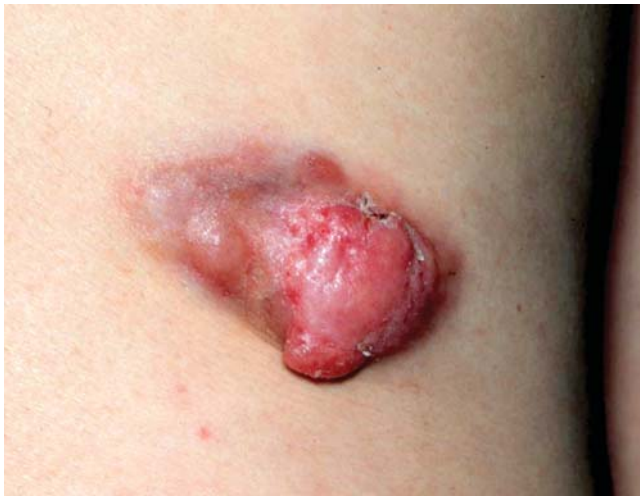

Figure 5: Dermatofibrosarcoma protuberans. Erythematous nodule on scar

(Figure 6). DFSP is made up by cells with large nuclei that show a slight degree of pleomorphism and low to moderate number of mitoses.[5] The tumor may reach the epidermis or leave the subjacent dermis area intact. The superjacent epidermis may be atrophic, normal, or ulcerated, depending on the degree of epidermal invasion by neoplastic cells. Recurrent cases may invade fascia, muscles, and bones.[16,29]

Immunohistochemistry may be useful in the differential diagnosis of DFSP, in which most cells are positive for the CD34 marker (antigen of human hematopoietic cells), although negative for factor XIIIa (fibrin stabilizing factor). On the other hand, dermatofibromas generally express factor XIIIa and are negative for immunomarking with CD34.

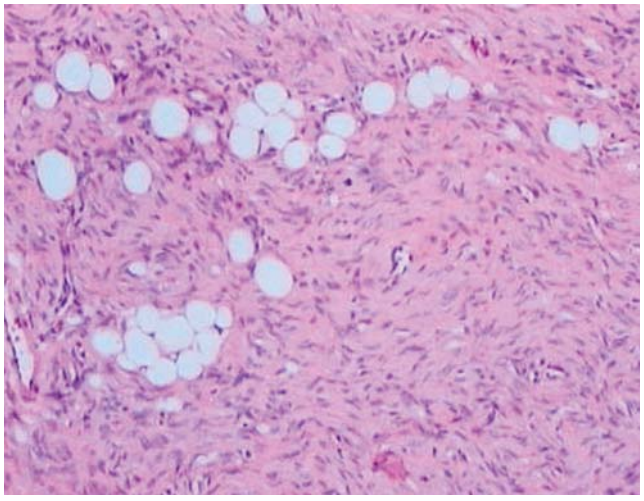

Figure 6: Dermatofibrosarcoma protuberans. Fusocellular neoplasm with micro-storiform pattern diffusely involving adipose tissue with a honeycomb aspect (HE 400X)

Positivity for protein S100 is a characteristic of neurofibromas. In differentiating it from DFSP with subcutaneous invasion, the use of desmin or myosin markers allows an easy distinction between DFSP and tumors of muscular origin with storiform morphology.[15]

Treatment

Treatment for DFSP is surgical. The first intervention is extremely important, since tumoral dissemination after an initial inadequate resection can lead to local uncontrolled growth or metastasis. DFSP is characterized by slow infiltrating growth. Recurrence rate after conventional surgery is around 60%, falling to 20% when margins greater than 4cm are used.[10] Mohs' micrographic surgery yields significantly higher cure rates (1.6% recurrence).[32-37] The role of radiotherapy in treating these tumors is not well established. Chemotherapy has been indicated for cases with metastases.[15,18]

Recent studies show DFSP tumoral response to the tyrosine kinase inhibitor (Imatinib), used both for metastatic disease and advanced local disease. Imatinib blocks the effect of the fusion protein COL1A1-PDGFβ to the PDGFβ receptor.[38-43]

Prognosis

Microscopic dissemination of the tumor by cell projections similar to tentacles under the skin make a complete surgical removal difficult.[27] Most local recurrences (between 50 and 75%) are noted three years after excision. Late recurrences, more than 10 years post-excision, although rare, have been described.[15,18,29,31] Consequently, patients must be examined every three to six months during the first three years after surgery and annually for the rest of their lives.

In spite of its local aggressiveness, DFSP rarely metastasizes; this occurs in approximately 1% to lymph nodes and 4% to distant organs. Because of hematogenic dissemination, the lungs are the primary site for metastatic involvement. Nevertheless, lesions in the brain, bones, and trachea have been described. Reports of distant metastases have been preceded by multiple local recurrences after inadequate initial excisions.[44]

ATYPICAL FIBROXANTHOMA

Atypical ibroxanthoma (AFX) is a malignant fibrohistiocytic neoplasm that predominantly affects photo-exposed surfaces of elderly individuals. It has a tendency for local recurrences and a low metastatic potential,[45] and has been considered a benign pseudosarcomatous lesion. Reports of metastases have established its true malignant nature.

Epidemiology and Pathogeny

Some authors believe that atypical fibroxanthoma represents a superficial form of the pleomorphic malignant fibrohistiocytoma (MFH) that affects deeper structures.[46] However, differences in clinical presentations justify a distinction between these lesions, and differences in their immunohistochemical profiles have been described.

Possible risk factors include chronic exposure to ultraviolet radiation and prior radiotherapy. The atypical fibroxanthoma occasionally originates in covered areas associated with radiodermatitis and in young individuals or children with xeroderma pigmentosum.[5,45] There is a greater incidence described in patients who received renal transplants.[6]

Clinical Presentation

AFX differs from MFH since it is superficial and better delineated tumor, and does not extensively invade subcutaneous tissues or deep structures such as fascia and muscle.[47] AFX presents as a solitary asymptomatic nodule, commonly ulcerated, in photodamaged skin. Typically, it does not surpass two centimeters in diameter. It preferentially affects nasal, malar, and auricular areas of elderly adults (average age 70 years). Approximately one fourth of cases occur on the trunk or limbs of younger individuals. These tumors generally are larger and less delimited.[5,47] Differential diagnosis is made with squamous cell and basal cell carcinomas, epidermoid cyst, and pyogenic granuloma.

Diagnosis

Histopathologically, AFX is characterized by bizarre cells randomly distributed, occasionally taking on a fascicular or storiform pattern. Cells are rounded or spindle, multinucleate, pleomorphic, with numerous typical or atypical mitoses. Inflammatory cells may be present. Rarely, necrosis may be observed; when it is present and significant, the diagnosis of malignant fibrohistiocytoma should be strongly considered.[5,47]

The immunohistochemical study is useful in the difficult distinction between AFX, spindle cell squamous cell carcinoma, and spindle cell melanoma. AFX is habitually negative for cytokeratins, unlike the spindle cell squamous cell carcinoma, and negative for protein S100, different from spindle cell melanoma.[48,30]

Treatment

Treatment for AFX is surgical. Since the tumor can extend to superficial subcutaneous tissue, excision with margin control is recommended. A 1cm margin, including subcutaneous tissue up to muscle fascia, should be used if histological control of margins is not possible during surgery.[49]

Prognosis

Metastases are rare. Prognostic factors related to metastases include greater invasion depth or invasion of skeletal muscles by the primary tumor, vascular or lymphatic invasion, tumoral necrosis, or recurrence.[5,50] Unfavorable prognostic factors are prior radiation of the tumor origin site and immunosuppression.

LEIOMYOSARCOMA

Leiomyosarcomas represent about 7% of all soft tissue sarcomas. The most common locations are intrabdominal and retroperitoneal. The superficial leiomyosarcoma is a rare neoplasm, comprising less than 3% of superficial sarcomas.[51]

Epidemiology and Pathogeny

When they affect the skin, these tumors may be subdivided into three main categories: cutaneous (dermal), subcutaneous, and secondary. The primary cutaneous form from aerector pili and sweat gland muscles, whereas the subcutaneous leiomyosarcoma derives from the muscle layer of vessels. Differences between these two subtypes are not always evident. However, for prognosis this distinction is extremely important, as the cutaneous leiomyosarcoma is only locally considered an aggressive tumor, while the subcutaneous form has a greater tendency to metastasize. Cutaneous leiomyosarcoma has a high potential for local recurrence (30 to 50%), and no case of distant metastases has been published so far. Subcutaneous leiomyosarcomas have high recurrence rates (50 to 70%) and a tendency to metastasize.[5,52]

Most of these tumors (75%) are reported in white-skinned individuals, affecting three times more women than men. They can appear at any age, but the greatest incidence is between 40 and 60 years of life.[52]

Clinical Presentation

Superficial leiomyosarcomas may occur on any part of the body, with show a greater predilection for lower limbs, especially the thighs. Fifty to 75% of lesions appear on lower limbs, 20 to 30% on upper limbs, 10 to 15% on the trunk, rarely affecting the face (1 to 5 %).[53,54]

They clinically present with solitary well-circumscribed nodules, generally with a soft consistency, and occasionally may develop pedicles or umbilications. Less frequently, they may be multinodular or multifocal. The skin over the cutaneous leiomyosar-

coma is usually erythematous or brownish in color, and in the subcutaneous form, may have a normal aspect. In general, dermal tumors appear adhered to the epidermis, while subcutaneous tumors are mobile. Ulceration with or without crusts is more frequently associated with the cutaneous form. Cutaneous tumors are smaller, not surpassing two centimeters, and have a slower growth than subcutaneous tumors. Pain upon compression is a symptom reported by 80 to 95% of patients. Pruritus, paresthesia, and bleeding are also frequent. Differential diagnosis should be made with dermatofibroma, lipoma, neurofibroma, epidermoid cyst, basal cell carcinoma, squamous cell carcinoma, and benign papilloma.[51,52]

Diagnosis

Cutaneous leiomyosarcomas are moderately- or well-differentiated sarcomas that originate in the dermis and tend to extend to subcutaneous cellular tissue. Classically, they consist of bundles of smooth muscle with spindle cells bearing large-volume and elongated nuclei ("cigar shaped"). The well-differentiated areas of the tumor show a greater concentration of these cells, while less-differentiated areas have cells with more irregular nuclei, anaplastic cells, and atypical giant cells with bizarre nuclei.[52-55] Subcutaneous forms are usually more circumscribed and delimited by a ring of compressed collagen fibers.[30,55] In the histopathological examination, it is necessary to identify more than one mitosis per field and smooth muscle cell anaplasia in order to establish the diagnosis. Smooth muscle cell bands can be identified with Masson's trichrome stain.[30,53] Histopathologically, the differential diagnosis includes fibrosarcoma, neurofibrosarcoma, malignant fibrohistiocytoma, neurilemoma, atypical fibroxanthoma, and dermatofibrosarcoma.[23,54]

Leiomyosarcomas express, as a whole, desmin and vimentin, and frequently, muscular actin. Cutaneous forms have a diffuse expression of protein S100. The smooth muscle actin á is considered by some authors as the most sensitive immunohistochemical marker for smooth cell differentiation.[53,56]

Treatment

Treatment for superficial leiomyosarcomas is ample excision, with lateral margins that vary from 3 cm to 5 cm, and deep lesions, including subcutaneous tissue to the fascia.[52,54] Local excision without adequate margins leads to relapses that tend to be more aggressive and involve deeper structures, and a greater risk for metastases.

Mohs' micrographic surgery has been used with success for treating cases of leiomyosarcoma, with lower recurrence rates and greater tissue preservation.[47]

Prognosis

Leiomyosarcomas, as other sarcomas when they are restricted to superficial tissues, is not an aggressive tumor and is associated with low mortality. Nevertheless, a 25% mortality is reported, although amply attributed to the subcutaneous leiomyosarcoma.[54,55]

The rate of local recurrence is approximately 30% for dermal tumors and 50% for subcutaneous tumors. In subcutaneous forms, 30% of patients present metastases. The metastasizing capacity of dermal leiomyosarcomas is still very controversial.[55]

LIPOSARCOMA

Although lipossarcomas are among the most common sarcoma of deep soft tissues in adults, primary cutaneous lipossarcoma is rare.[57]

Epidemiology and Pathogeny

The most recent WHO classification for soft tissue tumors acknowledges five categories of liposarcomas: well-differentiated (atypical lipoma), dedifferentiated, myxoid, round cell, and pleomorphic.[57-59]

Molecular biology and cytogenetics have collaborated towards a better classification of mesenchymal neoplasms. Characteristic karyotypical alterations have been demonstrated in certain lipomas and liposarcomas.[60]

Clinical Presentation

Most cases of superficial liposarcomas originate in subcutaneous cellular tissue and present as nodules with the consistency and density of fat, generally non-adhered to superficial planes.[58] Although rare, this type of tumor may have a primary dermal origin (approximately 1%) with a tendency toward exophytic growth, and present as a polypoid or pedunculated lesion.[57]

Diagnosis

Cases of liposarcomas that affect the subcutaneous layer are frequently of the lipoma-like (atypical lipoma) subtype. Morphologically, they consist mainly of mature adipocytes, with varied forms and sizes and the presence of stroma with highly nucleated and atypical cells with or without lipoblasts.[57,58] The terms 'atypical lipoma' and 'well-differentiated liposarcoma' should be considered as morphologically synonymous. The choice of one of them is based purely on the tumor location, whether superficial or deep, and not on histology criteria. The WHO preconizes that the term 'atypical lipoma' be used only for sub-

cutaneous tumors that exhibit low morbidity and an almost inexistent potential for dedifferentiation, but recommends maintaining the expression 'well-differentiated liposarcoma' for deep lesions.[59,61]

Treatment

Most cutaneous and subcutaneous liposarcomas can be treated surgically with complete excision of the lesion.[62]

The role of radiotherapy in treating deep lesions is well established. Its importance in the treatment of cutaneous or subcutaneous liposarcomas is restricted to inoperable lesion cases.[5]

Prognosis

Well-differentiated liposarcomas / atypical lipomas have excellent prognoses, with low rates of local recurrence and no reports of distant metastases.[58,61]

Even with high-grade morphological characteristics, the cutaneous liposarcoma presents the best prognosis when compared to deep lesions. Local recurrences may occur, but distant metastases are extremely rare. In spite of the good prognosis, because of the small number of cases, patients with cutaneous liposarcomas should be followed for long periods of time.[57]

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Malignant Peripheral Nerve Sheath Tumor (MPNST) is a sarcoma that originates in a peripheral nerve or in a neurofibroma.[62] A rare tumor, is usually develops in deep soft tissues. It normally demonstrates an aggressive behavior and has a mortality rate of approximately 50%.[63]

Several expressions have been used to name it, such as malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma, and malignant neurofibroma.[64]

Epidemiology and Pathogeny

About half of these tumors develop from neurofibromas in patients with or without type 1 neurofibromatosis (von Recklinghausen disease). However, less than 5% of individuals with type 1 neurofibromatosis (NF type 1) develop MPNST.

Analyses of molecular genetics suggest that NF1, the product of the gene implied in type 1 neurofibromatosis pathogenesis, is a tumor suppression gene whose inactivation may contribute to the pathogenesis of neural neoplasms associated to NF type I.[65]

Clinical Presentation

As is the case with other cutaneous variants of soft tissue sarcomas, cutaneous MPNST is extremely rare if compared to the classic deep form. Cutaneous MPNSTs that originate in patients with or without NF type 1 are tumors with a propensity for local relapses, even though they show a lower tendency for metastasizing. Cutaneous MPNSTs most frequently affect adults between 20 and 50 years of age. In patients with NF type I, these tumors appear earlier, with an average age of 30 years.[55] They involve the trunk and cephalic segment, although capable of developing in any region of the body. [66] When not related to neurofibromas, they more commonly arise from peripheral nerves of the trunk.[55] Clinically they present as subcutaneous nodules with a slow growth rate, and are generally observed months before diagnostic confirmation. Pain is a variable symptom, as it is more prevalent in patients with type 1 NF. A report of pain or growth of preexistent neurofibromas may be indicative of malignization.[62]

Diagnosis

On the histological examination, the tumor generally presents as a neoplasm of spindle cells with an infiltrating and destructive pattern, composed predominantly of bundles of spindle cells with light cytoplasms and undulated nuclei. There are focal variations in cellular density with myxoid hypocellular areas, interspersed with more cellular areas, especially in perivascular areas. Mitoses are rare, and tumoral necrosis is common. When focal rhabdomyosarcomatous differentiation is present, it is called a malignant Triton tumor.[55,62]

Immunohistochemical analysis is useful for the differential diagnosis between spindle cell tumors. Positivity for the S-100 protein is observed in percentages that vary from around 50 to 90% of MPNSTs.[5]

The differential diagnosis of cutaneous MPNST is made with cellular schwannoma, desmoplastic melanoma, and metastatic sarcomas. In cutaneous cases, the primary diagnostic challenge concerns the desmoplastic (neurotropic) melanoma, and a diagnostic confirmation requires evidence of neural differentiation and exclusion of melanocytic differentiation, something that can only be done by electronic microscopy (absence of melanosomes and presence of elements consistent with neural differentiation).[62] In the absence of this method, histological and immunohistochemical characteristics, such as absence of intradermal melanocytic differentiation and negativity for HMB-45 marking, may suggest the diagnosis of cutaneous MPNST.[5,63]

Treatment

Although cases of skin MPNST demonstrate a

benign clinical behavior, these tumors must be excised with ample and deep margins, reaching fascia, since they possess a high potential for local relapses. These recurrences generally present with a worsening of the histological grade or as larger and deeper lesions.[62,63]

Prognosis

The cutaneous MPNST has a better prognosis than its deep form, but approximately 40% of cases recur locally. Metastases, despite being rare, have been reported. Tumors associated to type 1 NF have a worse prognosis, probably because they are larger and deeper.[62,63,67]

EPITHELIOID SARCOMA

This is the most common sarcoma distal limbs (hand and wrists). It was only characterized as a distinct clinicopathological entity in 1970 when Enzinger described it as a sarcoma simulating a granuloma or carcinoma.[68,69]

Epidemiology and Pathogeny

Its origin is usually dermal or subcutaneous, but it can also arise from deep fáscia or in tenosynovial tissue. Data on genomic alterations in the epithelioid sarcoma are scarce. Studies suggest that modifications in chromosomes 8 and 22 may play a part in generating this tumor.[70,71]

Clinical Presentation

It presents as a localized slow-growing painless nodule, habitually on distal extremities of young adults, although there are cases described affecting children and elderly individuals (Figure 7). Despite its slow growth, it can be an extremely aggressive tumor with a clinical course characterized by high rates of local recurrence and metastatic potential, especially to lymph nodes and lungs.[69,71]

Diagnosis

The classic form is composed of pleomorphic epithelioid cells and spindle cells organized in nodular aggregates that frequently exhibit central necrosis[68] (Figure 8). In some cases of classic epithelioid sarcomas, the microscopic appearance resembles a benign granulomatous process. More recently, other less common histological variants of the tumor have been described. These subtypes include the "proximal type" or rhabdoid / large cell epithelioid sarcoma, the "fibroma-like" variant, and an angiomatoid epithelioid sarcoma variant.[71-73]

Because of its characteristic of being a mesenchymal tumor with an epithelioid phenotype,

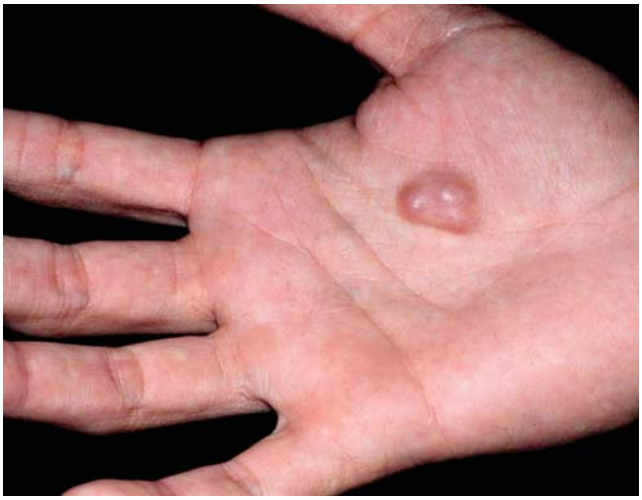

Figure 7: Epithelioid sarcoma. Solitary palmar nodule

immunohistochemically the epithelioid sarcoma reacts to an ample range of epithelial antibodies, such as cytokeratins and epithelial membrane antigen (EMA) (Figure 9) and mesenchymal antibodies, such as vimentin and CD 34.[71]

Treatment

Radical excision with ample margins is the treatment of choice for this tumor, which can be accompanied by chemotherapy or adjuvant radiotherapy adjuvant. The use of ample resection margins has shown a lower rate of local recurrence; nevertheless, there is no significant correlation between surgical margins and the probability of metastases.[69,71]

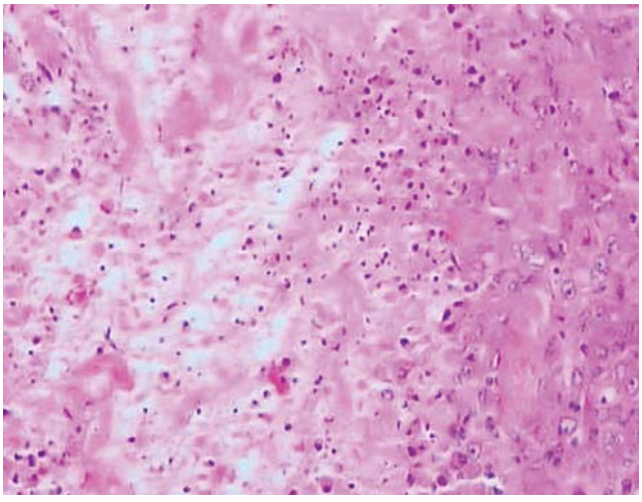

Figure 8: Epithelioid sarcoma. Neoplasm comprised of atypical epithelioid cells organized around area of geographic necrosis (HE 100X)

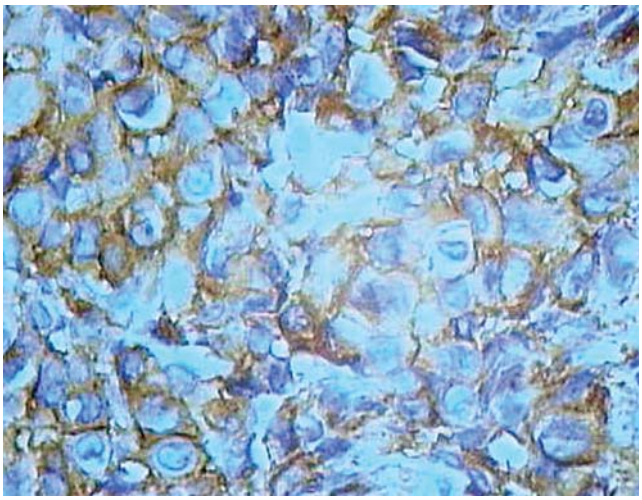

Figure 9: Epithelioid sarcoma. Positivity for epithelial membrane antigen (EMA) on surface of neoplastic cells (IHQ 400X)

Prognosis

Rates of local recurrence and metastases are 40% and 50%, respectively. The most frequently involved metastatic location is the pulmonary region, followed by lymph nodes and the brain.[69,71]

CONCLUSION

Cutaneous sarcomas are rare tumors, and dermatologists are the professionals who have the opportunity of making an earlier diagnosis of these neoplasms, thus improving their cure rates. It is of utmost importance that the dermatologist learn to recognize these tumors. A well-selected and well-applied initial treatment, especially from the surgical perspective, based on a correct diagnosis and staging, is extremely important for the prognosis of patients. Management of cases should be carried out by a multidisciplinary team involving dermatologists, pathologists, clinicians, and oncology surgeons, plastic surgeons, and radiotherapists. In the near future, molecular and cytogenetic investigations will aide in the classification of these neoplasms allowing a more accurate diagnostic and therapeutic individualization. ❑

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Questions and answers to questions

1. Dermatofibrosarcoma protuberans is usually located:
   a) on the head and neck
   b) on distal extremities
   c) on the perineum
   d) on the trunk

2. Which sarcoma can develop from a benign lesion?
   a) Dermatofibrosarcoma
   b) Malignant peripheral nerve sheath tumor
   c) Angiosarcoma
   d) Epithelioid sarcoma

3. Which lesion shows the greatest clinical resemblance to DFSP?
   a) Keratoacanthoma
   b) Cheloid
   c) Mycosis fungoides
   d) Lipoma

4. As to the prognosis of DFSP, the following are usually expected:
   a) frequent local recurrences progressing with metastases to lymph nodes
   b) frequent local recurrences rarely progressing with metastases
   c) frequent local recurrences with most patients progressing to death by hematogenic metastases to lungs and pelvic bones
   d) infrequent local recurrences and rare metastases

5. Which age group is most frequently affected by atypical fibroxanthoma (AFX)?
   a) 0 to 15 years of age
   b) 15 to 30 years of age
   c) 25 to 50 years of age
   d) over 50 years of age

6. Which sarcoma is a differential diagnosis with AFX?
   a) Epithelioid sarcoma
   b) Myxofibrosarcoma
   c) Malignant fibrohistiocytoma
   d) Fibrosarcoma

7. What is the foremost location of angiosarcomas?
   a) Head and neck
   b) Upper limb with chronic lymphedema
   c) Lower limbs
   d) Thorax

8. The sarcoma that originates on the upper limb with chronic lymphedema in women submitted to mastectomies with axillary lymph nodes resection is called:
   a) Bednar's tumor
   b) Stewart-Treves syndrome
   c) Enzinger's tumor
   d) Malignant Triton tumor

9. What is the histological type of this sarcoma?
   a) Dermatofibrosarcoma protuberans
   b) Kaposi's sarcoma
   c) Angiosarcoma
   d) Leiomyosarcoma

10. Which alternative best describes the usual presentation of the atypical fibroxanthoma:
   a) male 50-year-old patient presenting with nodule on back of approximately 3 cm, similar to a cheloid
   b) female 65-year-old patient, presenting with nodule on nasal dorsum of approximately 1 cm
   c) male 65-year-old patient, presenting with an ulcerated violaceous plaque on scalp, of approximately 6 cm
   d) female 50-year-old patient presenting with violaceous nodule on right upper limb, ipsilateral of the mastectomy

11. Which alternative represents a immunohistochemical characteristic of dermatofibroma useful for distinguishing it from DFSP?
   a) CD34 + S100 -
   b) CD34 + XIIIa factor -
   c) CD34 - S100 +
   d) CD34 - XIIIa factor +

12. According to current literature, which is the best treatment option for dermatofibrosarcoma?
   a) Surgery with ample margins (> 3 cm)
   b) Surgery associated with radiotherapy
   c) Micrographic surgery
   d) Tyrosine-kinase inhibitor (Imatinib)

13. What type of liposarcoma affects the subcutaneous layer?
   a) myxoid
   b) pleomorphic
   c) well-differentiated / lipoma-like
   d) round cells

14. The habitual clinical presentation of a liposarcoma is as:
    a) a frequently ulcerated subcutaneous nodule adhered to the dermis
    b) a subcutaneous nodule not adhered to superficial planes
    c) a cutaneous nodule in a photoexposed area
    d) a polypoid or pedunculated exophytic dermal nodule

15. Which is the favored location of leiomyosarcomas?
    a) Lower limbs
    b) Face
    c) Upper limbs
    d) Trunk

16. Which of these tumors has the best prognosis?
    a) Deep muscle leiomyosarcoma affecting skin by extension
    b) Dermal leiomyosarcoma
    c) Subcutaneous leiomyosarcoma
    d) Rhabdomyosarcoma

17. Which group of patients has the greatest propensity to develop a malignant nerve sheath type sarcoma (MPNST)?
    a) Patients with xeroderma pigmentosum
    b) Patients with Rothmund Thomson syndrome
    c) Patients with Gorlin's syndrome
    d) Patients with Von Recklinghausen disease

18. Tumor cells organized in irregular fascicles interlaced in a storiform pattern with some areas resembling a "cartwheel" or "whirlwind." This histological description refers to a:
    a) DFSP
    b) epithelioid sarcoma
    c) fibrosarcoma
    d) angiosarcoma

19. As to the epithelioid sarcoma, it is correct to affirm that:
    a) recurrences are frequent, but it has a low potential for metastases
    b) it is an aggressive tumor that affects the scalp of elderly men
    c) its growth is slow, and it can originate in a neurofibroma
    d) it has a high potential for recurrences and metastases, and affects distal extremities of young adults

20. The histological differential diagnosis of epithelioid sarcoma may be made with:
    a) dermatofibroma
    b) neurofibroma
    c) annular granuloma
    d) basal cell carcinoma

ANSWERS

Syphilis: diagnosis, treatment and control. An Bras Dermatol. 2006;81(2):111-126.

1. b	11. b
2. d	12. c
3. c	13. a
4. d	14. c
5. b	15. b
6. d	16. c
7. a	17. b
8. c	18. c
9. c	19. d
10. d	20. b