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REVIEW ARTICLE

Clinical update on cutaneous and subcutaneous sarcomas

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Abstract

Background: Cutaneous sarcomas are uncommon cancers that can have a wide range of clinical symptoms and lead to considerable cutaneous as well as systemic morbidity.

Aim: The objective of this review article is to discuss epidemiology, clinical features, diagnosis, and therapy of different types of cutaneous sarcomas.

Material and methods: Literature was screened to retrieve articles from PubMed/Medline and Google Scholar and related websites. Cross-references from the relevant articles were also considered for review. Review articles, clinical studies, systematic reviews, meta-analyses, and relevant information from selected websites were included.

Results and discussion: Cutaneous sarcomas have a negative effect on the quality of life. In their diagnosis, clinical presentation and histological evaluation are crucial. Complete surgical removal is the solution for more or less all cutaneous and subcutaneous sarcomas. The prognosis for cutaneous sarcomas is generally favorable since they tend to recur locally with distant metastases only on rare occasions. Patients having advanced disease should be treated in the setting of clinical trials if possible; choices include radiation therapy and systemic medicines. The value of innovative immunotherapy cannot be determined decisively at this time due to a paucity of relevant trials.

Conclusion: As cutaneous sarcomas are rarely diagnosed based on clinical findings, histology plays an important role in the diagnosis. They have a relatively favorable prognosis if treated properly. Patients should be treated at specialized centres.

KEYWORDS
metastasis, prognosis, Sarcoma

1 | INTRODUCTION

Sarcomas are malignant tumors that arise in solid mesenchymal tissues. Blood vessels, nerves, fibrous tissues, fat, muscle, and deep skin tissues can all effectuate soft tissue sarcomas. They can be found in every part of the body. Sarcomas are much less prevalent than other cancers.[1,2] The target of this review is to provide insight into cutaneous sarcomas that are frequently seen, with a focus on epidemiology, clinical features, diagnosis, and therapy. Commonly encountered cutaneous and subcutaneous sarcoma are listed in Table 1.[3,4]

2 | SARCOMA OF THE FIBROUS TISSUE

2.1 | Dermato-fibrosarcoma protuberans

Darier Ferrand tumor or Darier-Hoffmann tumor is another name for DFSP. It accounts for up to 1% of all soft tissue sarcomas. Dermatofibrosarcoma protuberans (DFSP) affects both genders and all races and manifests in early and mid-adulthood. Clinically, DFSP presents as a reddish, skin-colored, plaque with ≥1 nodule(s) located particularly on the trunk and limb(s). As the tumor has a tendency of delayed aggression and the clinical features are nonspecific, there occurs a delay between the onset of clinical features and the initiation of treatment. DFSP gradually leads to the formation of nodules within the initial plaque. After the appearance of nodules, growth is hastened and leads to the formation of ulcers which may lead to bleeding and/or become tender in up to one-fourth of cases.[5] DFSP is found in people with a history of scars, trauma, or burns in the past. The lesions are usually present for more than 5 years before being diagnosed. Swift growth or formation of ulcers pushes the patient to seek medical advice. Histopathology of DFSP shows a storiform pattern of unvarying, cytologically bland spindle cells associated with honeycomb-patterned infiltration up to the subcutis. Cytogenetics is a useful investigation for the diagnosis of DFSP. DFSP is thought to be of fibroblastic origin and is frequently associated with t(17;22) translocation and PDGFRB-COL1A1 fusion. Additional investigations include ultrasonography of lymph nodes, magnetic resonance imaging (MRI) to assess tumor extent and computed tomography (CT) thorax and abdomen, especially if suspected metastases. The gold standard treatment for DFSP is wide local excision, but Mohs micrographic surgery is a preferred choice with 2–5 cm of clear margin. Full microscopic removal of tumor margins minimizes the risk of recurrence. If the tumor is presented late in high reoccurrence zones (like head and neck areas), chemotherapy with Imatinib before surgery and radiotherapy after surgery improves the outcome of the disease. There is only a 5% chance of developing metastasis. The patient's prognosis is determined by the extent of surgical excision.[6,7]

TABLE 1 Commonly encountered cutaneous and subcutaneous sarcoma

Tissue of Origin	Sarcoma Variant
Fibrous tissue	Fibrosarcoma Malignant fibrous histiocytoma Dermatofibrosarcoma
Fat	Liposarcoma
Muscle	
Smooth muscle	Rhabdomyosarcoma
Striated muscle	Leiomyosarcoma
Blood vessels	Hemangiosarcoma Kaposi's sarcoma
Lymph vessels	Lymphangiosarcoma
Synovial tissue	Synovial sarcoma
Peripheral nerves	Neurofibrosarcoma
Cartilage and bone-forming tissue	Extraskeletal chondrosarcoma Extraskeletal osteosarcoma

2.2 | Fibrosarcoma (fibroblastic sarcoma)

Fibrosarcoma is a malignant mesenchymal tumor arising from the fibrous connective tissue. Infantile fibrosarcomas are fibrosarcomas that develop before the age of 15 years, but according to some researchers, infantile fibrosarcomas are only considered if they are identified before the age of two. Fibrosarcomas are the most common congenital soft tissue sarcoma seen in babies. Adult-type fibrosarcoma mainly affects adult males between the ages of thirty and fifty-five.[8,9]

Fibrosarcoma commonly manifests as a swelling in the libs, trunk, head, or neck. Histopathology sections reveal a dermal or subcutaneous spindle cell tumor. The tumor is made up of basophilic spindled cells that are relatively homogenous. The cancerous cells are typically organized in a "herringbone" pattern. Mitoses are typically straightforward to locate.

Fibrosarcoma in children is distinguished by a particular recurrent reciprocal translocation. The ETV6 (TEL) gene is fused to the neurotrophin-3 receptor gene NTRK3 (TRKS) at 15q25 in this translocation. In adults, no consistent anomaly is found.[10,11]

Immunohistochemistry (IHC) shows that vimentin positivity, whereas cytokeratin and S100 are negative, and actin is variable. Treatment consists of excision of the tumor. Radiation therapy can be added if there is a residual tumor or if the margins are positive. If the cancer is of a high grade, chemotherapy may be used. Infantile fibrosarcoma recurs in 40%–50% of cases but rarely metastasizes. Ninety per cent of people survive. Adult fibrosarcoma has a 50% recurrence rate and a 25% metastasis rate (lung, bone). If there are more cellular and mitotic activity, there would be more metastases. Survival rates are 41% after 5 years and 29% after 10 years.[12,13]

2.3 | Pleomorphic sarcoma without differentiation

It was originally termed malignant fibrous histiocytoma (MFH). Historically, it was believed to be the most common adult soft tissue sarcoma. It is usually seen in older persons (50 years and older), with a small male majority. This condition is more frequent in the lower extremities followed by upper extremities, trunk, and the head and neck region. The clinical presentation of PSD is a relatively painless, but briskly enlarging nodule with an indistinctive appearance. Tumors may be subcutaneous with no epidermal changes. Radiation-associated PFD is smaller in size and is usually seen in the parotid gland or neck region.[14] Osteosarcoma or MFH are the most common sarcomas found near orthopedic implants or after radiotherapy. When it appears on the skin, it is difficult to tell the difference between atypical fibroxanthoma and DFSP.[15,16]

Histopathology shows a storiform pattern (cells radiate from a central point) and irregular fascicles. Under a microscope abundance of chronic inflammatory cells along with a variable amount of

collagen production can be seen. Pleomorphic and unusual tumor cells are seen with foamy cytoplasm and prominent atypia amid an inflammatory collagenous stroma. Cytogenetics reveals a highly complicated karyotype, with frequent changes in the G1/S checkpoint genes. MRI findings usually reveal a well-delineated tumor that is dark on T1-weighted scans and bright on T2-weighted imaging. En masse resection with about a 2-cm clear margin is often restricted by closeness to functional organs in head and neck areas. Mohs micrographic surgery (MMS) is used for MFH management rarely. Adjuvant or neoadjuvant radiation and chemotherapy are frequently employed for tumors where clear margins cannot be obtained. Effective RT employs a radiation field that includes the tumor site and at least 5 cm of peripheral tissue, with doses ranging from 50 to 65 Gy. Chemotherapy is used for the management only of widespread diseases. The local recurrence rate is 25%–75%. MFH of the head and neck are more aggressive behavior than MFH of other areas. All high-grade pleomorphic sarcomas have a 50–60% five-year survival rate. Superficial location, modest size, and low grade are all good prognostic indicators.[17,18]

2.4 | Atypical fibroxanthoma

Atypical Fibroxanthoma (AFX) is an infrequent low-grade malignant cutaneous tumor with unknown differentiation that was first characterized by EB Helwig in the 1960s. The tumor is linked to a history of radiation, immunosuppression, and trauma. AFX is seen in the population of the seventh and eighth decades.

Patients may present with a tumor which can be exophytic, nodular, and/or plaque-like over sun-damaged skin, about an inch in diameter. AFX are more common in men. In histopathology, atypical fibroxanthoma is confined to the dermis with an overlaying epidermal collarette, mesial ulceration, and parakeratosis. In a comparative genomic hybridization analysis, Mihic-Probst et al found many aberrations of chromosomes shared by AFX and undifferentiated pleomorphic sarcoma (UPS)0.15 Only -1q, −3p, −5q, −11p, −11q and+7q, +5p, +11q, +12q were regarded noteworthy among those present in both cancers, with UPS being the most common tumor with these alterations. Markers including CD68, CD10, smooth muscle actin and vimentin are positive but not specific, but they are seen in more than half of tumor cells. The proliferation index Ki67 ranges from moderate to high. Treatment consists of resection with 2 cm surgical margins and a thorough assessment of the tumor margins. Recurrences are common via local infiltration. Positive margins during the first surgery, deeper invasion, and senescence are linked to recurrences and metastasis.[19,20]

3 | SARCOMA OF THE FAT TISSUE

3.1 | Liposarcoma

Adipocytes give rise to liposarcoma. Liposarcomas from the dermis or subcuticular tissue are few and far between and can be termed superficial liposarcomas.

They can be divided into 4 histological types:

1. well-differentiated,
2. dedifferentiated,
3. myxoid,
4. pleomorphic

Incidence of liposarcoma peaks between the ages of 50 and 70. After osteosarcoma, liposarcomas are the most prevalent variant of soft-tissue sarcoma.[21,22]

The etiology of liposarcoma is not known but the American cancer society has highlighted some factors which may trigger liposarcoma, which include cancer radiotherapy, familial cancer syndromes, disruption of the lymphatic system due to trauma and/or subjection to harmful chemicals. The commonest site of liposarcoma is the extremities. Myxoid liposarcoma located over the extremities presents as a deep mass. Patients frequently notice a deep-seated tumor in their soft tissue as a clinical presentation. Symptoms appear only when the tumor is quite large and exert pressure on the surrounding tissue which includes pain, oedema, or functional loss due to compression of nerves and vessels.[23]

Histopathology frequently shows the presence of lip blasts, i.e. cells with an abundance of clear multivacuolated cytoplasm and an eccentric darkly colored nucleus indented by the vacuoles.[24,25]

Cytogenetics shows t(12;16) (q13;p11) translocation with change in the CHOP gene and t(12;16) (q13;p11) translocation with changes in the CHOP gene.[26,27] Ultrasonography may not be able to differentiate between a liposarcoma and a benign lipoma, hence MRI is the first radiological investigation preferred. Surgical removal of the tumor with margins, occasionally radiation, and potentially chemotherapy are options for treatment. With a resection margin of 10 mm or greater, the recurrence rate is less than 10%. Radiation therapy is given after the surgery for the remaining cancerous cells to decrease the chance of recurrence. Chemotherapy reduces the fast-growing cells, the 2 FDA-approved drugs for liposarcoma are- eribulin mesylate and trabectedin.[28,29] Risk factors for local recurrence or progression include the morphology of a high-grade tumor, tumors of a large size (>5 cm) and insufficient or unsatisfactory resection.[30]

4 | SARCOMA OF THE MUSCLE

4.1 | Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a skeletal muscle-differentiated malignant mesenchymal tumor. It's the most frequent soft tissue sarcoma which is seen in children and adolescents.[31,32] Half of cases occur before age 10, with an additional peak occurring in adolescence.

Histologically RMS are classified into:

1. embryonal,
2. alveolar, and
3. pleomorphic.

RMS frequently manifests as a painless mass. Embryonal rhabdomyosarcoma (ERMS) is found in the head and neck region, genitourinary system, and retroperitoneum. Alveolar rhabdomyosarcoma (ARMS) most commonly affects the extremities.[33,34]

Under the microscope, embryonal rhabdomyosarcoma shows attributes of reminiscent fetal skeletal muscle along with myxoid and cellular interspersed with spindle and rounded cells. The alveolar variant has a nested proliferation that frequently has a dyshesive pattern showing an alveolar appearance as well as multinucleated neoplastic cells. The pleomorphic variant is typified by the disorganized orientation of pleomorphic cells associated with markedly eosinophilic cytoplasm. The neoplastic cells have abundant eosinophilic cytoplasm with a rhabdoid appearance and eccentric nuclei. Tumor cells in ARMS are tiny, having a spherical nucleus and little cytoplasm. These tumor cells' aggregates frequently become discohesive, forming gaps that resemble lung alveoli. Large, lobated hyperchromatic nuclei and unusual mitoses distinguish an anaplastic RMS fraction.[31]

In ARMS, PAX3 - FOXO1 is generated by t(2;13)(q35;q14) in about 60% of ARMS cases. PAX7 - FOXO1 is generated by t(1;13)(p36;q14) in about 20% of ARMS cases. Chromosome increases and losses are common in ERMS. Chromosome 11 loci have a higher chance of deletion of one among the two alleles in ERMS.[35]

Desmin, myogenin, and MYOD1 are the trio of indicators for primary cutaneous rhabdomyosarcoma with good sensitivity and specificity. Wide local excision with sentinel lymph node biopsy is the therapy of choice for rhabdomyosarcoma. In big or incompletely removed tumors, adjuvant or neoadjuvant radiation is frequently employed. Patients with primary breast alveolar rhabdomyosarcoma have a poor prognosis, with disseminated metastases commonly leading to death. Alveolar and pleomorphic subtypes have a substantially worse prognosis than embryonic subtypes. The clinical course of primary cutaneous rhabdomyosarcoma is potentially aggressive in both children and adults. High-risk RMS have approximately 20–40% 5-year survival rate. Early reporting and examination give chances for early detection of cutaneous RMS and prompt initiation of therapy.[36,37]

4.2 | Leiomyosarcoma

Leiomyosarcoma (LMS) accounts for about 5%–10% of all soft tissue sarcomas and is derived from the arrector pili muscle. LMS is categorized into 2 histological subtypes - dermal and cutaneous. LMS peaks around the sixth to the seventh decade. Every year, about one in 100000 persons are diagnosed with LMS. Clinical presentation includes irregular, asymmetrical, skin-colored or erythematous subcutaneous papules or nodules ranging from 0.3–3 cm in diameter that is sometimes painful under pressure and may bleed or ulcerate. Subcutaneous LMS presents as a large well-defined nodule.[38] Dermoscopic features of LMS consist of asymmetrical, ulcerated, multilobulated tumors with linear, irregular, and polymorphic atypical vessels, in addition to white structures, but they are non-specific.[39]

On histopathological examination, a poorly defined tumor nodule can be seen in the scanner view. The tumor is formed of proliferated spindle cells that generate rough bundles and fascicles. Spindle cells which are having cigar-shaped nuclei and noteworthy cytologic atypia in addition to mitotic figures are seen at high magnification. Kaddu defined a couple of growth patterns of LMS, a nodular pattern which is cellular and has nuclear atypia, and mitotic figures and a diffuse pattern that is less cellular and is having less mitotic figures, but having well-differentiated smooth muscle cells and fewer mitoses. Cytogenetics examination shows karyotypes that are frequently complicated and have no regular abnormalities. Alpha-smooth muscle actin (90%), HHF35 (90%), desmin and vimentin, (75%) are positive whereas CD117 is negative.[40] The definite treatment is surgery with a 3–5 cm clear lateral margin up to subcutaneous tissue and fascia. Although LMS is resistant to radiotherapy and chemotherapy, each responds differently. Chemotherapy and targeted therapies are the top choices for metastatic disease. This cancer frequently recurs locally or spreads to additional body structures. The lung is a common location for cancer metastasis. In the case of lesions invading the subcutis or subcutaneous leiomyosarcoma, metastases can occur in up to 43% of cases. Cutaneous LMS has a better prognosis compared to subcutaneous LMS. Local recurrences for LMS are not rare. As per statistics recurrence rates of cutaneous LMS is 0%–67% and for subcutaneous LMS are 19%–40%.[38,41]

5 | SARCOMA OF THE BLOOD VESSELS

5.1 | Kaposi's sarcoma

Moritz Kaposi, a Hungarian physician described Kaposi's Sarcoma. Kaposi's sarcoma is usually inactive, although it may be aggressive in certain areas. It is an antiproliferative tumor that presents clinically as multiple cutaneous and mucosal nodules.

Kaposi's sarcoma has It has 4 recognized epidemiologic-clinical forms; Classical, Endemic (in the African population), AIDS-associated and Iatrogenic. The types of Kaposi's sarcoma have been described in Table 2.

Clinical features may be different in different stages of the tumor. In the patch stage, macules of reddish or purple color are seen. The plaque stage is characterized by thick reddish, purple, or brown plaques whereas in the tumor stage nodules are formed. These stages can be seen in all four clinical subtypes of Kaposi sarcoma and multiple stages may be present at the same time.

In the patch stage vessels are dilated and cutting-through dermal collagen. Tumor vascular channels encircle and ensnare natural arteries, which is a promontory indication (classic but uncommon feature). Early lesions may be quite modest.[42]

In the plaque stage, slit-like vascular channels entering the deeper dermis are seen which are more widespread, compressed, and slit-like. Spindled endothelial cells proliferate infiltrating. Spindle cells invading and destroying eccrine coils is a common occurrence.

TABLE 2 Types of Kaposi's sarcoma

Type of Kaposi's Sarcoma	Affected population	Clinical features	Course
Classic	Old male usually in 6th to 7th decade of life	Usually found in lower extremities	Indolent, Survival → 10–15 years
Endemic (In African population)	Young African males, 2nd to 4th Decade of life	Localized nodular lesions or large exophytic, aggressive lesions	The nodules are indolent; for aggressive lesion, the survival is → 3–5 years
Iatrogenic	Immunosuppressed patients	Localized or widespread involvement	May regress when immunosuppressants are stopped
Epidemic (AIDS-associated)	People living with HIV-AIDS (PLHA)	The Head and neck, gastrointestinal tract and lungs are the most common sites	Fulminant, survival 1–3 years without Highly active antiretroviral therapy

In the tumor stage intersecting fascicles of homogeneous spindle cells produce discrete nodules. Blood is filled between gaps of spindle cells. Slit-like opening in a longitudinal section is also seen. Spaces resemble sieves in cross sections. Hyaline globules can be detected within the cytoplasm. In all stages, pleomorphism is modest, but mitoses are common. Severe pleomorphism is seen in a few poorly differentiated instances (must confirm with HHV8 immunostain to exclude angiosarcoma). Hemosiderin and extravasated erythrocytes are typical observations. In most situations, plasma cells are present.[43] There are no consistent abnormalities in the cytogenetics.

HHV8 may be seen in peripheral blood film examination and from the affected tissue. Radiology can be handy for the assessment of dissemination and depth. Treatment options for KS include symptomatic management, halting the progression of KS, cosmetic improvement (if needed), and relief from associated symptoms. There is no definite cure; however, there is a range of palliative treatments available. Immunosuppressive drugs are removed in the iatrogenic version. For AIDS-related Kaposi's Sarcoma, highly active antiretroviral treatment (HAART) is used. Surgical excision of symptomatic lesions (wide excision is unnecessary) for cosmetically disturbing KS lesions can be done. Topical alitretinoin, intralesional vinblastine, radiotherapy, laser ablation, cryotherapy, and photodynamic therapy are some local management options for bulky lesions. As of now, liposomal anthracyclines and taxanes are the main systemic cytotoxic treatment for KS. Other management options that have been tried include interferon alpha, thalidomide, antiherpes medications, imatinib, and matrix metalloproteinase inhibitors. The five-year relative survival rate is around 72%.[44,45]

5.2 | Angiosarcoma

Angiosarcoma is a malignant tumor with endothelial differentiation morphologically or immunophenotypically. Angiosarcoma accounts for up to 3% of all soft tissue sarcomas in adulthood. Mainly seen in males with M:F ratio of 3:1, and the peak is seen between the age of 65 and 70 years. It can be seen at any site. Angiosarcoma most commonly affects the skin of the head and neck (approximately 2/3rd of cases). Cutaneous angiosarcoma is the most frequent type, usually primary and develops in older persons' sun-exposed areas.

Cutaneous angiosarcoma in the following settings

1. Idiopathic angiosarcoma in the head and neck area
2. Angiosarcoma in association with long-standing lymphedema (Stewart-Treves syndrome);
3. Angiosarcoma after radiation therapy

Blue or purple macular, nodular, or plaque-like lesions are observed in these patients. Hemorrhage or ulceration can occur in advanced lesions. At the time of presentation, roughly 10% of patients had cervical lymphadenopathy.

All angiosarcomas exhibit comparable microscopic features, such as vascular gaps that are more or less evident and lined with atypia showing tumor cells. Endothelial cells pierce the stroma and papillary fronds of cells that protrude into the lumen line of the vascular gaps in low-grade lesions. Atypical cells and aberrant mitoses are more common in higher grade lesions.[46,47]

Cytogenetics shows upregulation of TIE1, KDR, TEK, and FLT. Overexpression of HIF1 alpha and HIF2 beta is seen. In radiation-induced and chronic lymphedema-associated angiosarcoma, FISH reveals a high degree of c-MYC gene amplification.[48]

In contrast-enhanced computed tomography of the lesion, soft tissue angiosarcoma looks like an irregular enhancing soft tissue mass. Radiological examinations like CT and MRI are used in preliminary stages, but they cannot be used in recurrent tumors as their specificity is low after radiotherapy of the lesion. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) can help in diagnosing recurrence.[49]

Differential diagnosis includes intravascular papillary endothelial hyperplasia, Kaposi sarcoma, Kaposi-like hemangioendothelioma, angiolymphoid hyperplasia, Kimura's disease, and amelanotic melanoma.[50]

The first line of management is radical surgery, but the recurrence rates are high. Hence, multimodality management can be helpful. Wide surgical excision, together with chemotherapy and radiotherapy, is the most common treatment option. Angiosarcoma

is being researched using targeted therapy and immunotherapy as promising new treatment options. Although characteristics such as tumor size, epithelioid component, high mitotic activity, and margin positive status have been linked to poor prognosis, these characteristics have yet to be validated for routine clinical use. The sites of metastasis can be the lungs, liver, cervical lymph nodes, spleen, and other organs. The average survival period after metastases was 4 months according to one research study. The result of cutaneous angiosarcoma management is quite disheartening with swift progression to mortality. Appreciation of variegated presentations of this entity and histopathological examination will lead to the beginning of early treatment.[51,52]

6 | SARCOMA OF THE LYMPH VESSEL

6.1 | Lymphangiosarcoma

It is an infrequent malignant tumor which arises from vascular endothelium in long-standing oedematous extremities. Most of the cases occur in association with postmastectomy lymphedema although a few cases occurred due to other causes of lymphoedema as well. Stewart and Treves first characterized it in six individuals with upper extremity lymphedema after mastectomy in 1948. Hence, it is also known as Stewart-Treves syndrome. Since lymphangiosarcoma is usually connected with post-mastectomy lymphedema, it affects women more than men. Lymphangiosarcoma might appear as a purple discoloration or a sensitive skin nodule on the front surface of the extremities. It develops into an ulcer with crusting and eventually becomes a large necrotic center including the skin and subcutaneous tissue.[53,54]

The exact etiology of angiosarcoma is unclear. Animal models showed chronic lymphedema is opportune for atypical vascular proliferation, which gradually leads to malignant changes in endothelial cells. Lymphedema also impairs local immunity, blocking immune detection.[55]

Angiosarcomas in patients of Stewart-Treves syndrome are histopathologically indistinguishable from angiosarcomas in non-lymphoedematous locations.[56] Karyotypes are frequently complicated and have no regular abnormalities. Soft tissue and skin of the afflicted limbs are implicated in improving vascular nodular soft problem tumors, as are indicators of edema inside subcutaneous tissues. Endothelial cells are identified by antibodies to a factor VIII-related antigen. CD34 antigen is a vascular endothelial cell marker that does not react with lymphatic endothelial cells. Antikeratin antibodies reveal no keratin in this malignancy, confirming that the tumor cells are not epithelial in origin. Laminin, CD31, collagen IV, and vimentin positivity can help identify the tumors.[57] Early amputation of the affected limb appears to be the most effective treatment for lymphangiosarcoma. Whether the use of chemotherapy or radiation therapy adjuvant to amputation can increase the chance of survival of patients with LAS remains to be determined. This is a tumor with a bad prognosis especially after the development of metastases, with a median survival rate of 2.5 years.[58]

7 | SARCOMA OF THE PERIPHERAL NERVES

7.1 | Neurofibrosarcoma/malignant peripheral nerve sheath tumor

Malignant peripheral nerve sheath tumor (MPNST) affects the connective tissue surrounding nerves. Malignant triton tumors are MPNSTs with a rhabdomyoblastomatous component. Some of these sarcomas may arise from stem cells of peripheral nerves, some can arise de novo, or some can develop from malignant transformations of pre-existing neurofibromas. Unusual or atypical clinical and imaging features can be present in MPNST. Clinically, there is a rapid growth, which may be asymptomatic or may be painful, associated with paraesthesia, atrophy of muscles, and. The margins of the tumor are not regular and ulcerations can be present on top of it.

MPNST can happen in the following circumstances; irregular (~50%), type 1 neurofibromatosis (40%–50%), and history of radiation therapy before (10%). In patients with NF1, plexiform neurofibroma is a common precursor lesion. Patients with NF1 have a lifetime chance of having MPNST of 8%–13%. About 10%–15% of plexiform neurofibromas progress to MPNST. It can occur in almost any anatomical place. The trunk and extremities are the most prevalent places (30%) followed by the head and neck. There is no preference for one sex over another. NF1 patients are usually younger than their sporadic and radiation-related counterparts.44 The lifetime risk of a patient with NF1 developing an MPNST appears to be in the range of 5%–10%.[59,60]

Histopathology examination demonstrates spindle-shaped cells, along with longitudinal, ovoid or rounded, or bulky nuclei, presenting hyperchromatism and varying degrees of pleomorphism, low magnification marbling with perivascular accentuation and homogeneous cytologic characteristics (alternating patches of hypocellularity and hypercellularity). Heterologous differentiation occurs in 10%–15% of instances. Rhabdomyoblast differentiation is linked to poor clinical outcomes. The perfect diagnosis can be done using electron microscopy and immunohistochemistry. The marker used is S-100 is positive in 17% to 56% of cases. Computed tomography examination can aid in the assessment of tumor extension. Magnetic resonance imaging (MRI) can show the nerve from which it has derived form and hence shows the peripheral tissue involvement.[61]

Cytogenetics reveals CDKN2A/CDKN2B and PRC2 inactivating mutations and Germline NF1 (in NF1 instances) mutation. Point mutations in BRAF V600 have been reported on occasion.[62] FDG PET can assist to distinguish MPNST from neurofibroma. Surgical excision with wide margins is the first-line treatment. The goal is to achieve complete excision of the tumor with a negative margin to get the best result in terms of local recurrence and distant metastasis. Adjuvant and/or neoadjuvant treatments include chemotherapy (e.g. high-dose doxorubicin) and, in some cases, radiation.[63] Radical surgery is imperative, and complementary radiotherapy increases the patient's survival rate by 5 years. Radiotherapy may also be used in cases of local recurrence and inoperable tumors. Methotrexate

can be administered alone or in combination with other cytotoxic drugs such as vinorelbine, vinblastine, or doxorubicin. Metastasis occurs in about 39% of individuals, with lung metastasis being the most prevalent. A big initial tumor (over 5 cm across), high-grade illness, co-existing neurofibromatosis, and the existence of metastases are all associated with a bad prognosis. Children have a dismal prognosis.[60,64]

8 | CONCLUSION

In everyday dermatology practice, cutaneous sarcomas are relatively infrequent. Aside from dermatofibrosarcoma protuberans, which are more common in the mid-aged population, skin sarcomas are more common in the elderly. Because these sarcomas are rarely diagnosed based on clinical findings, histology is crucial in the diagnosis. Given the omnipresent availability of web-based knowledge and information, it is critical to emphasize to patients that, unlike deep connective and soft tissue sarcomas, cutaneous sarcomas have a relatively favorable prognosis if treated properly. Patients should be treated at specialized centres and, if possible, as part of a clinical study in the rare case of metastases.

AUTHOR CONTRIBUTIONS

Jyoti Kumari: Writing and revising the manuscript. Kinnor Das: Review and revising the manuscript. Anant Patil: Review and revising the manuscript. Clay J Cockerell: Review and revising the manuscript. Mohamad Goldust: Conception, writing, review, and revising the manuscript

DISCLAIMER

We confirm that the manuscript has been read and approved by all the authors and that the requirements for authorship as stated earlier in this document have been met and that each author believes that the manuscript represents honest work.

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