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Original Article

Soft Tissue Tumours with Epithelioid Morphoogy

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Abstract

Background: To study the morphological findings of soft tissue sarcomas with epithelioid morphology and their distribution with respect to the age, gender and location.

Methods: In this descriptive study, soft tissue sarcomas (n=100) with epithelioid morphology were evaluated by two histopathologists Cinical and morphological features like age, gender, site and type of tumor were quantified and documented. Epithelioid Morphology was defined as cells with polygonal to polyhedral shape, abundant cytoplasm and round nuclei .All cases were diagnosed with help of a panel of immunohistochemical (IHC) stains, i.e., CK ,EMA, Desmin, S100, CD31, CD34, INI-1, CD99 and TFE3 in conjunction with clinical history and morphology. lCA and HMB45 IHC stains were also utilized to rule out the possibility of a lymphoproliferative disorder and melanoma.

Results: Mean age of presentation was 36 years, with patients ranging in age from 1 to 80 years. There were n=37 females as compared to n=44 males. Most common site was thigh (n=21) followed by arm (n=13), head and neck region (n=5) and inguinal region (n=4).Epithelioid sarcoma (n=29) was the most common soft tissue sarcoma in our study followed by sclerosing epithelioid fibrosarcoma (n=10), alveolar soft part sarcoma (n=9), biphasic synovial sarcoma and epithelioid angiosarcoma (n=8), epithelioid malignant peripheral nerve sheath tumours (MPNST) (n=7), epithelioid hemangioendothelioma, undifferentiated epithelioid sarcoma, epithelioid angiomyolipoma and epithelioid leiomyosarcoma(n=6). rare tumors included in the study were 2 cases of epithelioid rhabdomyosarcoma and one case each of pseudomyogenic hemangioendothelioma, malignant rhabdoid tumor and dedifferentiated liposarcoma with rhabdoid features.

Conclusion: Soft tissue sarcomas with epithelioid morphology require careful morphological and immunohistochemical evaluation to differentiate them from carcinomas, lymphomas and melanoma because of the differences in their clinical management and prognosis.

Introduction

Soft tissue sarcomas constitute 1% of all malignant neoplasms. Epithelioid morphology, a defining feature of most carcinomas and melanomas characterizes many of these soft tissue tumors, and therefore knowledge of these tumors is imperative to avoid misdiagnosis. Soft tissue sarcomas represent a heterogeneous group of rare malignant neoplasms. These tumors account for almost 1% of all adult solid malignancies and about 20% of pediatric tumors.[1]Sarcomas can be divided into three broad categories based on their light microscopic appearance on H&E. These categories include the spindle cell sarcomas, round cell sarcomas and sarcomas with epithelioid morphology.Epithelioid morphology can be defined as polygonal to polyhederal cells with abundant cytoplasm, round to oval nuclei and distinct nucleoli. Epithelioid morphology literally meaning epithelial like is characteristic of carcinomas, however it can be seen in almost all tumor lineages especially melanomas. Soft tissue sarcomas with epithelioid morphology therefore present a unique challenge to the pathologist who has to differentiate it from carcinomas, melanomas and other soft tissue sarcomas of similar morphology.[2,3]

Sarcomas known to display epitheliod morphology include Epithelioid Sarcoma,epithelioid Malignant Peripheral Nerve Sheath Tumor, epithelioid Angiosarcoma, sclerosing epithelioid fibrosarcoma, Pseudomyogenic Hemangioendothelioma, Malignant Extra renal Rhabdoid tumor , Synovial Sarcoma, Epithelioid Rhabdomyosarcoma, Epithelioid Leiomyosarcoma and Myxofibrosarcoma.[3,4,5] A thorough knowledge of these entities and use of immunohistochemical stains enables us to make definite diagnosis in majority of these cases.

Patients and Methods

Histology slides of the 100 cases of soft tissue sarcomas with epithelioid morphology were evaluated by two histopathologists with special interest in soft tissue pathology. Epithelioid Morphology was provisionally defined as cells with polygonal to polyhedral shape, abundant cytoplasm and round nuclei. Soft tissue

sarcomas with rhabdoid features were also included in the study. The cases were selected solely on the basis of morphology. Clinical and morphological features like age, gender and site were assessed and documented. Cases with poor fixation, history of radiation therapy or carcinosarcomas were excluded from this study. All of the reported cases were diagnosed with help of a panel of immunohistochemical (IHC) stains; AE1/AE3, EMA, Desmin, CD31, CD34, INI-1, CD99 and TFE3 in conjunction with clinical history and morphology. LCA and HMB45 IHC stains were also utilized to rule out the possibility of a lymphoproliferative disorder and melanoma.

Results

Mean age of presentation was 35.80±*15.57* years, with patients ranging in age from 1 to 80 years. There were n=51 females as compared to n=49 males in our study. Most common site was lower limbs (n=37) followed by upper limbs (n=25), head and neck region (n=9) and chest and abdomen (n=15). Epithelioid Sarcoma (n=29) was the most common soft tissue sarcoma (Table 1).Rare tumors included in the study were 2 cases of epithelioid rhabdomyosarcoma and one case each of pseudomyogenic hemangioendothelioma, malignant rhabdoid tumor and dedifferentiated liposarcoma with rhabdoid features. The panel varied from case to case depending on the morphology and the closest histological and clinical differentials. Most common IHC stains positive in Epithelioid sarcoma were cytokeratin AE1/AE3, EMA and CD34. INI-1 was recently acquired by our institute and it showed loss of expression in cases it was applied. Synovial sarcoma was positive for Cytokeratin, EMA , CD99(100%) and TLE 1(100%). FISH studies were not performed in these cases. Epithelioid Hemangioendothelioma and epithelioid angiosarcoma were in most cases positive for CD31 and CD34. ERG, FLI-1 and factor-VIII were also used in a few cases to support the diagnosis. Epithelioid leiomyosarcoma was positive for SMA, Caldesmon and Desmin. Both the cases of Epithelioid Rhabdomyosarcoma were positive for Myogenin and Desmin. Epithelioid MPNST was positive in all cases for s100 and negative for both HMB45 and Melan A. New neural markers SOX-10 and PGP 9.5 were applied 0n one case each and showed positive staining. HMB-45 was consistently positive in all cases of epithelioid angiomyolipoma (Table 2;Figure 1-3). Undifferentiated epithelioid sarcoma was a diagnosis of exclusion in cases which did not show any specific lineage.

Table 1 Summary of the important clinical features according to individual tumor type

Type of tumour	Total No. of cases	Mean age ±S.D (in years)	Male to female ratio	Most common Sites
Epithelioid Sarcoma	29	33.24± 13.19	2.63:1	Upper and lower limbs
Sclerosing epithelioid fibrosar-coma	10	40.59± 19.07	2:3	Chest and abdomen, upper limb, lower limb and back
Alveolar soft part sarcoma	9	32.56± 5.46	1:2	Lower limb
Biphasic synovial sarcoma	8	31.38± 14.69	1:1	Upper and lower limbs
Epithelioid angiosarc-oma	8	49.00± 17.79	1:3	Chest and abdomen, Head and neck
Epithelioid MPNST	7	37.29± 12.50	2:5	Upper and lower limb
Epithelioid Hemang-ioendoth-elioma	6	34.00± 10.01	2:1	Chest and abdomen, upper and lower limb
Epithelioid Angiom-yolipoma	6	31.50± 17.80	2:1	Kidney, Liver
Epithelioid Leiomyo-sarcoma	6	43.33± 17.01	0:6	Uterus, Lower limb
Undifferent iated Epithelioid Sarcoma	6	43.50± 20.20	1:2	Upper and lower limb

Colour Page

Table 2: IHC markers used in the major subtypes

Tumor Subtype	CK	EMA	CD34	CD31	S100	HMB45	TFE3
Epithelioid Sarcoma	+(100%)	+(100%)	+(80%)	Negative	Negative	Negative	NA
Sclerosing epithelioid fibrosarcoma	+(50%)	Negative	Negative	NA	+(20%)	Negative	NA
Alveolar Soft part sarcoma	Negative	Negative	NA	NA	Negative	Negative	+ (100%)
Biphasic synovial sarcoma	+(67%)	+(100%)	Negative	NA	Negative	NA	NA
Epithelioid angiosarcoma	Negative	Negative	+(57%)	+(43%)	Negative	Negative	NA
Epithelioid MPNST	Negative	NA	Negative	Negative	+(100%)	Negative	NA
Epithelioid Hemangioendothelioima	Negative	NA	+(100%)	+(100%)	Negative	NA	NA
Epithelioid angiomyolipoma	Negative	NA	NA	NA	NA	+(83%)	NA
Epithelioid Leiomyosarcoma	+(40%)	Negative	NA	NA	Negative	NA	NA

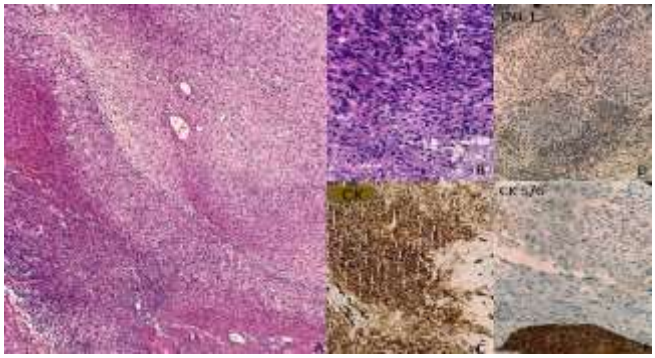

Figure 1: (A) Low power H&E of epithelioid Sarcoma. The tumor shows a well-circumscribed growth pattern on low magnification. Infiltrative growth pattern often in the form of single cells and small tumor cell nests. Central necrosis, a common feature of epithelioid sarcoma is also seen. (B) High power H&E showing polyhedral looking tumor cells.(C) The tumor shows positive expression of CK (D) CK 5/6 is negative in tumor cells with positive internal control(E) Loss of INI-1 expression.

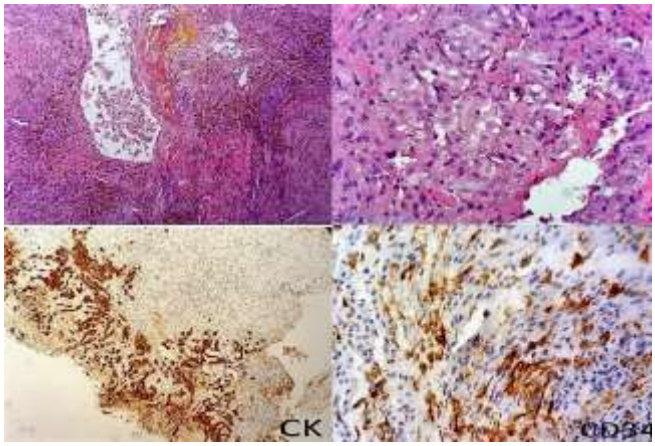

Figure 2:(A,B) H&E Epitheliodangiosarcoma.Microscopically areas of well-formed anastomosing vessels to solid sheets of epithelioid cells with abundant eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli. The vascular spaces are lined by markedly atypical endothelial cells. Extensive haemorrhage and necrosis are frequently present. (C) Cytokeratin expression in Epithelioidangiosarcoma. (D) CD34 staining in tumors cells.

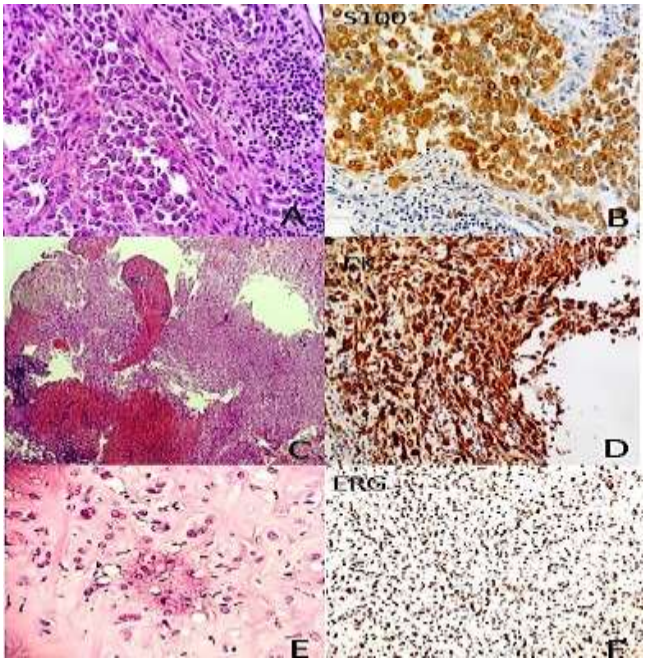

Figure 3: (A) H &E showing Epithelioid Malignant peripheral nerve sheath tumor. The neoplastic cells typically grow in a distinctly nested pattern, at least in part, with other areas usually showing a cord-like pattern of growth. (B) Diffuse S100 staining in MPNST (C) H&E of a rare case of pseudomyogenichemangioendothelioma. The tumor shows Infiltrative margins with loose fascicular and sheet- like architecture. Plump spindle cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm. There are focal prominent stromal neutrophils. (D) Cytokeratin staining in a case of pseudomyogenichemangioendothelioma (E) H&E showing epithelioid hemangioendothelioma. The tumor is composed of endothelial cells forming small sized vessels. The tumor cells form lumens of various sizes which occasionally contain red blood cells. Sometimes the intracytoplasmic vacuoles are so large that they compress the nucleus and give signet ring cell morphology. There is a sclerotic background. (F): ERG immunohistochemical stain showing positive expression in tumor cells.

Discussion

Soft tissue sarcomas comprise a heterogenous group of tumors with variable behavior, prognosis and

treatment depending on the type, grade and stage. Therefore, correct diagnosis of these tumors is of utmost importance. Clinical data including exact site, age of the patient and radiological findings are essential for diagnosis. First step in diagnosis of a sarcoma is determination of the pattern and cytological features to make a differential which can be later confirmed using immunohistochemistry and cytogenetics. Most sarcomas display either spindle cell or round cell morphology and only a few variants display epithelioid features. Epithelioid morphology is more commonly associated with carcinoma and melanoma. Presence of epithelioid features can be a diagnostic challenge to the pathologist who has to differentiate them not only from other sarcomas, but also carcinomas (notably sarcomatoid carcinomas) and melanomas. Immunohistochemistry, as an adjunct can help in making the definite diagnosis. [6-10]

Most of sarcomas in our study were of adult age group. A single case of malignant rhabdoid tumor was included in the study. The patient was 2 months old at presentation presented with mass in sub hepatic region. The tumor cells were a mixture of rhabdoid and spindle shaped cells displaying loss of expression of INI-1 and positive staining for CK.

Epithelioid sarcoma was the most common sarcoma in our study.Mean age and site of the patients were comparable to other studies. The tumors consistently expressed epithelial markers (pan CK, EMA) and CD34. Loss of INI-1 expression (SMARCB-1) is now considered the standard for diagnosis and is applied in any tumor where differential diagnosis includes epithelioid sarcoma.

Sclerosing epithelioid fibrosarcoma(SEF) was diagnosed mainly on its histological appearance of epithelioid round to oval cells arranged in cords and acini in a sclerotic background. [14,15] Hybrid features i.e sarcoma showing features of both sclerosing epithelioid fibrosarcoma and low grade fibromyxoid sarcoma was identified in one case.Most cases showed only focal positivity for keratins and muscle markers. MUC-4 is considered the most specific and sensitive marker for SEF.[16] The new marker was positive in two out of 4 cases it was applied on.

TFE3 was by far the best IHC stain for Alveolar soft part sarcoma. PAS positivity served a useful adjunct with the morphology. Most cases of biphasic synovial sarcoma were positive for epithelial markers. TLE-1 is considered an extremely sensitive marker of synovial sarcoma, and is now included in our panel. Translocation for X:18 was not performed in any of these cases which is now considered gold standard for diagnosis. However, all new cases are being confirmed by FISH. [17]

Epithelioid angiomyolipoma is a potentially aggressive lesion and part of spectrum of poorly understood PEComa group of tumors. Most tumors in our study were renal in origin except one which was identified in liver. The category of undifferentiated epithelioid sarcoma was reserved for neoplasms which displayed epithelioid morphology but did not fall into any known category.

One rare case of recently identified entity pseudomyogenic hemangioendothelioma was also diagnosed. The 24 year male presented with lytic lesion of right proximal humerus and microscopic examination showed bland looking epithelioid to spindle shaped cells with moderate eosinophilic cytoplasm. The neoplasm was positive for SMA, FLI-1, CK and CD31. Pseudomyogenic hemangiomas present as subcutaneous nodules but are known to invade muscle and bone. The main differential is epithelioid sarcoma. However, negativity for CD34 and intact INI-1 expression differentiates it from the latter.[18]

Conclusions

1.The rare occurence of these tumors, their deceptive morphology and inconsistent expression of most immunostains makes diagnosis of these tumors a challenge for the pathologist.

2.A multi-disciplinary approach along with immunohistochemistry and cytogenetics is the best approach to diagnose these tumors. In case of doubt referrel to a specialist soft tissue pathologist should also be considered.

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