Proximal-type Epithelioid Sarcoma with Chondroid and Osseous Differentiation: A Diagnostic Challenge

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Summary

Proximal-type epithelioid sarcoma is characterized by more aggressive behavior, and by its predominance of large epithelioid cells having intracytoplasmic hyaline inclusions imparting rhabdoid appearance to tumor cells. They show loss of SMARCB1 protein (INI1) on immunohistochemistry. Osseous differentiation is known in epithelioid sarcoma, but chondroid differentiation is extremely uncommon. We found only one case with chondroid differentiation in epithelioid sarcoma of distal-type after extensive literature search. We present a case of proximal-type epithelioid sarcoma having both chondroid and osseous differentiation, making first case of its kind.

Keywords: Epithelioid sarcoma; Proximal-type; Chondroid differentiation; Osseous differentiation; INI1 loss

Introduction

Epithelioid sarcoma (ES), an aggressive soft tissue sarcoma with uncertain histogenesis was firstly described by Enzinger in 1970.[1] Two clinicopathological subtypes are recognized: the classic or distal form, characterized by its proclivity for acral sites, and the proximal type, arising mainly in proximal/truncal regions. Though dystrophic calcification and metaplastic bone formation are detected in 20% of cases,[2] chondroid differentiation is extremely uncommon and only one case has been documented in literature till date.[3] Here, we describe a case of proximal type of ES with chondroid differentiation and its close differential diagnoses.

Case Report:

A 27 year old young gentleman presented with a mass in the right upper thigh, operated outside. Magnetic resonance imaging (MRI) done outside revealed a 9x6.5x5cm ill defined heterogenous signal intensity solid cystic mass in subcutaneous plane on posteromedial aspect of right thigh. There was no muscle or bone involvement. It was reported elsewhere by two pathologists at two different places as extraskeletal osteosarcoma and chondroblastoma-like tumor of soft tissue having mild to moderate nuclear atypia respectively. The patient came to our institute seven months later for further management, ours being a tertiary care cancer hospital.

Slides were reviewed in the pathology department. Sections showed epithelioid cells in sheets and perivascular arrangement, having abundant eosinophilic cytoplasm and moderate nuclear pleomorphism. Also there were rhabdoid cells having intracytoplasmic hyaline inclusions and eccentric nucleus with prominent nucleoli, multinucleated bizarre tumor cells and few cells with intranuclear inclusions. The tumor showed osseous and chondroid metaplasia at many places. There was micro, macro and pericellular chicken-wire calcification, osteoclastic giant cells, dispersed hemosiderin laden macrophages, dilated blood spaces and few areas of necrosis. Mitotic figures were very sparse and atypical mitotic figures were not seen. On immunohistochemistry tumor cells showed diffuse and strong staining for epithelial membrane antigen (EMA), whereas high molecular cytokeratin 5/6 (CK5/6) was negative. Tumor cells were positive for cluster differentiation 34 (CD34) and friend leukemia integration 1 transcription factor (FLI1) but negative for cluster differentiation 31 (CD31). Integrase interactor 1 (INI1) was characteristically lost in tumor cells. Also the tumor was negative for special AT-rich sequence-binding protein 2 (SATB2), smooth muscle actin (SMA), S-100, SRY-related HMG-box 10 (SOX 10), p63, desmin, cluster differentiation 99 (CD99) and anaplastic lymphoma kinase 1 (ALK1). Based on histomorphology and immunohistochemistry, diagnosis of proximal-type epithelioid sarcoma with osseous and chondroid differentiation was rendered.

Patient underwent re-excision of the tumor bed, which did not show any residual tumor. Six months later, patient developed local recurrence. Inguinal block dissection was done along with excision of the recurrent tumor. Inguinal lymph nodes did not show metastasis and the patient is doing well with 14 months of follow-up till now.

Discussion

Epithelioid sarcoma represents <1% of adult

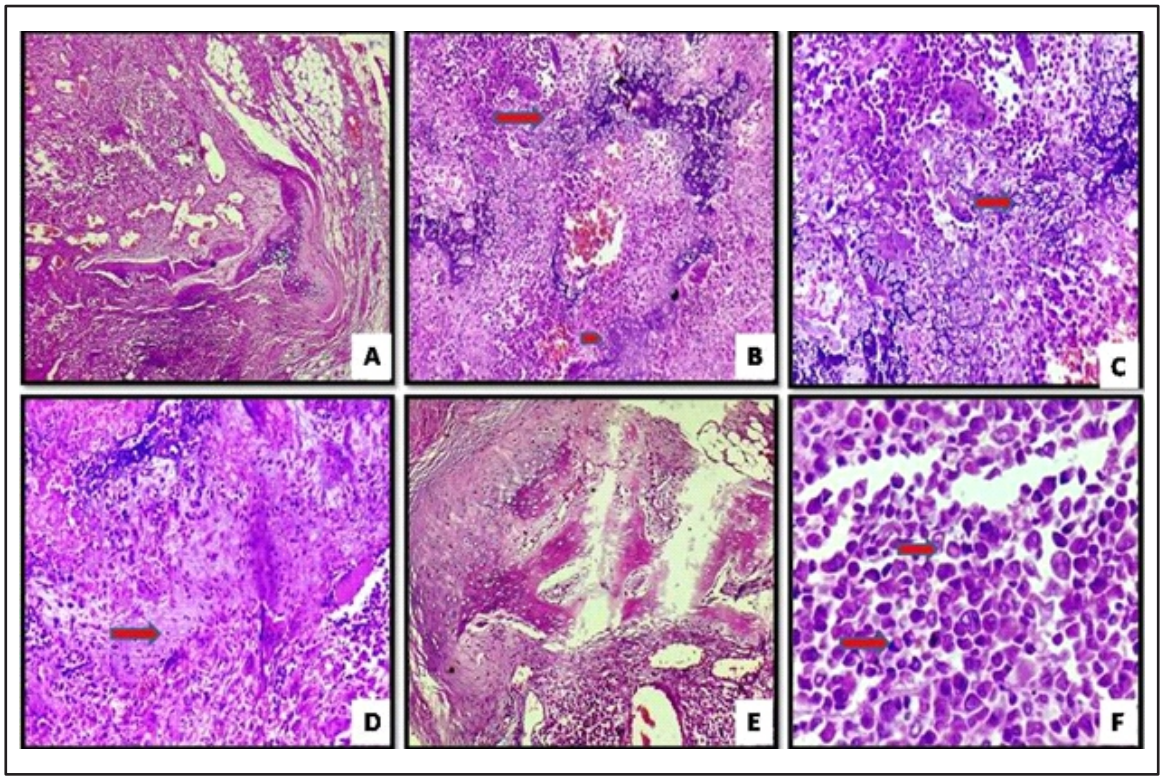

Figure 1: A-Tumor in subcutaneous plane, metaplastic bone and cartilage at periphery (40X, H&Ea); B-Microcalcification (arrow) and chondroid differentiation (arrow head) (100X, H&Ea); C-Tumor with osteoclastic giant cells and pericellular chicken-wire calcification (arrow) (200X, surrounded by tumor cells (200X, H&Ea); F-Epithelioid tumor cells having rhabdoid appearance (arrow) (400X, H&Ea). a-Hematoxylin and eosin

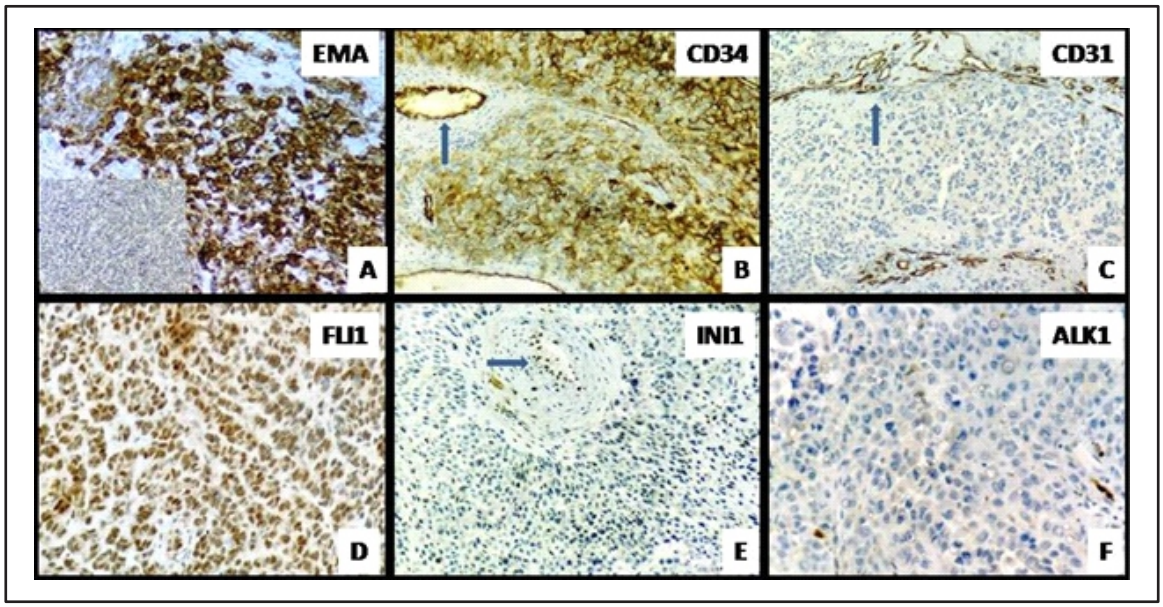

Figure 2: A-Tumor cells are strong and diffusely positive for EMA, Inset-Negative for CK5/6; B-Tumor cells positive for CD34. Internal control, vascular endothelial cells are positive (arrow); C-Tumor cells negative for CD31. Internal control, vascular endothelial cells are positive (arrow); D-Tumor cell nuclei positive for FLI1; E-Tumor cells show loss of INI1, retained in vascular endothelial cells (arrow); F-Tumor cells negative for ALK1
EMA-Epithelial membrane antigen; CK-Cytokeratin; CD-Cluster of differentiation; FLI1- Friend leukemia integration 1 transcription factor; INI1- Integrase interactor 1; ALK1- Anaplastic lymphoma kinase 1

soft tissue sarcoma [WHO 2020]. The proximal-type subtype tends to arise in deep soft tissue, affecting pelviperineal, genital, and inguinal regions most often. It affects predominantly young to middle aged adults.[2]

Grossly, proximal-type ES presents as solitary

or multiple grey-white nodules ranging from 1 to 20 cm with areas of haemorrhage and necrosis.[4] On microscopy, it shows multinodular and sheet-like growth of large epithelioid cells with enlarged vesicular nuclei and prominent nucleoli. Cells with rhabdoid features are frequently observed. Occasional cases with prominent myxoid stroma have been reported.[5] The major differential diagnoses comprise of epithelioid malignant peripheral nerve sheath tumor (MPNST), malignant extrarenal rhadoid tumor (MERT), myopithelial tumors, malignant melanoma (MM), epithelioid angiosarcoma, epithelioid leiomyosarcoma (LMS), rhadomyosarcoma (RMS), extraskeletal osteosarcoma, epithelioid fibrous histiocytoma and undifferentiated carcinoma. Among all these entities, loss of expression of nuclear protein, INI1 by IHC is seen in epithelioid MPNST, MERT and myoepithelial carcinoma. Epithelioid MPNSTs may be positive for cytokeratin and EMA occasionally, they show diffuse and strong S-100 and SOX 10 immunoreactivity.[4] MERT express EMA, cytokeratin, Sal-like protein 4 (SALL4), glypican-3 but is always negative for CD34. Myoepithelial tumors can show cartilaginous differentiation in 10% cases and they express EMA, cytokeratin, S-100 along with myoepithelial markers like glial fibrillary acid protein (GFAP), Calponin and p63.[6] Malignant melanomas typically express human melanoma black-45 (HMB-45) and S-100, but not EMA or CD34. Epithelioid angiosarcoma may be positive for cytokeratin and CD34. Also, many epithelioid angiosarcomas have a diffuse sheet-like growth pattern, mimicking ES. But they express marker for endothelial differentiation, CD31 and absent to weak EMA expression. Although, approximately 30% of LMS are immunoreactive for cytokeratin and EMA, they also express SMA, desmin and H-caldesmon. Tumor cells in RMS express desmin and myoD1 or myogenin. Extraskeletal osteosarcomas are typically SATB2 positive and EMA negative unlike ES. Fibrous histiocytoma with epithelioid morphology shows expression of ALK1 and is also negative for EMA and CD34. The distinction between proximal-type epithelioid sarcoma and undifferentiated carcinoma is probably the most difficult consideration. The absence of squamous or glandular differentiation, focal or negative CK5/6 expression, and presence of CD34 reactivity favor the diagnosis of ES over undifferentiated carcinoma. CD34 is almost always negative in carcinomas.[4]

In our case, with chondroid differentiation and pericellular chicken-wire calcification, other differential diagnoses considered were chondroblastoma-like osteosarcoma and chodroblastoma-like chondroma of soft tissue. The chondroid and osteoid matrix were of benign nature with osteoid matrix lined by benign osteoblasts, suggesting metaplastic nature of matrix, excluding osteosarcoma. Chondroblastoma-like tumor of soft tissue was also the differential diagnosis, in view of fair circumscription, low mitosis, chondroid and osteoid matrix, osteoclastic giant cells and chicken-wire calcification. One of the eight cases described by Cates JM et al showed local recurrence as in our case.[7] However, no data is available on loss of INI1 in these tumors which are believed to be variants of chondroma of soft tissue.

Both classic and proximal types of ES are associated with almost complete loss of SMARCB1 (INI1) nuclear protein expression, encoded by SMARCB1 gene located at 22q11.23.[8] SMARCB1 biallelic deletion can be demonstrated by FISH (Fluorescent In-Situ Hybridisation) or by immunohistochemical loss of INI1 protein expression. We performed INI1 IHC in this case to confirm SMARCB1 deletion.

Treatment consists of early local radical excision or amputation with regional lymph node dissection as nodal metastasis is an ominous feature. ES has a high risk for local recurrence and metastasis and requires long-term follow-up, given that recurrence or metastasis may occur many years after the initial diagnosis. Proximal type behaves even more aggressively.

Our case developed local recurrence six months after initial diagnosis. Re-excision and inguinal block dissection was performed. Inguinal lymph nodes did not show metastasis. The patient was followed-up with computed tomography (CT) every six months. With 14 months follow-up, he is doing good and is free of disease. However, long term follow-up and clinicoradiological correlation is necessary to know the disease prognosis and outcome.

Conclusion:

Chondroid differentiation is extremely uncommon in epithelioid sarcoma. Present case is the first of its kind having both chondroid and osseous differentiation in proximal-type subtype. Exclusion of other close mimickers is of utmost necessity to set up a proper treatment plan consisting of radical excision/amputation and regional lymphadenectomy with long term follow-up, being it an aggressive disease with poor prognosis.

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