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Recurrent Epitheloid Cell Sarcoma of Scapular region: A Case Report and Review of Literature

Authors
Raza MW, Verma S, Prasad SN, Misra MP

Abstract
Epithelioid sarcoma is a rare variety of malignant soft tissue sarcoma of uncertain differentiation that affects young adults mostly involves upper arm especially arm and wrist. It has a high rate of recurrence and metastasis. A 55-year-old male presented in December 2011 with a swelling over right scapular region (near angle of scapula). The patient gave a history of swelling from 6 months. Local excision was done 2 times from 2014 to 2016. Each time the recurrence was just distal to previous one. For the third recurrence just adjacent to it wide local excision was done. Immunohistochemistry (IHC) showed expression of Vimentin, Pan-CK: Focal positive, EMA: Focal positive, LCA: negative, CD-99: Negative,. IHC confirmed the diagnosis of epithelioid sarcoma of axillary region. Patient received adjuvant chemotherapy followed by local radiotherapy. Patient remained asymptomatic for 2 years when follow up PET-CT was suggestive of lung metastasis. Thus, doxorubicin based chemotherapy has been planned.
Keywords: *Doxorubicin, epithelioid sarcoma, immunohistochemistry, wide local excision, Scapula.*

Introduction

Epithelioid sarcoma is a rare variety of soft tissue sarcoma affecting 20-40 years of age group. Laskowski in 1961 described it as “sarcoma aponeuroticum” because of its involvement of aponeuroses and surrounding structures. The term "epithelioid sarcoma" was coined by Enzinger in 1970.[1] It involves upper extremities in approximately 60% of cases.[2] with high risk of recurrence and metastasis.[3] Because of its epithelial and mesenchymal differentiation, this tumor is often mistaken for chronic inflammatory processes, necrotizing granulomas, and various fibrohistiocytic tumors. Gender, involved site, age at diagnosis, tumor size, and pathology are the prognostic factors[5]. Female patients show a more favorable outcome. Proximal lesions show worse prognosis as compared to the distal lesions.[3] It is the second and the sixth most common soft tissue sarcoma in the hand and upper extremity respectively.[2,4] Tumors show a better outcome if presented in earlier age group.[5] Tumors >2 cm in diameter and tumors with necrosis, vascular invasion have been correlated with worse outcome.[3]

This article reviews the epidemiology, prognostic factors, clinical features, pathogenesis, diagnosis and management of epithelioid sarcoma.

Case Report

A 55 years male presented with a swelling over right scapular region (near angle of scapula) from 6 months which was progressively increasing in size in Dec 2011. For which excision was done in

Aug 2012. Patient did not take any adjuvant treatment and developed a recurrence just adjacent to lateral margin of previous excision in form of small nodule lesion in right axilla in March 2014 for which 2nd time excision of lump was done in Sep 2014. He remained asymptomatic for 2 years and then again developed recurrence laterally from previous disease site in axillary fold in 2016. Biopsy and IHC Vimentin: Positive, Pan-CK: Focal positive, EMA: Focal positive, LCA: negative, CD-99: Negative, CD-30: Negative, HMB-45: Negative, Desmin- Negative confirmed it to be epitheloid cell sarcoma. Preop MRI right shoulder showed mass lesion size 4 x 3.6 x 2.8 cm with altered signal intensity in right posterior axillary fold and ill defined interface with infraspinatus as well as teres minor muscle. Pre op PETCT showed similar MRI findings with sub centimetric bilateral axillary lymphnode, subcentrimetric bilateral external iliac and right superficial inguinal lymph node. He underwent wide local excision followed by adjuvant chemotherapy and radiotherapy 50Gy in 25 fractions in 5 week.

Patient again developed a nodular lesion in January 2018 which was more distal than prior at right arm. PET CT showed FDG avid well defined hypodense lesion in posterior compartment of right arm, measuring 4.2x5.8 cm starting just distal to metallic clips and multiple lung metastasis.

FNAC confirmed it to be epitheloid sarcoma. Patient again underwent local excision with histopathology consistent with epitheloid sarcoma. Patient is currently undergoing doxorubicin base palliative chemotherapy.

Table 1

PATHOLOGIC DIFFERENTIAL DIAGNOSIS
Granulomatous process
"Amelanotic" melanoma
Synovial sarcoma
Ulcerating squamous cell carcinoma
Nodular fasciitis
Nodular tenosynovitis
Rhabdomyosarcoma
Clear cell sarcoma
Squamous cell carcinoma
Fibrosarcoma
Fibrous xanthoma
Liposarcoma
Fibromatosis/fibroma
Spindle cell sarcoma
Granular cell myoblastoma

Table 2

Stains	%Reactivity
Vimentin	>75%
Cytokeratin	>75%
Epithelial membrane antigen	>75%
CD34	50-75%
Smooth muscle actin	50-75%
Muscle specific antigen	50-75%
Desmin	50-75%
S-100	<5%
HMB	<5%

Discussion

A recent study based on surveillance, epidemiology, and end results database, showed that the incidence has been increasing with 5.2% per year since 1973 and in 2005, the incidence was 0.4 case per million.[3] This tumor commonly affects 20-40 years of age group (mean age 27 years) and affected male-female ratio is 1.8:1.[4] Females carry a favorable prognosis in epithelioid sarcoma.[5] Studies have failed to reveal any geographical or racial predisposition for the rare disease.[2,5]

Epithelioid sarcoma mostly presents as a firm or hard swelling arising from dermis or deep tissue at the origin site. This may be misdiagnosed as ganglion cyst or giant cell tumor of the tendon sheath. It is mostly painless or nontender but in about 20% cases it may be painful or tender.[5] The three variants of ES are epithelioid, spindled, and mixed, with the principal form being epithelioid. These cells are large, round, oval, or polygonal, with abundant, deeply acidophilic cytoplasm and a

clear or vesicular, centrally placed nucleus[2,6]. About 13% of cases have multifocal tumors at presentation, while 13% have distant metastasis[7]. An important variation from the rest of the sarcomas is the tendency for lymph node metastasis. Other sarcomas with lymphatic spread include synovial sarcoma, clear cell sarcoma, angiosarcoma, rhabdomyosarcoma and embryonal sarcoma. In a long-term clinical study, 45% patients of epithelioid sarcoma developed metastasis in the lung (51%), lymph nodes (34%) and scalp (22%)[5]. In our report also, patient presented with recurrent epithelioid sarcoma with metastasis to lung.

Epithelioid sarcoma rarely can cause demineralization or cortical thinning of the adjacent bone.[5] Soft tissue swelling can be visualized in some cases by conventional X-ray. Rarely, speckled patterns of calcification are seen. MRI is the imaging modality of choice prior to biopsy and histopathologic diagnosis. The role of MRI is primarily determining the extent of the tumor and in differentiating doubtful cases of recurrence from postoperative changes due to multiple excisions.[8] One study on 160 soft tissue sarcomas, based on positron emission tomography (PET) - computerized tomography imaging showed 3 cases of epithelioid sarcomas, and all three were PET positive.[9]

Tissue biopsy is the diagnostic modality of choice to diagnose sarcoma, and IHC differentiates the different types of sarcomas including epithelioid sarcoma. The proportion of spindle cells to epithelioid cells varies among tumors which may be arranged in a whorled pattern. It leads to the histological appearance of several benign and malignant entities (Table 1)

In gross appearance, a white nodule with infiltrating margins is one of the basic features of epithelioid sarcoma. Microscopically, the tumor consists of ovoid or polygonal epithelial cells well blended with fusiform eosinophilic cells with intracytoplasmic vacuoles.[5] Distinct sheets of polygonal cells with spindle cells as seen in biphasic synovial sarcoma are not visualized in the traditional variant. Pseudogranulomatous proliferation of cells is seen around a necrotic acellular central zone. Multinuclear giant cells can be present in a small number of tumors.[5] INI1, located on the chromosome 22 (22q11.2), is a member of SWI/SNF multi subunit chromatin remodeling complex. The loss of this tumor suppressor gene is associated in more than 80% epithelioid sarcoma.[10] Diagnosis is aided by consistently positive staining with the immunoreactants vimentin, epithelial membrane antigen, and cytokeratin.[11,12] Other stains, such as CD34, may also be positive. Vimentin reactivity is present in almost all cases.[5],[13] (Table 2) CA-125 can be used as a serum marker to monitor metastasis. S100 and p63 are typically negative and differentiate from synovial sarcoma. CD34 is expressed in 50-60% of epithelioid sarcomas[14] but is negative in carcinoma.

Management: Surgery

A wide total surgical excision with clear margins (amputation or wide en bloc excision) is the main treatment modality for ES (15-17) Wide local excision is the primary treatment modality in epithelioid sarcoma. Some studies showed up to 77% recurrence rate after marginal resection in epithelioid sarcoma.[5] Patients with small (<5 cm) superficial tumors or small deep tumors that can be resected with wide margins (>1 cm) or complete resection with the investing fascial barriers are candidates for surgery without radiation therapy[18,19]. Thus, most authors recommend wide resection or tumor bed resection despite the dysfunction and morbidity associated with it.[7,8] However, epithelioid sarcoma tend to spread proximally in the same limb (distant to the original tumor) leading some to consider less radical treatment for local control. Amputation can be considered in case of multiple recurrences or if there is not a significant loss of function. However, it does not decrease the risk of local metastasis.[5] Since lymphatic spread can occur in epithelioid sarcoma, sentinel lymph node biopsy and regional lymph node dissection has been

proposed by some authors.[20] However, further research is needed as outcome literature of this technique for sarcomas is lacking.

Adjuvant therapy: Because of slow growing nature and rarity of epithelioid sarcoma, it is very difficult to have long-term follow-up to compare and evaluate different adjuvant treatment modalities

Radiotherapy

While the efficacy of radiation therapy as an adjunct to surgery has been clearly demonstrated in soft tissue sarcomas, studies of ES are limited due to small sample size and limited follow up. External beam radiotherapy was also tried in some institutes for primary and recurrent cases[21] for limb salvage, but it has not shown to increase overall survival as compared to amputation.[22] These factors include narrow or positive surgical margins, local recurrence after prior surgery, tumor size of 5 cm, lesions deep to or invading the superficial fascia, high grade, and younger than 50 years[12] In a paper from Massachusetts General Hospital authors tried to establish role of radiotherapy in eight patients of epitheloid cell sarcoma in conjuction with surgery or alone. They concluded that Local control and survival for this group of patients is similar to that for other patients with upper extremity or high grade sarcomas. They also concluded that radiation combined with surgery achieves a low rate of local recurrence, and a high likelihood of maintaining a functional extremity and good cosmesis.[23] Some authors reported that a radiation dose of >64 Gy was associated with improved local control, and major complications were associated with a dose of >68 Gy[24]. 5-year survival in epithelioid sarcoma is approximately 50-70%.[19]

Chemotherapy: A randomized phase III trial by Lorigan P.et al 2007, in 326 patients with various subtypes of advanced soft tissue sarcoma compared Doxorubicin (doxo) versus with two different treatment schedules of ifosfamide (continuous IV infusion vs. bolus ifosfamide). Results showed no difference between the three arms. The progression free survival was 2.52 months (doxo group) versus 2.16 months (ifosfamide group) and overall survival of 12 months (in doxo group) versus 10.92 months (ifosfamide group) (p =0.076) [25].

The phase III EORTC 62012 trial compared doxorubicin versus doxorubicin with ifosfamide. It showed higher response rate and progression free survival with the combination but no statistically significant improvement in overall survival (PFS: 7.4 months (doxo + ifosfamide) and 4.6 months (doxo alone group) p =0.003); overall survival: 14.3 months (doxo + ifosfamide) versus 12.8 months (doxo alone) p =0.076). The combination therapy had higher grade 4 toxicities. Results support the use of intensified doxorubicin and ifosfamide only if specific goal is tumour shrinkage and not in palliative settings.[26]

In a randomized phase III trial by Seddon et al 2017 Doxorubicin vs. Docetaxel/Gemcitabine: doxorubicin was studied against combination of gemcitabine and docetaxel in first line treatment of advanced unresectable or metastatic soft tissue sarcoma. The results showed no significant difference[27].

Immunotherapy: In a retrospective study conducted on STS patients, PD-L 1 expression was found in 100% of patients with epithelioid sarcoma, 53% of SS, 38% of rhabdomyosarcoma, 33% of Ewing sarcoma[28]. Efficacy of PD-L1 inhibitors need to be validated.

Conclusion

Epithelioid sarcoma is a rare slow growing sarcoma with high risk of recurrence and metastasis. Post excision the tumor bed and margins need to be addressed with adequate doses of radiotherapy. Doxorubicin is to be given as first line for metastasis. Epithelioid sarcoma still remains difficult and challenging.

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