Epithelioid Sarcoma in a child presenting as a submandibular mass

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Key words: Soft tissue sarcoma; Epithelioid sarcoma; Paediatric; Submandibular
African Health Sciences 2010; 10(4): 400 - 404

Epithelioid sarcoma (ES) is a clinical curiosity with uncertain histogenesis[1]. Histologically, two variants have been described: the "classic or distal" variant, which usually affects distal extremities of adolescents and young adults between 15 and 35 years of age , particularly in the hand and foot, and consists of a subcutaneous or deeper nodular proliferation of rounded to plump cells with abundant eosinophilic cytoplasm palisading around areas of necrosis[2], while the "proximal" variant , first described in 1997 by Guillou et al. [3], is found mostly in the pelvic, perineal, and genital tracts of young to middle-aged adults and characterized by a proliferation of epithelioid-like cells with rhabdoid features in the absence of a granuloma-like pattern.

In this monograph we report a case of pediatric epithelioid sarcoma presented as a submandibular mass and to the best of our knowledge it has not been previously documented in this place.

A nine –year old female child presented with a firm fixed lobulated mass near the left angle of the mandible with a provisional diagnosis of enlarged submandibular lymph node. Fine needle aspiration cytology (FNAC) of the mass was performed and revealed a spindle cell lesion with myxoid back ground suggestive of nodular fasciitis. Excisional biopsy of the mass was done. A round, lobulated mass was received measuring 4x3x3cm, cut –sections were homogenous with foci of necrosis.

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Histologically, the tumor cells have nodular proliferation (Fig. 1A) of large polygonal to spindle-shaped cells with epithelioid appearance and abundant eosinophilic cytoplasm palisading around areas of necrosis and simulating a granulomatous process (Fig. 1B). The tumor cells were uniformly immunoreactive to cytokeratin (CK) (Fig. 1C), epithelial membrane antigen (EMA) (Fig. 1D), vimentin (Fig. 2A), CD34 (Fig. 2B), neuron-specific enolase (NSE) (Fig. 2C), and CD 138 (Fig. 2D). The tumor cells showed no immunoreactivity to S-100 protein, HMB-45, smooth muscle actin (SMA), sarcomeric actin, desmin, CD31, factor VIII, CD99 and CD117 (Table 1). The patient had an uneventful postoperative recovery with no recurrence after one year of follow-up. No adjuvant chemotherapy or radiotherapy was given to the patient.

Figure 1: A - showing the nodularity of epithelioid sarcoma (thick arrow) with areas of necrosis arrow head)
H&E X 100 B - showing large polygonal cells with epithelioid appearance (thick arrows)and abundant eosinophilic cytoplasm palisading around areas of necrosis (arrow head)and simulating a granulomatous process,
H&E, X400, C – showing diffuse brown cytoplasmic immunoreactivity to cytokeratin (arrow head), strepavidin-biotin- immunoperoxidase,
X400, D - showing brown membranous and cytoplasmic immunoreactivity to epithelial membrane antigen(arrow head), strepavidin-biotin-immunoperoxidase, X400.

Figure 1: A - showing the nodularity of epithelioid sarcoma (thick arrow) with areas of necrosis arrow head)

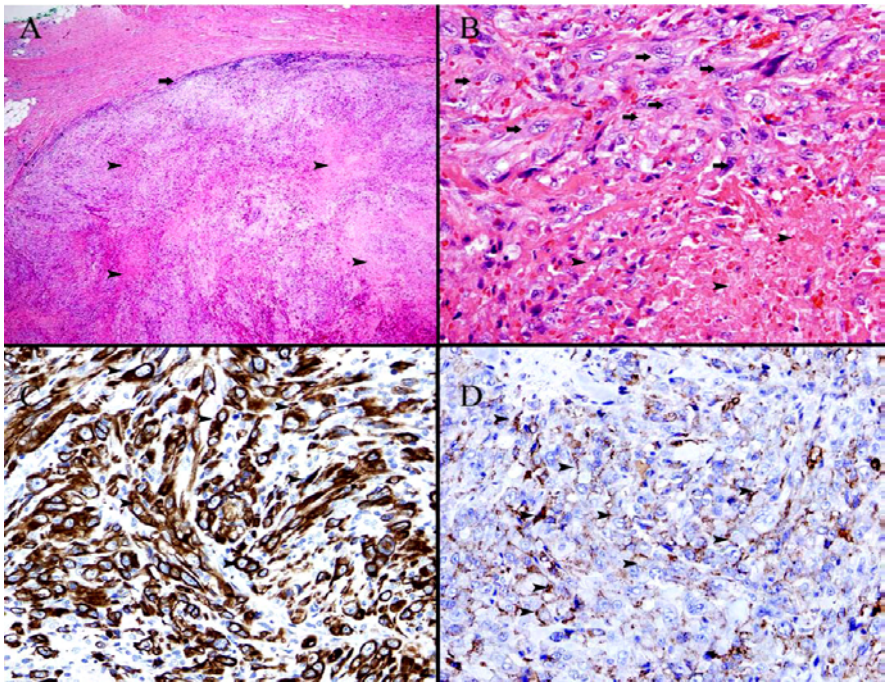

Figure 2: A - diffuse brown cytoplasmic immunoreactivity to vimentin(arrow head), strepavidin-biotin- immunoperoxidase X400, B - diffuse brown cytoplasmic immunoreactivity to CD34(arrow head), strepavidin-biotin- immunoperoxidase, X400, C- diffuse brown cytoplasmic immunoreactivity to neuron specific enolase (arrow head), strepavidin-biotin- immunoperoxidase, X400, D- brown membranous and cytoplasmic immunoreactivity to CD138 (arrow head), strepavidin-biotin- immunoperoxidase, X1000.

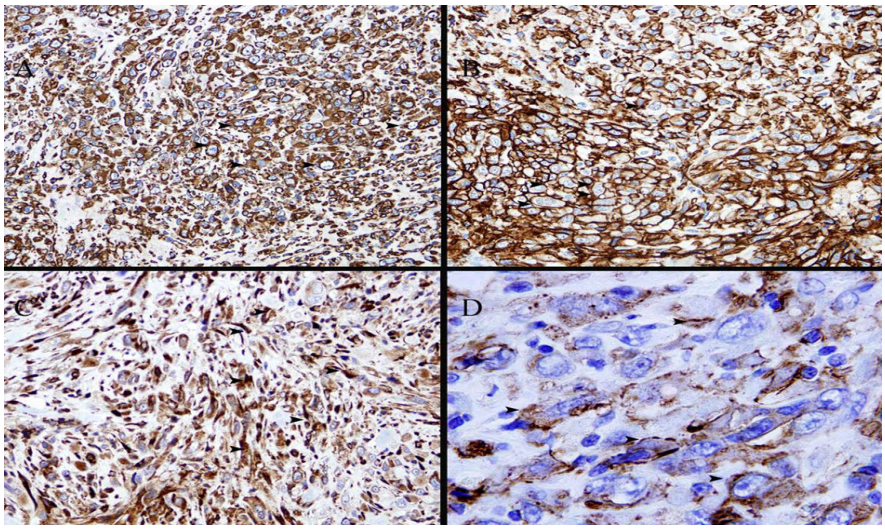

Table 1: **The primary antibodies which are used in the immunohistochemical staining**

No	Primary Antibody	Type	Clone	Company	Dilution	Method	Staining pattern	Reaction
1	Cytokeratin	Monoclonal	AE1/AE3	Dako	1:50	Streptavidin biotin	Cytoplasmi	Positive
2	EMA	Monoclonal	E29	Dako	1:50	Streptavidin biotin	Cytoplasmic	Positive
3	CD34	Monoclonal	QBEnd 1	Dako	1:50	Streptavidin biotin	Cytoplasmic	Positive
4	CD 138	Monoclonal	M15	Dako	1:50	Streptavidin biotin	Membranous Cytoplasmic	Positive
5	Vimentin	Monoclonal	V9	Dako	1:50	Streptavidin biotin	Cytoplasmic	Positive
6	NSE	Monoclonal	BBS/NC/ VI-H14	Dako	1:50	Streptavidin biotin	Cytoplasmic	Positive

Continuation of table 1

No	Primary Antibody	Type	Clone	Company	Dilution	Method	Staining pattern	Reaction
7	S100	Monoclonal	MAC387	Dako	1:50	Streptavidin biotin	Cytoplasmic	Negative
8	CD31	Monoclonal	JC70A	DAKO	1:50	Streptavidin biotin	Membranous Cytoplasmic	Negative
9	HMB-45	Monoclonal	HMB-45	Dako	1:50	Streptavidin biotin	Cytoplasmic	Negative
10	SMA	Monoclonal	1A4	Dako	1:50	Streptavidin biotin	Cytoplasmic	Negative
11	Sarcomeric Actin	Monoclonal	Alpha-Sr-1	Dako	1:50	Streptavidin biotin	Cytoplasmic	Negative
12	Desmin	Monoclonal	D33	Dako	1:50	Streptavidin biotin	Cytoplasmic	Negative
13	CD117	Polyclonal		DAKO	1:100	Streptavidin biotin	Membranous Cytoplasmic	Negative
14	CD99	Monoclonal	12E7	Dako	1:50	Streptavidin biotin	Membranous Cytoplasmic	Negative
15	Factor VIII	Polyclonal		DAKO	1:2000	Streptavidin biotin	Membranous Cytoplasmic	Negative

NSE: neuron specific enolase EMA: epithelial membrane antigen SMA: smooth muscle actin.

It was only after Enzinger's report of sixty two cases in 1970[4] that ES received widespread recognition as a distinctive tumor type. ES is notorious for being misdiagnosed[5]. Our patient was clinically misdiagnosed as enlarged submandibular lymphnode, since the mass had a round and smooth contour with firm consistency making it similar to an enlarged lymphnode. Furthermore, the FNAC was misleading too showing features of spindle cells with myxoid background; non-specific features leading to a wrong diagnosis. The use of FNAC as a diagnostic modality for the pathologic evaluation of soft tissue neoplasms is uncommon and controversial[6].

Paediatric ESs are rare neoplasms. More than seventy cases of paediatric ES have been documented[1-12], however, no report of ES in the submandibular region. It is noteworthy to mention here that the tumor in our patient shows both histological and behavioral features of distal type of ES despite its occurrence in a proximal area.

The immunohistochemical profile of ES is quite interesting and shows immunoreactivity to CK, EMA, CD34, Vimentin, NSE, and CD138. Many immunohistochemical studies[7-12] have shown similar staining patterns (Table 2), however, none have reported CD138 expression in ES, which is to best of our knowledge, the first time being documented in ES. CD138 (Syndecan-1) is a cell-surface heparan sulfate proteoglycan, that links the cytoskeleton to the interstitial matrix and plays a role in cellular adhesion and proliferation processes. Via its heparan sulphate chains, CD138 binds to a variety of growth and angiogenic factors and acts as a classical co-receptor for growth factor receptors, thus promoting cell proliferation and tumor formation[13].

Table 2: Literature review of immunohistochemical studies in comparison with our results

Ref No.	CK	EMA	CD34	VIM	CD138	Actin	Des	HMB	S100	NSE	CD68	VIII	CD31	CD99	CD117
7	+	+				-	-		-	-	-				
8	+	+	+	+		-	-	-	-		-		-		
9	+	+	+	+		-	-	-	-		-		-		
10	+	+		+											
11	+	+	+	+		+	-		-						
12	+	+		+		+	-		+	+	-				
Present study	+	+	+	+	+	-	-	-	-	+	-	-	-	-	-

CK : cytokeratin EMA: epithelial membrane antigen VIM: vimentin Des: desmin.

ES is usually confused histologically with a variety of lesions including; granulamatous lesions, rheumatoid nodules, fibromatosis, an ulcerating squamous cell carcinoma and soft tissue sarcomas with epithelioid features such as angiosarcoma, malignant peripheral nerve sheath tumor (MPNST), rhabdomyosarcoma, leiomyosarcoma and synovial sarcoma (SS) [11].

Both morphological and immunohistochemical staining patterns are helpful in solving the differential diagnosis. The negative immunoreactivity to CD68 differentiates epithelioid sarcoma from granulomatous processes, rheumatoid nodule and other histiocytic lesions. The immunoreactivity to CK, EMA, CD34 and vimentin differentiates epithelioid sarcoma from squamous cell carcinoma and other epithelial tumors[11], while the combination of negative immunoreactivity to CD31, factor VIII, S100, SMA and desmin with positive immunoreactivity to CK, EMA, CD34 and vimentin rules out angiosarcoma, MPNST, rhabdomyosarcoma and leiomyosarcoma. The differentiation from SS is very difficult since they almost have similar immunohistochemical prolfile. However, absence of the biphasic pattern, nodularity with central necrosis, well circumscription and absence of immunoreactivity to CD99 can differentiate ES from SS. In addition, SS is characterized by the presence of SYT-SSX fusion oncogene. Demonstration of the t(X;18) by cytogenetics or fluorescence in situ hybridization will enable us to differentiate between synovial sarcoma and ES. Moreover, TLE expression is a consistent feature of SS[14].

The origin of ES remains controversial[1-12]. A recent analysis of the immunohistochemical pattern of both epithelial and mesenchymal markers led to the conclusion that ES is a mesenchymal tumor capable of partial epithelial transformation[15].

ES is known to recur and metastasize even after wide excision and the reported metastatic rate is between 30% and 45%[1,2,4,5]. The tumor metastasizes through lymphatic and blood vessels to regional lymph nodes, skin, lungs, heart, pleura, liver, pericardium, bone and soft tissue of the other parts of the body. Lungs are the most common site of distant metastasis[1,5]. Unlike most soft tissue sarcomas, the involvement of lymph nodes are frequently described[1,5]. Baratti et al. reported lymphnode metastasis in 30% of ES[5].

Surgery is the gold standard method of treatment. Adequate treatment requires radical en bloc excision as early as possible along with extensive lymph node dissection. The role of radiotherapy and chemotherapy is controversial[1-12]. Baratti et al. found no significant survival difference between patients who received and who did not receive adjuvant chemotherapy or radiotherapy[5]. In our patient, the mass was excised completely and no adjuvant therapy was given postoperatively. There was no evidence of local recurrence, lymph node involvement or distant metastasis for more than one year of clinical and radiological follow-up of our patient.

Older age, male sex, proximal or axial location, depth, tumor size, mitotic figures,

necrosis, vascular invasion, tumor haemorrhage , local recurrence, nodal metastases, and the extent of surgery, were identified as adverse prognostic factors[5].

Conclusion

ES can occur in the submandibular region and can show both histological and behavioral features of the distal type despite its occurrence in a proximal site.

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