Soft tissue sarcomas in Mosul: a pathologic evaluation

Ahmad F. Lazim* Bedoor AK. Al-Irhayim**
Al-Jamhory Teaching Hospital-Mosul; **Department of pathology. College of Medicine, University of Mosul.

ABSTRACT

Objective: Histochemical and immunohistochemical examination of soft tissue sarcomas(STS) in Mosul to assess the value of these techniques in verifying the primary diagnosis.

Methods: Paraffin embedded tissue blocks of 35 cases of soft tissue sarcomas collected over a period of 20 months in Mosul, were utilized. H&E, reticulin ,and Van Gieson's staining techniques and immunohistochemical marker for S-100 protein were applied to all the cases.

Results: Soft tissue sarcoma accounts for 16.4%of the total of 213 cases of benign and malignant soft tissue neoplasms,with a mean age of 30.5 years ,and a male preponderance(Male: Female ratio of1.7:1). The most common histologic subtypes are extraskeletal Ewing's sarcoma(ES), dermatofibrosarcoma protuberans(DFSP) ,and spindle cell sarcoma, not other wise specified (NOS). The extremities are affected in 51.4% of all cases, particularly the lower limbs. The majority of soft tissue sarcomas belong to the high grade category by applying French Federation of Cancers Centers Sarcoma Group (FFCCSG) and American Joint Cancer Committee (AJCC) grading schemes .Both reticulin and Van Gieson's stains have been successfully depicting the growth patterns of different subtypes. Immunoreactivity for S-100 protein was positive in two cases.

Conclusions: High quality H&E stained sections remain the best method for establishing the diagnosis of sarcomas .Reticulin stain proved extremely helpful in subclassifying sarcomas and S-100 protein was instrumental in changing the diagnosis of sarcoma in one case.

الخلاصة:

الهدف: استعمال الفحوصات الكيمياوية النسيجية والكيمياوية النسيجية المناعية للتوصل إلى التشخيص النهائي لسرطانات (غرن) الأنسجة الرخوة في الموصل.

النموذج المستخدم: القوالب الشمعية الخالصة بنسيج ٣٥ حالة لسرطانات (غرن) الأنسجة الرخوة خلال فترة ٢٠ شهر.

الطريقة: استعمال الصبغات النسيجية (H&E, reticulin, Van Gieson's) الكيمياوية النسيجية المناعية من نوع S-100 protein في كل الحالات.

النتائج: مثلت حالات سرطانات (غرن) الأنسجة الرخوة نسبة ١٦,٤% من أصل ٢١٣ حالة شملت أيضاً الحالات الحميدة وكان معدل العمر ٣٠,٥سنة مع زيادة طفيفة للمصابين من الذكور نسبة للإناث (١٠٧:١) أكثر الحالات هي من نوع (ES) Ewing's sarcoma.

الاستنتاج: الصبغة النسجية من نوع H&E هي أفضل طريقة للتشخيص مع بقية الصبغات المستخدمة.

Soft tissue sarcomas (STS) are heterogeneous group of malignant neoplasms which arise predominantly from the embryonic mesoderm[1,2].They are tumors of extra skeletal connective tissues of the body, grouped together owing to similarities in clinical presentation, pathologic appearance and biologic behavior[3]. They define a group of histologically and genetically diverse cancers that account for approximately 1% of all adult malignancies[3,4]. Sarcomas can occur any where in the body ,particularly in the extremities in 29% of the cases; trunk (19%); retroperitoneum (15%); or the head and neck (9%)[5].

The most commonly diagnosed subtypes are malignant fibrous histiocytoma; leiomyosarcoma; liposarcoma; synovial sarcoma, and malignant peripheral nerve sheath tumors (MPNST)[6,7].

Rhabdomyosarcoma is most common in childhood[6,7]. On the other hand, nonrhabdomyosarcomatous soft tissue sarcomas (NRSTS) account for nearly three percent of childhood malignancies[8]. Soft tissue sarcomas usually afflict old persons, with a median age of 56 years, and a male; female ratio of 1:1[9]. Reticulin stain is of particular importance in demonstrating the reticular fibers (type III collagen) and basement membrane material (type IV). However, it is useful to depict hemangiopericytoma, vascular smooth muscle, fibrosarcoma versus endothelial cell tumors, MPNST[10,11]. Van Gieson stain is suitable to confirm fibroblastic nature of a lesion on attempting to decide whether a spindle cell tumor is a fibrosarcoma or leiomyosarcoma[10,11]. S-100 protein is demonstrated in 50 to 90 % of MPNST[12].

The main objectives of this study are subtyping of already diagnosed sarcomas by applying reticulin stain, Van Gieson stain, and immunohistochemical marker S-100 protein, assess histologic grading by reevaluation of H&E stained sections,as well as finding out the relative frequency of soft tissue sarcomas in Mosul, age and gender distribution.

Materials and methods:

A retrospective pathologic evaluation of 35 cases of soft tissue sarcomas, which had been diagnosed throughout a period extending from 1st January 2004 till 1st August 2005 in Mosul city.

The following histopathological techniques were performed to each case.

1- Routine H&E staining method was applied for subtyping, and grading of soft tissue sarcomas utilizing FFCCSG and AJCC grading schemes.

2- Special stains; Reticulin stain (Gordon and Sweets) and Van Gieson's stain were performed to outline the distribution of reticulin and collagen fibers in various subtypes[13,14].

3-Standard avidin-biotin peroxidase complex (ABC) immunohistochemical technique for the detection of S-100 protein monoclonal antibody[15].

Results:

There were 35 cases of soft tissue sarcomas with a mean age of 30.5 years (age range 2-82years), and a slight male preponderance (male: female ratio of 1.7:1).

The most common histologic subtypes are extra skeletal Ewing's sarcoma (6 cases:17.2%), Dermatofibrosarcoma protuberans DFSP (5 cases :14.3%), spindle cell sarcoma (NOS) (4 cases: 11.4%). Fibrosarcoma, malignant fibrous histiocytoma (MFH), embryonal rabdomyosarcoma, and Liposarcomas, each represents 3 cases (8.6%). However, other subtypes (synovial sarcoma, hemangiopericytoma, Kaposi's sarcoma, neuroblastoma, and clear cell sarcoma) accounted for 23% of all sarcomas.

Age and sex distribution within the various subtypes is outlined in table(1).

The most common primary sites are extremities (51.4%), particularly the lower limbs; retroperitoneum and trunk (14.3%),whereas other various locations are relatively rare (34%), as assigned in table (2).

Staining patterns:

The cartwheel growth pattern of DFSP(figures 1&2), fibrosarcoma (figures 3&4) and the proliferating pericytes in hemangiopericytoma are clearly identified in H&E, Reticulin and Van

Gieson's stained sections, whereas the epithelial and sarcomatous elements of biphasic synovial sarcoma are readily seen in both H&E and reticulin stained sections (figure5). Peripheral neuroblastoma has the characteristic of well circumscribed masses of small round cells in a fibrillary stroma .Kaposi's sarcoma shows fascicles of plumpy spindle cells, easily recognized by H&E stain.Spindle cell sarcoma (NOS) case is depicting a marked nuclear hyperchromasia and intense S-100 protein immunoreactivity(figures 6&7). Both FFCCSG and AJCC grading systems are applied in all cases, majority of which were related to the high grade category as illustrated in table (3).

Table (1): Age and sex distribution of soft tissue sarcomas subtypes.

Subtypes of Sarcomas	No.(%)	Male	Female	Mean age (age range) yrs
ES\PNET	6(17.2)	4	2	17(5-35)
DFSP	5(14.3)	5	0	26(16-50)
MFH	3(8.6)	1	2	55(50-82)
Fibrosarcoma	3(8.6)	2	1	42(16-55)
Embryonal rhabdomyosarcoma	3(8.6)	3	0	15(4-26)
Well differentiated liposarcoma	2(5.7)	2	0	46(38-54)
Hemangiopericytooma	2(5.7)	1	1	26.5(20-33)
Synovial sarcoma	2(5.7)	2	0	28(21-35)
Neuroblastoma	2(5.7)	0	2	9.3(2.5-16)
Myxoid liposarcoma	1(2.8)	0	1	26
Kaposi sarcoma	1(2.8)	0	1	35
Clear cell sarcoma	1(2.8)	0	1	43
Spindle cell sarcoma (NOS)	4(11.4)	2	2	48(22-52)
Total	35(100)	22	13	30.5(2.5-82)

Table (2): Primary sites of soft tissue sarcomas throughout the body.

Site	No.(%)
Lower extremity	10 (28.6)
Upper extremity	8 (22.9)
Trunk & Retroperitoneum	5 (14.3)
Miscellaneous	12 (34.3)
Total	35 (100)

Table (3): FFCCSG and AJCC grading systems in various sarcomas.

Grade	No. (%)
FFCCSG System	
Grade I	9(25.
Grade II	9(25.7)
Grade III	17(48.6)
AJCC system	
G1	9(25.7)
G2	3(8.6)
G3	9(25.7)
G4	14(54.28)

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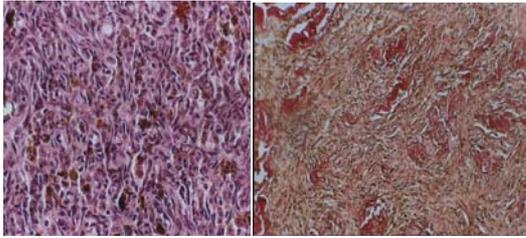
Figure(1) (left) Cartwheel growth pattern in DFSP(H & E stain).
Figure(2)(right) Subcutaneous connective tissue surrounding DFSP is seen infiltrated by the neoplastic spindle cells(Van Gieson's stain).
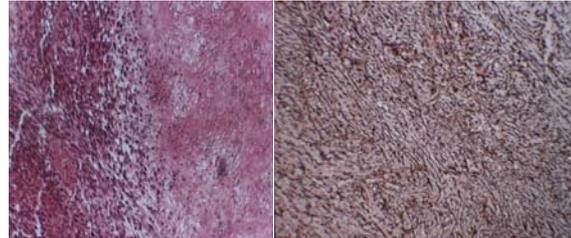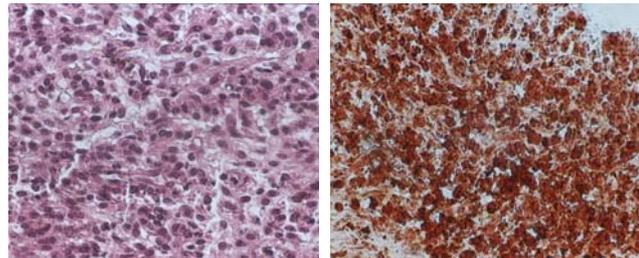

Figure(3) (left) High grade fibrosarcoma with extensive necrosis (H & E stain).
Figure(4)(right) Reticulin fibers surrounding individual cells in a well differentiated fibrosarcoma(reticulin stain).

Figure(5) The epithelial nests are sharply enclosed within reticulin network in biphasic synovial sarcoma(reticulin stain).

Figure(6) (Left) Spindle cell sarcoma (NOS)has a marked nuclear hyperchromasia (H & E stain).
Figure(7)(right) Intense positivity of S-100 protein in a case of spindle cell   sarcoma (NOS).

Discussion:

According to standard   knowledge, soft tissue sarcomas account for 1-2% of all malignant neoplasms[3,4,16-19]. However, in this study they represented 16.4% of soft tissue neoplasms [Benign: Malignant ratio of 100:18], and this is not much different from   that recognized in a previous study from Mosul in 1997(21% with Benign: Malignant ratio of 100:25)[20]. The mean age recognized (30.5 years) with a male: female ratio of 1.7:1 is relatively akin to the findings of other authors which   vary   between   1-3:1[17,20-23].   The extremities are more prone to be targeted by sarcomas, in particular, the lower limbs, and this   was   also   observed   in   similar studies[1,6,9,17,24].ES/PNET and DFSP were the most frequent soft tissue sarcomas found in our study, which was different from other surveys[25-28].

Malignant   fibrous   histiocytoma   was considered as the most common soft tissue sarcoma in adult life[1,6,3], while liposarcoma

and leiomyosarcoma were the prevailing subtypes by others[17,21]. ES/PNET is a rare childhood malignancy which is histologically similar to skeletal ES[25]. In this study   the relative frequency, the male predilection and the age incidence were close to others [25-27] and half of the six cases encountered were recognized in the lower extremities as was documented by others[27]. These findings highlight the well known facts about these tumors as being aggressive and of   high grade[26,27].

Dermotofibrosarcoma protuberans was the second most common malignancy in this study (14.3%), showed a tendency to affect young adults with a predilection for the upper extremities. The age of patients, the   site distribution of their tumors as well as   the grading status are concordant with those described by Sabine et al 2002[28]. Reticulin and Van Gieson's stains were very helpful in outlining   the   individual   spindle   cells   as

reported by others[10,11]. There was no immunoreactivty for S-100 protein, since they lack the specific Immunohistochemical markers[12,28].

Malignant fibrous histiocytoma is the most common subtype according to some reports[24,29], but in the current study, it resided fourthly in order of frequency and presenting only in adults as assigned by others[29,30]. It frequently occurs in the extremities and retroperitoneum[29,30]. All the cases of MFH have predominantly the storiform–pleomorphic pattern, high grade with significant foci of necrosis and ample mitotic figures, as described by Chibon et al[31]. The reticulin staining pattern simulated that of DFSP and fibrosarcoma, by outlining the individual cells and blood vessels[10,11]. Van Gieson's stain showed dispersed fine collagenous fibrils, while the tumor cells were not reactive for S-100 protein as observed by other authors[12,16,32]. Fletcher et al[33], and Meister et al[34] attested a retrospective evaluation of cases of MFH depending on newly defined histopathologic criteria and observed that these cases can be reclassified into other entities.

Fibrosarcoma, represents about 10 % of musculoskeletal sarcomas with an age range of 35-55 years and often arising in the soft tissue of the extremities[35]. These features are similar to our findings. Two cases of fibrosarcoma are related to the high grade category, being very cellular with marked cytologic atypia, brisk mitotic activity, and evident necrosis, whereas the other case is of a low grade with morphologic resemblance to the normal fibroblasts. Reticulin fibers were observed clearly surrounding individual cells at their poles, as was described by others[11,14,36,37].

Embryonal rhabdomyosarcoma is the most common soft tissue sarcoma in childhood accounting for 5% of all childhood malignancies[38,39] with male predominance[38]. In the present study it was diagnosed in three males with a mean age of 15 years, so its frequency of 8.6% (3 cases) is close to that of Hussein[20] in which embryonal rhabdomyosarcoma accounted for 12.5% of all

sarcomas. One case showed predominance of round cell component with an intense immunoreactivity for S-100 protein, however, both ES/PNET and embryonal rhabdomyosarcoma can show this positivity[40,41]. All the cases of embryonal rhabdomyosarcoma fell within the high grade group (grade 4, G4), akin to other studies[42].

Liposarcoma was predominantly afflicting adults (40-60 years), arising mostly in the lower extremities. These findings are similar to others[43,44]. The single case of myxoid liposarcoma occured in an adult female in her third decade which is characteristic of this cancer as stated by Smith et al[45,46]. Likewise, S-100 protein was negative in the three cases as noticed by others[12]. Both well differentiated and myxoid liposarcomas were low grade malignancies, an observation matching those in comparable studies[45,46].

Hemangiopericytoma is an uncommon stromovascular neoplasm that arises from the pericytes of Zimmermann[47]. It has been described in all age groups[47], with an equal sex distribution[48]. The retroperitoneum, extremities, head and neck are more frequently involved sites[47-49]. It was attested in two cases, a male and a female, of 20 years and 33 years respectively. Both cases were of high grade lesions with a high mitotic count > 4/10 HPF[48], marked cellularity and pleomorphism with areas of hemorrhage and necrosis.Reticulin stain was very useful in depicting the reticulin meshwork surrounding packed pericytes as described by others[50].

Biphasic and monophasic synovial sarcomas were recognized in two cases in the present study (5,7% of the soft tissue sarcomas). The patients were both males of 21years and 35 years respectively with tumours in lower extremities. Similar clinical features were described by others[51-53]. In these studies, synovial sarcomas accounted for 5-20% of all malignant soft tissue neoplasms, most frequently affecting young adults with a slight male predominance, and primarily located in the extremities. Biphasic synovial sarcoma was perfectly demonstrated by reticulin stain, which outlined the well defined epithelial cell nests as well as the sarcomatous spindle cell

component. The mechanisms involved in its epithelial differentiation are still unknown[54]. Van Gieson's stain did not have particular pattern in synovial sarcoma, and no immunoreactivity for S-100 protein was recognized, as mentioned by others[12,52].

Neuroblastoma is the most common neoplasm during infancy[55], being extremely rare in children older than 5 years (with boy: girl ratio of 1.2)[56]. Peripheral neuroblastoma , on the other hand ,is a tumor of soft tissue which is morphologically similar to neuroblastoma but can occur at any age[19]. The two cases in our study occurred in females 2.5 and 16 years. both were characterized morphologically by relatively well defined nests of small round cells in a fibrillary stroma. These nests were outlined by thin fibrous bands which were intensely stained by reticulin stain. Neuroblastoma in the present study belongs to the high grade lesions (G4, undifferentiated)[55]. S-100 protein was negative in our and in other studies[12,57].

Kaposi's sarcoma is appreciated as grade II (G2) malignancy according to FFCCSG and AJCC grading schemes. Its occurrence was in an adult female who was a recipient of kidney transplant. The tumor was multicenteric including the lower extremity, as observed by Papadopulose et al[58]. Histologically it is recognized as a highly angiogenic tumor characterized by aberrant proliferation of vascular structures and enhanced vascular permeability as attested by others[59,60,61].

Spindle cell sarcomas (NOS) are also dictated by other authors[31,62], as representing 2 % of all sarcomas of the soft tissues. The case included in this study showed strong immunoreactivity for S-100 protein. Thus, the diagnosis was changed to MPNST(malignant peripheral nerve sheath tumor) rather than fibrosarcoma since the positivity for this marker can be demonstrated in 50-90 % of cases[46,62].

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