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HISTOPATHOLOGICAL STUDY OF SOFT TISSUE TUMOURS AND CORRELATION OF HISTOLOGIC GRADE OF SARCOMAS WITH PROLIFERATIVE MARKER KI-67

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ABSTRACT

INTRODUCTION: Soft tissue tumours have diagnostic and therapeutic challenge due to a wide variety of histomorphological patterns. Soft tissue sarcomas are relatively infrequent and constitute less than 1 % of all malignant neoplasms. Immunohistochemical evaluation of Ki-67 is a rapid prognostic tool to assess the cellular proliferation better than mitotic index.

METHODS: A prospective study was conducted with a total of 100 cases of soft tissue tumors to analyze the frequency and histomorphology. Soft tissue sarcomas were graded by FNCLCC grading system and were subjected to Ki-67 evaluation. Spearman's Rho and Pearman's correlation coefficients were calculated to determine the correlation between the histologic grade and Ki-67 index.

RESULTS: Soft tissue tumours constituted only about 1.3% of all neoplasms. Benign tumours (50%) outnumbered intermediate (11%) and malignant soft tissue tumours (39%). Soft tissue tumours were more common in males (52%) than females (48%) and frequently observed in the sixth decade. The sites of predilection were upper extremities for benign tumours and lower extremities for malignant tumours. Most common benign soft tissue tumour was Neurofibroma (19%) followed by Schwannoma (14%). Undifferentiated pleomorphic sarcomas were the most common malignant soft tissue tumour (28%). In FNCLCC grading, most of the sarcomas were grade III (42%). Ki-67 index was low in grade I sarcomas, variable in grade II sarcomas and high in grade III sarcomas. Spearman's rho and Pearman's correlation R values were 0.77 and 0.75 respectively and p value is less than 0.05.

CONCLUSION: There is positive correlation between the histologic grade and Ki-67 proliferative index in soft tissue sarcomas. Ki-67 index can be used as an independent prognostic factor to predict the risk of distant metastasis. Prospective evaluation of Ki-67 should be carried out in patients with soft tissue sarcomas for planning adjuvant treatment modalities.

KEYWORDS : Soft tissue Sarcomas, FNCLCC grading, Ki-67.

INTRODUCTION:

Soft tissue tumours are highly heterogenous group of tumours that are classified histologically according to their resemblance to adult mesenchymal tissue[1]. Benign tumours outnumber malignant soft tissue tumours[2]. Malignant soft tissue tumours constitute only less than 1 % of all malignant neoplasms. Malignant lesions have high rate of local recurrence and distant metastasis and are given adjuvant treatment modalities. Immunohistochemistry is of great value and is extensively used to accurately classify these neoplasms. Thus the histopathological classification of soft tissue tumours based on their behavior is important to decide the treatment.

FNCLCC grading is the standard grading system used in the morphological evaluation of sarcomas. Since histologic grading is prone for subjective variation, many prognostic markers have been studied in soft tissue sarcomas. Most promising proliferative marker to assess the risk of distant metastasis and tumour mortality in sarcomas is Ki-67. Prospective evaluation of Ki-67 can be used for predicting the overall survival rate in patients with sarcomas and accordingly the treatment can be planned.

OBJECTIVES:

1. To study the frequency and histopathological features of benign and malignant soft tissue tumors and to assess the histologic grade of soft tissue sarcomas morphologically by FNCLCC (Federation Nationale des Centres de Lutte Contre le Cancer) grading system.
2. To correlate the histologic grade with expression of immuno histochemical proliferative marker Ki 67 in selected cases of soft tissue sarcomas.

MATERIAL AND METHODS:

A prospective study was conducted with a total sample of 100 cases of soft tissue tumors, including both benign and malignant tumors. Incisional biopsy specimens, lipomas and soft tissue tumours modified by neo-adjuvant chemotherapy or radiotherapy were excluded. Operated resection specimens were fixed in 10% neutral buffered formalin for 12 hours. Representative bits were taken from the tumour, surgical margins and lymph nodes. They were processed routinely and multiple 4 to 6 micron thin paraffin sections were obtained. Stained slides were evaluated and tumours were classified as benign or malignant based on cellularity, nuclear atypia and presence or absence of atypical mitotic figures. Malignant soft tissue sarcomas were histologically graded using the FNLCC grading system which included assessment of tumour differentiation score, mitotic count per 10 high power fields and tumour necrosis volume. Selected cases of soft tissue sarcomas were subjected to Ki-67 evaluation using MIB-1 antibody. Ki-67 score based on percentage of nuclear positive tumour cells and labeling index were evaluated. Spearman's Rho and Pearman's coefficient correlation studies were done to assess the strength of correlation between histologic grade and Ki-67 index. p value was derived to determine the statistical significance level of the study.

OBSERVATION AND RESULTS:

Soft tissue tumours constituted only about 1.3% of all total neoplasms diagnosed during the study period. Majority of soft tissue tumours were benign constituting about 50%, followed by malignant tumours (39%) and intermediate grade tumours (11 %) (Chart 1).

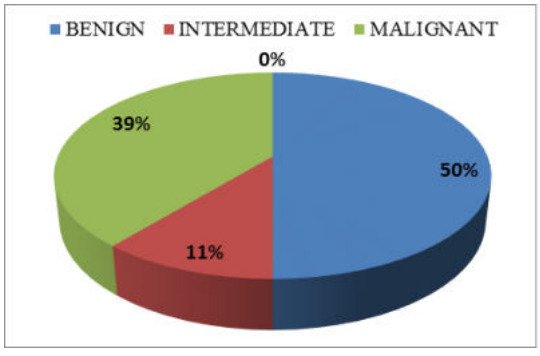

Chart 1- Distribution Of Tumors According To Behaviour

The age range was 1 to 80 years with mean age of 42.11 years. Majority of soft tissue tumours occurred in the age group of 50-59 years (23%) and the least number of tumours occurred in the age group of <10 years (4%). Male to female ratio was 1:0.9 indicating that the incidence was slightly higher in males.

Most of the soft tissue tumours involved the lower extremity in about 32% of cases followed by 25% cases in upper extremity and 14% cases in head and neck region. The site of predilection was upper extremities for benign tumours and lower extremities for malignant soft tissue tumours.

Table 1 - Distribution Of Soft Tissue Tumors According To Who Classification

TUMOUR TYPE		PERCENTAGE
ADIPOCYTIC TUMOURS	WELL DIFFERENTIATED LIPOSARCOMA	4%
	MYXOID LIPOSARCOMA	4%
	DEDIFFERENTIATED LIPOSARCOMA	3%
	TOTAL	11%
FIBRO/ MYOFIBRO-BLASTIC TUMOURS	FIBROMATOSIS	2%
	GIANT CELL FIBROBLASTOMA	1%
	JUVENILE HYALINE FIBROMATOSIS	1%
	DERMATOFIBROSARCOMA PROTRUBERANS	4%
	FIBROSARCOMA	6%
	INFANTILE FIBROSARCOMA	1%
	TOTAL	15%
FIBROHISTIOCYTIC TUMOURS	BENIGN FIBROUS HISTIOCYTOMA	5%
VASCULAR TUMOURS	HAEMANGIOMA	6%
SMOOTH MUSCLE TUMOURS	LEIOMYOMA	2%
	LEIOMYOSARCOMA	2%
	TOTAL	4%
SKELETAL MUSCLE TUMOURS	ALVEOLAR RHABDOMYOSARCOMA	1%
PERIVASCULAR TUMOURS	GLOMANGIOMA	1%
NERVE SHEATH TUMOURS	NEUROFIBROMA	19%
	SCHWANNOMA	14%
	MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR	3%
	TOTAL	36%
UNDIFFERENTIATED TUMOURS	UNDIFFERENTIATED PLEOMORPHIC SARCOMA	11%
TUMOURS OF UNCERTAIN DIFFERENTIATION	MYXOMA	1%
	SYNOVIAL SARCOMA	7%
	ALVEOLAR SOFT PART SARCOMA	1%
	EXTRASKELETAL MYXOID CHONDROSARCOMA	1%
	TOTAL	10%

Table 1 analyses the distribution of soft tissue tumours according to WHO classification. Nerve sheath tumours (36%) were the most common comprising of 19% neurofibromas, 14% schwannomas and 3% malignant peripheral nerve sheath tumours. Fibroblastic tumours (15%) were the second most common tumours with 6% of them contributed by fibrosarcomas. Undifferentiated pleomorphic sarcomas and adipocytic tumours constituted about 11% of soft tissue tumours. Among benign tumours, Neurofibroma was the most common (38%) followed by Schwannoma (28%) and Haemangioma (12%). The incidence of benign soft tissue tumours was equal in both males and females with ratio of 1:1. Benign soft tissue tumours were common in the age group of 20-29 years in males and 40-49 years in females constituting about 32% each. The most common intermediate soft tissue tumours were Dermatofibrosarcoma protruberans (37%) followed by Well differentiated liposarcoma / atypical lipomatous neoplasm (27%). They were common in males with male to female ratio of 1.2:1. Among males, 33.33 % of cases occurred in the first decade. Among females, 60% of cases occurred in the sixth decade.

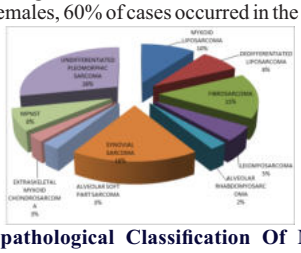

Chart 2- Histopathological Classification Of Malignant Soft Tissue Tumours

The most common malignant soft tissue tumour constituting about 28.20% was Undifferentiated pleomorphic sarcoma followed by Liposarcoma and Synovial sarcoma (17.95% each) as shown in Chart 2. They were common in males with male to female ratio of 1.2:1 and in the sixth decade (50-59 years) constituting about 33.33% of cases in both males and females.

42% of soft tissue sarcomas were 'grade 3' according to FNCLCC grading system followed by 37% of 'grade 2' sarcomas and 21% of 'grade 1' sarcomas. Out of 18 'grade 3' sarcomas, 9 cases were Undifferentiated pleomorphic sarcomas constituting about 50% of cases followed by 3 cases of dedifferentiated liposarcomas (16.66%). Most frequent among 'grade 2' sarcomas were synovial sarcoma (37.5%) and fibrosarcoma (25%). Most frequent among 'grade 1' sarcomas were well differentiated and myxoid liposarcomas each accounting for about 33.33%.

Table 2- Correlation Between Fnclcc Grading And Ki-67 Index In Selected Cases Of Sarcomas

S. NO.	DIAGNOSIS	FNCLCC GRADE	KI 67 SCORE	KI67 INDEX
1	WELL DIFFERENTIATED LIPOSARCOMA	1	1	LOW
2	DEDIFFERENTIATED LIPOSARCOMA	3	3	HIGH
3	FIBROSARCOMA	2	2	HIGH
4	INFANTILE FIBROSARCOMA	2	2	HIGH
5	UNDIFFERENTIATED PLEOMORPHIC SARCOMA	3	2	HIGH
6	MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR	3	2	HIGH
7	LEIOMYOSARCOMA	3	3	HIGH
8	ALVEOLAR RHABDOMYOSARCOMA	2	1	LOW
9	SYNOVIAL SARCOMA	2	1	LOW
10	ALVEOLAR SOFT PART SARCOMA	2	1	LOW

- Spearman's Rho correlation (R) = 0.77 with p value of 0.005
- Pearman's correlation coefficient (R) =0.75 with p value of 0.007

Grade 1 sarcomas had a low Ki-67 index with score of 1 (1-25%). Among Grade 2 sarcomas, two cases had high Ki-67 index with score of 3 (more than 50%) and three had low Ki-67 index with score of 2 (26-50%). All the four grade 3 sarcomas had high Ki-67 index (Table 2). Spearman's rho and Pearson's correlation coefficients were calculated and the p value was less than 0.05. The relationship between tumour histologic grade and Ki-67 index is statistically significant. Hence Ki-67 index has a positive correlation with histological grade.

DISCUSSION:

Soft tissue tumours form a complex group composed of benign tumours, intermediate locally aggressive, intermediate rarely metastasizing and malignant tumours [1]. These tumours have a wide variety of morphological patterns. Hence the present study has been undertaken to analyze the histopathological features of soft tissue tumours and their incidence in relation to age, sex and site. Because of the lowest incidence of sarcomas among malignant neoplasms, there is difficulty in diagnosing and providing appropriate treatment for metastasis free survival especially in patients with high-risk sarcomas. The study has attempted to establish the correlation between the histologic grade and Ki-67 index and efficiency of Ki-67 expression in assessing cellular proliferation and prognosis in sarcomas.

Incidence of soft tissue tumours in the present study was 1.3% of all neoplasms diagnosed which is comparable with studies by Mirza Asif Baig where the overall incidence of soft tissue tumours was 1.6% [2]. Benign tumours (50%) were more common than malignant tumours (39%) with benign to malignant ratio of 1.3:1 which is comparable with Kransdorf MJ et al study [3] where the benign to malignant ratio was 1.5: 1. Most benign soft tissue tumours were seen in the age group of 20-50 years with the mean age of 35 years. Intermediate and malignant soft tissue tumours were commonly seen in the age group of 50-59 years with the mean age of 60 years. Similar results were observed by Batra et al and Kinjal Bera [4,5]. The incidence of soft tissue tumours was slightly higher in males with male to female ratio of 1:0.9

which is comparable with studies by Myher Jensen and Janaki et al where the ratio was 1:1 [6,7]. The sites of predilection in the present study were lower extremities (56%) for malignant tumours and upper extremities (36%) for benign soft tissue tumours. These results are comparable with studies conducted by Kransdorf et al , Batra et al and Janaki et al [4,7,8]. Nerve sheath tumours (66%) were the most common benign soft tissue tumors after excluding lipomas followed by vascular tumours (12%). These results are comparable with studies conducted by Agravat AH et al, Bashar et al and Vikas V. Narhire et al[9-11]. Undifferentiated Pleomorphic sarcoma was the most common malignant soft tissue tumour in the present study (28.20%) followed by Liposarcoma and Synovial sarcoma (17.95%). This is in agreement with studies conducted by Kransdorf et al, Aydin et al, Henry J. Mankin et al, Mirza Asif Baig and Krishnakanth et al where Undifferentiated pleomorphic sarcoma was the most common malignant tumour[8,12-14]. Undifferentiated pleomorphic sarcomas were more common in the sixth decade with male to female ratio of 1.8:1 and the site most commonly involved was thigh. These results are comparable with studies by Henry J Mankin, Kransdorf MJ and Sharan Weiss [8,13,15]. Liposarcomas were more common in the sixth decade with male to female ratio of 2.5:1and the site most commonly involved was retroperitoneum. These are in agreement with studies conducted by Geeta Dev et al [16], Kransdorf MJ et al and Mirza Asif Baig.

Soft tissue sarcomas were graded by FNCLCC grading system as proposed by Trojani et al[17]. Most of the sarcomas were grade 3 (42%) followed by grade 2 (37%) and grade 1 (21%). This is comparable with studies by Hiroshi Hashimoto et al and Aydin et al [12,18]. Ki67 cut-off value was in the range of 10% (Choong et al) to 40% (Levine et al) for sarcomas[19,20]. Ki-67 proliferative index was defined as the percentage of tumor cells showing nuclear positivity with a reference cutoff value of 20–40%.

Ki-67 immunoquantitation revealed the following:

1. Grade 1 sarcoma shows low Ki-67 index (Score 1; 1-25%)
2. Grade 2 sarcomas show both low and high Ki-67 index. (Scores 2 and 3; 26-50% and >50%)
3. Grade 3 sarcomas show high Ki-67 index. (Score 3; >50%)

Heslin et al emphasized the importance of Ki-67 marker as an independent prognostic factor to determine the risk of distant metastasis and tumour related mortality[21]. High Ki-67 proliferative index can be useful in the selection of high-risk sarcomas for systemic adjuvant chemotherapy or radiotherapy to provide metastasis free survival and low Ki-67 index can be used to avoid overtreatment and aggressive side effects of the adjuvant therapy. Spearman's Rho and Pearman's correlation coefficients were calculated. p value derived was 0.005 ($p<0.05$) and hence the correlation between FNLCC histologic grade and Ki67 index is strong and statistically significant. These results are comparable with studies by Sahin et al, Aydin et al and Sumiti Gupta et al[12,22,23].

CONCLUSION:

Soft tissue tumours are highly heterogenous group of tumours with diagnostic and therapeutic challenge. They are classified by WHO as benign, intermediate and malignant tumours based on their behavior. Assessment of morphological histologic grade is essential because of its usefulness in predicting the prognosis of soft tissue sarcomas. Due to advancement in molecular studies, immunohistochemical expression of Ki-67 in sarcomas can be easily used to assess the cellular proliferation rate better than the mitotic score used in the FNLCC grading system. Ki-67 can be effectively used as an independent prognostic marker to assess the risk of distant metastasis and tumour related mortality. Based on Ki-67 labelling index, patients with high-risk primary soft tissue sarcomas can be given adjuvant chemotherapy or radiotherapy for metastasis free survival in tertiary care centers.

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