ROLE OF HISTOPATHOLOGY IN DIAGNOSIS OF SOFT TISSUE TUMORS AT TERTIARY CARE CENTER

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ARTICLE INFO

Received : 15 February, 2022

Accepted : 19 July, 2022

Published : 15 November, 2022

ORA 304

DOI: https://doi.org/10.3126/bjhs.v7i2.49294

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Citation

Role of Histopathology in Diagnosis of Soft Tissue Tumors at Tertiary Care Center. Nikita Gautam, Ramesh Makaju, Rachana Dhakal, Dipika Basnet, Binita Lama. BJHS 2022;7(2)18. 1758-1764.

ABSTRACT

Introduction

Soft tissue tumors (STTs) are a diverse group of neoplasms. It varies from the most common benign tumors to some self-limited lesions and rare malignant soft tissue tumors. Because of the overlap in their clinical and radiological characteristics, histopathology is crucial in determining their diagnosis.

Objectives

To study the relative frequencies of types of soft tissue tumors (benign, intermediate and malignant) as well as their histological pattern in relation to age, gender and site of distribution.

Methodology

This was a retrospective study conducted over a period of three years from January 2018 to December 2020 in the Department of Pathology, Dhulikhel Hospital, Kavre Nepal. This study included STTs of all the anatomical sites excluding STTs of the female reproductive system. The tumors were classified as benign, intermediate, or malignant using the WHO 2013 classification of soft tissue and bone tumors. The sarcomas were further graded into grades 1, 2, and 3 using the FNCLCC (French Fédération Nationale des Centres de LutteContre le Cancer) grading system. Immunohistochemistry (IHC) and special staining procedures were also performed as and when required.

Result

A total of 198 STTs were studied, of which benign cases were 191 (96.45%), intermediate 03 (1.52%) and malignant 04 (2.03%) in number. The most common type of STTs was vascular tumors 77(38.89%) followed by adipocytic tumors 52(26.26%) and nerve sheath tumors 13(6.56%). STTs were most common in the third decade of life, with the head and neck region being the commonest site. All four malignant tumors were categorized using the FNCLCC grading system. There were three cases of Grade 2 sarcoma and one case of Grade 3 sarcoma.

Conclusion

The most common benign tumors were vascular tumors followed by adipocytic tumors and nerve sheath tumors. STTs were most common in the third decade of life. Benign tumors were more common than malignant tumors. In comparison to malignant tumors, benign tumors were found at a younger age group. STTs were found mainly in the head and neck region followed by upper and lower limbs. Despite the fact that molecular diagnostics is gaining popularity in the field of soft tissue tumors, histopathology still remains the gold standard.

KEYWORDS

Benign, FNCLCC grading, Histopathology, Malignant, Soft Tissue Tumors, Vascular.

INTRODUCTION

Soft tissue tumors (STT) are typically characterized as mesenchymal proliferations that develop in the extra-skeletal non-epithelial tissue of the body, excluding the viscera, meninges, and lymphoreticular system.[1] Soft tissue tumor comprise for about 1% of all adult malignancies and 15% of pediatric malignancies.[2] Although the etiology of STTs is still unclear, they have been linked to irradiation, heat burns, chemicals, trauma, viruses, genetic factors, and immunosuppression. STTs are classified into several types based on their cells of origin, including adipocytic, fibroblastic, fibrohistiocytic like, vascular, pericytic, skeletal muscle, smooth muscle, chondro-osseous, gastrointestinal stromal tumors (GIST), and nerve sheath lesions.[3]

STTs have a wide range of morphological and histological differences that can be detected under microscopic examination.[4] There is a relationship between the type and site of tumors along with the patient'ssymptoms, age and gender. STTs can develop at any age and at almost any anatomical site. However, the histologic distribution of these tumors has been found to be rather specific for a particular age group and anatomical location.[5] The majority of benign soft tissue tumors are superficial and have a diameter of less than 5 cm.[6] Both benign and malignant STTs, typically manifest as a painless mass. A biopsy is required when a patient with no history of trauma presents with a swelling or when the swelling persists after 6 weeks following local trauma.[5]

Soft tissue tumors present a challenge not only to pathologists but also to treating surgeons due to their diverse biological behavior, that varies from benign self-limited lesions to highly aggressive malignant lesions with a significant risk of metastasis and mortality.[3,4] Hence, histopathological diagnosis with negative margins is critical for reducing the chance of recurrence, assisting in improved patient treatment, and predicting the prognosis of the tumor.[7] Thus, the purpose of this study was to assess the distribution of STTs by age, gender, and anatomical site as well as to determine the histopathological type, in order to better understand the various types of soft tissue tumors.

METHODOLOGY

This three-year retrospective study was conducted in the Department of Pathology at Dhulikhel Hospital - Kathmandu University Hospital (DH-KUH) from January 2018 to December 2020. The Institutional Review Committee (IRC no: 62/2021) granted the ethical clearance certificate. This study included STTs of all the anatomical sites excluding STTs of the female reproductive system. A total of 198 specimens in the department of pathology were studied. Relevant baseline data such as age, gender, clinical diagnosis, tumor site, histologic types and tumor grade were obtained from the histopathological records. The tumors were classified using the WHO 2013 classification of tumors of soft tissue and bone as benign, intermediate and malignant.[8] The sarcomas were further graded according to FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) grading system into grades 1, 2 and 3 respectively based on degree of differentiation, mitotic count per high power field and amount of necrosis.[8] Immunohistochemistry (IHC) and special staining procedure were also performed as and when required. The frequencies of benign, intermediate, and malignant lesions were then recorded. The collected data was entered into Microsoft Excel, and descriptive data analysis was carried out using Statistical Package for Social Sciences (SPSS) 20.0 software. The findings were presented as frequencies and percentages.

RESULTS

A total of 198 soft tissue tumors were studied of which benign cases were 191 (96.45%), intermediate 03 (1.52%) and malignant 04 (2.03%) (Figure No.1)

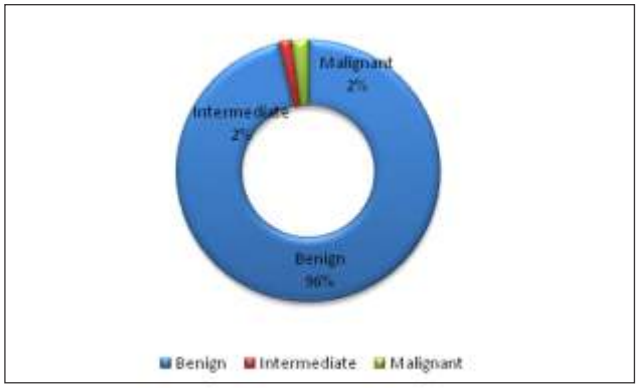

Figure 1: Grades of soft tissue tumors

Overall, the ratio of benign to malignant STTs was 47.7:1.Male to female ratios in benign, intermediate and malignant tumors was 1.05:1, 2:1 and 3:1 respectively with an overall ratio of 1.08:1. (Table No. 1)

Table 1. Grades of soft tissue tumors in males and females

Grades	Male	%	Female	%	Total	%
Benign	98	95.14	93	97.9	191	96.45
Intermediate	02	1.94	01	1.05	03	1.52
Malignant	03	2.92	01	1.05	04	2.03
Total	103	100	95	100	198	100.00

Benign lesions were found in 98 (95.14%)males and 93 (97.9%) females. Malignant lesions were found in 03(2.92%) males and 01(1.05%) females. The occurrence of these tumors ranged from 1 to 75 years of age with a mean age of 36.94 SD ±17.20years. Soft tissue tumors were predominant in the third decade of life 45 (22.73%). (Table No.2)

Table 2: Age and sex distribution of soft tissue tumors

Age(years)	Male	Female	Total	%
1-10	4	5	9	4.54
11-20	16	10	26	13.13
21-30	23	22	45	22.73
31-40	21	22	43	21.72
41-50	17	14	31	15.66
51-60	10	13	23	11.62
61-70	9	7	16	8.08
71-80	3	2	5	2.52
Total	**103**	**95**	**198**	**100.00**

Table 3: Site of soft tissue tumors

Site	Benign n%	Intermediate n%	Malignant n%	No%
Head and Neck	54(27.27)	0(0%)	0(0%)	54(27.27)
Upper limb	49(24.74)	0(0%)	1(0.5)	50(25.25)
Lower limb	36(18.18)	3(1.52)	1(0.5)	40(20.20)
Trunk	31(15.65)	0(0%)	2(1.01)	33(16.67)
Back	21(10.61)	0(0%)	0(0%)	21(10.61)
Total	191(96.45%)	3(1.52%)	4(2.03%)	198(100)

The commonest site of STTs were head and neck region 54(27.27%) that included all benign tumors followed by upper limb 50(25.25%) that included benign and malignant tumors and lower limb 40(20.20%) that included benign, intermediate and malignant tumors. (Table No.3)

In our study vascular tumors 77(38.89%) were the most common type of all STTs that was mostly found in the head and neck region. Among the vascular tumors, capillary hemangiomas 35(45.45%) were the commonest type occurring predominantly in males 21 (60%). The adipocytic tumor 52(26.26%) was the second most common type of all STTs. This was mostly present in the upper limbs 15(28.84%). Among adipocytic tumors, lipomas 50(96.1%) was the most common type seen in the majority of the females 27(54.0%). The third most common type of STTs were nerve sheath tumors 22 (11.11%). Among these, schwannomas 13(59.09%) was the most common type and predominant in females 8 (61.53%).

Out of 20 (10.10%) cases of so-called fibrohistiocytic tumors, benign fibrous histiocytoma/dermatofibroma was the most common type 13(65%). All of the fibro histiocytic tumors were benign, with the exception of a giant cell tumor of soft tissue that belonged to the intermediate category.

Fibroma of the tendon sheath 5(50%) was the most common STTs among the fibroblastic/myofibroblastic tumor 10(5.05%). All were benign except solitary fibrous tumor and Dermatofibrosarcoma protuberans, which were of intermediate category with 1(10%) case each. Glomus tumor 4 (100%) was the only perivascular/pericytic tumor in our study while synovial sarcoma 2 (66.67%) was the common tumor of unknown differentiation. In this study, 7 cases of cutaneous leiomyoma (3.53%), 2 cases of benign gastrointestinal stromal tumors (1.01%), and 1 case of extra skeletal osteosarcoma (0.5%) were also diagnosed. (Table No 4,5)

Out of 198 cases, all four malignant tumors were graded using the FNCLCC grading system based on the degree of differentiation, mitotic count per high power field and amount of necrosis. It included three cases of Grade 2 (Score 5) sarcomas, with one case each of alveolar soft part sarcoma, synovial sarcoma and extra skeletal osteosarcoma. Similarly, one case of synovial sarcoma was graded as Grade 3 (Score 6). In our study, immunohistochemistry and special stain findings correlated well with the histopathological findings. Synovial sarcomas were positive for TLE-1, CK, EMA, and CD-99 on immunohistochemistry. Alveolar soft part sarcoma was diagnosed on the basis of special stain (Periodic Acid Schiff Stain; positive for intracellular crystalline material). However, immunohistochemistry and special stain was not performed for extra skeletal osteosarcoma due to financial constraint of the patient.

Table 4: Classification of Soft tissue tumors based on histological type and grading (WHO 2013)

Types of soft tissue tumor	Benign n/%	Intermediate n/%	Malignant n/%	Total
Adipocytic (n=52;26.26%)				
Lipoma	50(25.25)	0(0%)	0(0%)	50(25.25)
Angiolipoma	2(1.01)	0(0%)	0(0%)	2(1.01)
Nerve sheath (n=22;11.11%)				
Schwannoma	13(6.56)	0(0%)	0(0%)	13(6.56)
Neurofibroma	8(4.04)	0(0%)	0(0%)	8(4.04)
Granular cell tumor	1(0.5)	0(0%)	0(0%)	1(0.5)
Vascular (n=77; 38.89%)				
Pyogenic granuloma	23(11.61)	0(0%)	0(0%)	23(11.61)
Capillary hemangioma	35(17.67)	0(0%)	0(0%)	35(17.67)
Cavernous hemangioma	13(6.56)	0(0%)	0(0%)	13(6.56)
Lymphangioma	6(3.03)	0(0%)	0(0%)	6(3.03)
Fibroblastic/Myofibroblastic (n=10;5.06%)				
Fibroma of Tendon sheath	5(2.52)	0(0%)	0(0%)	5(2.52)
Nodular fasciitis	3(1.51)	0(0%)	0(0%)	3(1.51)
Dermatofibrosarcoma protuberans	0(0%)	1(0.5)	0(0%)	1(0.5)
Solitary fibrous tumor	0(0%)	1(0.5)	0(0%)	1(0.5)

Tumor of uncertain differentiation (n=3;1.52%)				
Alveolar soft part sarcoma	0(0%)	0(0%)	1(0.5)	1(0.5)
Synovial sarcoma	0(0%)	0(0%)	2(1.01)	2(1.01)
Pericytic/Perivascular (n=4;2.02%)				
Glomus tumor	4(2.02)	0(0%)	0(0%)	4(2.02)
Smooth muscles (n=7;3.53%)				
Cutaneous leiomyoma	7(3.53)	0(0%)	0(0%)	7(3.53)
Chondro-osseous (n=1;0.50%)				
Extra skeletal Osteosarcoma	0(0%)	0(0%)	1(0.5)	1(0.5)
So called Fibrohistiocytic tumor (n=20;10.10%)				
Benign Fibrous Histiocytoma/Dermatofibroma	13(6.56)	0(0%)	0(0%)	13(6.56)
Localized Tenosynovial giant cell tumor	6(3.03)	0(0%)	0(0%)	6(3.03)
Giant cell tumor of soft tissue	0(0%)	1(0.5)	0(0%)	1(0.5)
Gastrointestinal stromal tumors (n= 2;1.01%)				
Benign gastrointestinal stromal tumors	2(1.01)	0(0%)	0(0%)	2(1.01)
Total	**191(96.45%)**	**3(1.52%)**	**4(2.03%)**	**198**

Table 5: Tumors according to histological type and gender

Types of tumors	Male	Female	Total	%
Adipocytic (n=52)				
Lipoma	23(11.61)	27(13.64)	50	25.25
Angiolipoma	1(0.5)	1(0.5)	2	1.01
Nerve sheath (n=22)				
Schwannoma	5(2.52)	8(4.04)	13	6.56
Neurofibroma	5(2.52)	3(1.51)	8	4.04
Granular cell tumor	0	1(0.5)	1	0.5
Vascular (n=77)				
Pyogenic granuloma	10(5.05)	13(6.56)	23	11.61
Capillary hemangioma	21(10.61)	14(7.07)	35	17.67
Cavernous hemangioma	8(4.04)	5(2.52)	13	6.56
Lymphangioma	3(1.51)	3(1.51)	6	3.03
Fibroblastic/Myofibroblastic (n=10)				
Fibroma of Tendon sheath	4(2.02)	1(0.5)	5	2.52
Nodular fasciitis	1(0.5)	2(1.01)	3	1.51
Dermatofibrosarcoma protuberans	0	1(0.5)	1	0.5
Solitary fibrous tumor	1(0.5)	0	1	0.5

Tumor of uncertain differentiation (n=3)				
Alveolar soft part sarcoma	1(0.5)	0	1	0.5
Synovial sarcoma	1(0.5)	1(0.5)	2	1.01
Pericytic/Perivascular (n=4)				
Glomus tumor	2(1.01)	2(1.01)	4	2.02
Smooth muscles (n=7)				
Cutaneous leiomyoma	3(1.51)	4(2.02)	7	3.53
Chondro-osseous (n=1)				
Extra skeletal Osteosarcoma	1(0.5)	0	1	0.5
So called Fibrohistiocytic tumor (n=20)				
Benign Fibrous Histiocytoma/Dermatofibroma	6(3.03)	7(3.53)	13	6.56
Localized Tenosynovial giant cell tumor	5(2.52)	1(0.5)	6	3.03
Giant cell tumor of soft tissue	1(0.5)	0	1	0.5
Gastrointestinal stromal tumors (n=2)				
Benign gastrointestinal stromal tumors	1(0.5)	1(0.5)	2	1.01

DISCUSSION

Soft tissue tumors have long attracted the interest of clinicians and pathologists. This heterogeneous category includes a wide range of tumors with close histological similarities with few differences that can be identified only by accurate and meticulous microscopic examination. A total of 1343 specimens were received in the department of pathology during the study period of which 198 specimens (14.72%) of STTs were studied as per inclusion criteria.

Overall, benign soft tissue tumors (96.45%) were more common than malignant tumors (2.03%) which was similar to a study.[7] However, estimating the relative frequency of benign and malignant soft tissue tumors is difficult since many benign tumors are asymptomatic and are generally not reported to clinicians. The higher frequency of benign lesions in our study could be due to the fact that this was a single-center study. On the basis of grading of STTs, 96.45% were benign, (1.52%) were intermediate grade and (2.03%) were malignant. This finding is comparable to a study in which the incidence of these tumors was (95.75 %), (1.70 %), and (2.55 %) respectively.[7]

In our study the STTs was more common in males (52.02%) than females (48.0%) with a male to female ratio of 1.08:1. Vahini G.et al found these tumors in (62.8%) of males and (37.2%) in females with a male: female ratio of 1.69:1.[9] Baste B.D. et al found these tumors in (64.3%) of males and (35.7%) of females with a male: female ratio of 1.8:1.[5] Damani et al found these tumors in (62.13%) of males and (37.87%) of females with the male: female ratio of 1.64:1.[7] These findings are comparable with our study results. Overall benign STTs were mainly seen in the third decade of life (22.73 %) in our study. Other studies have shown almost similar results of (22%) and (20.9%) respectively.[10,11] The frequency of malignant STTs was low (2.02%) in our study. It was found in the second to sixth decades of life. However, previous studies have reported malignant STTs to be more common in the sixth decade of life.[10,12] This disparity could be due to a lower number of malignant cases in our study.

The most common site of occurrence of STTs in our study was the head and neck region (27.27%) that constituted all benign tumors followed by upper limb (25.25%) and lower limb (20.20%). Similar findings were observed in other studies.[7,12] Among the malignant cases 2 cases were seen in trunk and 1 case each in upper and lower limbs respectively. The lower extremities were the most common site for malignant STTs according to few studies.[11,12]

Vascular tumors (38.89 %) were the most common type of all benign STTs followed by adipocytic tumors (26.26%). This finding is consistent with the findings of Igho et al.[1] Adipocytic tumor was the most common soft tissue tumor according to a study.[10] In the other hand leiomyoma was the commonest tumor of soft tissue according to other studies.[4,5,7] Among vascular soft tissue tumors, capillary hemangioma (45.5%) was the commonest vascular tumor according to a study.[11] Soft tissue sarcomas accounted for less than 1% of all malignant tumors. Due to the rarity of these tumors, there is a paucity of literature on soft tissue sarcomas in developing countries.[10]

In our study the overall incidence of malignant soft tumors was low (2.02%). The most common type of malignant tumors was synovial sarcoma (1.01%) and alveolar soft part sarcoma (0.50%) (Fig.1, Fig.2). These tumors were found in the trunk and extremities. On grading of the malignant tumors using the FNCLCC grading system there was 3 cases of Grade 2(Score 5) sarcomas that included 1 case each of alveolar soft part sarcoma, synovial sarcoma and extra skeletal osteosarcoma. Similarly, one case of synovial sarcoma was included in Grade 3 (Score 6) on the basis of degree of differentiation, mitotic count per high power field and amount of necrosis. This finding is in contrast to a study undertaken by Singh HP et al, in which 70 (25.9%) of 270 cases were malignant. There were 27 Grade 3 tumors and

24 Grade 2 tumors among the 54 tumors that were graded. In rest of the cases the tissue was scant and there was no prognostic significance of grading as in MPNST and angiosarcoma.[10]

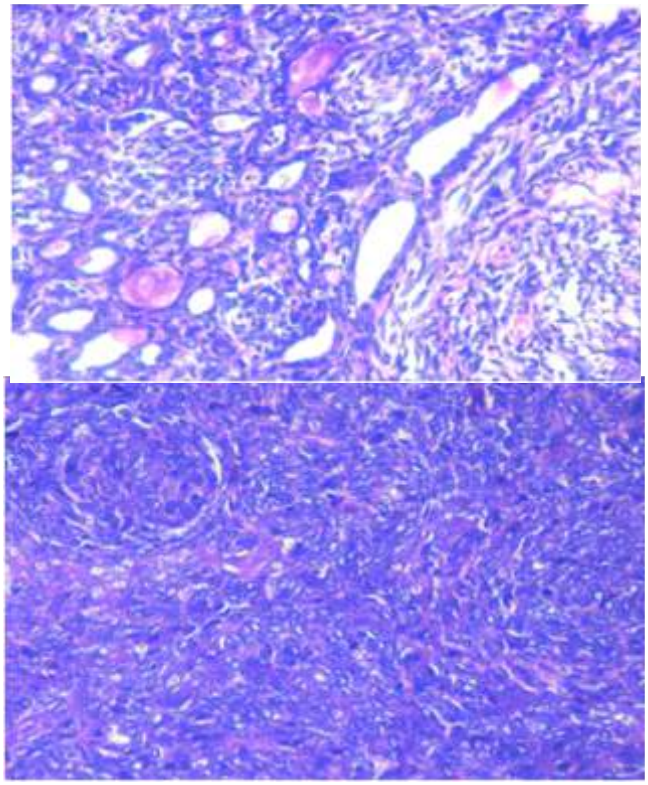

Figure 1: Synovial sarcoma: It shows a biphasic tumor with epithelial and spindle cell component.

A) Epithelial component is arranged in solid nests, trabeculae, some forming glandular pattern. (H&E, 40X).
B) Spindle cells are arranged in fascicles with ovoid nucleus, inconspicuous nucleoli, coarse chromatin and scant cytoplasm. (H&E, 40X).

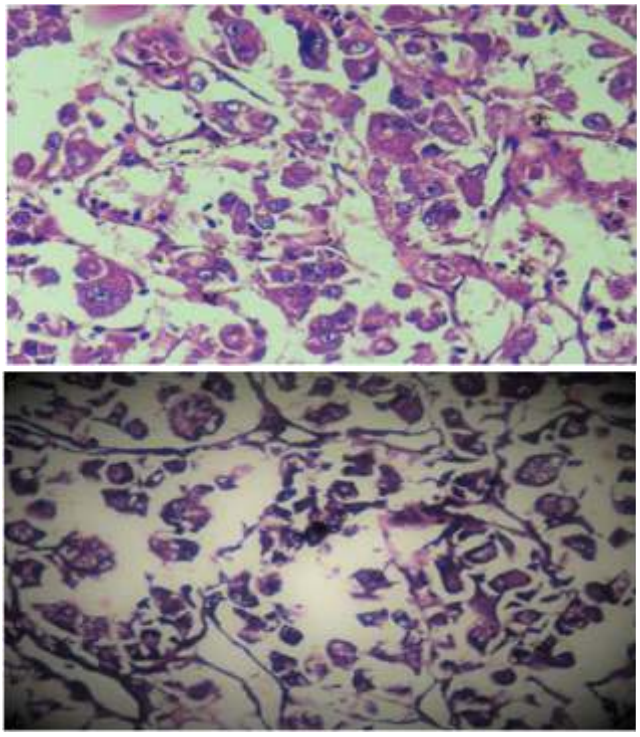

Figure 2: A. Alveolar soft part sarcoma: Tumor cells are arranged in nests and pseudo alveolar pattern, separated by fibrous stroma. Individual cells have large polygonal cells, vesicular nuclei, prominent nucleoli and abundant eosinophilic granular cytoplasm, some shows vacuolation. (H&E, 40X).

B. PAS positive intracellular rod-shaped crystalline material also seen. (H&E, 40X).

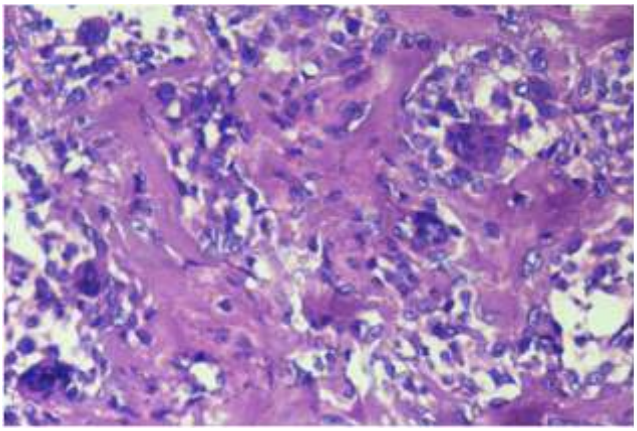

Figure 3 : Tenosynovial giant cell tumor: Composed of numerous mononuclear cells admixed with numerous multinucleated giant cells scattered throughout the lesion. (H&E, 40X).

On grading of the malignant tumors using the FNCLCC grading system there was 3 cases of Grade 2(Score 5) sarcomas that included 1 case each of alveolar soft part sarcoma, synovial sarcoma and extra skeletal osteosarcoma. Similarly, one case of synovial sarcoma was included in Grade 3 (Score 6) on the basis of degree of differentiation, mitotic count per high power field and amount of necrosis. This finding is in contrast to a study undertaken by Singh HP et al, in which 70 (25.9%) of 270 cases were malignant. There were 27 Grade 3 tumors and 24 Grade 2 tumors among the 54 tumors that were graded. In rest of the cases the tissue was scant and there was no prognostic significance of grading as in MPNST and angiosarcoma.[10]

Thus, it is concluded that STTs include a diverse group of tumors with limited studies being conducted using the FNCLCC grading system. The FNCLCC grading system aids in determining the prognosis of malignant tumors, while IHC helps in the diagnosis of cases with histopathological features that are similar to carcinomas and sarcomas.

CONCLUSION

The current study provides a reasonable understanding of the frequency, grade, and histological diagnosis of soft tissue tumors. STTs were more common in males than in females. The majority of those affected were between the ages of 21 to 30 years. Overall benign soft tissue tumors were the most common tumor and vascular tumors were the commonest type. Among all types of vascular tumors, capillary hemangiomas were the most common.

STTs were more frequently observed in the head and neck region. Despite the development of special stains, immunohistochemistry, in situ hybridization (ISH), and cytogenetic approaches, histopathological examination continues to be the gold standard for diagnosing soft tissue tumors.

RECOMMENDATION

As adjunct to histopathological examination, immunohistochemistry (IHC) provides a practical approach particularly to differentiate between benign, intermediate and malignant soft tissue tumors and also to diagnose and differentiate malignant tumors of similar histomorphological picture.

LIMITATIONS OF THE STUDY

This study was conducted in a single center. Therefore, the current study cannot reflect the actual incidence of soft tissue tumors. As a result, these findings cannot be generalized at the national level. Immunohistochemistry, in situ hybridization (ISH), and cytogenetic techniques are all reliable and widely used diagnostic tools. However, in few cases of soft tissue tumors, there exists a complexity in patterns of expression of many antigens, hence a single antibody does not help. So, the use of panels of antibodies becomes necessary but their cost is the major drawback.

ACKNOWLEDGEMENTS

We are thankful to all the staffs of the Department of Pathology of Dhulikhel Hospital, for their assistance and active participation in our research.

CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURE

None

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