Soft Tissue Sarcomas: Pattern Diagnosis or Entity?

Pages with reference to book, From 272 To 275

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Abstract

Soft tissue sarcomas (STS) are a diverse and heterogeneous group of tumours The sub-classification of these tumours is of importance for both prognosis and treatment. Classically, sub- categorization is based purely on histomorphological grounds, but as new techniques evolve, a more, conclusive and accurate diagnosis can be made. This study describes the prevalence of soft tissue sarcomas in adults diagnosed at The Aga Khan University Hospital (AKUH) and the impact of immunohistochemistry(IHC) on the precise sub-categorization of these tumours. The study included 364 adults (age 16+) who were diagnosed as soft tissue sarcoma in the past six years (May 1991 - July 1997) at the Histopathology lab of the AKUH. Where indicated, tu.mours were stained with a panel of antibodies using the PAP technique. Of these, 237(65%) were male and 127 (35%) were female. The median age at which all sarcomas were diagnosed was 39,5 years. The most common site was the lower extremity (29%). The most frequently diagnosed sarcoma was leiom yosarcoma (13%), followed by malignant nerve sheath tumour (12%), rhabdomyosarcoma (10%) and liposarcoma (10%). Cases were further analyzed by dividing them into two groups, each group comprised of all sarcomas diagnosed during the specified period. In the period 1991 - 1994, only 16% of cases were further analyzed usig IHC, while in the period 1995-1997, IHC was performed on 59% of cases. In the 1991-1994 group, a conclusive diagnosis was made in 57% of the cases and in the 1995-1997 group in 78%. A Chi-square test was performed, which proved that these results were statistically significant. Soft tissue sarcoma is one of the key areas in surgical pathology where immunohistochemistry plays an important role in both precise diagnosis and sub-categorization (JPMA 48:272, 1998).

Introduction

Soft tissue tumours are mesenchymal proliferations that arise in extraskeletal, non-epithelial tissue of the body, exclusive of the viscera, glia and reticuloendotheiuin[1]. Soft tissue sarcomas are malignant tumours capable of local recurrence and distant metastases. Some tumours such as dermatofibrosarcoma protuberans rarely metastasize, while others such as malignant fibrous histiocytoma do so more frequently. Thus the tenn sarcoma alone is insufficient to classify them and they must be sub-categorized according to histomorphology and line of differentiation. This is important forboth prognosis as well as for treatment.

The description of a soft tissue neoplasm as being round cell, spindle cell or pleomorphic sarcoma, that is based on pattern, is not adequate to understand the behaviour of the tumour[1]. Thus recent classification is based on the line and degree of differentiation. Tumours that are well differentiated can be diagnosed on histomorphology alone. However, some tumours are poorly differentiated and H&E examination is an inadequate means of providing a confirmatory diagnosis. For instance, a tumour with spindle shaped cells could be fibrosarcoma or monophasic synovial sarcoma. Hemangiopericytoma like pattern may be seen focally in several different sarcomas[2], such as synovial sarcoma[3]. In a pleomorphic sarcoma, it may be impossible to sub- categorize the tumour purely on histomorphological grounds. Today, new techniques like immunohistochemistry (IHC), electron microscopy and cytogenetic analysis have evolved, which have increased diagnostic accuracy of soft tissue sarcoma (STS). IHC for tissue specific markers has proved of great value and is being increasingly used to accurately classify these neoplasms.

Many studies have been performed in the West, however, relatively few have been carried out in Asia and particularly Pakistan. The risk factors and demographics of ourpopulation are different which may result ma different age of the population at risk. Therefore, this study describes the prevalence of soft tissue sarcoma and its subtypes, in a hospital-based sample and characterizes them according to age, sex and anatomic location. The second purpose of this study is to look objectively whether the judicious use of immunohistochemistiy increases the number of cases in whichaconclusive diagnosis can be made.

Material and Method

Data was collected from the surgical pathology files of The Aga Khan University Hospital. The study included at all adult cases (16 years and above) of soft tissue sarcoma diagnosed during the six year period, May 1991 to July 1997. Cases were then characterized according to their histomorphological subtypes, age, sex and anatomic location of the tumour.

Further analysis was performed by dividing the cases into two groups. The first group contained all cases diagnosed during the period May 1991 to December 1994 and the second group contained all cases diagnosed in the period January 1995 to July 1997. In each group, the number of cases on which immunohistochemistty was performed was noted. In addition, the numbers of confirmed diagnoses were recorded.

The diagnosis was considered confirmed if the report said “features are those of’ or “features are consistent with”. Cases where only a suggestive diagnosis or differential diagnosis was given were not included in the confirmed category. A Chi square test was performed to show whether the results were statistically significant.

Immunohistochemistry was recommended/performed on only those cases where a definitive diagnosis could not be made on purely histomorphological grounds. During the period 1991-1994, IHC was not performed on all recommended cases, as the patient was required to pay an additional fee.However, in the period 1995- 1997, the cost of IHC was included in the initial cost and all recommended cases had immunohistochemistry performed.

Besides routine H&E, histochemical stains such as PAS, Reticulin, Tnchrome etc., were also performed. Where recommended, immunohistochemical analysis was perfonned using peroxidase anti-peroxidase (PAP) technique. The differential diagnosis on routine H&E exaniination was the factor that determined which antibodies would be included in the primary panel. On an average, 3-5 antibodies were included in a standard immunohistochemical battery. The most common antibodies included in the panel were vimentin, desmin, myoglobin, smooth muscle actin, S-100, cytokeratin and neuroectodermal markers. Data of this study was analyzed partly through Epi Info and partly manually.

Results

During the six year period May, 1991 - July, 1997. 364 cases of soft tissue sarcoma in adults (age 16 years and above), were diagnosed at the Histopathology Lab, of The Aga Khan University Hospital (AKUH). Of these, 237 (65.1%) were male and 127 (34.9%) were female, giving a male to female ratio of 1.9:1.

Table I. Distribtuion of sarcomas by age.

Age	No. of cases	Percentage
16-30	120	33.0
31-45	103	28.3
46-60	84	23.1
61 and above	51	14.0
Unknown	6	1.7

Table I describes the distribution of STS in various age groups. The largest percentage, 33.0% (120 cases) of sarcomas was seen in the 16-30 years age group. The median age at diagnosis of sarcoma was 39.5 years, with a range of 16-85.

Table II. Anatomic distribution of soft tissue sarcomas.

Location	No. of cases	Percentage
Head and neck	38	10.4
Thorax	35	9.6
Abdomen	41	11.3
Pelvis	28	7.7
Upper limb	57	15.7
Lower limb	104	28.6
Unknown	61	16.8

Table II describes the anatomic distribution of sarcomas. Most tumours, 104 (28.6%) originated in the soft tissue of the lower limb. The next most common location was the upper limb, followed by the abdomen. Less common sites of the tumour were the head and neck, thorax and pelvis. In a-large number of biopsy specimens, the location of the tumour was not specified.

Sarcomas were then studied on the basis of their histological subtypes as shown in Table III.

Table III. Distribution of hitological entities in 364 cases.

Histomorphological subtype	No. of cases	Percentage
Leiomyosarcoma	46	12.6
Malignant nerve sheath tumor	42	11.5
Rhabdomyosarcoma	38	10.4
Liposarcoma	35	9.6
Synovial sarcoma	32	8.8
Not otherwise specified	30	8.2
Malignant fibrous histiocytoma	25	6.9
Fibrosarcoma	23	6.3
Dermatofibrosarcoma protuberans	22	6.0
Primitive neuro-ectodermal tumor	19	5.2
Extra skeletal Ewing's sarcoma	13	3.6
Extra skeletal chondrosarcoma	13	3.6
Hemangiopericytoma	8	2.2
Non Hodgkin's lymphoma	6	1.7
Epitheloid sarcoma	5	1.4
Kaposi's sarcoma	2	0.8
Hemangioendothelioma	2	0.6
Angiosarcoma	1	0.3
Osteosarcoma	1	0.3
Alveolar soft part sarcoma	1	0.3

Leiomyosarcoma was the mOst frequently diagnosed STS, 46 cases (12.6%) foliwed closely by malignant nerve sheath tumour (MNST) 42 cases (11.5%), rhabdornyosarcoma 38 cases (10.4%), liposarcoma 35 cases (9.6%) and synovial sarcoma 32 cases (8.8%). A large number of sarcomas fell into the "Not otherwise specified" (NOS) category, referring to an undifferentiated or uncharacterizable tumour of mesenchymal origin. Malignant fibrous histiocytorna (MFH!), fibrosarcoma and dermatofibrosarcoma (DP) were also common entities.

The five most common sub-categories were then studied on the basis of age, sex and location.

Table IV. Distribution of the top five sarcomas.

Sarcoma type	M:F ratio	Age Median	range	Most common location (%)
Leiomyosarcoma	1.7:1	44.5	(23-80)	Lower limb 23.9
MNST	2.5:1	36.0	(19-74)	Lower limb 35.7
Rhabdomyosarcoma	2.5:1	25.5	(16-71)	Lower limb 23.7
Liposarcoma	1.7:1	47.0	(23-85)	Lower limb 40.0
Synovial sarcoma	1.1:1	29.0	(16-65)	Lower limb 43.8

Table IV shows this distribution. In each morphological subtype more males were diagnosed with STS than females and the lower limb was the most common site of the tumour. The median age varied greatly with the youngest 25.5 years for rhabdomyosarcoma and the eldest 47 years for liposarcoma.
The second part of the study aimed at seeing the role of immunohistochemistry in the diagnosis and sub-categorization of STS. To fulfill this goal, cases were divided into two groups and compared on the basis of the increase in use of IHC versus an increase in the number of confirmed diagnosis. The first group consisted of all adult cases diagnosed with STS in the period May 1991 to December 1994 and the second group comprised those cases diagnosed between Januaiy 1995 and July 1997. During the first period, immunohistochemistry was a relatively new procedure at the AKUH. When patients were requested to have immunohistochenustry performed, many did not comply due to the additional cost. Therefore, from 1995 onward the cost of IHC was subsidized, a uniform fee was charged to all patients and IHC was performed wherever necessaiy.
In the period 1991 - 1994, 15.8% of cases had IHC analysis perfonned, while in the period 1995 - 1997, 58.5% had IHC. In comparison, the numbers of confinned diagnosis in 1991-1994were57%whiledunngtheperiod 1995-1997, were 78%. A “confirmed diagnosis” was recorded when the report stated “features are those of’ or “features are consistent with”. Cases, which had a differential diagnosis, were not included in the confirmed category.
In order to prove that these results were statistically significant, a Chi-square test with a confidence interval of 95% and a significance level >3.84, was performed (Table V).

Table V. Impact of immunohistochemistry on providing a conclusive diagnosis.

	Conclusive diagnosis	Inconclusive diagnosis	Total
IHC performed	131	17	148
No IHC performed	121	95	216
Total	252	112	364

Chi square test with 95% confidence interval and significant value >3.84
Chi-square value = 43.54

The test compared cases in which immunohistochemistry was performed with those in which only H&E examination was done. The results showed that with the use of immunohistochemistry, there was a significant increase in the number of cases in which a conclusive diagnosis could be made.

Discussion

This study showed that STS occur at a much younger age in our population (39.5 years) as compared to the West (64 years)[4]. The most common subtypes were leiomyosarcoma, MNST, rhabdomyosarcoma, liposarcorna. and synovial sarcoma. Western studies show MPH and liposarcoma to be the two most common STS with a typical incidence in middle aged and elderly[5]. MFH, which typically occurs around 68 years in the West[4], occurred at 55.5 years in this study and was the sixth common subtype. Liposarcoma, the second most common histotype in most Western literature ranked fourth in our study. The median age of diagnosis was 59 years in the West[4] and 47 years in this study.

There are several possible reasons for this difference, including different risk factors etc. One of the main reasons is the fact that the Pakistani popuation has an average life expectancy of 59 years. Much of the population consists of adolescents and young adults. As there are fewer individuals in the older age groups, there are fewer cases of sarcomas that commonly occur in the elderly.

According to Fletcher[6,7], MFH eventually may not be retained as an entity as it is an easy category in which all pleomorphic STS, which show only subtle differentiation, like focal storiform pattern, are placed. With careful histological, IHC and ultrastructural analysis it is possible to identify some degree of differentiation in most of these tumours, such as smooth or skeletal muscle differentiation, allowing them to be recalcified as pleomorphic leiomyosarcoma or rhabdomyosarcoma. The judicious use of IHC in this study may also have contributed to the decreased numbers of MFH in our series.

Pleomorphic rhabdomyosarcoma is most frequently seen in childhood and adolescence[8]. Immunostaining for muscle related antigens like desmin, myoglobin and actin is useful here[9].

Diagnosis of MNST is usually based on demonstrable origin from a nerve, neurofibroma or neurofibromatosis type 1. However, there is little agreement on diagnostic criteria outside this setting. As a result, different studies show varied incidence of MNST. Histological grounds are often inadequate to separate MNST from fibrosarcoma.

However, based on histology specific to MNST (such as nuclear shape, nuclear pallisading, perivascular tumor cell whirling, the presence of heterologous elements) and with the help of special stains, immunohistochemistry and electron microscopy, one can differentiate between MNST,

fibrosarcoma and monophasic synovial sarcoma.

This study showed that an increase in the use of immunohistochemistry has contributed to improve diagnostic accuracy. The inununoenzymatic techniques like immunoperoxidase are very sensitive and easy to interpret with light microsocpy. In cases where the tumour is well differentiated and typical histological features are present, IHC is not required. However, in those tumours that are poorly differentiated, one can only provide a differential diagnosis, IHC is then extremely useful. For instance, PNET, extra skeletal Ewing's sarcoma and solid variant of alveolar rhabdomyosarcoma are all small round cell sarocmas[10]. These tumours are usually indistinguishable with light microscopy. Staining with desmin and muscle specific actin may therefore be useful to distinguish rhabdomy osarcoma from Ewing's and PNET.

Immunohistochemically, PNET should be positive for vimentin, neuron specific enolase and atleast one other "neural" marker[11]. Another diagnostic problem often encountered is the close resemblance of monophasic synovial sarcoma and fibrosarcoma, which could result in misdiagnosis. Synovial sarcoma almost always expresses keratin and epithelial membrane antigen, in addition to vimentin[12] and thus a precise distinction can be made. However, results of IHC must be interpreted with care and knowledgeofpossible aberrantexpressione.g., S-lOO protein, neuron specific enolase and cytokeratin may be detected occasionaly in rhabdomyosarcoma[13]. . Focal cytokeratin reactivity is occasionaly reported in MNST, leiomyosarcoma[14] and MFH, creating diagnostic problems.

Immunohistochemistiy has made a significant contribution to the diagnosis of soft tissue sarcomas. It provides an additional tool by which one can analyze poorly differentiated sarcomas and characterize them. Its specificty, sensitivity, cost effectiveness and applicability to routinely processed material, clearly make it an essential part of diagnostic pathological studies for soft tissue tumours.

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