RESEARCH ARTICLE

ADJUNCTIVE ROLE OF IMMUNOHISTOCHEMISTRY TO TRADITIONAL HISTOMORPHOLOGY IN DIAGNOSIS AND ACCURATE TYPING OF SOFT TISSUE SARCOMA

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ABSTRACT

Background: Soft tissue sarcomas, compared with carcinomas and other neoplasms, are relatively rare and constitute less than 1% of all cancers. Immunohistochemistry (IHC) especially a panel approach is an important adjunct to histopathological morphology and plays an important role in Soft tissue sarcoma diagnosis and accurate typing.

Aims & Objective: Current study is to evaluate the utility of histopathology and immunohistochemistry in soft tissue sarcoma diagnosis and accurate typing.

Material and Methods: Total of 50 cases of soft tissue sarcoma studied from January 2010 to October 2012. All cases were reported using routine (H&E) Hematoxylin- eosin stain and other ancillary techniques including panel approach of immunohistochemistry.

Results: Histomorphology confirmed diagnosis in 22 % cases. In 78 % cases it was contributory to IHC. IHC provide confirmative diagnosis (Single diagnosis) in 45 cases (90%), definitive diagnosis (with two possibilities) in 4 cases (8%) and noncontributory in 1case (2%).

Conclusion: Despite the rapid development of molecular genetic techniques, IHC still remains the most important diagnostic tool in the diagnosis of soft tissue tumours aside from recognition of morphologic features and clinical correlation. One of its major utilities is to correctly identify a tumour as mesenchymal or nonmesenchymal origin and then accurate typing done according to specific cell lineage. IHC is specifically useful in tumours of uncertain cell lineage and primitive round cell tumours. Indeed IHC has brought Brown revolution in sarcoma diagnosis and accurate typing. But important not to forget histopathology which provide the basic platform for the panel approach of IHC.

Key-Words: Soft Tissue Sarcoma; Histomorphology; Immunohistochemistry

Introduction

Soft tissue can be defined as “nonepithelial extraskeletal tissue of the body exclusive of the reticuloendothelial system, glia, and supporting tissue of various parenchymal organs”. It is represented by the voluntary muscles, fat and fibrous tissue, along with the vessels serving these tissues. By convention it also includes the peripheral nervous system because tumours arising from nerves present as soft tissue masses and pose similar problems in differential diagnosis and therapy.[1] Currently, nineteen histological types and over 50 different subtypes of soft tissue sarcoma are being recognized. Soft tissue sarcomas, compared with carcinomas and other neoplasms, are relatively rare and constitute less than 1% of all cancers. Also benign tumours out number malignant soft tissue tumours.[2] This may be because cells in soft tissue, in contrast to tissues that more commonly give rise to malignancies, are not continuously dividing cells.[2] The relative infrequency and sometime subtle presentations make soft tissue sarcomas difficult to detect. This hampers the acquisition of expertise in diagnosis and treatment of these tumours. Therefore, referral to specialized centres is greatly advocated. Careful diagnosis, disease staging and treatment planning by a multidisciplinary team of sarcoma specialists have improved the outcome for STS (Soft tissue sarcoma) patients. There are many techniques available for the diagnosis of malignant soft tissue tumours. Histopathology has been and always will be the cornerstone to tumour diagnosis. Apart from Histopathology other ancillary methods like histochemical stains, immunohistochemistry, ultrastructural studies and recently growing

cytogenetic study are often indispensable for reaching diagnosis. Immunohistochemistry (IHC) has emerged as the most valuable adjunct to Hematoxylin and Eosin (H&E) staining in diagnostic histopathology.[1] No other method during the past fifty years has had such a major impact on histopathology. The first approach consists in ruling out non-mesenchymal tumour, followed by trying to define mesenchymal cell lineage. This approach, achieved with a panel of commonly used antibodies, which helps narrow down the differential to a more manageable level. In addition, there are specific tumour types requiring a more refined set of immunohistochemical antibodies.

To Quote Clive R. Taylor one of the pioneers in the field,[3] "Immunochemistry has elevated histopathology from something resembling an art form to something more closely resembling a science". Indeed IHC has brought a 'Brown Revolution' to histopathology laboratories. Given the bewildering number of STSs and likewise continuously growing list of IHC antibodies used in STSs diagnosis, this study concentrates on Histopathological diagnosis and the applicability of IHC in diagnosing cases clinically suspected to have soft tissue sarcoma.

Materials and Methods

The present study was undertaken to study the significance of Histopathology and IHC for accurate characterization and further subtyping of malignant soft tissue tumours. Age, gender and site wise distribution also evaluated. Total 50 cases were studied, from January 2010 to October 2012 including 5 referred cases with paraffin tissue block from the other centers. All surgical biopsies, specimens and referred cases for review were received at histopathology department for accurate diagnosis, confirmation of malignancy and further subtyping of tumour with the aid of IHC. There were 24 males and 26 females, and their age ranged from 3 years to 80 years with the mean age of 40 years. After histopathological examination, relevant panel of immunohistochemical antibodies was applied using peroxidase anti-peroxidase method. The final diagnosis was achieved after correlating histopathological, immunohistochemical and other findings. Specimens were surgical biopsies like Image guided core needle biopsies, open biopsies & resected specimens. Gross examinations of specimens were done under heads of overall appearance, size, ulceration, fungation, consistency, appearance of cut surface including presence of necrosis, haemorrhage, and other specific findings. Tissue sections were taken from representative location, various level of lesion, from surgical margin, normal tissue & lymph node if identified in received tissue. Specimens are fixed as early as possible by 10% neutral buffered formalin preferably within 1 hour of surgery of the patient. Fixation period of 24 hours for large specimen and minimum 6-8 hours for small and core needle biopsy was followed. After routine paraffin processing, sections were cut and stained by Hematoxylin-eosin method and relevant panel of immunohistochemical antibodies were applied after thorough histopathological analysis. Diagnosis were made according to criteria & grading of malignant soft tissue tumour. One of the sections representatives of malignancy, devoid of necrosis was selected for examining the expression of different markers by IHC. In each staining series a known positive control section was taken. The technique used was based on PAP (peroxidase anti-peroxidase) method. The positive control was examined for the presence of coloured end product at the site of target antigen (DAB chromogen – brown end product). The presence of these colours with appropriate staining pattern was interpreted as a positive staining result, indicating proper performance of kit reagents). Test specimen stained was then examined. Presence of coloured end product in target cells also according to specific pattern of staining for different IHC marker in positive cells should also reveal the correct pattern of staining (membranous, cytoplasmic, nuclear, diffuse, dot-like or perinuclear), such as nuclear staining for S-100, myogenin & membrane staining for cytokeratin.[4] Taken into consideration before labelling positive result and absence of such findings indicate negative result. Only intact cells were examined for presence or absence of staining since necrotic and degenerated cells often stain non-specifically. In present study weak/ moderate/strong staining was considered as positive staining, no staining considered as

negative staining and equivocal staining considered inconclusive. Panel approach of IHC was followed by thorough histopathological examination. After histopathology tumour type depending on morphology like Spindle cell, Round cell, Epithelioid cell, Pleomorphic type, with chondroid or osseus differentiation and undifferentiated type. Proper panel of IHC markers were followed according to guidelines which specifically saved tissue and time both for accurate diagnosis.

Results

There were 24 males and 26 females, and their ages ranged from 3-80 years with the mean age of 40 years. The maximum numbers of cases were in the age group of 41-50 years (28%) while minimum numbers in 0-10 years (6%). Maximum number of cases have intra-abdominal/ retroperi-toneal site which accounted for 17 cases (34%) out of 50 specimens followed by upper & lower extremities in 13 cases (26%), head & neck, chest, back, inguinal region, mediastinal, scrotal and others. Most common diagnosis was that of Spindle cell type, which accounted for 26 of the 50 cases (52%) Followed by Round cell type accounted for 15 of 50 cases (30%), Pleomorphic type 7 cases (14%), Epithelioid sarcoma 1 case (2%). Other typical morphology like well differentiated liposarcoma accounts for 1 case (2%). Most common diagnosis were GIST and Undifferentiated sarcoma not otherwise specified 7 cases (14%) each, followed by Ewings sarcoma /PNET were 6 cases (12%), Synovial sarcoma were 5 cases (10%), 4 cases (8%) of Liposarcoma & Rhabdomyosarcoma each, 3 cases (6%) of Leiomyosarcoma & Fibrohistiocytic sarcoma each, 2 cases (4%) of Dermatofibrosarcoma protuberance & Malignant peripheral nerve sheath tumour each, Other cases like Neuro-blastoma, Extraskeletal Myxoid Chondrosarcoma also identified. Rare tumours like Rhabdoid tumour, Kaposi sarcoma, Atypical ossifying fibromyxoid tumour also diagnosed. Histopathological morphology confirmed the diagnosis in 22 % cases and in rest of 78 % cases it was contributory to IHC in deciding correct panel of antibodies and interpretation of IHC. Immunohistochemical staining confirmed the diagnosis (Single diagnosis) in 45 cases (90%), IHC was contributory to definitive diagnosis (with two possibilities) in 4 cases (8%), and was noncontributory in only 1 case (2%) that was mainly due to inadequate biopsy in which even the primary panel was not possible. Apart from positive control in IHC cases were followed like one case of synovial sarcoma of lung was subjected to cytogenetic and molecular analysis had t (x; 18) and supported diagnosis made on histopathology with help of IHC. This suggest accuracy and reliability of IHC in diagnosis of such crucial lesions.

Table-1: Distribution of Study Cases according to Age

Age (years)	No. of Cases	Percentage
0-10	3	6
11-20	5	10
21-30	5	10
31-40	7	14
41-50	14	28
51-60	8	16
61-70	5	10
71 onwards	3	6
Total	**50**	**100**

Table-2: Distribution of Study Cases on the Basis of Location of Tumour

Sites	No. of Cases	Percentage
Upper & Lower Extremities	13	26
Intra-abdominal / Retroperitoneal	17	34
Head & Neck	2	4
Chest wall, Trunk , Back & axillary	7	14
Lung	3	6
Inguinal	3	6
Uterus and Kidney	2	4
Scrotal	2	4
Mediastinal	1	2
Total	**50**	**100%**

Table-3: Distribution Study according Types of Sarcoma Diagnosed

Types	N	%
Gastrointestinal Stromal Tumour	**7**	14
Synovial sarcoma	5	10
Ewing's sarcoma/PNET	6	12
Liposarcoma	4	8
Rhabdomyosarcoma	4	8
Leiomyosarcoma	3	6
MPNST	2	4
Undifferentiated Sarcoma (most probably MFH)	7	14
DFSP	2	4
Fibrohistiocytic sarcoma	3	6
Kaposi sarcoma	1	2
Rhabdoid Tumour	1	2
Neuroblastoma	1	2
EMC	1	2
Ossifying Fibromyxoid tumour	1	2
Pleuropulmonary blastoma	1	2
Others	1*	2
Total	50	100

* Others includes case was round cell tumour on Histopathology but turned out to be other malignancy by IHC

Table-4: Comparison of Various Studies where IHC Contributed to Diagnosis

Study Group	Total Case	Diagnosis on IHC
Bashyal R et al (2011)[10]	40	36 (90%)
Coindre et al (1986)[8]	144	130 (90.00%)
Vege et al (1994)[12]	145	124 (85.5%)
Ahmed Z et al (2006)[11]	265	249 (93.03%)
Pity I et al (2011)[13]	127	112 (88.2%)
Bianchini et al[14]	43	35(81.4%)
Current Study	50	49 (98.00%)

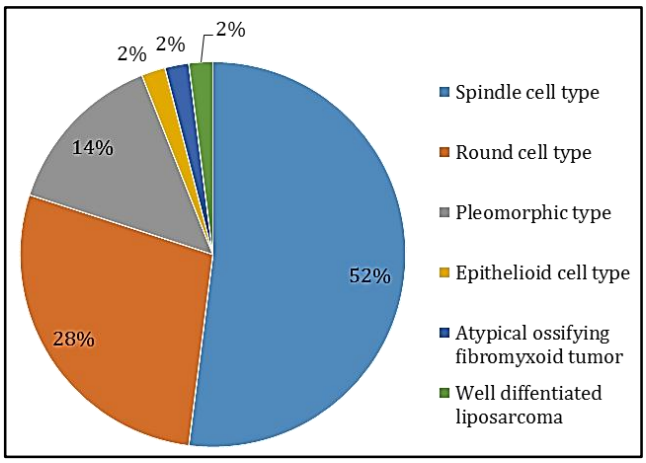

Figure-1: Distribution Study according to Histological (Morphological) Types

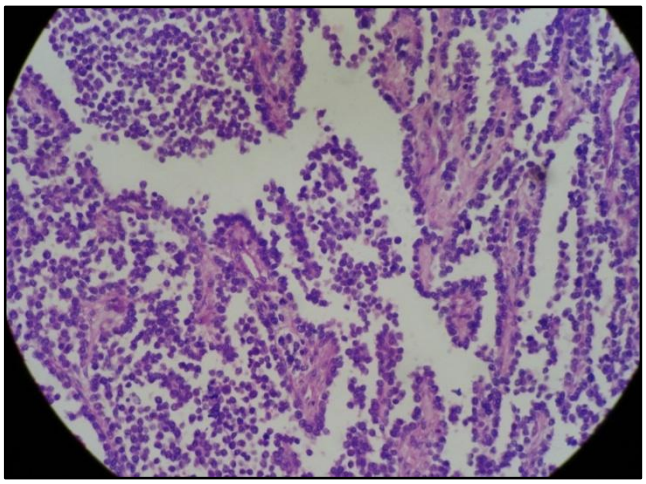

Figure-2: Alveolar Pattern of Malignant Round Cells in Alveolar Rhabdomyosarcoma (H & E X40)

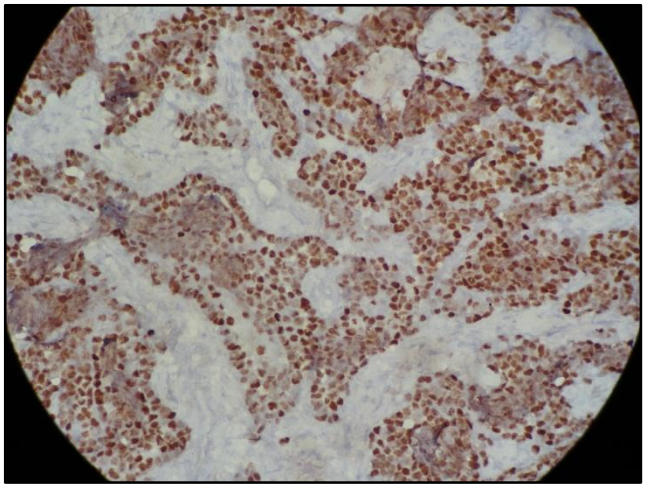

Figure-3: Case of Rhabdomyosarcoma showing Diffuse & strong Myogenin Nuclear Positivity (IHC-DAB X40)

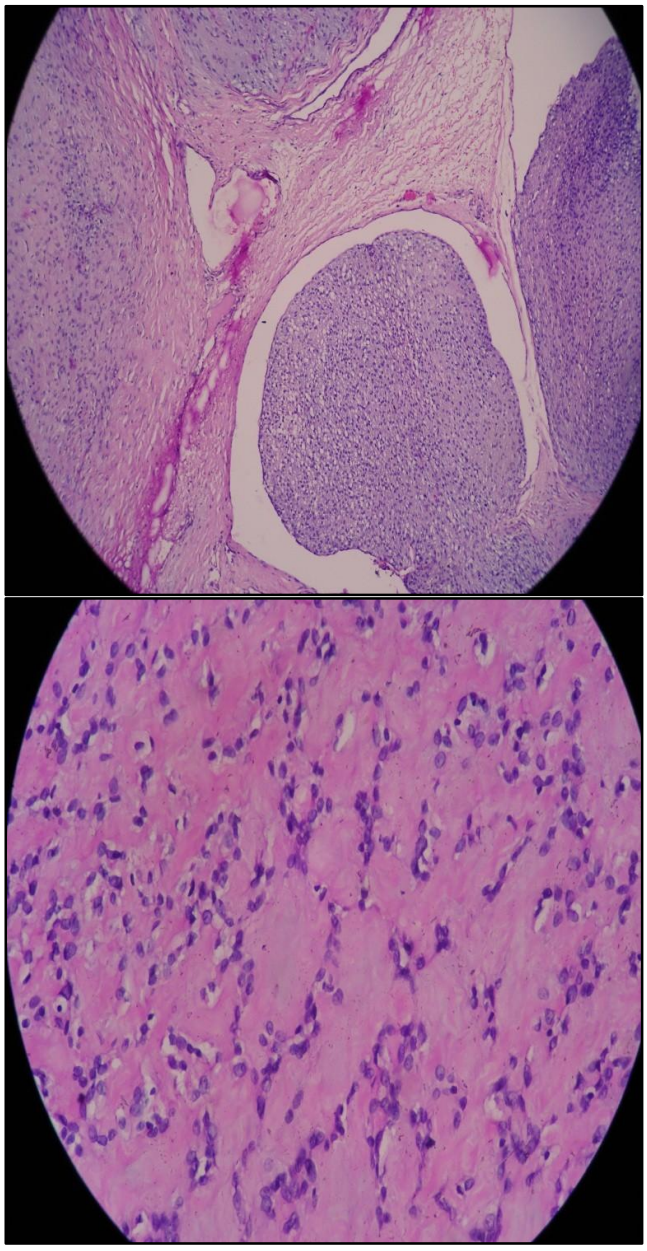

Figure-4: Atypical Ossifying Fibromyxoid Tumour: (A) Cells are arranged nests and lobule (H & E X10) (B) Cells arranged in cords in myxoid matrix (H & E X40)

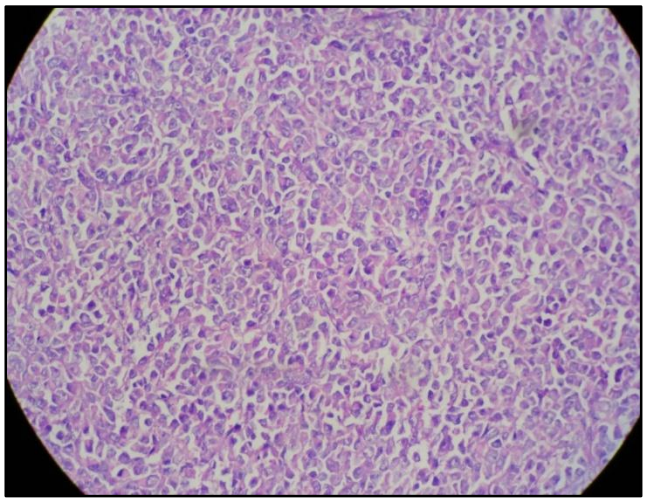

Figure-5: Rhabdoid Tumour: Large Sheets of epithelioid looking cells with abundant eosinophilic cytoplasm. Few cells with para nuclear intra cytoplasmic hyaline inclusions. (H & E X40)

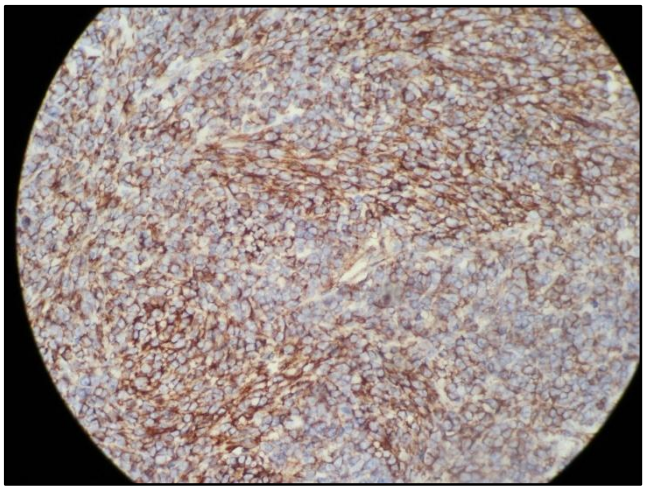

Figure-6: Rhabdoid Tumour with CD99 Positivity (IHC-DAB X40)

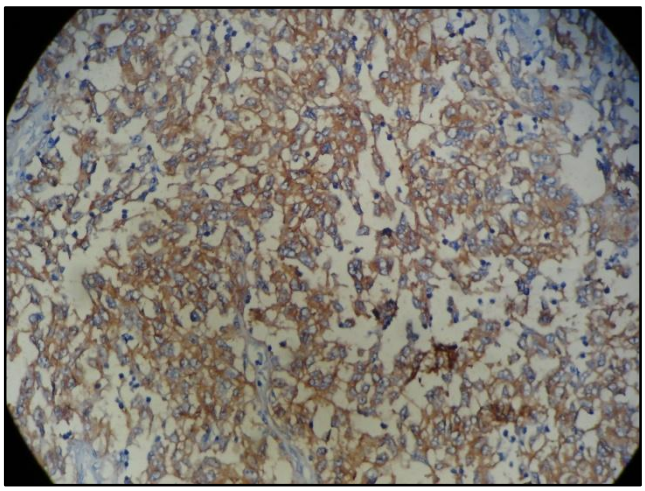

Figure-7: CD117 Strong and Diffuse Positivity in GIST (IHC-DAB X40)

Discussion

The optimal treatment of patients with malignancy depends on establishing accurate diagnosis by using a combination of clinical, radiological, histopathological and other data especially in soft tissue sarcoma. Radiographic diagnosis can be useful, but they cannot accurately predict histology or whether a lesion is benign or malignant. Therefore, all lumps that persist or grow should be biopsied if possible. In broad sense at first we need to establish whether it is mesenchymal or non mesenchymal because treatment, outcome, prognosis and survival differs. Subtypes of various sarcoma also having significance in terms of treatment options, prognosis and survival. In some instances, it is difficult or impossible to make correct diagnosis and subtyping of malignant soft tissue tumours because of varied clinical presentation or atypical histopathological features. With the help of recent advances in technology like IHC, molecular techniques, electron microscopy, it has now become possible in the large majority of cases to accurately subtype malignant soft tissue tumours. The most challenging aspect of diagnostic surgical pathology is determining the histogenesis of malignant soft tissue tumours and accurately subtypes them. Earlier histochemical stains such as mucicarmine, PAS stain etc. were used but these types of histochemical stain lack true specificity in terms of defining particular cell or tumour type.[2] The accuracy of ultrastructural diagnosis is very high by electron microscopy but the main drawbacks are requirement of capital intensive set up, need for fixation in gluteraldehyde, limitation of sample size and of course the high cost. On the other hand Immunohistochemistry has become most important tool that has made possible to diagnose and subtype malignant soft tissue tumours accurately. Its advantages include its remarkable sensitivity and specificity, its applicability to routinely processed, formalin fixed material, and compatibility to most common fixatives. Clinical relevance of immunohistological typing: It is very important to determine whether a neoplasm is epithelial, lymphoid or mesenchymal in origin, as treatment protocols for these three types are radically different. For e.g. Lymphomas are highly sensitive to radiotherapy and chemotherapy and patients survive longer than patients with carcinoma do. Also with the diagnosis of lymphoma, unnecessary radical surgery or other inappropriate forms of therapy may be avoided. The application of a panel of antibodies chosen in accordance with the differential diagnoses considered on histopathological morphology like Spindle cell, Round cell, Epithelioid cell, Pleomorphic type, with chondroid or osseous differentiation and undifferentiated type. Proper panel of IHC markers followed according to guidelines is very useful which specifically saved tissue and time both for correct diagnosis and typing of sarcomas.[5-9] More antibodies are being produced against a range of cellular antigens, but certain limitations exist. In some of cases Immunohistochemical studies do not discriminate between neoplastic and non-neoplastic lesions or between benign and malignant cell (e.g. between nodular fascitis and leiomyosarcoma).[1] These distinctions have to be made by conventional histopathological morphology. Even with larger

panel of antibodies, there remains a paucity of specific antibodies that allow for '100% unequivocal, definitive diagnosis' in every case. So histopathological cytomorphology is must as a primary screening of sarcomas, almost provide final diagnosis in few cases and gold standard in diagnosing sarcomas like for e.g. well differentiated Liposarcoma and is must before proceeding towards IHC panel of antibodies.

In current study the histopathological morphology include most common diagnosis was that of Spindle cell type 26 cases (52%) followed by Round cell type 14 cases (28%), pleomorphic type 7 cases (14%), epithelioid sarcoma, 1 (2%) case of Atypical ossifying fibromyxoid tumour and other typical morphology like liposarcoma accounts for 1 case (2%) each of sarcoma out of 50 studied. Such incidence pattern depends on the age of presentation as round cell tumours are more common in childhood and young age whereas the spindle cell and pleomorphic tumours are common in older age groups.

According to Bashyal R et al (2011)[10] studied 40 cases of round cell tumours of which accurate histological diagnosis was possible with the aid of IHC in more than 89% cases.[10] Ahmed et al (2003)[11] studied 20,000 biopsies of which 157 cases of Malignant spindle cell tumours IHC accurately diagnose 154 cases (98.09%) and 108 cases of Round cell tumours from which IHC accurately diagnose 95 cases (87.96%). So overall IHC was 93.03% accurate in typing the sarcoma.[11] Vege et al (1994)[12] studied 145 consecutive biopsies with the diagnosis of undifferentiated or poorly differentiated tumour in order to classify them into lymphoid, epithelial or mesenchymal in origin. Which included 21 cases of sarcoma. It was possible to arrive at a histogenetic diagnosis on immunostaining in 85.5% of the cases. Pity I et al (2011)[13] reported 127 cases as undifferentiated malignant tumours over a 12 month period. Application of immuno-histochemistry resulted in characterization of 112 (88.2%) cases. In 15 cases (11.8%) immunohisto-chemistry was noncontributory. Sarcoma cases were 17 cases (13.4%) respectively. Coindre et al (1986)[8] observed 144 undifferentiated cancers, of which 130 tumours (90.00%) classified by immunohistochemical study , which comprised 82 non-Hodgkin's lymphomas, 32 carcinomas, 7 melanomas, 7 sarcomas and 2 others. Study included 7 cases out of 144 cases diagnosed as sarcoma. Bianchini et al[14] studied 43 undifferentiated tumours out of which 35 cases (81.4%) cases were accurately diagnosed including majority of soft tissue tumours.

Present study was based on 50 malignant soft tissue tumours. It was possible to arrive at a diagnosis in 49 (98.00%) out of 50 cases studied. So our study is well supported by evidenced above mentioned previous studies showing vital role of IHC in soft tissue sarcoma especially when they are undifferentiated. On evaluation of soft tissue sarcoma by panel approach of IHC. It was apparent that few markers are more specific to particular lesion and very helpful in diagnosis. Like in case of Spindle cell sarcoma especially in retroperitoneal location CD117 is indicating diagnosis of Gastrointestinal Stromal Tumour (GIST) with support of other negative and positive markers and in current study CD117 was positive in all the cases of GIST. Finding was supported by study of Hornick and Fletcher et al. (2002)[15] and other[5] which also showed the same result.

Myogenin is most specific marker for establishing origin from skeletal muscle like Rhabdomyosarcoma. S. Kumar, et al.[16] studied 69 cases of rhabdomyosarcoma all showing strong expression of myogenin. Current study also shows all 4 cases of rhabdomyosarcoma showing strong positivity by myogenin.

CD34 positivity in Spindle cell tumour more favoring diagnosis of Dermatofibrosarcoma protuberans which is helpful in diagnosing DFSP and distinguishing it from other tumours like dermatofibroma, benign fibrous histiocytoma etc.[17]

Diagnosis of Synovial sarcoma requires demonstration of both the epithelial and mesenchymal markers in support with other markers like BCL2 was positive in all cases of synovial sarcoma in current study.

In current study the gender wise distribution shows out of 50 cases, 24 cases (48 %) were male while 26 cases (52 %) were females detected of

having soft tissue sarcoma. The male to female ratio was 0.92: 1. The contrasting result compared to evidence that soft tissue sarcoma are more common in males[1,2,18] may be due to more number of females attending government hospitals than males. Males may be attending private centres more than females. The difference may be due to economic reasons.

Most common site of incidence in current study is intra-abdominal/retroperitoneal site which accounted for 17 cases (34%) followed by upper & lower extremities in 13 cases (26%), head & neck region, chest wall, trunk, back and others rare location like lung, scrotum and mediastinal. Other study also shows majority of sarcomas arises in extremities and intra-abdominal location.[1]

Conclusion

From the present study, it is apparent that the impact of diagnostic IHC for the surgical pathology is legendary and plays an important role in the diagnosis of soft tissue tumours. One of its major utilities is to correctly identify a tumour as being of mesenchymal or nonmesenchymal origin. Once mesenchymal origin has been established, histologic subtyping according to specific cell lineage may be achieved with the use of lineage-specific markers. Tumours of uncertain cell lineage and tumours with primitive small round cell morphology are often characterized by a unique IHC phenotype. In this group of tumours, immunohistochemistry is most widely applied and is of greatest value.[9] Despite the rapid development of molecular genetic techniques, IHC still remains the most important diagnostic tool in the diagnosis of soft tissue tumours aside from recognition of morphologic features and clinical correlation. As surgical pathology is still based on skill in morphological interpretation, one cannot achieve success by diagnostic IHC alone without having a sound foundation in histopathologic analysis. The discovery of neoplasm-associated antigens has not only made the more accurate diagnosis of malignant soft tissue tumours feasible but has also shed light on the extensive immunophenotypical heterogeneity of even the most closely linked malignancies. A panel approach is always recommended so that an antigenic profile of positive as well as negative markers will provide the most accurate characterization of tumour. Awareness of the diagnostic utility of several tissue or organ specific immunomarkers should help meet one of the most significant challenges in diagnostic pathology. Though IHC is not most rapid and cost effective method for displaying morphological analysis of neoplasm, molecular technique and electron microscopy should be integrated selectively in future at the discretion of the pathologist to provide rapid and comprehensive solutions for problematic cases. Cytogenetics & molecular analysis will be of paramount importance for the diagnosis in future.

In cases of soft tissue tumours diagnostic approach should be to remember few points like,

- Appropriate history & thorough clinical examination
- Diagnostic radiology.
- Good histopathological morphology.
- Adequate & appropriately directed panel of antibodies by IHC.
- If required help of other techniques like cytogenetics & molecular analysis or ultrastructural study by electron microscopy and others.

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