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HISTOPATHOLOGICAL STUDY OF SOFT TISSUE TUMORS IN CORRELATION WITH IMMUNOHISTOCHEMISTRY AND / OR HISTOCHEMISTRY FINDINGS

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Abstract

Background: Soft tissue tumors are a heterogeneous group of tumors with a wide range of clinical behavior. Soft tissue tumors frequently pose as diagnostic problems for surgical pathologists, because of their rarity and overlap in their histological features. The present work aims at the study of soft tissue tumors in various age groups of patients with special reference to confirming the diagnosis made on Histopathology with immunohistochemistry and/or histochemistry, wherever required. Once the diagnosis of benign or malignant nature of the tumor has been established, the next important step is definite typing of the tumor and assigning a histological grade for sarcomas. To study the Soft tissue tumors histologically and correlate the findings with immunohistochemistry and/or histochemistry findings and categorize these tumors according to recent classification.

Material and Methods: The present study was done on 542 cases of soft tissue tumors received at Department of pathology, Siddhartha medical college, Vijayawada from June'2008 to June'2010 as retrospective study and prospectively from June 2010 to June'2012. Tissues were routinely processed and Sections from paraffin blocks were taken and routine hematoxylin and eosin staining performed. Special stains such as Periodic acid schiff's stain, Masson trichrome stains .Immunohistochemistry with Vimetin, Desmin, S-100 and CD-31 was done for the tumors wherever required. The results of histopathology were compared with the results of immunohistochemistry and / or histochemistry.

Results: Benign soft tissue tumors were observed with highest frequency in 4th decade (24.02%) followed by 5^{th} decade (22.44%) and Lipoma was the most common benign soft tissue tumor accounting for 56.69%. Soft tissue sarcomas were observed with highest frequency in 5^{th} & 6^{th} decades (41.18%) and Malignant fibrous histiocytoma was the most common soft tissue sarcoma accounting for 32.35%. The correlation of histopathological diagnosis with IHC/HC was 80%.

Conclusion: Histopathological diagnosis of Soft tissue tumors is important factor for treatment strategy, predicting survival rates and metastasis. Wherever there is suspicion of the

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diagnosis the histopathological diagnosis has to be confirmed by immunohistochemistry and/or histochemistry.

Keywords: Soft tissue tumors, Sarcoma, Lipoma, Histochemistry, Immunohistochemistry.

Introduction

Soft tissue tumors are a highly heterogeneous group of tumors that are classified on a histogenic basis according to the adult tissue they resemble. Soft tissue can be defined as non-epithelial 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 and peripheral nervous system because tumors arising from nerves present as soft tissue masses.[1] Embryologically, soft tissue is derived principally from mesoderm, with some contribution from neuroectoderm.

Soft tissue tumors frequently pose as diagnostic problems for surgical pathologists, because of their rarity and overlap in their histological features. Despite these difficulties, 80%of soft tissue tumors are easily diagnosed by light microscopy and with the aid of special stains.[2] Soft tissue tumors need thorough clinical evaluation supported by radiological evaluation. Biopsy is the critical step with FNAB and needle core biopsy playing important role. Histological grade is the single most important factor for treatment strategy, predicting survival rates and metastasis.[3]

For having a definite diagnosis, the histopathological diagnosis is to be confirmed by immunohistochemistry or histochemistry wherever there is suspicion of the diagnosis; or the definite diagnosis could not be made on the biopsy. Benign soft tissue tumors out number malignant tumors by a wide margin. Soft tissue sarcomas, compared with carcinomas and other neoplasms are relatively rare and constitute fewer than 1% of all cancers.[4] Development of a useful and comprehensive histologic classification of soft tissue tumors has been a relative slow process. Earlier classifications have been based more on the nuclear configuration than the type of tumor cells.

The world health organization classification of soft tissue tumors was first published in 1969 and revised in 1994 as a collective effort by pathologists in ten countries in 2002.[5] Weiss and Goldblum (2001) have used a revised WHO classification with some modifications to classify these tumors. Grading of soft tissue sarcomas was first proposed by Broders et. al (1939),[6] using a combination of histological features for fibrosarcoma. Markkhede et al (1982),[7] suggested a grading system that used four grades of malignancy based on cellularity, cellular pleomorphism and mitotic activity. In their study the grade correlated well with survival rates.

Histochemistry: It is the use of special stains such as Periodic acid Schiff reagent(PAS), Masson's Trichrome, Van Gieson, Reticulin stain etc, to demonstrate cell and tissue structure and function for a making a diagnosis on diseased tissues.

Immunohistochemistry: Immunohistochemistry is the use of antibody-based reagents for localization of specific epitopes in tissue sections. In recent years, immunohistochemistry has become a powerful tool to assist the surgical pathologist in many clinically critical settings. It plays an important role in the diagnosis of soft tissue tumors. One of its major utilities is to correctly identify a tumor as mesenchymal or non mesenchymal origin. Once mesenchymal

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origin has been established, histologic subtyping according to specific cell lineage may be achieved with lineage-specific markers.

Table 1: **Common immunohistochemical markers used for soft tissue tumors**

Antibodies to	**Expressed by**
Vimentin	Sarcomas, melanoma
Desmin	Benign and malignant smooth and skeletal muscle tumors
Neurofilaments	Neuroblastic tumors
Smooth muscle actin	Benign and malignant smooth muscle tumors, myofibroblastic tumors
Myogenin, MyoD1	Rhabdomyosarcoma
S-100 protein	Melanoma, benign and malignant peripheral nerve sheath tumors, cartilaginous tumors,
Epithelial membrane antigen	Carcinomas, epithelioid sarcoma, synovial sarcoma perineurioma, meningioma
CD31,vWF	Benign and malignant vascular tumors
CD34	Benign and malignant vascular tumors, solitary fibrous tumor, dermatofibrosarcoma protuberans
CD99	Ewing's sarcoma/primitive neuroectodermal tumor
CD68	Macrophages, fibrohistiocytic tumors

Table 2: Specific tumor types, normal counterparts, and useful IHC markers

Tumor type	**Normal cell counterpart**	**Useful marker(s)**
Angiosarcoma	Endothelium	CD31, CD34, FLI-1, von Willebrand factor, ulexlectin
Leiomyosarcoma	Smooth muscle	Muscle (smooth) actins, desmin, caldesmon, myosin heavy chain
Rhabdomyosarcoma	Skeletal muscle	MyoD1, myogenin; desmin
Ewing's sarcoma/PNET	?	CD99 ,FLI-1
Synovial sarcoma	?	Cytokeratin, EMA
Malignant peripheral nerve sheath tumor	Nerve sheath	S-100, CD57, NGF receptor, EMA, claudin-1, Glut-1
Liposarcoma	Adipocyte	S-100 protein, MDM2
Chondrosarcoma	Chondrocyte	S-100 protein
Osteogenic sarcoma	Osteocyte	Osteocalcin
Kaposi sarcoma	Endothelium	CD31, CD34, VEGFR3, LANA
Gastrointestinal stromal tumor	Interstitial cells of Cajal	CD117a (c-kit), CD34, protein kinase C ϑ

Material and Methods

542 cases of soft tissue tumors received at Department of pathology, Siddhartha Medical College, Vijayawada were studied both prospectively and retrospectively from June’2008 to

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June'2010 as retrospective study and the prospectively from June 2010 to June'2012. Biopsy specimens received were fixed in 10% buffering formalin. Grossing was done taking 1 block for each cm of the tumor along with areas of necrosis. Sections were taken from the tumor in relation to skin and other structures. Sections were included from all surgical margins. Tissues were routinely processed, Sections from paraffin blocks were taken and routine hematoxylin and eosin staining performed.

Special stains: Periodic acid schiff's reagent stain: PAS positive substances – Magenta, Nuclei –Blue. Masson trichrome stain: Nuclei – Blue black, Cytoplasm, muscle and acidophil granules – Red Collagen, cartilage, mucin, basophil granules – Blue / green

IHC: Immunohistochemistry was done for the tumors wherever required. Immunohistochemistry was done with the following stains. Vimetin, Desmin, S-100, CD-31, CD-34, CD-68, NSE, EMA.

The results of histopathology were compared with the results of immunohistochemistry and / or histochemistry.

Results

In this study of 542 cases, 508 were benign (93.72%) and 34 cases were malignant (6.28%), with a ratio of 15: 1. Lipoma (56.69%) was the most common benign soft tissue tumor, followed by hemangioma (15.74%), and neurofibroma (5.74%). Among the malignant tumors malignant fibrohistiocytoma (MFH) is the most common (32.35%) followed by liposarcoma (8.82%) & synovial sarcoma (8.82%).

Table 3: Distribution of Benign Soft Tissue Tumors in the Major Groups

S. No.	Tumor type	No. of cases	% of cases
1	Fibroma	18	3.54%
2	Fibromatosis	5	0.98%
3	Benign fibrous histiocytoma	15	2.96%
4	Lipoma	288	56.69%
5	Capillary hemangioma	37	7.28%
6	Granuloma pyogenicum	38	7.48%
7	Cavernous hemangioma	5	0.98%
8	Lymphangioma	5	0.98%
9	Glomus tumor	2	0.39%
10	Giant cell tumor of tendon sheath	9	1.78%
11	Pigmented villonodular synovitis	3	0.59%
12	Neurofibroma	29	5.71%
13	Schwannoma	18	3.54%
14	Benign nerve sheath tumor	8	1.58%
15	Ganglion	28	5.51%
	TOTAL	508	100%

Lipoma was the most common benign soft tissue tumor accounting for 56.69%.

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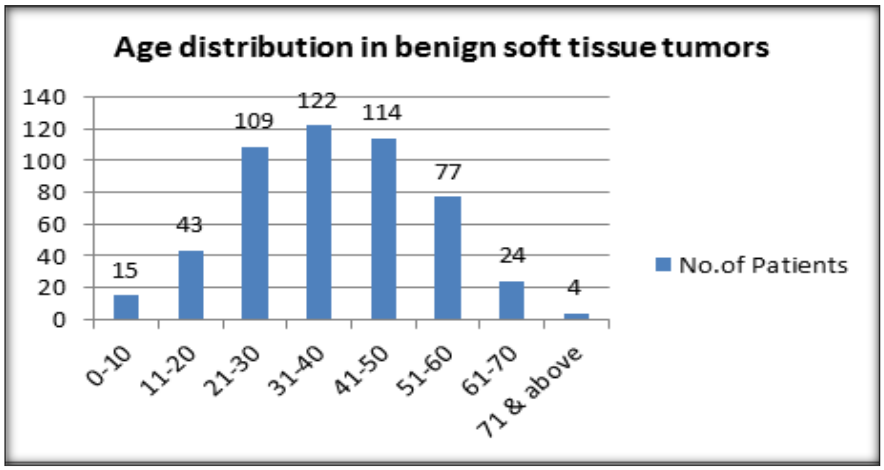
Table 4: Distribution of Soft Tissue Sarcomas in the Major Groups

S. No.	Tumor Type	No. of cases	% of cases
1	Fibrosarcoma	1	2.94%
2	Dermatofibrosarcoma protuberans	6	17.66%
3	Malignant fibrous histiocytoma	11	32.35%
4	Liposarcoma	3	8.82%
5	Rhabdomyosarcoma	1	2.94%
6	Angiosarcoma	3	8.82%
7	Malignant peripheral nerve sheath tumor	2	5.88%
8	Extraskeletal Ewings sarcoma	2	5.88%
9	Esthesio neuroblastoma	1	2.94%
10	Extraskeletal Chondrosarcoma	1	2.94%
11	Synovial sarcoma	3	8.82%
	Total	34	100%

Malignant fibrous histiocytoma was the most common soft tissue sarcoma accounting for 32.35%.



Benign soft tissue tumors were observed with highest frequency in 4th decade (24.02%) followed by 5th decade (22.44%).

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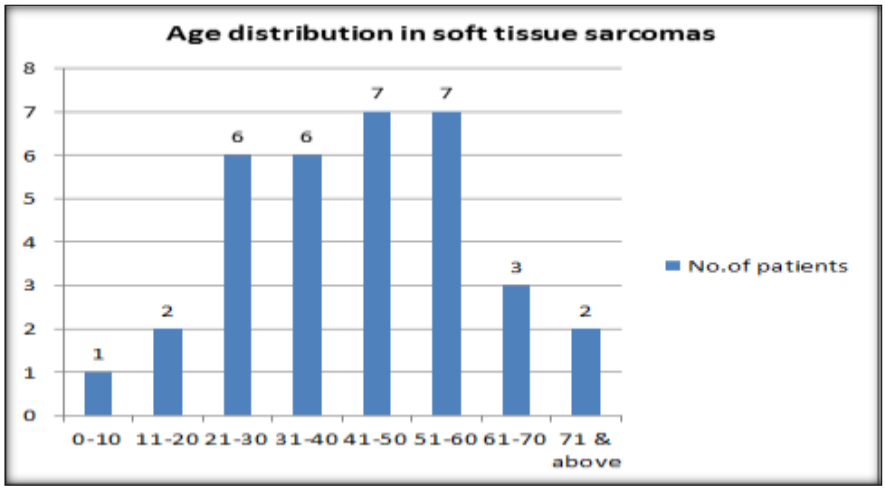
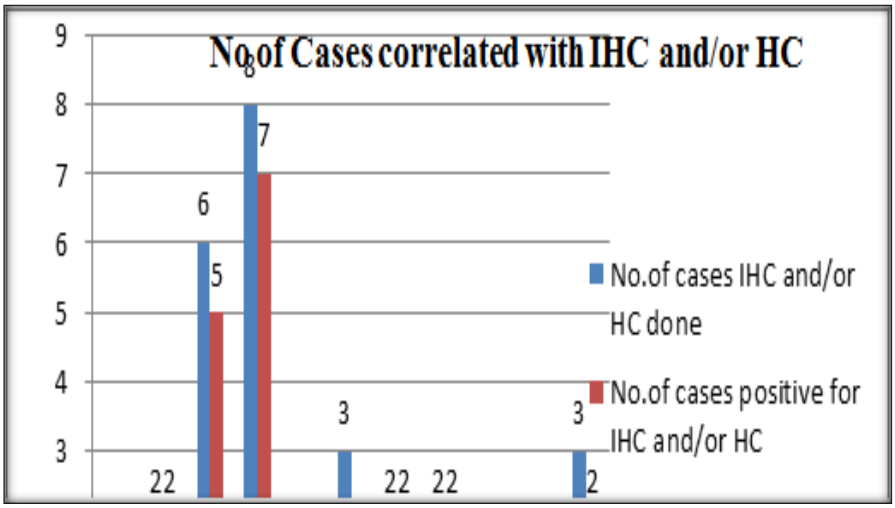


Soft tissue sarcomas were observed with highest frequency in 5th & 6th decades (41.18%).



The correlation of histopathological diagnosis with IHC/HC was 80%.

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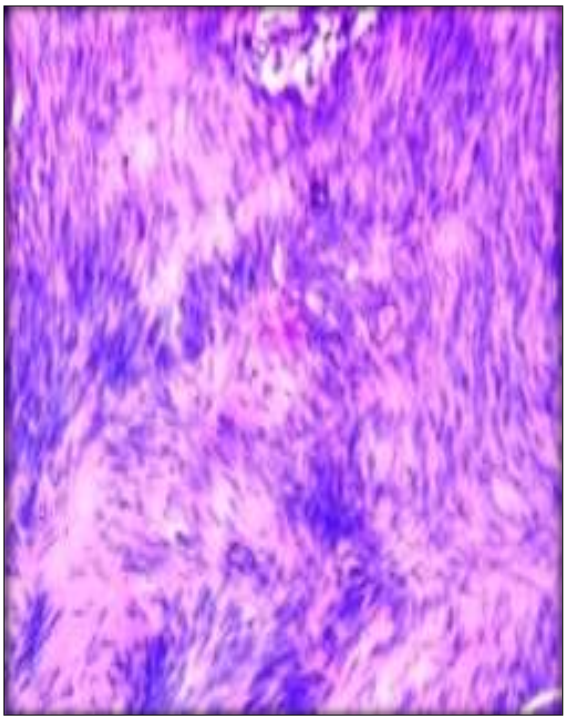

Figure 1: Fibroma 40X, H&E showing fascicles of spindle cells

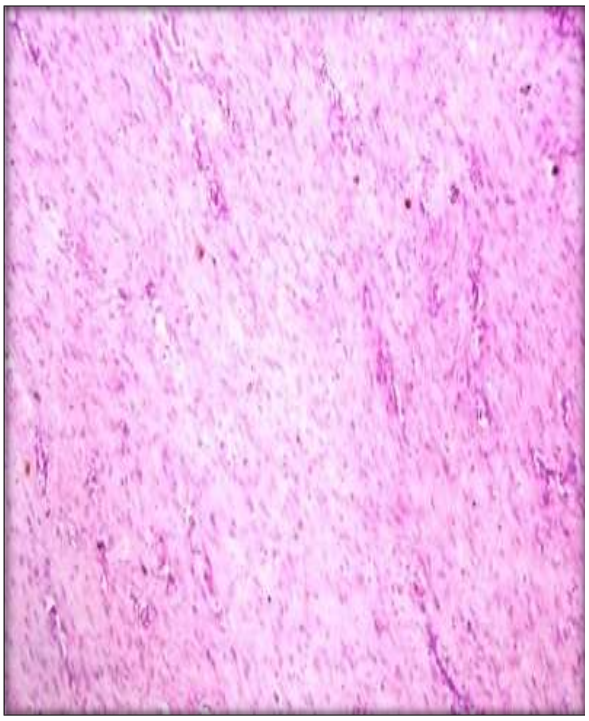

Figure 2 : Abdominal Fibromatosis 10X, H&E showing hypocellular areas of spindle cells

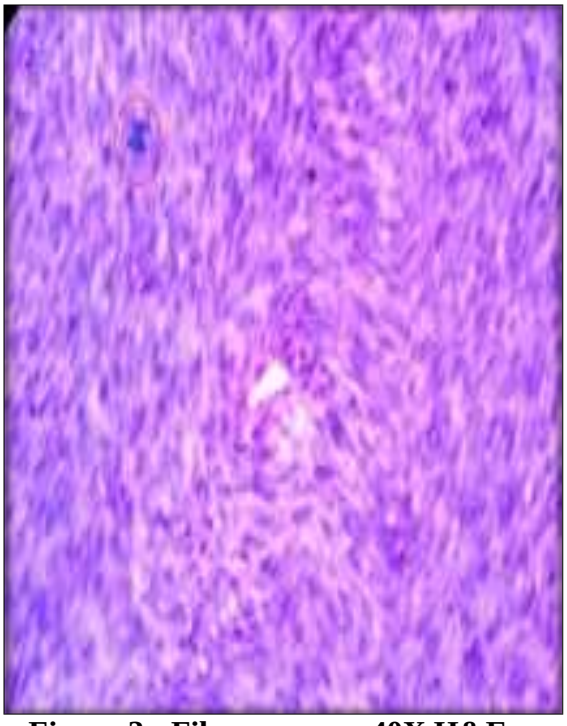

Figure 3: Fibrosarcoma 40X H&E, Spindle Cells with high grade nuclear features

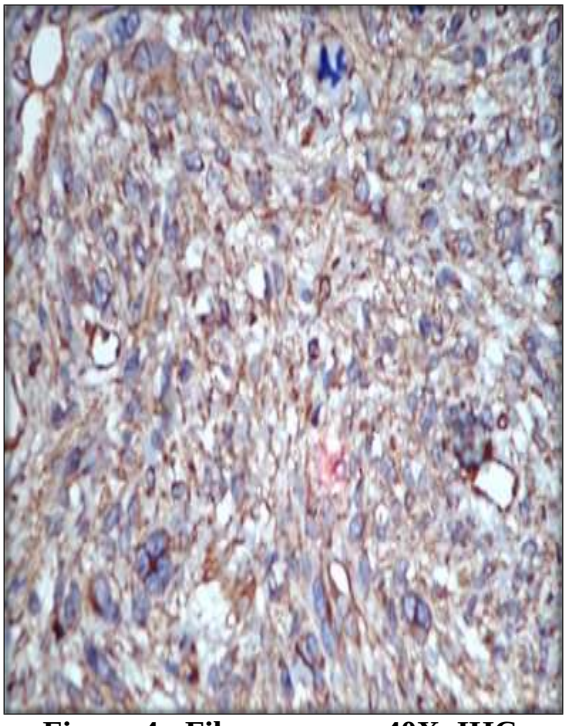

Figure 4: Fibrosarcoma 40X IHC, Vimentin positivity

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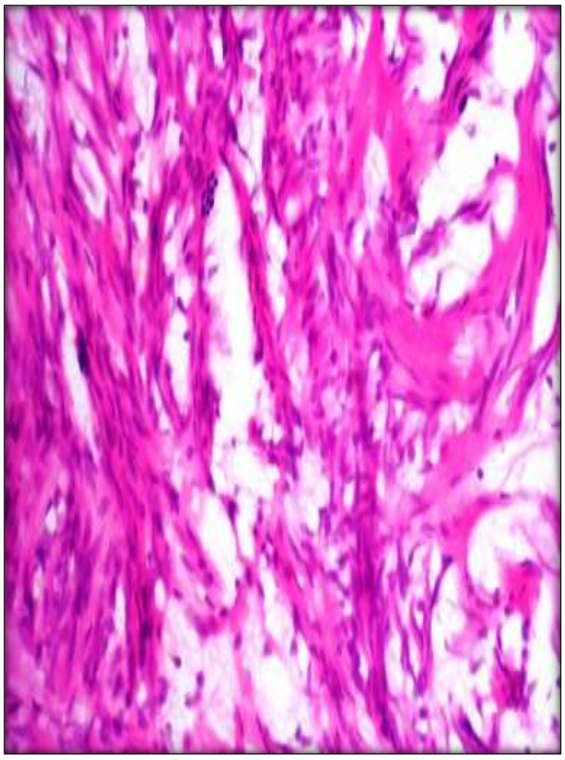

Figure 5: Benign Fibrous Histiocytoma 40X H&E, Uniform spindle cells with few giant cells

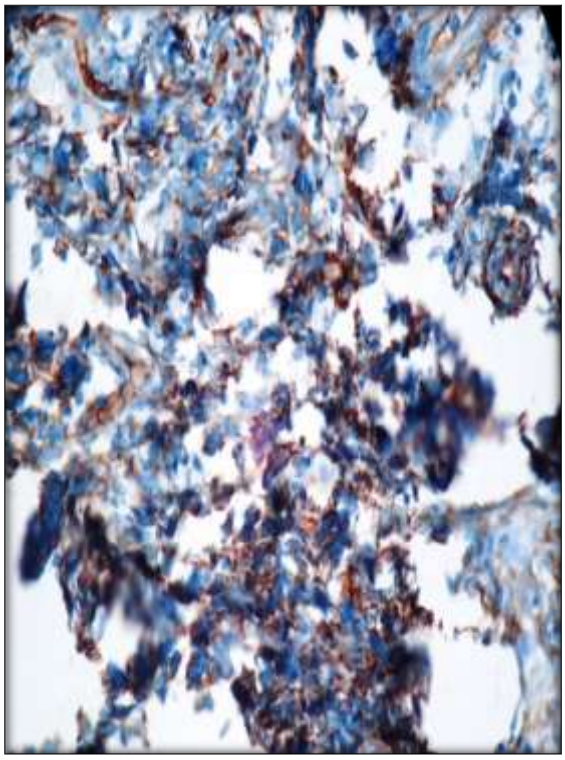

Figure 6 : Benign Fibrous Histiocytoma 40X IHC, CD34 positivity

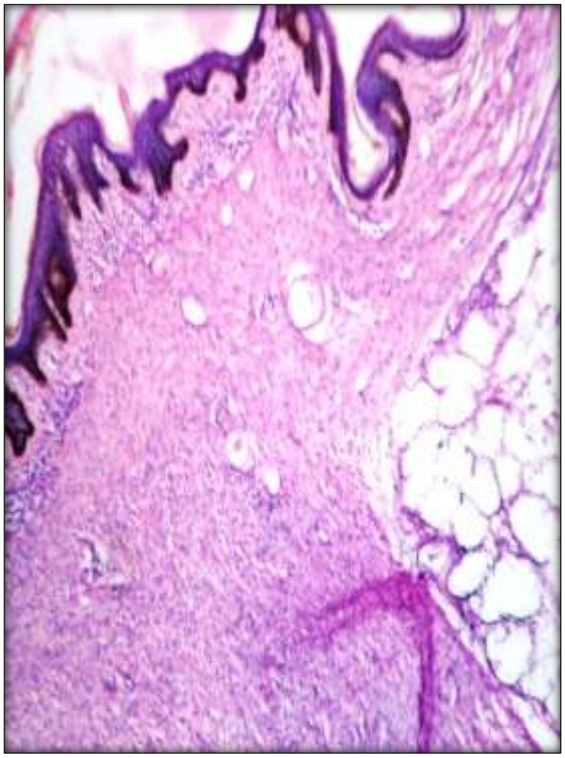

Figure 7: Dermatofibrosarcoma protuberans 10X H&E, tumor cells in storiform pattern extending into

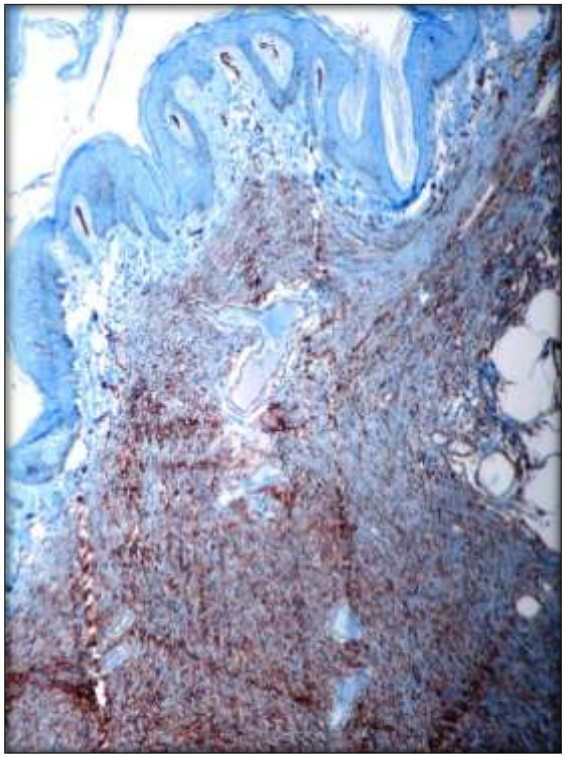

Figure 8: Dermatofibrosarcoma protuberans 10X IHC CD34 positivity

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subcutaneous fat

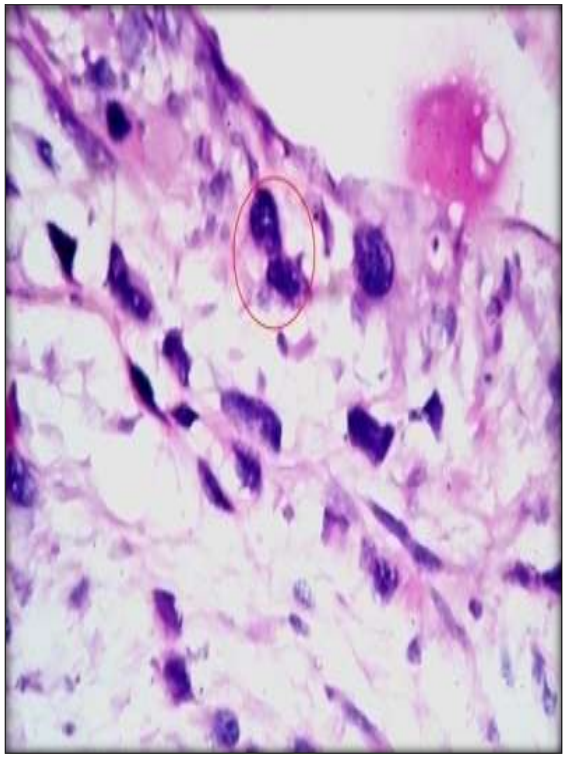

Figure 9: Malignant Fibrous Histiocytoma 40X H&E, pleomorphic tumor cells, few bizarre cells

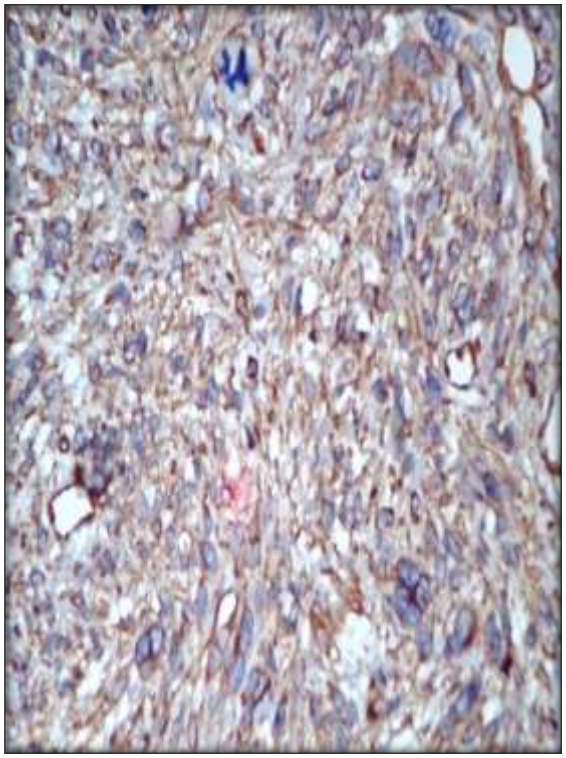

Figure 10: Malignant Fibrous histiocytoma 40X IHC Vimentin positivity

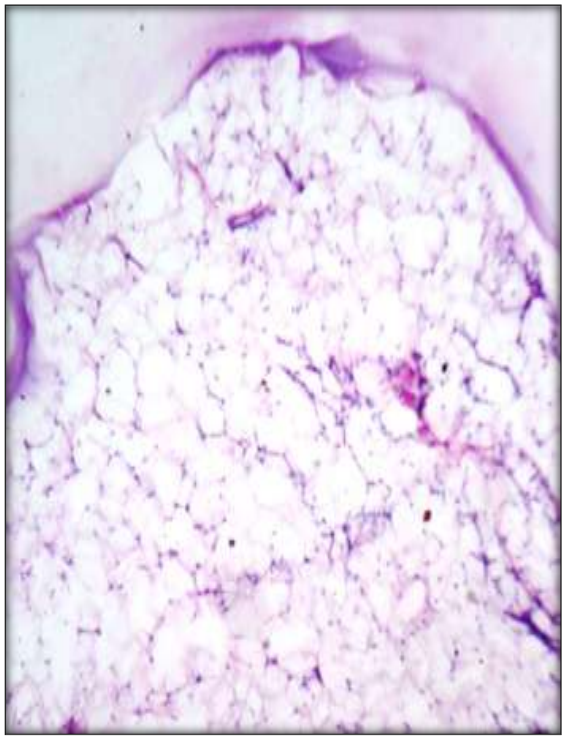

Figure 11: Lipoma 10X H&E, Proliferating adipocytes

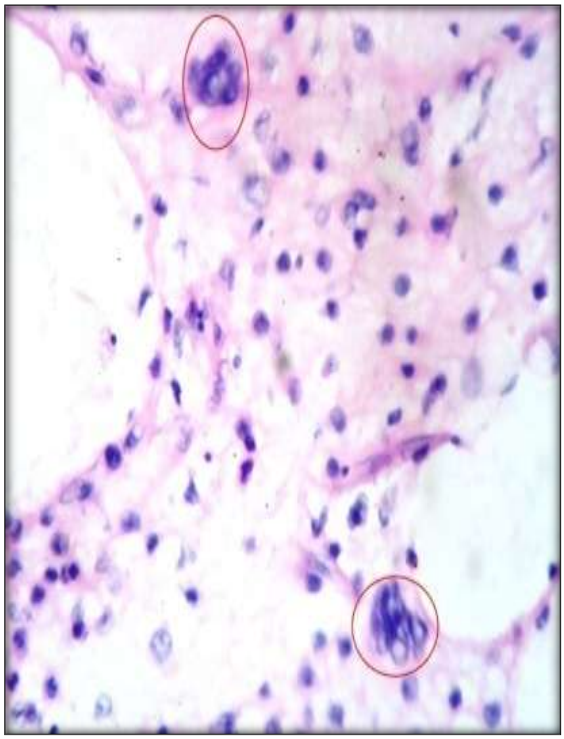

Figure 12: Myxoid Liposarcoma40X H&E Lipoblasts of varying stages along with

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stromal mucin

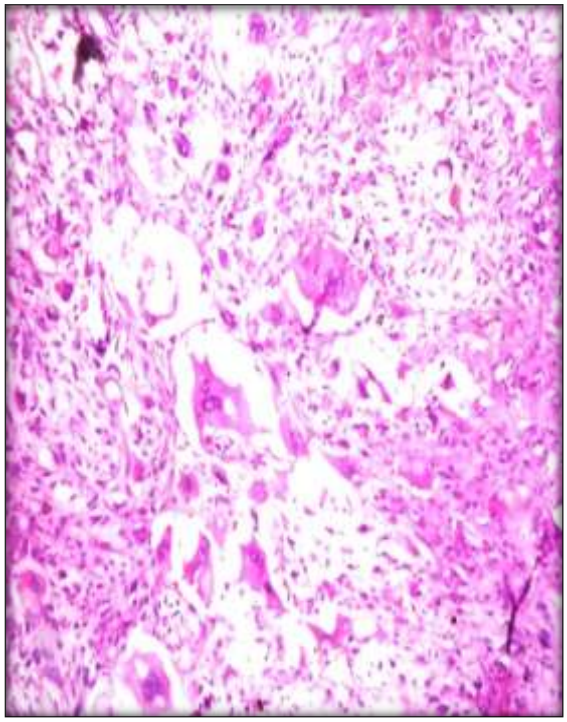

Figure 13: Rhabdomyosarcoma 10X H&E Predominantly spindle cells with scattered rhabdomyoblasts

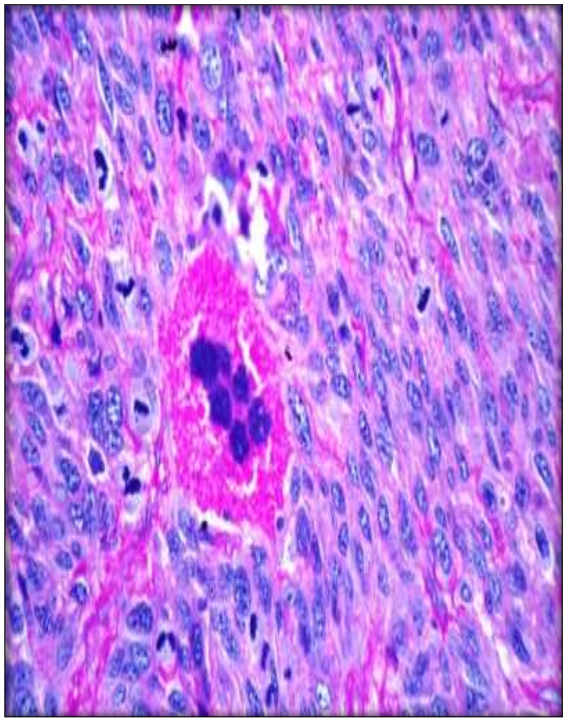

Figure 14: Rhabdomyosarcoma 40X PAS Intracellular granular positivity

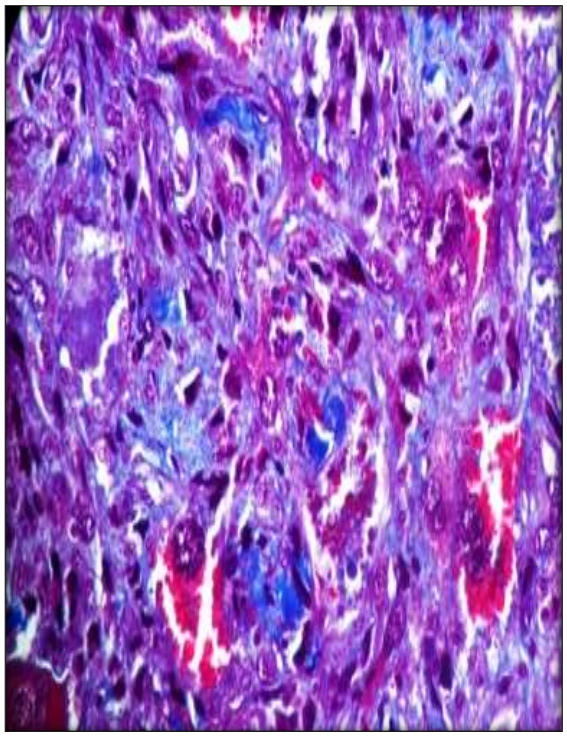

Figure 15: Rhabdomyosarcoma 40X Masson's Trichrome showing fibrous tissue

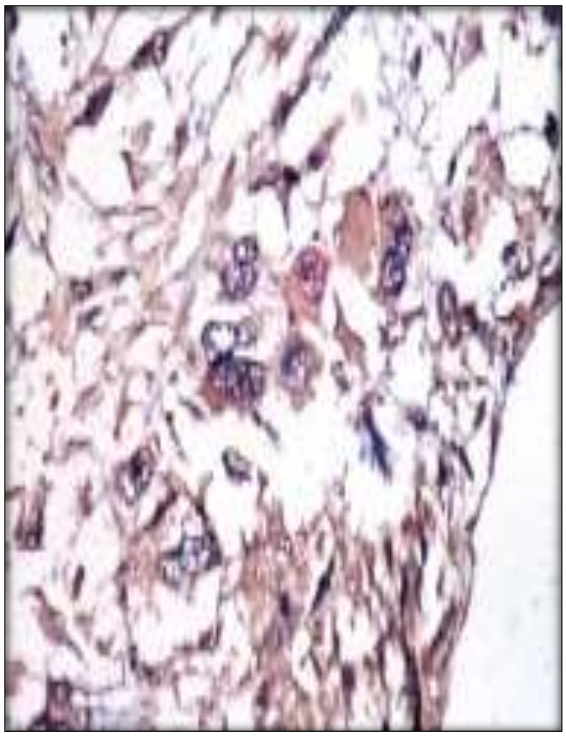

Figure 16: Rhabdomyosarcoma 40X IHC, Desmin positivity in large pleomorphic cells

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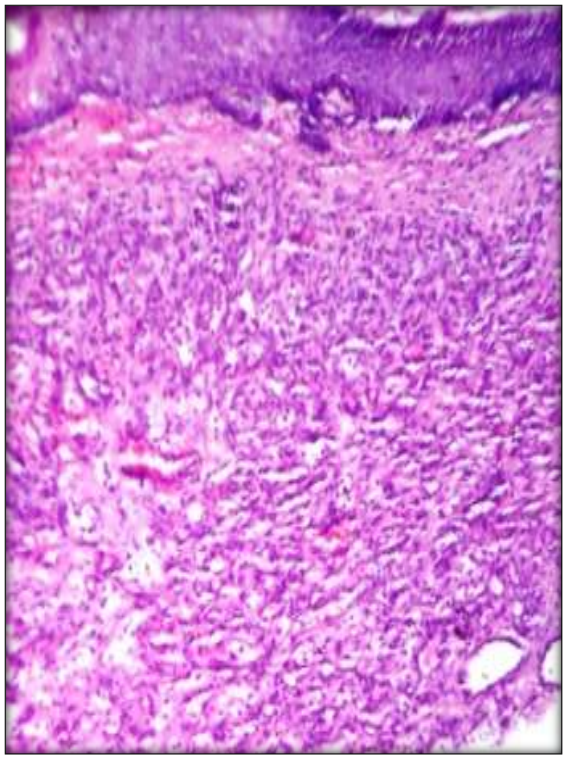

Figure 17: Capillary Hemangioma 10X H&E, Small vessels lined by flattened mature endothelium

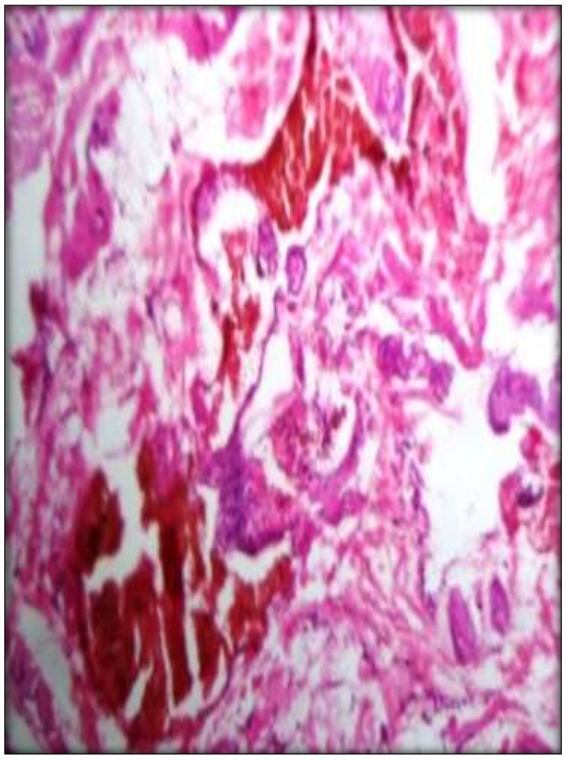

Figure 18: Cavernous Hemangioma 10X H&E Large thin walled vascular spaces

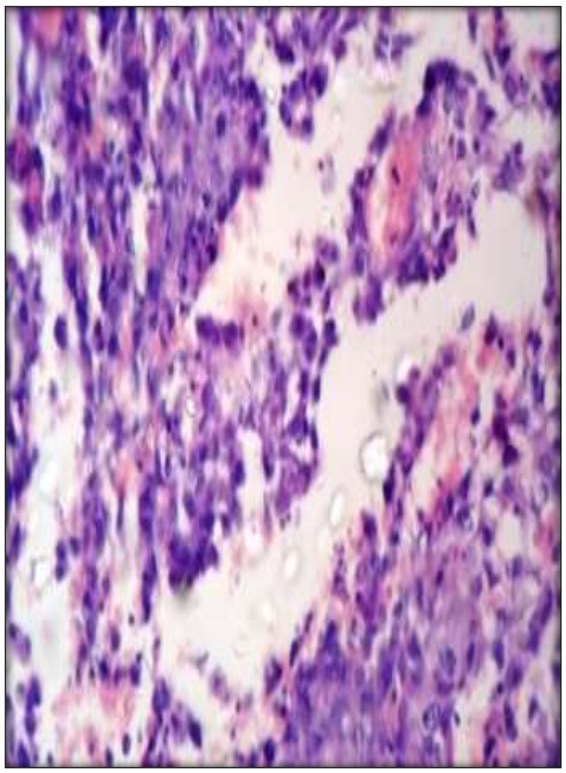

Figure 19: Angiosarcoma 40X H&E, Infiltrative growth between collagen bundles

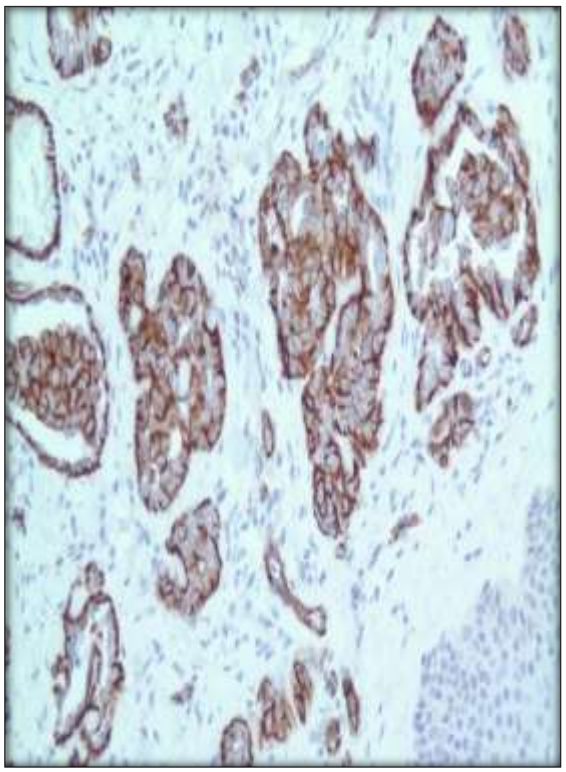

Figure 20: Angiosarcoma 40X IHC CD31 positivity

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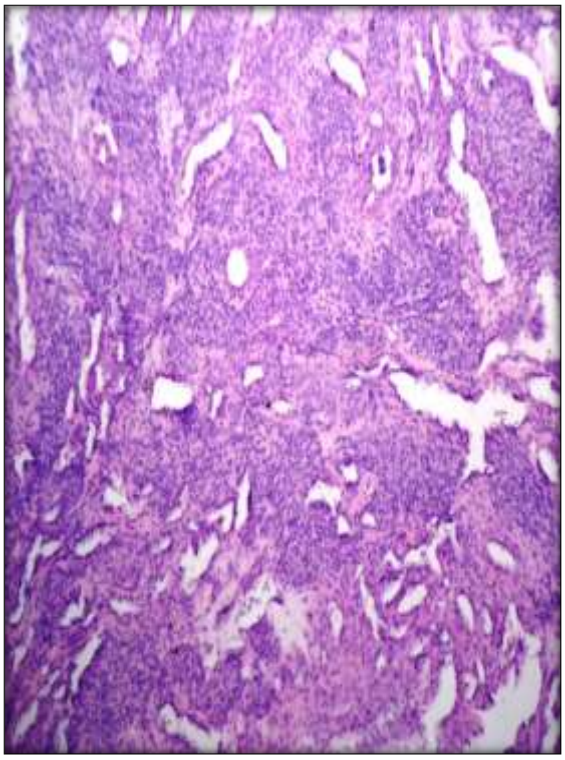

Figure 21: Glomus Tumor 10X H&E solid sheets of glomus cells interrupted by vessels

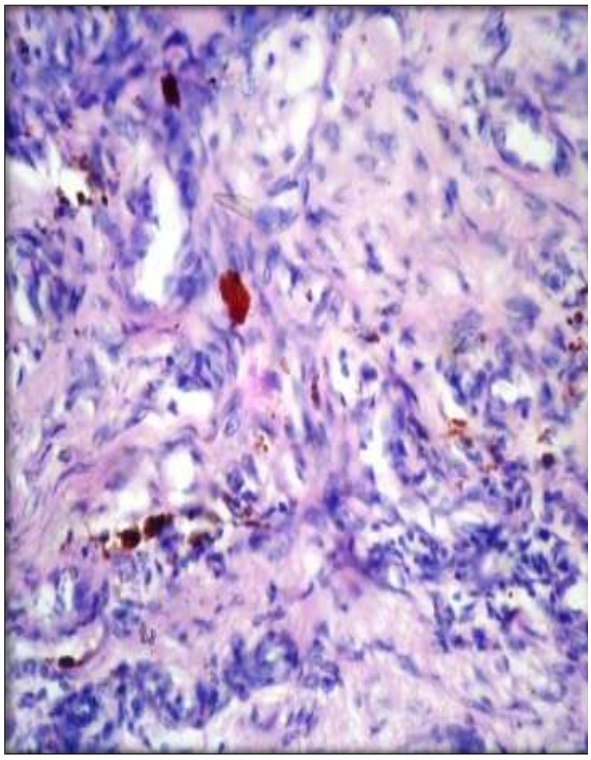

Figure 22: Pigmented Villonodular Synovitis 40X H&E Giant cells admixed with round cells, hemosiderin pigment

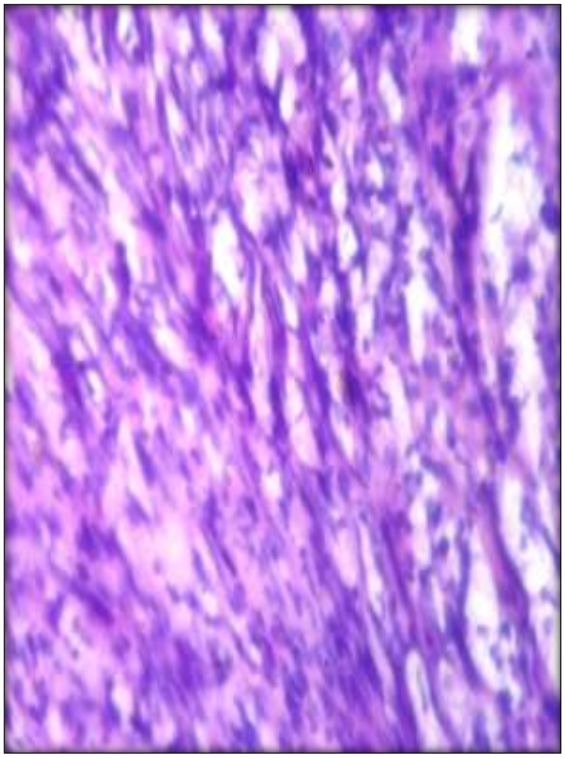

Figure 23: Neurofibroma 40X H&E Cells with wavy darkly stained nuclei along with collagen

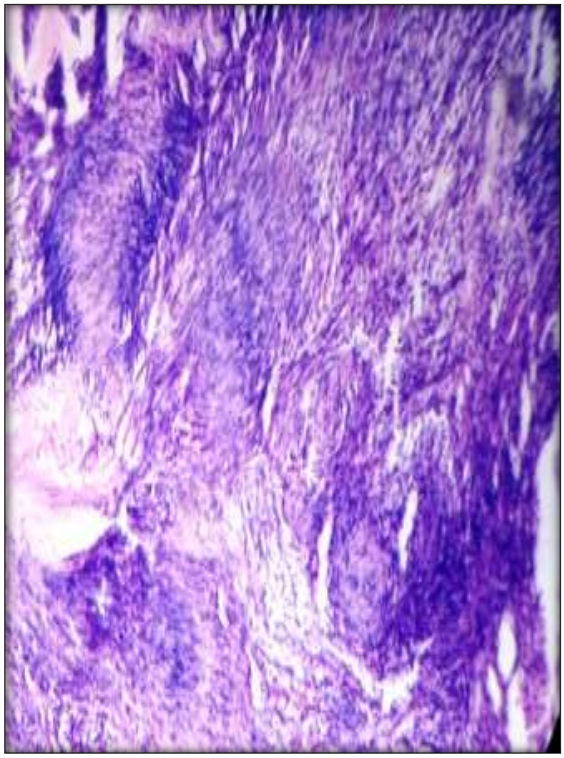

Figure 24: Schwannoma 10X H&E Alternating Antoni A and Antoni B areas

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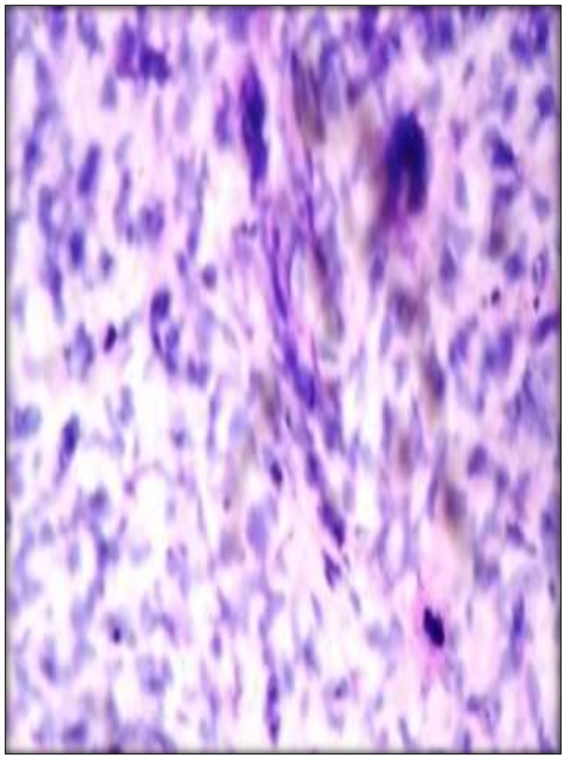

Figure 25: Malignant Peripheral Nerve Sheath Tumor 40X H&E Cells with buckled nuclei and atypical mitotic figures

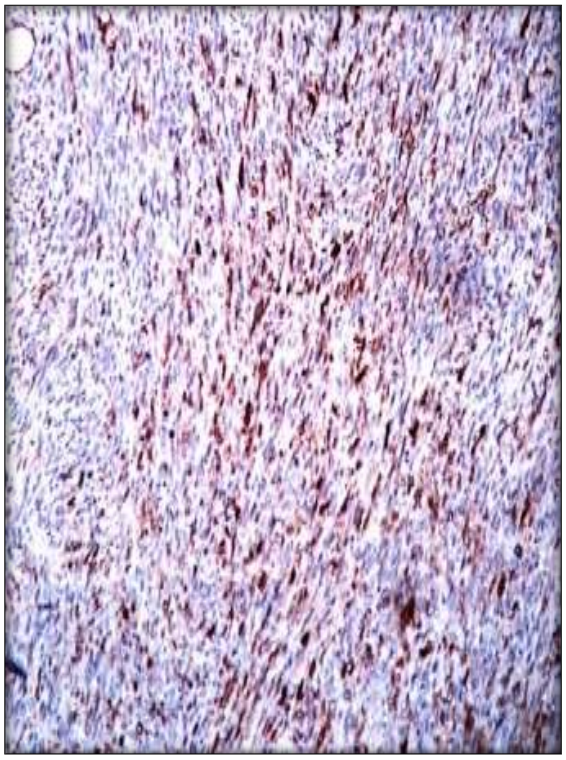

Figure 26: MPNST 10X IHC S100 positivity

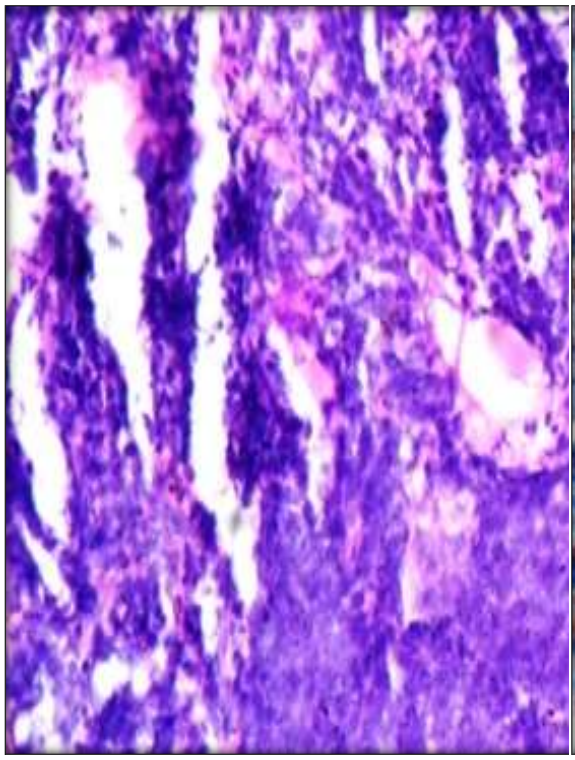

Figure 27: Extraskeletal Ewings Sarcoma 40X H&E Monotonous small

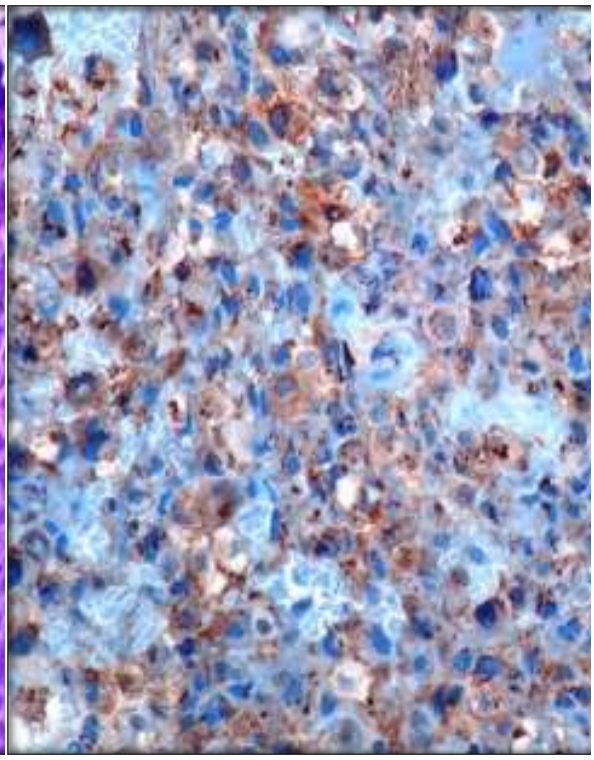

Figure 28: Extraskeletal. Ewings Sarcoma 40X IHC CD99 positivity

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round cells with scanty cytoplasm

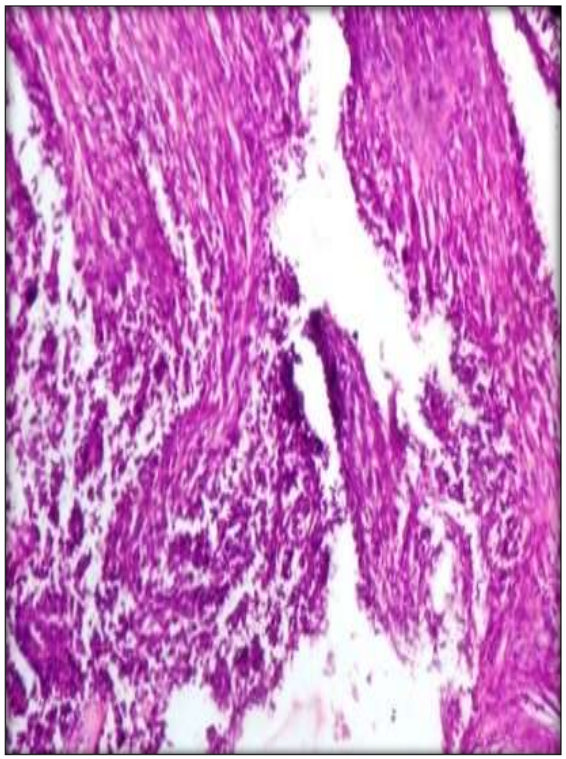

Figure 29: Synovial Sarcoma 10X H&E Biphasic type – Epithelial structures with malignant spindle cells

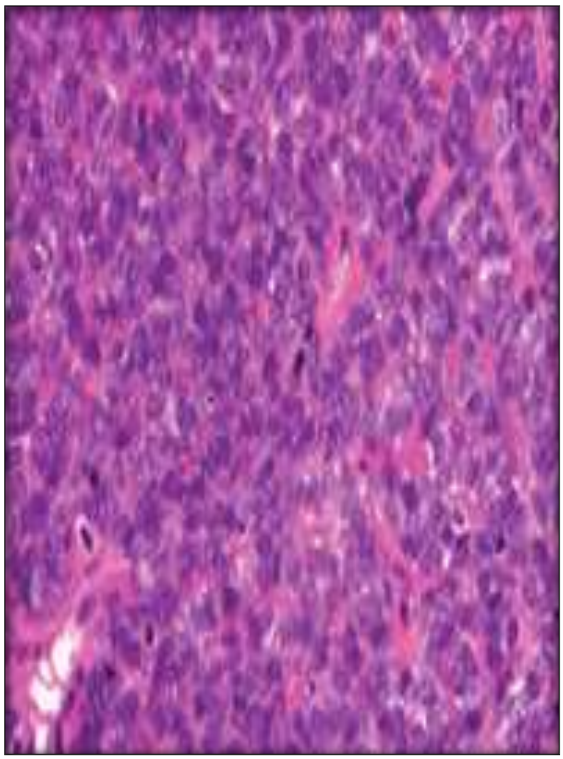

Figure 30: Synovial sarcoma 10X PAS highlighting secretions

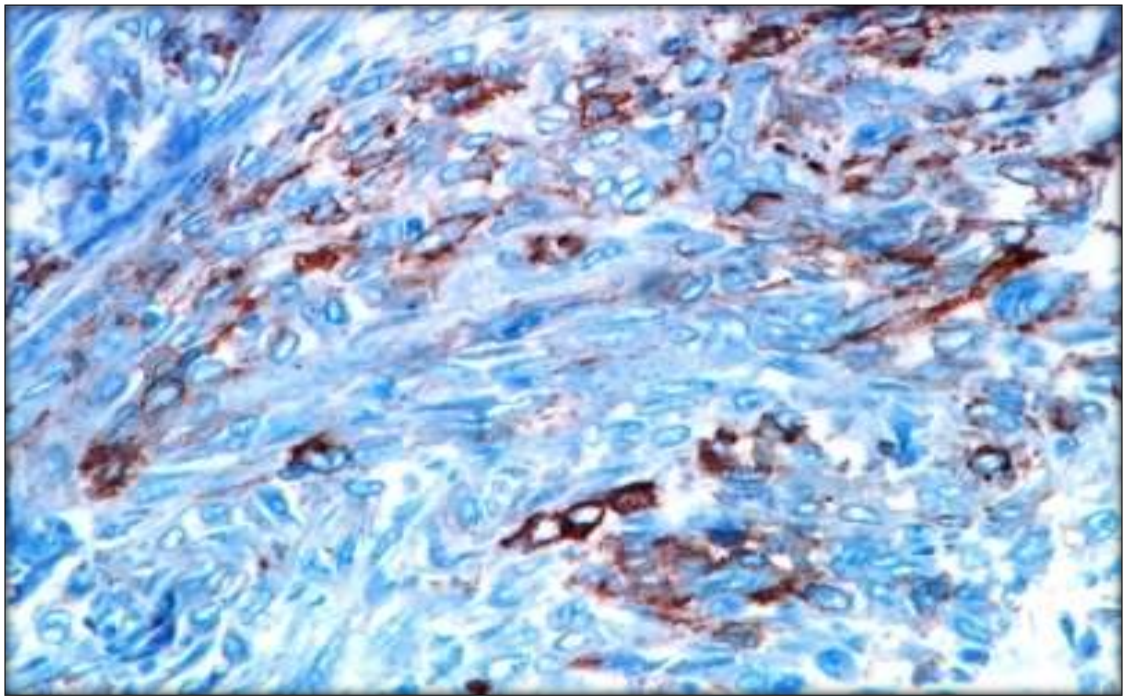

Figure 31: Synovial sarcoma 40X IHC EMA focal positivity

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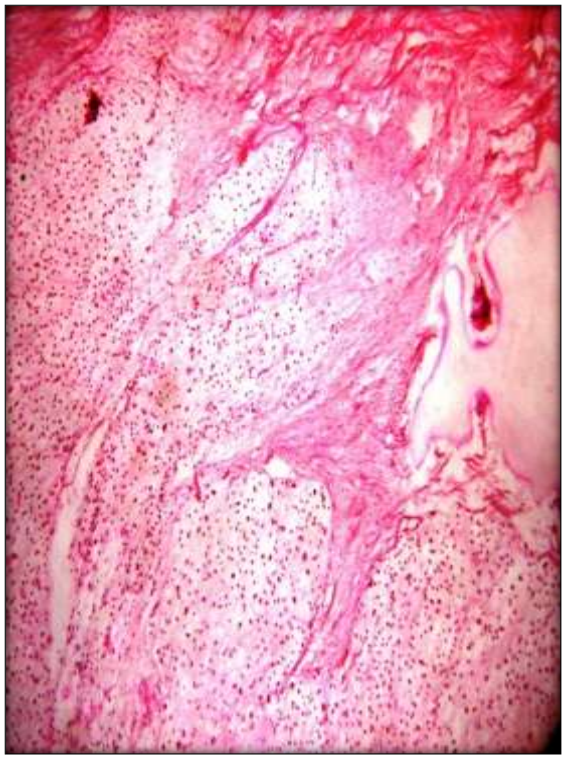

Figure 32: Extraskeletal Chondrosarcoma 10X H&E Atypical chondrocytes in cords and strands

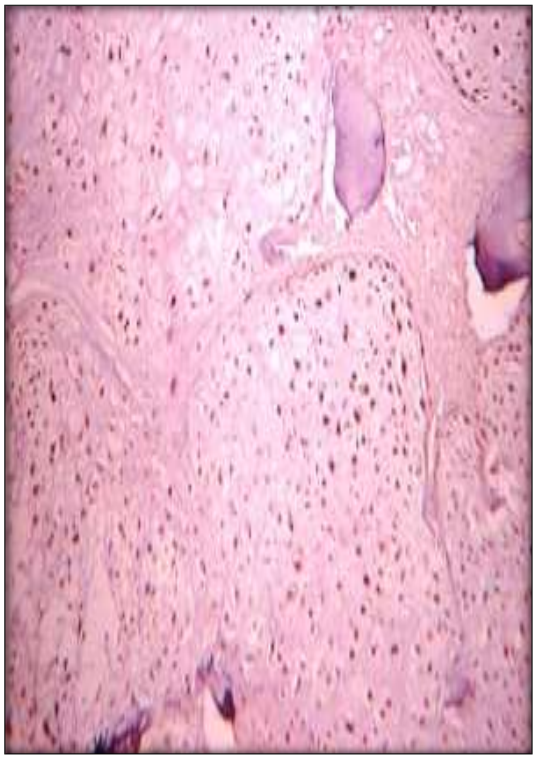

Figure 33: Extraskeletal Chondrosarcoma 40X IHC S100 positivity

Discussion

Soft tissue tumors resemble to a variable degree their prototype tissues. However, because of their pleuripotentiality and common mesenchymal derivation they show wide morphological range and may present similar growth characteristics lacking morphologic individuality. Immunohistochemistry has greatly enhanced our capabilities to properly classify certain entities. In any case, it is important to acquire as much information as possible regarding the following factors: (1) general clinical information (age, sex, previous medical history, etc), (2) specific information about the tumor itself (location, size, relationship to surrounding tissues, rate of growth, etc), (3) histopathological features (cellularity, growth pattern, matrix production, cell size and shape, atypia and anaplasia, mitoses, necrosis, etc), (4) antigenic profile, and, (5) whenever necessary, electron microscopic features and molecular data. In the present study of 542 cases, 508 were benign (93.72%) and 34 cases were malignant (6.28%). Lipoma (56.69%) was the most common benign soft tissue tumor, followed by hemangioma (15.74%), and neurofibroma (5.74%). Among the malignant tumors malignant fibrohistiocytoma (MFH) is the most common (32.35%) followed by liposarcoma (8.82%) & synovial sarcoma (8.82%). The most common age group for benign tumors was fourth and fifth decade while the majority of malignant tumors developed in the fifth and sixth decade.

In the study of Bashar A. Hassawi et al,[8] of 502 cases, 431 cases (85.9%) were benign & 71 cases (14.1%) were malignant. Lipoma was the most common benign soft tissue tumor, followed by hemangioma, lymphangioma, and neurilemmoma. Among the malignant tumors fibrosarcoma was the most common, followed by liposarcoma, and rhabdomyosarcoma. The

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age of benign tumors was evenly distributed from childhood to advanced age, while the majority of malignant tumors developed in adult age group.

In the study of Chae Koo Lee et al,[9] of 336 soft tissue tumors 79 were malignant and 257 were benign tumors. Among malignant tumors, fibrosarcoma, neurogenic sarcoma, fibroliposarcoma and leiomyosarcoma were especially prevalent, and among benign tumors hemangioma, lipoma, fibroma and neurofibroma were more commonly encountered. Average ages of malignant and benign soft tissue tumors were 37 and 33 years respectively.

IHC Correlation of the Present Study with Other Studies

Study / **Tumor (IHC/HC)**	**Present Study**	**Declerck D et al,[12]**	**C W Lawson et al,[13]**	**Gabhane et al,[10]**	**Oliveira A M et al,[11]**	**Abenoza P et al,[14]**
Fibrosarcoma (vimentin)	100%					
Benign Fibrous histiocytoma (CD34)	100%					
Dermatofibrosarcoma Protruberans (CD34)	83.33%	81.6%				
Malignant fibrous histiocytoma (vimentin)	87.5%		100%			
Rhabdomyosarcoma (Desmin)	100%					
Rhabdomyosarcoma (PAS)	100%					
Rhabdomyosarcoma (MT)	100%					
Angiosarcoma (CD31)	33.33%					
Malignant Peripheral Nerve sheath tumor (S100)	100%			40%		
Extraskeletal Ewings Sarcoma (CD99)	100%					
Esthesioneuroblastoma (NSE)	0%					
Extraskeletal Chondrosarcoma (S100)	100%				17%	
Synovial Sarcoma (EMA)	66.66%					97%

In this study, the correlation of histopathological diagnosis with immunohistochemistry and/ or histochemistry diagnosis was 80 %.

Conclusion

Soft tissue tumors are composed of numerous and complex diagnostic entities. Because of this complexity and some tumors with a deceptively bland histologic appearance, soft tissue

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tumors may pose a major diagnostic challenge to the general practicing pathologist. Immunohistochemistry plays an important role in the diagnostic accuracy of soft tissue tumors. It is useful to differentiate mesenchymal and non mesenchymal tumors. It is useful for histologic subtyping with the use of lineage-specific markers. IHC along with histochemistry is useful in confirming the histopathological diagnosis, which is an important factor for treatment strategy, predicting survival rates and metastasis.

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