Original Article

Histopathological Spectrum of Myxoid Soft-Tissue Neoplasms in a Tertiary Care Center with a Special Focus on Vascular Patterns: A 13-Year Compilation

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Abstract

Introduction: Myxoid soft-tissue tumors are a diverse group of tumors which have similar histomorphology but have varied genetic sequence and clinical outcome, hence differentiating and diagnosing them is a challenge for any pathologist. This study describes the various histomorphological spectrum and vascular pattern of various myxoid soft-tissue tumors. **Materials and Methods:** This was a retrospective and prospective observational study of myxoid soft-tissue tumors over a period of 13 years. A total of 224 cases with myxoid morphology were included and were examined morphologically with a special focus on the vascular pattern. SPSS v 24 was used for statistical analysis. **Results:** The predominant lesions were benign in 164 (73.21%) cases, followed by malignant lesions in 43 (19.19%) cases and intermediate lesions 17 (7.58%) cases. Both benign and malignant lesions showed a male preponderance and were seen to arise predominantly from the extremities. The most common benign myxoid lesions in this study were of neural origin with myxoid neurofibroma constituting 65 (29.01%) cases, followed by schwannoma 38 (16.9%) cases. Myxoid dermatofibrosarcoma protuberans was the most common intermediate lesion. Tumors with adipocytic differentiation were the predominant lesions among the malignant group, i.e myxoid liposarcoma seen in 17 (7.5%) cases. **Conclusions:** Vascular pattern in the myxoid lesions are subtle yet crucial in arriving at a histo-morphological diagnosis. Further studies correlating the vascular pattern with the genetic profile of these tumours can help arriving at a histo-morphological diagnosis of myxoid lesions.

Keywords: Crow's feet vessels, histomorphology, liposarcoma, myxoid, neurofibroma, soft tissue, vascular pattern

Introduction

Myxoid soft-tissue tumors are a diverse group of lesions having characteristic abundant myxoid extracellular matrix possessing diverse clinicopathological spectrum. Any soft tissue tumour can present with myxoid areas ranging from benign to malignant. However, they are consistently associated with entities like myxoid liposarcoma, low-grade fibro-myxoid sarcoma, extraskeletal myxoid chondrosarcoma, myxofibrosarcoma, myxo-inflammatory fibroblastic sarcoma, and myxoid dermatofibrosarcoma protuberans.[1-4] Differential diagnosis of myxoid tumors is always challenging. The cellular organization, nuclear atypia, and vascular pattern aid the distinction. Many of these myxoid lesions have similar histopathological features, and it is extremely difficult for a pathologist to predict the behavior of these lesions.[5,6] Hence, there are greater chances of underestimating a high-grade tumor and vice versa. This mandates the use of ancillary techniques such as immunohistochemistry and molecular tests with clinical correlation for arriving at an accurate diagnosis.[1]

This study's objectives are to describe the histomorphological spectrum and vascular pattern among various myxoid soft-tissue tumors, to describe their demographic distribution, and to categorize these as benign, intermediate, and malignant. Differentiating various myxoid lesions requires careful

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evaluation of clinical, radiological, histological, and vascular patterns for initial categorization of tumor type for further immunological and molecular tests. In this study, we describe distinguishing histological and vascular patterns among various lesions and review of literature of myxoid soft-tissue tumors.

Materials and Methods

This was a retrospective and prospective descriptive observational study of myxoid soft-tissue tumors over a period of 13 years from January 2007 till December 2019, observed in Shimoga Institute of Medical Sciences, Shimoga, Karnataka. A list of all soft tissue lesions were made after reviewing the past 10 year registers and computer database (2007- 2016). From 2017, all the soft tissue neoplasm received in the department were also included for the study. The Hematoxylin and Eosin stained slides were retrieved from the storage facility and reviewed. All the cases showing myxoid changes were included in the study (n= 224). The clinical data and imaging, whenever available were correlated

The hematoxylin and eosin (H and E)-stained slides of these cases were reviewed to assess the histological features, especially the vascular pattern. The biopsy tissue received in the department of pathology was fixed overnight in 10% buffered formalin and submitted for processing. Paraffin sections were cut 4–6 microns in thickness, and routine H and E staining was performed. As per the WHO 2020 classification of soft-tissue tumors, the 224 cases included in the study were classified. Special stains and immunohistochemistry were performed whenever necessary. Radiological imaging and operative findings were scrutinized to know the anatomical extent of the tumor. Results were subjected to appropriate statistical analysis using SPSS v 24 software and the data are presented in the form of tables and charts. The demographic data were analyzed using means, proportions, and percentages.

Results

In this study, the predominant lesions were benign in 164 (73.21%) cases, followed by malignant lesions in 43 (19.19%) cases and intermediate lesions 17 (7.58%) cases [Table 1]. Benign and malignant lesions were seen predominantly in males; however, the intermediate lesions showed a female preponderance. The maximum benign lesions were seen in the age group of 21–30 years while that of intermediate lesions were seen in the age group of 41–60 years and malignant lesions in the age group of >60 years [Table 1]. Both benign and malignant lesions were seen to arise predominantly from the extremities.

The most common benign myxoid lesions in this study were of neural origin with myxoid neurofibroma constituting 65 (29. 01%) cases, followed by schwannoma 38 (16.9%) cases [Table 2]. Myxoid dermatofibrosarcoma protuberans was the most common intermediate lesion in this study with 15 (6.7%) cases. However, tumors with adipocytic differentiation were the predominant lesions in the malignant group, i.e myxoid liposarcoma seen in 17 (7.5%) cases [Table 2]. Figure 1a-e shows the various vascular patterns encountered in the myxoid soft-tissue neoplasms in this study.

Discussion

Mesenchymal tumors are one of the most challenging fields of diagnostic pathology for they are difficult to categorize just with histomorphology. Many a times, a mesenchymal tumor of neural origin may simulate that of fibrohistiocytic origin or that of any other differentiation, especially when associated with a myxoid change, and requires ancillary techniques to diagnose accurately. Refinement of classification schemes in the 2020 WHO blue book has eased the situation a bit and helps to take better therapeutic decisions.[7] The diagnostic accuracy of myxoid sarcomas ranges from 20% to 30% as mere histopathological features are insufficient to make an accurate diagnosis as it is done in epithelial malignancies.[8,9] Besides, they are rare and hence pathologists are not continuously exposed to these soft-tissue tumors to develop an expertise for accurate diagnosis.[7]

Virchow introduced the term "myxoma" to describe a soft-tissue tumor, histologically resembling the structure of

Table 1: The demographic details of various myxoid soft-tissue lesions categorized as benign, intermediate, and malignant

Category	*n* (%)	Mean age (years) Male: female ratio	Age group (years), *n* (%)	Site, *n* (%)
Benign	164 (73.21)	32.5 1.2:1	<40, 100 (60.9) 40-60, 24 (14.6) >60, 40 (24.3)	EX: 72 (43.9) HN: 18 (10.9) TA: 68 (41.4) DO: 6 (3.6)
Borderline	17 (7.58)	41.5 1:1.6	<40, 2 (11.7) 40-60, 15 (88.2)	EX: 2 (11.7) TA: 12 (70.5) DO: 3 (17.6)
Malignant	43 (19.19)	51.5 1:1.8	<40, 3 (6.9) 40-60, 12 (27.9) >60, 28 (65.1)	EX: 29 (67.4) HN: 2 (4.6) TA: 9 (20.9) DO: 3 (6.9)

EX: Extremities, HN: Head and neck, TA: Trunk and abdomen, DO: Deep body cavity and other organs

Table 2: Various myxoid soft-tissue tumors in this study with their vascular pattern, mitotic figures, and key diagnostic features

	Diagnosis, *n* (%)	Vascular pattern	Mitotic count	Key histological pattern and differentiating features considered
Benign	Myxoma, 21 (12)	A-20, H-1	I-21	Superficial/intramuscular, avascular and hypocellular, CD 34 +
	Angiomyxoma, 9 (5.4)	Ti-7, Th-2	I-7, II-2	Superficial, subcutis, multilobulated, poorly circumscribed spindle and stellate fibroblasts; thin-walled vessels
	Myxolipoma, 12 (7.3)	A-10, H-1, Ti-1	I-11, II-1	Superficial, mature adipocytes, hypovascular, no lipoblast
	Myxoid nodular fasciitis, 18 (10.9)	Ti-6, Th-10, C-2	I-13, II-5	Subcuticular, scant vascularity, short fascicles with tissue culture pattern, SMA +
	Myxoid neurofibroma, 65 (39.6)	Ti-45, Th-20	I-65	Spindle cells, neurofibrillary background, mast cells
	Ossifying fibromyxoid tumor, 1 (0.6)	Ti-1	I-1	Bone shell, thin vessels
	Schwannoma, 38 (23.1)	Ti-9, Th-28, C-1	I-38	Spindle cells, mast cells, Schwannian stroma, S-100 +
Borderline	Aggressive angiomyxoma, 2 (11.7)	Th-2	II-2	Deep seated, thick vessels, infiltrative margin
	Myxoid dfsp, 15 (88.2)	Ti-10, Th-3, C-1, Cf-1	I-14, II-1	Infiltrative sheets, bland spindle cells, thin vessels, scant mitosis
Malignant	Myxofibrosarcoma, 7 (16.2)	C-6, Cf-1	II-3, III-4	Subcutis occasionally intramuscular-Curvilinear vessels, hypo-Moderate cellularity
	Low-grade fibromyxoid sarcoma, 5 (11.2)	Ti-1, Ar-4	I-1, II-4	Intramuscular/deep-seated, arcuate vessels and MUC 4 +
	Myxoid liposarcoma, 17 (39.5)	Ti-1, C-2, Cf-14	II-13, III-4	Intramuscular, crow's feet/curvilinear vessels, univacuolated lipoblasts. MDM 2 +
	Malignant peripheral nerve sheath tumor, 6 (13.9)	Ti-2, Th-4	II-2, III-4	Marbling due to hypo- and hypercellular areas, monotonous hyperchromatic spindle cells, S 100, SOX 10 +
	Myxopapillary ependymoma, 4 (9.3)	Ti-2, Th-2	I-2, II-2	Ependymal canals lined by well-differentiated tumor cells
	Extraskeletal chondrosarcoma, 4 (9.3)	Ti-2, Th-2	I-1, II-3	Cords, trabeculae of tumor cells, hypovascular

Mitotic figures: I-0-5/10 HPF, II-5-10/10 HPF, III->10/10 HPF. A: Avascular, H: Hypovascular, Ti: Thin walled, Th: Thick walled, Ar: Arcuate, C: Curvilinear, Cf: Crow's feet vessels, SMA: Smooth muscle Actin, HPF: High-power field, S 100: Proteins are soluble in 100%, i.e., saturated, ammonium sulfate at neutral pH, SOX 10: SRY-box transcription factor 10, MUC 4: Mucin 4, MDM 2: Mouse double minute 2 homolog

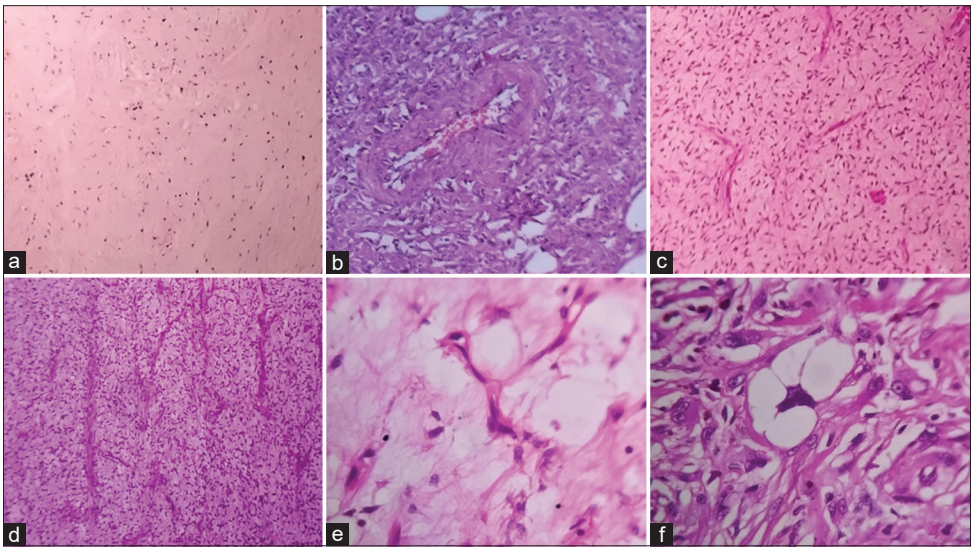

Figure 1: (a) Avascular myxoid pattern seen in myxoma (H and E, ×10), (b) Thick-walled vessels (H and E, ×40), (c) Curvilinear vessels (H and E, ×40), (d) Long arcade vessels (H and E, ×40), (e) Crow's feet vessels seen in myxoid liposarcoma (H and E, ×40), (f) Lipoblast in a De-differentiated liposarcoma (H and E, ×40)

the umbilical cord and had recognized the recurrent nature of some myxomatous tumors,[10] and it clarified that it is difficult to predict the exact clinical behavior of these different tumors based on their myxoid morphology alone. This group of tumors exhibits a broad range of biological behavior varying from those which are entirely benign to locally aggressive (but non metastasizing) behavior to those which are frankly malignant; hence, accurate histopathological diagnosis is essential to decide clinical management. Histological criteria (e.g. tumor demarcation, growth and vascular pattern, and nuclear

atypia) remain the hallmarks of diagnosis,[4] especially in a resource-limited setting as many of these neoplasms lack a distinct immunohistochemical profile. However, distinct chromosomal recurrent translocations have been identified in several myxoid sarcomas, including t (12;16) (q13; p11) FUS-DDIT3 in myxoid liposarcoma, t (7;16) (q34; p11) FUS-CREB3 L2 in low-grade fibromyxoid sarcoma, and t (9;22) (q31; q12) EWSR1-NR4A3 in extraskeletal myxoid chondrosarcoma which can be easily utilized for accurate diagnosis using dual-color, break-apart fluorescence *in situ* hybridization probes spanning the genomic regions.[11]

Lipoma with myxoid change is a common occurrence, and diagnostic clues include superficial location, monotonous adipocytes with mild pleomorphism, the absence of lipoblast, hypovascularity, and the absence of mouse double minute 2 homolog (MDM-2). In our series, majority of the myxoid lipoma showed avascular and uniform adipocytes with scant mitotic figures. In retroperitoneal cases,[2] the absence of lipoblasts, spindle cells, and the absence of MDM-2 helped us to reach the final diagnosis. Retroperitoneal myxoid neurofibromas were easily differentiated by their spindle cells, neurofibrillary stroma, and mast cells. Histologically myxoid liposarcoma consisted of undifferentiated nondescript small spindle cells and small univacuolated lipoblasts in a myxoid background. Delicate branching thin-walled crow's feet-like capillaries [Figure 1e] were consistently seen in all myxoid liposarcomas with low mitotic count unlike other malignant lesions. Multivacuolated lipoblasts were seen at periphery and in dedifferentiated areas [Figure 1f]. Myxoid liposarcoma at intramuscular plane had greater vascularity, lipoblasts, and variation in size of cells that differentiated it from myxoma in two cases.

Myxomas are paucicellular, relatively avascular lesions having small, bland, spindle- or stellate-shaped nuclei and inconspicuous cytoplasm. Abundant areas of myxoid stroma, which focally extend into deep muscle fibers at the periphery, were seen in two cases [Figure 1a]. The absence of vessels and pleomorphism in most cases excluded both myxoid liposarcoma and myxofibrosarcoma. S-100 protein negativity helped to exclude a myxoid neurofibroma or low-grade malignant peripheral nerve sheath tumor.

Most of the nodular fasciitis were uncapsulated but well-circumscribed lesions composed of myofibroblast having plump nuclei and loose collagenous stroma showing variable myxoid changes. The stroma contained delicate thin-walled capillaries, extravasated red blood cells, and scattered inflammatory cells, mainly lymphocytes and less often neutrophils. One case in a child had extensive myxoid change, but immunological CD 34 positivity and extravasated red cells, the absence of chicken-wire vessels, and tissue culture-like distribution of cells helped us in differentiating it from other myxoid lesions.

Angiomyxomas were mainly seen in adults at vulvovaginal region, head-and-neck region, on the trunk, and usually presented as a superficial, slowly growing nodular mass involving the dermis and subcutis. They were multilobulated, poorly circumscribed myxoid mass having plump, spindle, and stellate fibroblasts; numerous thin-walled vessels; and inflammatory cells. Occasional mitoses were seen, but pleomorphism was absent; three of our cases show mild nuclear hyperchromasia, which is probably degenerative. Two deep (aggressive) angiomyxomas were included in the study. These were large, arising from vulval region and showed prominent, thick walled, regularly spaced vascular channels with uniform less cellularity and infiltrative margin.

In our series, myxoid liposarcomas were distinguished from their myxoid counterparts by their greater vascularity and the presence of univacuolated lipoblasts. The close differentials such as intramuscular lipoma usually lack these features and myxofibrosarcoma usually have nuclear hyperchromasia, pleomorphism, and characteristic curvilinear vessels. Useful clues for round included retained crow's feet vessels, and small areas of mucin pooling. S-100 positivity and keen search for the presence of lipoblasts were most useful in two of our cases.

Myxoid pattern lesions are predominantly mesenchymal tumors (epithelial tumors with myxoid/mucoid matrix such as pleomorphic adenoma and colon carcinoma usually have characteristic features to diagnose accurately without ancillary techniques) which represent a group of neoplastic and nonneoplastic entities characterized by a background containing a prominent amount of myxoid or mucoid substances.[1] The extracellular myxoid matrix is heterogeneous and its chemical composition varies with tumor type and grade.[4] The myxoid matrix is made of glycosaminoglycans and albumin.[2] The varying nature of glycosaminoglycans is due to the differing amounts of hyaluronic acid, heparan sulfate, chondroitin-4, and chondroitin-6 sulfates and hence results in different tumor types and grades.[2] Although there is little difference in the chemical composition of the matrix in these tumors, it was found that extracellular matrix (ECM) formation in intramuscular myxoma is impaired compared to Grade I myxofibrosarcoma. Rho/Rock pathway and integrin activation, cell migration, and invasion result from increased rigidity of ECM and hence result in malignant transformation.[12] Histochemical analysis of myxoid matrix is replaced by newer immunological techniques nowadays. However, myxoid change is usually inversely related to metastatic rate in some tumors (e.g. myxofibrosarcoma and myxoid liposarcoma).

Conclusions

Despite many recent developments in ancillary techniques such as special stains, immunohistochemistry, *in situ* hybridization, and molecular genetics, the key histomorphological patterns and vascular features of myxoid soft-tissue tumors are still relevant for the baseline differentiation of these tumors and hence act as a guide for ancillary techniques for accurate diagnosis.

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Conflicts of interest
There are no conflicts of interest.

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