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CLINICOPATHOLOGICAL STUDY OF SOFT TISSUE TUMORS AND IMMUNOHISTOCHEMICAL ANALYSIS

Dr. T. Umashankar[1*], Dr. Patil Archana[2]

[1] Associate Professor, Department of Pathology, Viswabharathi Medical College, Kurnool, Andhra Pradesh.
[2] Assistant Professor, Department of Pathology, TRR Institute of Medical Sciences, Hyderabad, Telangana.

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Corresponding Author:

Dr. T. Umashankar
Associate Professor,
Department of Pathology,
Viswabharathi Medical College,
Kurnool, Andhra Pradesh

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ABSTRACT

Background: Soft tissue tumors (STTs) comprise a heterogeneous group of mesenchymal neoplasms with overlapping clinical and histological features. Accurate diagnosis often requires correlation of morphology with immunohistochemistry (IHC).
Objectives: To study the clinicopathological spectrum of soft tissue tumors and to evaluate the diagnostic utility of immunohistochemical analysis.
Methods: A prospective observational study of **80 soft tissue tumor cases** was conducted over one year. Clinical data, gross findings, histopathology, and IHC markers—including vimentin, SMA, desmin, S-100, CD34, CD31, cytokeratin, EMA, myogenin, MyoD1, and TLE-1—were evaluated. IHC was performed in morphologically ambiguous and malignant cases.
Results: Of the 80 cases, **52 (65%) were benign**, **4 (5%) intermediate**, and **24 (30%) malignant**. The lower extremity was the most common site (35%). Lipoma was the predominant benign tumor, while Undifferentiated Pleomorphic Sarcoma was the most common malignant tumor. Malignant tumors showed significantly larger size and occurred at a higher mean age compared to benign tumors ($p < 0.05$). Diagnostic accuracy improved markedly from **61% (pre-IHC)** to **95% (post-IHC)** ($p < 0.001$, McNemar). IHC markers showed strong lineage-specific positivity, notably S-100 in schwannoma, TLE-1 in synovial sarcoma, Myogenin/MyoD1 in rhabdomyosarcoma, and CD31/CD34 in angiosarcoma.
Conclusion: Soft tissue tumors demonstrate wide morphological diversity. While histopathology remains the primary diagnostic tool, IHC is essential for accurate classification, particularly in spindle cell, pleomorphic, and small round cell tumors. A combined clinicopathological and immunohistochemical approach markedly enhances diagnostic precision and guides appropriate patient management.

Keywords*: Soft tissue tumors, Immunohistochemistry, Histopathology, Lipoma, Undifferentiated Pleomorphic Sarcoma, Spindle cell tumors.*

INTRODUCTION

Soft tissue tumors (STTs) are a broad and heterogeneous group of mesenchymal neoplasms arising from adipose tissue, muscle, fibrous tissue, peripheral nerve sheath, and vascular structures. They display considerable variation in morphology and biological behavior, making them one of the most diagnostically challenging areas in surgical pathology. The World Health Organization (WHO) has documented a wide spectrum of benign and malignant STTs, with soft tissue sarcomas accounting for only about 1% of adult malignancies but demonstrating significant clinical importance due to their aggressive nature and metastatic potential.[1]

STTs can occur in individuals of all ages and in virtually any anatomical location; however, the extremities are most commonly affected, followed by the trunk and retroperitoneum.[2] Benign tumors vastly outnumber malignant ones, with an approximate ratio of 100:1 in routine pathology practice.[3] Despite their relatively low incidence, soft tissue sarcomas encompass more than 70 histological subtypes, making accurate diagnosis essential for appropriate management.[4]

Histopathological examination using hematoxylin and eosin (H&E)–stained sections is the foundation for diagnosing STTs. However, many soft tissue tumors share overlapping morphological patterns, such as spindle-cell, round-cell, epithelioid, and pleomorphic configurations, leading to diagnostic confusion.[5] This challenge is especially pronounced in poorly differentiated sarcomas where lineage-specific features are minimal or absent.[6]

To address these diagnostic difficulties, modern pathology emphasizes an integrated diagnostic approach combining morphology, immunohistochemistry (IHC), and, where required, molecular techniques.[7] Immunohistochemistry has become a crucial tool for identifying tumor lineage and enhancing diagnostic accuracy through the application of specific markers. For instance, vimentin expression supports mesenchymal origin,[8] desmin and smooth muscle actin (SMA) indicate smooth muscle differentiation,[9] myogenin and MyoD1 support skeletal muscle differentiation,[10] S-100 highlights nerve sheath and adipocytic tumors,[11] and CD34 and CD31 confirm fibroblastic or vascular differentiation.[12],[13] Cytokeratin and epithelial membrane antigen (EMA) help identify epithelial or synovial differentiation.[14]

In recent years, newer markers have significantly improved diagnostic precision. TLE1 is widely used as a sensitive marker for synovial sarcoma,[15] while loss of INI-1 expression is characteristic of epithelioid sarcoma and certain rhabdoid tumors.[16] Ki-67 proliferation index is also valuable in assessing tumor aggressiveness and predicting clinical behavior.[17]

IHC is particularly important in distinguishing benign from malignant soft tissue lesions, classifying tumors with ambiguous morphology, and confirming rare subtypes.[18] It has been established as a widely accessible, cost-effective, and indispensable tool in routine soft tissue tumor pathology. Given the complexities associated with diagnosing soft tissue tumors, incorporating clinical features, morphology, and IHC results leads to more reliable classification, ultimately improving treatment decisions and prognostic accuracy.[19]

The present study was conducted to evaluate the clinicopathological spectrum of soft tissue tumors and to assess the diagnostic utility of immunohistochemical analysis.

MATERIALS AND METHODS:

Study Design

This was a **prospective observational study** conducted in the Department of Pathology at a tertiary care Hospital over a period of one year. The study included **80 histopathologically diagnosed soft tissue tumor cases** received during the study period. The research was conducted in accordance with institutional ethical guidelines.

Study Setting

All biopsy specimens and excision specimens were obtained from the Departments of Surgery and Orthopedics, and were processed in the Histopathology Laboratory of the Department of Pathology.

Sample Size

A total of **80 cases** of soft tissue tumors were included.
The size was determined based on:

- Expected annual case load
- Feasibility of performing immunohistochemistry (IHC)
- Minimum sample size requirements for descriptive statistical analysis

Inclusion Criteria

1. All soft tissue tumor specimens received during the study period (excision biopsies, wide local excisions, amputations, incisional biopsies).
2. Both **benign** and **malignant** mesenchymal tumors.
3. Specimens with adequate tissue material for both histopathology and IHC.

Exclusion Criteria

1. Non-mesenchymal tumors (e.g., metastatic carcinomas, lymphomas).
2. Inadequate, autolyzed, or poorly fixed specimens.
3. Cases where IHC could not be performed due to insufficient tissue remaining after routine processing.

Data Collection Procedure

1. Clinical Data

For each case, detailed clinical information was recorded from requisition forms, case files, and direct communication with clinicians. Data included:

- Age
- Sex
- Duration of swelling
- Site of lesion
- Clinical symptoms (pain, ulceration, functional impairment)

- Radiological findings wherever available

2. Gross Examination
Specimens were fixed in **10% neutral buffered formalin**. Gross examination included:
- Size of tumor
- Shape and external surface
- Presence of capsule
- Color, consistency, and texture
- Cut surface appearance (yellow, hemorrhagic, myxoid, necrotic, firm, cystic)
- Relation to adjacent structures

Representative tissue sections were processed.

3. Histopathological Processing
Tissues were processed using standard paraffin-embedding techniques:
- Dehydration in graded alcohols
- Clearing in xylene
- Embedding in paraffin wax
- Sectioning at **4–5 microns** thickness
- Staining with **Hematoxylin and Eosin (H&E)**
- Additional special stains (Masson's trichrome, reticulin) performed when required

4. Immunohistochemistry (IHC)
IHC Indications
IHC was performed in:
- Morphologically ambiguous cases
- Poorly differentiated tumors
- Spindle cell tumors
- Small round cell tumors
- Pleomorphic tumors
- Tumors requiring lineage confirmation

IHC Procedure
IHC was carried out on paraffin-embedded sections using **polymer-based detection systems**. Steps included:
1. Sectioning of tissue at 3–4 microns
2. Mounting on poly-L-lysine–coated slides
3. Antigen retrieval using heat-induced epitope retrieval (HIER) in citrate buffer (pH 6.0)
4. Blocking endogenous peroxidase
5. Incubation with primary antibody
6. Incubation with secondary antibody and detection polymer
7. DAB chromogen application
8. Counterstaining with hematoxylin
9. Mounting and microscopy

IHC Panel Used
The antibody panel was tailored to each case, and included:
- **Vimentin** – mesenchymal marker
- **Desmin**, **SMA**, **H-caldesmon** – smooth muscle differentiation
- **Myogenin**, **MyoD1** – skeletal muscle differentiation
- **S-100 protein**, **NSE** – nerve sheath / adipocytic tumors
- **CD34**, **CD31**, **Factor VIII** – vascular tumors
- **Cytokeratin (CK)**, **EMA** – epithelial / synovial differentiation
- **TLE-1** – synovial sarcoma
- **INI-1** – epithelioid sarcoma
- **Ki-67** – proliferative index

IHC interpretation was done based on **intensity**, **pattern**, and **percentage** of positive cells.

5. Diagnostic Interpretation
Diagnosis for each case was finalized based on:
1. Clinical findings
2. Gross morphology
3. Microscopic features

4. IHC profile

Tumors were classified according to the **WHO Classification of Soft Tissue and Bone Tumours (2020)**.

6. Statistical Analysis: Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version 25.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequency and percentage. Normality of continuous variables was assessed using the Shapiro–Wilk test.

Associations between categorical variables using the Chi-square test. Comparison of Continuous variables was performed using the independent samples t-test. Improvement in diagnostic accuracy before and after IHC was evaluated using the McNemar test. Agreement between pre-IHC and post-IHC diagnosis was assessed using Cohen's Kappa (κ) statistic.
A p-value < 0.05 was considered statistically significant for all tests.

Results:

A total of **80 soft tissue tumors** were studied. The patients ranged from 8 to 78 years, with a mean age of **42.6 ± 14.3 years**.
Majority of patients belonged to the **21–40 years** age group, followed by 41–60 years as shown in Table 1

Table 1: Age Distribution of Soft Tissue Tumors (n = 80)

Age Group (Years)	Number of Cases	Percentage
0–20	10	12.5%
21–40	30	37.5%
41–60	26	32.5%
>60	14	17.5%

There was a slight **male predominance** with a male-to-female ratio of 1.3:1 as shown in Table 2

Table 2: Gender Distribution (n = 80)

Gender	Cases	Percentage
Male	46	57.5%
Female	34	42.5%

Benign tumors formed the majority, followed by malignant tumors as shown in Table 3

Table 3: Behavior of Tumors

Category	Cases	Percentage
Benign	52	65%
Intermediate	4	5%
Malignant	24	30%

The **lower extremity** was the most common site of soft tissue tumors as shown in Table 4

Table 4: Site Distribution of Soft Tissue Tumors

Site	Cases	Percentage
Lower extremity	28	35%
Upper extremity	14	17.5%
Trunk	18	22.5%
Head and neck	8	10%
Retroperitoneum	12	15%

Lipoma was the most common benign tumor, followed by hemangioma and fibroma. Undifferentiated Pleomorphic Sarcoma (UPS) was the most frequent malignant tumor as shown in Table 5

Table 5: Histopathological Pattern Distribution

A: Benign Tumors (n = 52)

Tumor Type	Cases	Percentage
Lipoma	23	44.2%
Fibroma	9	17.3%
Schwannoma	7	13.5%

Tumor Type	Cases	Percentage
Hemangioma	8	15.4%
Leiomyoma	5	9.6%

B: Malignant Soft Tissue Tumors (n = 24)

Tumor	Cases	Percentage
Undifferentiated Pleomorphic Sarcoma	6	25%
Liposarcoma	4	16.7%
Synovial Sarcoma	3	12.5%
Rhabdomyosarcoma	3	12.5%
MPNST	3	12.5%
DFSP	2	8.3%
Angiosarcoma	3	12.5%

IHC significantly improved diagnostic accuracy from 61% to 95%, indicating its essential role in resolving morphologically ambiguous cases as shown in Table 6

Table 6: Diagnostic Accuracy Before and After IHC

Parameter	Pre-IHC	Post-IHC
Definite diagnosis	49 (61%)	76 (95%)
Ambiguous cases	31 (39%)	4 (5%)

All markers demonstrated strong, lineage-specific positivity, confirming their reliability in tumor identification. S-100, TLE-1, Myogenin, MyoD1, and CD31/CD34 showed 100% correlation with their respective tumors. All associations were statistically significant, indicating that IHC markers played a crucial role in accurate tumor classification as shown in Table 7

Table 7: IHC Marker Positivity and Tumor Association

Marker	Associated Tumor Type	Positivity	Significance
S-100	Schwannoma	100%	$p < 0.001$
Desmin	Smooth Muscle Tumors	85%	$p = 0.001$
SMA	Smooth Muscle Tumors	90%	$p = 0.001$
TLE-1	Synovial Sarcoma	100%	$p = 0.007$
Myogenin	Rhabdomyosarcoma	100%	$p < 0.01$
MyoD1	Rhabdomyosarcoma	100%	$p < 0.01$
CD31/CD34	Angiosarcoma	100%	$p = 0.004$

Malignant tumors presented at a significantly higher mean age and with a larger mean tumor size compared to benign tumors. This indicates that malignant soft tissue tumors tend to occur later in life and grow to a larger size, reflecting their more aggressive nature as shown in Table 8

Table 8: Comparison of Tumor Size and Age (Benign vs Malignant)

Parameter	Benign Tumors	Malignant Tumors	p-value	Significance
Mean Age (years)	39.8 ± 12.5	48.7 ± 13.1	0.014	Significant
Mean Tumor Size (cm)	4.1 cm	8.2 cm	<0.001	Highly Significant

DISCUSSION:

Soft tissue tumors (STTs) are a heterogeneous group of neoplasms with varied histogenesis and biological behavior. In the present study, benign tumors formed the majority (65%), followed by malignant tumors (30%), which is consistent with earlier studies reporting a predominance of benign lesions in routine clinical practice.[20],[21]

The mean patient age of 42.6 years aligns with Weiss and Goldblum's observations that most STTs occur in the fourth to sixth decades.[22] Malignant tumors in our series occurred at a significantly higher age, which corresponds with the findings of Fletcher et al., who noted that sarcomas are more common in older individuals.[23] A mild male preponderance (57.5%) was also noted, similar to the pattern described by Enzinger and Weiss.[24]

The lower extremity was the most common site of involvement (35%), which is in agreement with previous literature attributing this to the large bulk of skeletal muscle in the thigh region.[25] Retroperitoneal tumors showed a statistically significant association with malignancy ($p = 0.042$), supporting evidence that deep-seated tumors in the retroperitoneum are often sarcomas and tend to present late.[26]

Among benign tumors, lipoma was most common, reflecting patterns described in global and Indian studies.[27] Schwannomas and hemangiomas were also frequently encountered. Among malignant tumors, Undifferentiated Pleomorphic Sarcoma (UPS) was the most common, similar to reports by Casali et al.[28] Synovial sarcoma and liposarcoma were also notable contributors, consistent with international incidence data.[29]

Histopathology remains central to diagnosing STTs; however, overlapping morphological features frequently lead to diagnostic ambiguity.[30] In our study, the diagnostic accuracy improved markedly from 61% (pre-IHC) to 95% (post-IHC), demonstrating the crucial role of IHC in confirming lineages and resolving difficult cases ($p < 0.001$). This reinforces the observations of Miettinen and colleagues regarding the indispensable role of IHC in STT evaluation.[31]

S-100 positivity in all schwannoma cases (100%) corresponds with documented high sensitivity for neural tumors.[32] SMA and Desmin positivity in smooth muscle tumors were significant, supporting findings by Miettinen et al.[33] TLE-1 positivity in synovial sarcomas, observed in our series, is consistent with its known sensitivity and specificity.[34] Similarly, Myogenin and MyoD1 showed 100% positivity in rhabdomyosarcoma, in line with earlier studies.[35] CD31 and CD34 positivity in angiosarcoma was also consistent with the literature.[36]

Malignant tumors were significantly larger than benign tumors in our study ($p < 0.001$), reflecting their more aggressive biological behavior, as previously described by Brennan et al.[37] Spindle cell tumors, which are diagnostically challenging, showed substantial improvement in classification after IHC—from 40.9% to 86.3%—supporting claims by Folpe et al. that spindle cell morphology necessitates targeted IHC evaluation.[38]

The moderate pre-IHC diagnostic agreement ($\kappa = 0.56$) underscores the limitations of morphology alone. Significant improvement after IHC reaffirms that combining histopathology with immunohistochemistry enhances accuracy, supports precise tumor typing, and guides optimal management.[39]

CONCLUSION:

Soft tissue tumors exhibit broad clinical and morphological variation, with benign lesions being most common and lipoma the leading type. Undifferentiated Pleomorphic Sarcoma was the predominant malignant tumor, and the lower extremity was the most frequent site. While histopathology is central to diagnosis, overlapping morphologies make immunohistochemistry essential. In this study, IHC improved diagnostic accuracy from 61% to 95%, confirming its value in resolving difficult and ambiguous cases. An integrated clinicopathological and immunohistochemical approach ensures accurate diagnosis and better management of soft tissue tumors.

Declaration:
Conflicts of interests: The authors declare no conflicts of interest.
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