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Original Article

Epithelioid Sarcoma: Clinicopathological Spectrum and Its Diagnostic Challenges

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ABSTRACT

Epithelioid sarcoma (ES) is a rare, aggressive soft tissue malignancy with epithelioid morphology that poses significant diagnostic challenges due to overlap with other tumors. **Aims**: To outline clinicopathological features of ES, identify its immunohistochemical (IHC) profile, and highlight diagnostic pitfalls. **Methods**: A retrospective cross-sectional study of 400 soft tissue tumors (July 2023–August 2025) at a tertiary center screened for epithelioid morphology (n=4 confirmed ES). Clinicopathological data, histomorphology, and IHC (CK, EMA, vimentin, S100, CD34, INI1, H3K27me3) were reviewed. **Results**: Of 400 tumors, 3.5% were malignant (n=14), with 4 showing epithelioid morphology reclassified as ES (3 classic/distal, 1 proximal). Mean age: 40 years (range: 29–49); male predominance (75%). Sites: thigh/trunk (75%), perineal (25%). All showed INI1 loss (100%); CK/EMA/vimentin positive (100%). Rhabdoid cells correlated with proximal type. One case metastasized to lungs; one patient died within 10 months. **Conclusion**: INI1 loss is diagnostic; integrated clinicopathological-IHC approach enhances accuracy. Early multidisciplinary management is crucial for this aggressive tumor.

Keywords*: Epithelioid sarcoma, soft tissue tumors, INI1 loss, immunohistochemistry, diagnostic pitfalls.*

INTRODUCTION

Epithelioid sarcoma (ES) is a rare, aggressive soft tissue malignancy accounting for <1% of all soft tissue tumors. It typically presents as slow-growing, painless dermal/subcutaneous masses in the distal extremities of young adults, yet shows 40–45% rates of local recurrence and metastasis. Its epithelioid morphology and immunophenotypic overlap with melanoma, carcinoma, and other sarcomas create significant diagnostic challenges, making immunohistochemistry (IHC) essential for accurate identification.

AIMS AND OBJECTIVES

1. To outline the clinicopathological features of epithelioid sarcoma across age, gender, location, and morphological patterns.
2. To identify the immunohistochemical profile for epithelioid sarcoma using a targeted diagnostic panel for precise diagnosis.
3. To identify major diagnostic pitfalls due to its morphological overlap.

MATERIALS AND METHODS

Study Design: Retrospective cross-sectional study.
Study Setting: Tertiary hospital-based single-center study.
Study Duration and Period: 2 years; July 2023 to August 2025.

Sample Size: n=400 (with 4 tumors having morphology of epithelioid sarcoma).
Case Retrieval: Patient particulars and clinical details were obtained from the Medical Records Department (MRD) section of the study center.
Case Selection: Histopathologically diagnosed soft tissue tumors (June 2023–2025) were included.
Screening and Clinical Data: Tumors with epithelioid morphology were screened; demographic and anatomical data were recorded.

Cytohistomorphological Review: Architectural patterns, necrosis, stroma, and cell morphology were evaluated. Blocks were re-sectioned for IHC.

Immunohistochemistry: IHC performed using panel: CK, EMA, vimentin, S100, CD34, INI1, H3K27me3.
Final Diagnosis: Diagnosis established by correlating morphology with IHC findings.
Statistical Analysis: Descriptive statistics; chi-square test for morphology vs. INI1 status.

RESULTS

Of 400 soft tissue tumors, 385 (96.25%) were benign and 14 (3.5%) malignant (Table 1). Malignant types included adipocytic (21.45%), tumors of uncertain differentiation (28.57%), and others (Table 2). Four cases showed epithelioid morphology on H&E, initially diagnosed as epithelioid rhabdomyosarcoma (25%), epithelioid angiosarcoma (25%), epithelioid MPNST (25%), and epithelioid leiomyosarcoma (25%) (Table 3). Reclassification confirmed 3 classic/distal ES and 1 proximal ES, all with INI1 loss (100%).

Demographics: Mean age 40 years (range 29–49); male:female ratio 3:1 (Figure 1). Anatomical distribution: lower limb/thigh (75%), perineal/inguinoscrotal (25%) (Figure 2). IHC: CK/EMA/vimentin positive in 100%; CD34 positive in 75%; INI1 loss in 100% (Table 4). Rhabdoid cells present in 75% (proximal type). Fine-needle aspiration cytology showed epithelioid cells in clusters (Figure 3).

Detailed case summaries (Table 5): One case metastasized to lungs; one patient died within 10 months post-diagnosis.

Table 1: Distribution of total no. of soft tissue tumors (n=400)

CATEGORISATION OF SOFT TISSUE TUMORS	NUMBER OF CASES:	PERCENTAGE %
NO. OF BENIGN SOFT TISSUE TUMORS	385	96.25%
NO. OF MALIGNANT SOFT TISSUE TUMORS	14	3.50%
TOTAL	399~ 400	100%

Table 2: Types of Malignant Soft Tissue Tumors/Sarcomas (n=14)

TYPE OF SARCOMA	LOCATION IN BODY:	NO. OF CASES	% of case
ADIPOCYTIC(LIPOSARC OMAS) TUMORS	THIGH, DEEP SOFT TISSUE, RETROPERITON EUM	3 (1: WELLDIFFERENTIATED, 1: PLEOMORPHIC, 1: MYXOID)	21.45
2)FIBROBLASTIC/ MYOFIBROBLASTIC TUMORS	HAND	1 (ADULT FIBROSARCOMA)	7.14
3)SMOOTH MUSCLE/LEIOMYOSARCOMA	UTERUS, INGUINOSCROTAL	2	14.28
4)SKELETAL MUSCLE /RHABDOMYOSARCOMA	PARASPINAL MUSCLE, HEAD & NECK	2 (1:ALVEOLAR,1:PLEOMORPHIC)	14.28
5)VASCULAR TUMORS	THIGH	1 (ANGIOSARCOMA)	7.14
7)PERIPHERAL NERVE SHEATH TUMORS	THIGH	1 (MPNST)	7.14
8)TUMORS OF UNCERTAIN DIFFERENTIATION	TRUNK, HEAD & NECK, LOWER LIMB	4 (1:SYNOVIAL,2:EXTRASKELETAL EWINGS, 1:SPINDLE CELL SARCOMA)	28.57
	TOTAL NO. OF CASES :	14 IN TOTAL	100

Table 3: Soft tissue sarcoma with epithelioid morphology (n=4)

Category on H&E	Number of cases	Percentage
EPITHELIOID RHABDOMYOSARCOMA	1	25%
EPITHELIOID ANGIOSARCOMA	1	25%
EPITHELIOID MPNST	1	25%
EPITHELIOID LEIOMYOSARCOMA	1	25%
	TOTAL	100%

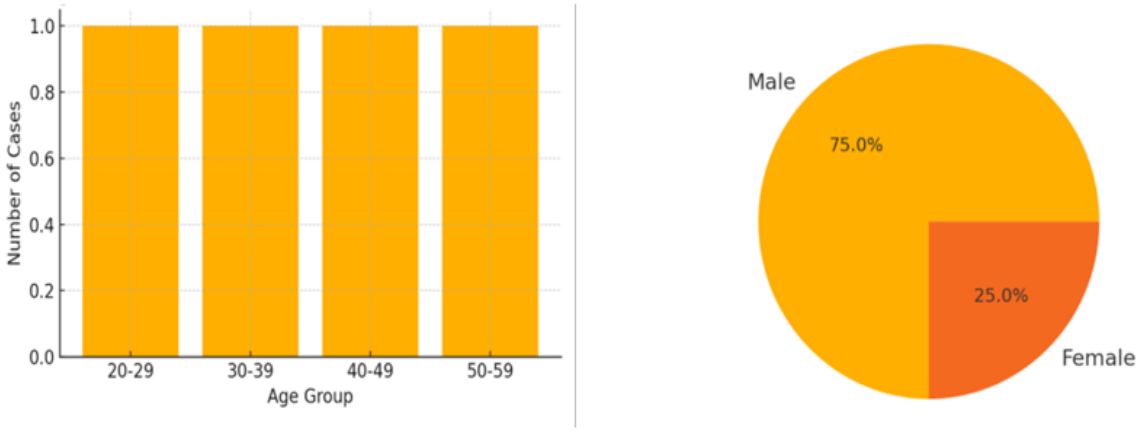

Figure 1: Distribution of different cases of ES according to age and gender:

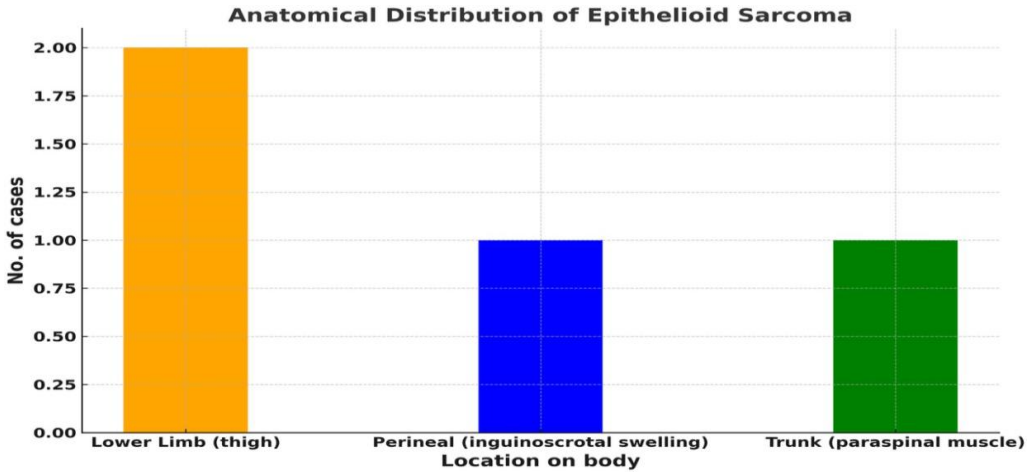

Figure 2: Anatomical distribution of epithelioid sarcoma:

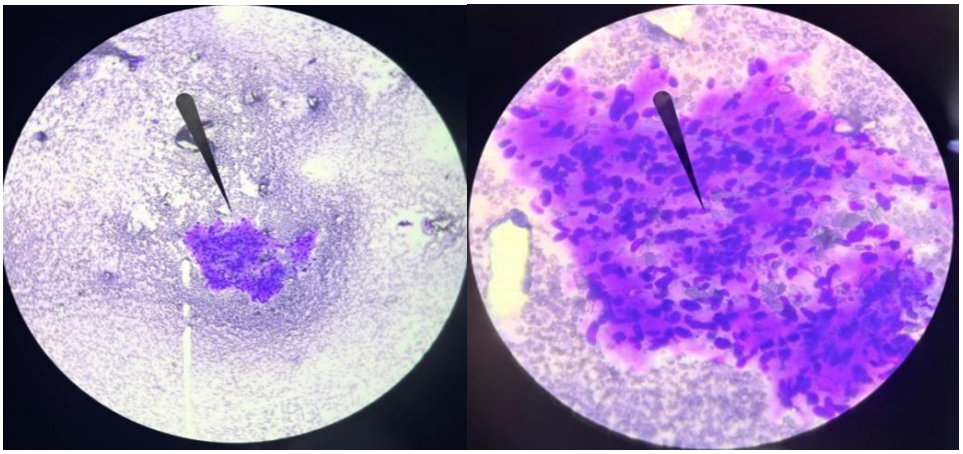

Figure 3: On FNA:

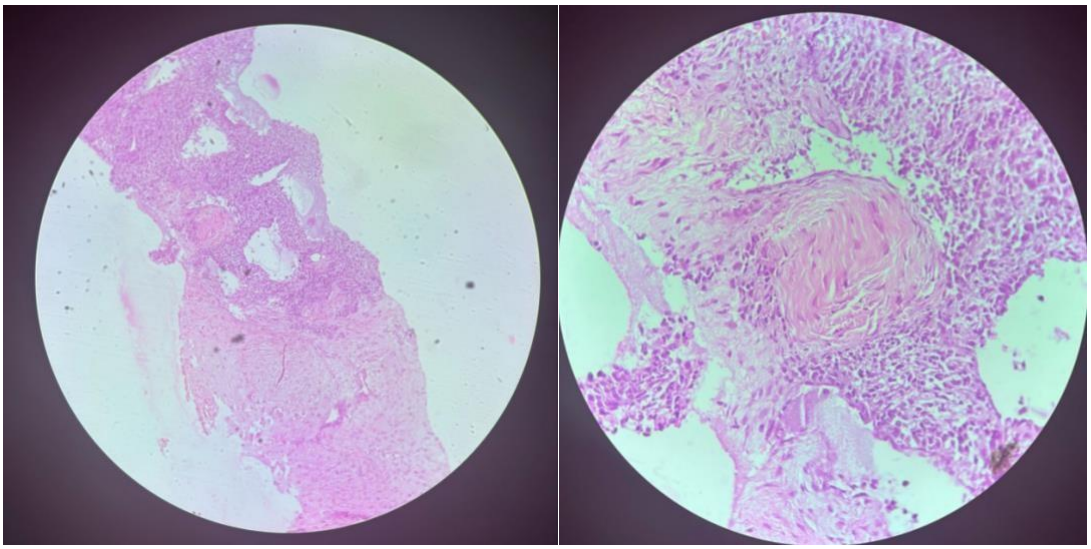

Figure 4: On HPE: Epithelioid MPNST: A)-10X H&E, B) -40X H&E

Table 4: IHC Expression Status of Soft Tissue Sarcoma having epithelioid morphology (n=4)

IHC MARKER	POSITIVE STATUS	NEGATIVE STATUS
CYTOKERATIN	4	0
EMA	4	0
VIMENTIN	4	0
CD34	3	1
INI1 LOSS *	3	1
DESMIN	2	2
MYOD1	1	3
S100	1	3
H3K27meu	1	3
SOX10	0	4

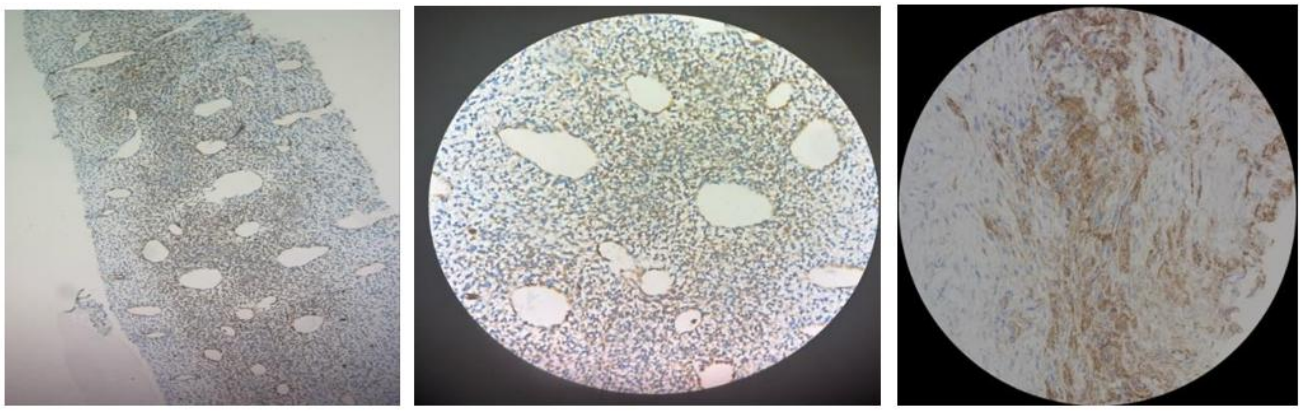

Fig: CYTOKERATIN +

Fig: VIMENTIN+ + +

Fig: EMA +

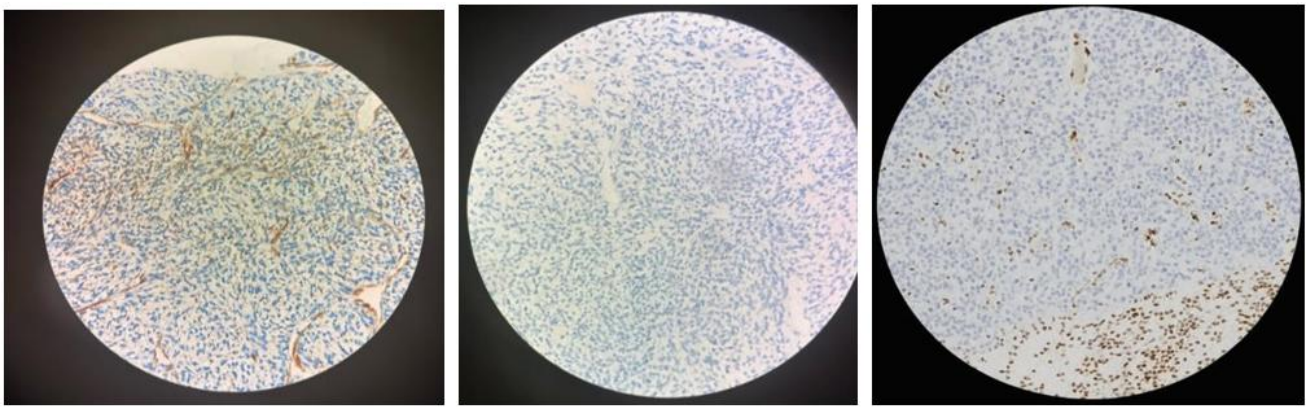

Fig: CD34 + Fig: S100 neg Fig:INI1 loss noted

Table 5: Epithelioid Sarcomas with clinicopathological features, HPE diagnosis, IHC panel, final diagnosis & follow-up

Sl no.	AGE	GENDER	LOCATION	CLINICAL FEATURES	HPE DIAGNOSIS	RHABDOID CELLS +/-	IHC PANEL	FINAL DIAGNOSIS	METASTASIS	TREATMENT AND FOLLOW- UP
1	29 years	MALE	PARASPINAL MUSCLE	RAPIDLY ENLARGING PAINFUL MASS	EPITHELIOID RHABDOMYOSARCOMA	+	CD34+, DESMIN+,CK+ ,MYOD1+, INI1 LOSS	PROXIMALES	ABSENT	SURGERY FOLLOWED BY 9 CYCLES OF INTENSIVE CHEMOTHERAPY .NOW ON MAINTENANCE THERAPY
2	37 years	FEMALE	THIGH	PAINFUL ENLARGING MASS, RED NODULES ON SKIN	EPITHELIOID ANGIOSARCOMA	_	CD34/31+,CK+	CLASSIC/ DISTALES	PRESENT, TO LUNGS	SURGERY + 6 CYCLES OF CHEMOTHERAPY
3	45 years	MALE	THIGH	SWELLING WITH DISCHARGING PUS	EPITHELIOID MPNST	+	S100-,CD34 +,SOX10- ,INI1LOSS,H3 K27MEU RETAINED	PROXIMALES	ABSENT	1 CYCLE OF RT FOLLOWED BY 2 CYCLES OF CHEMOTHERAPY
4	49 years	MALE	INGUINOSCROTAL SWELLING	PAINLESS MASS	EPITHELIOID LEIOMYOSARCOMA.	+	SMA+,DESMIN+, INI1 LOSS PATCHY	PROXIMALES	ABSENT	SURGERY + CHEMOTHERAPY, DIED WITHIN 10 MONTHS OF DIAGNOSIS

DISCUSSION

The present study demonstrates a strong correlation between morphology (rhabdoid cells presence) and likelihood of proximal epithelioid sarcoma, supporting previous literature. INI1/SMARCB1 loss was consistently diagnostic across cases, reinforcing its role as the single most reliable marker for epithelioid sarcoma differentiation. High degree of mimicry with carcinomas, angiosarcoma, MPNST, granulomatous lesions led to frequent initial misdiagnosis. Combined histomorphology and focused IHC panel (CK, EMA, CD34, INI1 loss) increases diagnostic accuracy significantly. Early

recognition is vital due to aggressive behavior, evidenced by metastasis in one case and poor outcome in another (Table 6).

The study by Hasegawa et al. (2001), a retrospective analysis, examined proximal-type epithelioid sarcoma and found that all tumors were positive for cytokeratin (CK), epithelial membrane antigen (EMA), and vimentin, with 14 out of 20 cases exhibiting a MIB1 index of 30% or more. This led to the conclusion that proximal epithelioid sarcoma represents a rare form of undifferentiated sarcoma characterized by epithelioid features and a poor prognosis.

In a similar retrospective study, Jagdale et al. (2009) reported on 5 cases of proximal epithelioid sarcoma and 2 cases of classic epithelioid sarcoma. Immunohistochemically, all tumors reacted positively for CK, EMA, vimentin, and Ca-125, while also demonstrating loss of INI1 expression. The authors concluded that the co-expression of epithelial and mesenchymal markers, combined with reactivity for CD34 and Ca-125 along with INI1 loss, is key to clinching the diagnosis of epithelioid sarcoma.

Asano et al. (2015) conducted another retrospective study focusing on prognostic factors, noting that proximal epithelioid sarcoma and large, deep-seated tumors were more frequent in adults. They identified lymph node metastasis as having the strongest negative impact on survival, with tumor sizes greater than 5 cm and positive surgical margins also associated with poor outcomes. This work confirms epithelioid sarcoma as a high-grade sarcoma with generally poor survival rates.

Das et al. (2021), in a case-control study, reported a median age of diagnosis for epithelioid sarcoma at 34 years (range: 17-80 years), with INI1 loss observed in all confirmed cases. The study emphasized that loss of INI1 is a characteristic feature, and highlighted tazemetostat—an FDA- approved therapy—as a promising option for metastatic cases.

In the present study from Gauhati Medical College and Hospital (GMCH) Guwahati (2023-2025), also a retrospective analysis, rhabdoid morphology combined with deep soft tissue involvement was identified as a key indicator raising suspicion for proximal epithelioid sarcoma. Furthermore, INI1 loss emerged as the most critical marker for differentiating it from mimics. Overall, the findings underscore that an integrated clinicopathological and immunohistochemical (IHC) approach is essential for accurate diagnosis.

Limitations:

- Retrospective design dependent on archival blocks and available clinical documentation.
- Limited follow-up period.

CONCLUSION

Epithelioid sarcoma is rare but aggressive. Rhabdoid morphology with deep location raises suspicion for proximal epithelioid sarcoma. INI1 loss is the most critical diagnostic marker. An integrated clinicopathological + IHC approach is essential for accurate diagnosis. Early detection and multidisciplinary management improve patient outcomes.

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