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Epithelioid Sarcoma on Fine Needle Aspiration Cytology: A Case Series Highlighting Diagnostic Challenges

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KEYWORDS

Epithelioid sarcoma, fine needle aspiration cytology, soft tissue sarcoma, INI1 (SMARCB1), immunohistochemistry,

Abstract

Background

Epithelioid sarcoma is a rare malignant soft tissue tumor that poses significant diagnostic challenges, particularly on fine needle aspiration cytology (FNAC), owing to its wide morphological variability and close resemblance to inflammatory and other neoplastic conditions. Early cytological recognition is crucial to avoid misdiagnosis and treatment delay.

Objective

To describe the cytomorphological spectrum of epithelioid sarcoma on FNAC and to highlight the diagnostic utility and limitations of FNAC through a **case series** with histopathological and immunohistochemical correlation.

Methods

This case series includes **three patients** with epithelioid sarcoma presenting at different anatomical sites with variable clinical duration and presentation. FNAC was performed in all cases, followed by histopathological examination of biopsy or excision specimens. Cytological findings were systematically correlated with histopathology and immunohistochemistry.

Results

FNAC smears across all cases were moderately to highly cellular and demonstrated dispersed epithelioid to plasmacytoid tumor cells with occasional spindle-shaped cells in a necrotic background. The tumor cells exhibited abundant cytoplasm, eccentrically placed nuclei, vesicular chromatin, and prominent nucleoli, with mild to marked nuclear pleomorphism. Histopathological examination revealed nodular tumors composed of sheets and nests of plump oval to polygonal cells with eosinophilic cytoplasm, frequent mitotic activity, areas of myxoid change, and extensive necrosis. Immunohistochemistry showed tumor cell positivity for cytokeratin and epithelial membrane antigen (EMA) in all cases, with complete loss of nuclear INI1 (SMARCB1) expression, confirming the diagnosis of epithelioid sarcoma, including both conventional and proximal-type variants.

Conclusion

Epithelioid sarcoma remains a significant diagnostic challenge on FNAC due to its cytomorphological heterogeneity and overlap with other malignancies. The presence of plasmacytoid or rhabdoid cells, necrotic background, and mixed cellular population on cytology should raise suspicion for this entity. FNAC serves as a valuable initial diagnostic tool; however, definitive diagnosis requires histopathological confirmation and immunohistochemical correlation, particularly demonstration of INI1 loss. Awareness of the cytological spectrum of epithelioid sarcoma is essential for accurate diagnosis and timely management.

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INTRODUCTION

Epithelioid sarcoma is an uncommon malignant mesenchymal neoplasm occurring in both paediatric and adult populations, characterized by epithelioid cellular morphology and expression of epithelial markers.[1] The tumor is broadly classified into two distinct subtypes: conventional (distal) type and proximal type.[1,2] The conventional variant typically comprises epithelioid to spindle-shaped cells arranged in a characteristic pseudogranulomatous pattern with central necrosis, whereas the proximal type is composed predominantly of large epithelioid cells with rhabdoid morphology and demonstrates more aggressive clinical behavior.[1,2] Immunohistochemically, epithelioid sarcoma consistently shows positivity for cytokeratin and epithelial membrane antigen (EMA), along with a distinctive loss of nuclear INI-1 (SMARCB1) expression, which serves as a valuable diagnostic marker.[3]

The cytological diagnosis of epithelioid sarcoma is particularly challenging due to significant morphological overlap with a variety of other neoplasms exhibiting epithelioid features.[4] Fine needle aspiration cytology (FNAC) is most commonly utilized in recurrent or metastatic disease, especially when the lesion is superficially located and easily accessible for sampling. The cytopathological literature on epithelioid sarcoma remains limited, consisting largely of isolated case reports and small case series.[4,5,6,7] Consequently, the full spectrum of cytomorphological features of this tumor is not yet completely characterized. In view of these diagnostic challenges and limited cytological documentation, the present case is reported to highlight the FNAC features of epithelioid sarcoma with histopathological and immunohistochemical correlation.

- M. Miettinen *et al.*

CASE REPRESENTATION

Case 1

A middle-aged male presented with a slowly progressive mass over the left gluteal region, first noticed approximately 15 years prior to presentation. The lesion was initially small and asymptomatic but gradually increased in size and eventually ulcerated. There was no history of trauma or significant comorbid illness.

On clinical examination, a large ulcerated mass with irregular margins and areas of necrosis was noted over the left gluteal region. Fine needle aspiration cytology (FNAC) was performed from the lesion. The smears were moderately cellular and showed dispersed round to polygonal tumor cells along with occasional spindle-shaped cells. The cells had abundant cytoplasm and eccentrically placed nuclei with prominent nucleoli, imparting a plasmacytoid appearance. Nuclear pleomorphism was mild to moderate. The background revealed extensive necrosis and cellular debris. Based on these findings, a malignant soft tissue neoplasm was suspected.

A wedge biopsy was subsequently performed. Grossly, a greyish-white to greyish-brown soft tissue fragment measuring 2 × 2 cm was received. Histopathological examination revealed a nodular tumor composed of plump oval to polygonal cells arranged in sheets and nests. The tumor cells exhibited eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, with mild to moderate pleomorphism and frequent mitotic activity (12 per 10 high-power fields). Occasional spindle-shaped cells were noted at the periphery of tumor nodules. Areas of myxoid change, extensive necrosis, and mild inflammatory infiltrate were also present.

Immunohistochemical analysis showed tumor cell positivity for cytokeratin and epithelial membrane antigen (EMA), with complete loss of nuclear INI1 (SMARCB1) expression. These findings confirmed the diagnosis of epithelioid sarcoma, proximal type.

Case 2

A 32-year-old female presented with a painless, slowly enlarging nodular swelling over the dorsum of the right hand for 3 years. The lesion had gradually increased in size without ulceration or skin discoloration. There was no prior surgical intervention or trauma at the site.

Local examination revealed a firm, non-tender subcutaneous nodule measuring approximately 3 × 2 cm. FNAC yielded moderately cellular smears composed predominantly of dispersed and loosely

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cohesive epithelioid cells. The tumor cells were round to polygonal with moderate to abundant cytoplasm and centrally to eccentrically placed nuclei showing vesicular chromatin and conspicuous nucleoli. Occasional spindle-shaped cells were identified. Mild nuclear pleomorphism was present. The background showed focal necrosis and scattered inflammatory cells. A cytological impression of a malignant epithelioid soft tissue tumor was rendered, with differential diagnoses including epithelioid sarcoma and carcinoma.

Wide local excision of the lesion was performed. Histopathological examination revealed a multinodular tumor involving the dermis and subcutaneous tissue. The nodules were composed of epithelioid cells arranged in sheets and short fascicles, with central areas of necrosis giving a pseudogranulomatous appearance. The tumor cells showed eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli, and moderate mitotic activity. Peripheral spindle cell areas were also identified.

On immunohistochemistry, the tumor cells were diffusely positive for cytokeratin and EMA, with retained vimentin expression. Nuclear expression of INI1 was completely lost in tumor cells. A final diagnosis of conventional (distal-type) epithelioid sarcoma was made.

Case 3

A 45-year-old male presented with a recurrent mass in the left inguinal region. He had undergone excision of a similar lesion at the same site 4 years earlier, the details of which were unavailable. The current lesion had been progressively increasing in size for 8 months and was associated with mild discomfort.

Clinical examination revealed a firm, ill-defined deep-seated mass measuring approximately 6 × 5 cm. FNAC smears were highly cellular and demonstrated dispersed large epithelioid cells with abundant dense cytoplasm. The nuclei were eccentrically placed, pleomorphic, and showed prominent nucleoli. Several cells exhibited rhabdoid morphology. Occasional spindle cells were present. The background was hemorrhagic with extensive necrosis. Based on cytological features, a diagnosis of malignant epithelioid neoplasm was considered, favoring epithelioid sarcoma.

Core biopsy was performed for confirmation. Histological sections showed a poorly circumscribed tumor composed of sheets of large epithelioid cells with rhabdoid features infiltrating the surrounding soft tissue. The cells displayed abundant eosinophilic cytoplasm, marked nuclear pleomorphism, prominent nucleoli, and frequent atypical mitoses. Extensive necrosis was noted.

Immunohistochemically, the tumor cells showed strong positivity for cytokeratin and EMA. There was complete loss of nuclear INI1 expression. Based on morphological and immunophenotypic findings, a diagnosis of proximal-type epithelioid sarcoma was established.

necrosis, and mild inflammatory infiltrate were also noted.

Immunohistochemical analysis revealed that the tumor cells were positive for cytokeratin and epithelial membrane antigen (EMA). Notably, there was a loss of nuclear INI1 expression in tumor cells, confirming the diagnosis of epithelioid sarcoma.

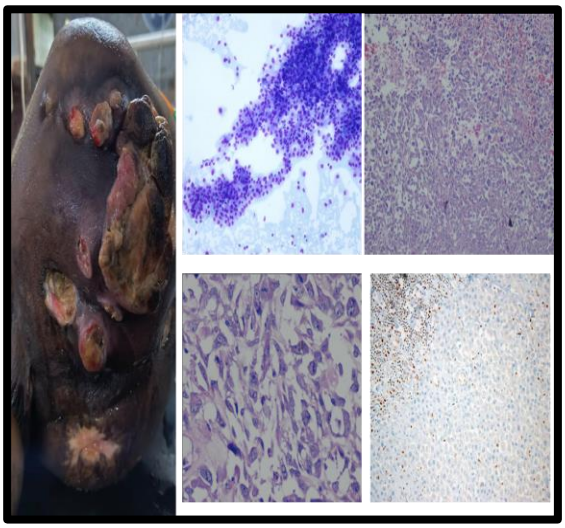

Figure 1-5

- Clinical photograph showing a large, ulcerated, irregular mass involving the left gluteal region with areas of necrosis, consistent with a long-standing soft tissue tumor.

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- Fine needle aspiration cytology smear showing dispersed round to polygonal tumor cells with occasional spindle-shaped cells in a necrotic background (MGG stain, ×100).
- Histopathological section demonstrating a nodular growth pattern composed of sheets and nests of plump oval to polygonal tumor cells with eosinophilic cytoplasm and areas of necrosis (Hematoxylin and Eosin stain, ×100).
- High-power view showing tumor cells with vesicular nuclei, prominent nucleoli, mild to moderate pleomorphism, and occasional spindle cells at the periphery (Hematoxylin and Eosin stain, ×400).
- Immunohistochemistry showing loss of nuclear INI1 (SMARCB1) expression in tumor cells, confirming the diagnosis of epithelioid sarcoma (INI1, ×200).

Discussion

Epithelioid sarcoma is a rare and aggressive soft tissue sarcoma that continues to pose significant diagnostic challenges due to its marked morphological heterogeneity and close resemblance to a wide spectrum of benign and malignant entities. In the present case series, the tumors demonstrated considerable variation in clinical presentation, anatomical location, and disease duration, yet shared characteristic cytomorphological and immunophenotypic features that were critical in establishing the diagnosis. The presence of epithelioid morphology with plasmacytoid and rhabdoid features, deep soft tissue involvement, and extensive necrosis observed across the cases—particularly in proximally located lesions—raised strong suspicion for proximal-type epithelioid sarcoma, a variant known for its aggressive behavior and unfavorable prognosis.[8]

The correlation between rhabdoid morphology and proximal-type epithelioid sarcoma observed in our series is consistent with previously published literature. Hasegawa et al. (2001), in their landmark clinicopathological study of 20 cases, characterized proximal-type epithelioid sarcoma as a distinct entity composed predominantly of large epithelioid cells with rhabdoid features and aggressive clinical behavior. All tumors in their series expressed cytokeratin and epithelial membrane antigen (EMA), supporting epithelial differentiation, and most showed a high proliferative index, underscoring their malignant potential.[9] The morphological and immunophenotypic features observed in the proximal-type tumors in our series closely parallel these findings.

One of the most consistent and diagnostically valuable features across all three cases in the present series was the complete loss of nuclear INI1 (SMARCB1) expression. This finding served as a decisive factor in confirming the diagnosis in each case, particularly in the setting of overlapping cytomorphology. The uniform loss of INI1 reinforces its role as the single most reliable immunohistochemical marker for epithelioid sarcoma differentiation. Similar observations were reported by Jagdale et al. (2009), who emphasized that co-expression of epithelial markers (cytokeratin, EMA) with mesenchymal markers such as vimentin, along with CD34 positivity and INI1 loss, is critical in establishing a definitive diagnosis in both proximal and conventional epithelioid sarcoma.[10]

Fine needle aspiration cytology, although a valuable initial diagnostic modality, remains particularly challenging in epithelioid sarcoma due to its pronounced cytological mimicry. In the present case series, FNAC smears consistently revealed dispersed epithelioid to plasmacytoid tumor cells with occasional spindle-shaped cells and a necrotic background, leading to a broad differential diagnosis that included carcinoma, angiosarcoma, malignant peripheral nerve sheath tumor (MPNST), and granulomatous lesions. This high degree of morphological overlap is well documented and frequently results in initial misdiagnosis, as also highlighted in previous studies.[11,12] The presence of necrosis and inflammatory background, especially in long-standing or recurrent lesions, further compounds the diagnostic difficulty.

Prognostic implications of epithelioid sarcoma were evident when the findings of the present series were viewed in light of existing literature. Asano et al. (2015), in their retrospective analysis of 44 patients,

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identified proximal tumor location, large tumor size, deep soft tissue involvement, lymph node metastasis, and positive surgical margins as adverse prognostic factors.[13] In our series, cases with deep-seated and proximal-type morphology exhibited features traditionally associated with aggressive biological behavior, emphasizing the importance of early and accurate diagnosis even though long-term follow-up data were limited.

The clinical relevance of early recognition is further supported by the findings of Das et al. (2021), who reported universal loss of INI1 expression across all confirmed cases of epithelioid sarcoma in their cohort. Their study also highlighted the emerging role of targeted therapy, particularly tazemetostat—an FDA-approved EZH2 inhibitor—for patients with metastatic or unresectable disease.[14] Awareness of this therapeutic implication further underscores the importance of precise pathological diagnosis.

Additional retrospective studies by Frezza et al. (2020), Zhang et al. (2021), and Shi et al. (2021) have consistently documented high rates of local recurrence, metastasis, and poor clinical outcomes in epithelioid sarcoma, reinforcing its aggressive nature.[15,16,17] Kashyap et al. (2022), in an Indian tertiary-care center experience, similarly emphasized delayed diagnosis and unfavorable outcomes, particularly in proximal-type tumors, highlighting the relevance of these findings in the Indian subcontinent.[18]

In summary, this case series highlights the diagnostic complexity of epithelioid sarcoma on FNAC and underscores the importance of recognizing key cytomorphological clues, including plasmacytoid or rhabdoid cells, necrotic background, and mixed cellular populations. While FNAC serves as a valuable screening tool, definitive diagnosis requires histopathological confirmation and immunohistochemical correlation, particularly demonstration of INI1 loss. Heightened awareness of the cytological spectrum of epithelioid sarcoma among cytopathologists is essential to facilitate early diagnosis, guide appropriate management, and potentially improve patient outcomes.

Conclusion

This case underscores the diagnostic complexity of epithelioid sarcoma on FNAC and highlights the pivotal role of INI1 loss in confirming the diagnosis. Given the tumor's aggressive behavior and therapeutic implications, heightened awareness among cytopathologists and the use of an integrated clinicopathological and immunohistochemical approach are essential for early and accurate diagnosis.

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