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BRIEF REPORT

WILEY

Rhabdomyosarcoma with epithelioid morphology: A challenging cytologic diagnosis in a pleural effusion

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Abstract

Rhabdomyosarcomas (RMS) are rare malignant skeletal muscle tumors that present more commonly in pediatric populations. The WHO currently classifies RMS into four types, embryonal, alveolar, pleomorphic, and spindle cell/sclerosing variants. Epithelioid rhabdomyosarcoma (EpiRMS) is another rare, recently described subtype of RMS presenting in older patients with a male predominance and has a rapidly progressive clinical course with frequent metastases. EpiRMS closely mimics poorly differentiated carcinoma or melanoma, demonstrating discohesive large epithelioid cells with abundant eosinophilic cytoplasm, frequent glassy cytoplasmic inclusions, large vesicular nuclei, and prominent nucleoli. We present a case of metastatic rhabdomyosarcoma with features reminiscent of EpiRMS presenting as a pleural effusion, closely followed by an inguinal lymph node biopsy. The malignant cells in the pleural fluid were diffusely positive for desmin, negative for MyoD1, myogenin, S100 and SOX10, and retained INI-1 expression. Subsequent lymph node biopsy demonstrated identical malignant epithelioid cells that were positive for desmin, myoD1 and myogenin, and a cytological diagnosis of "metastatic rhabdomyosarcoma, favor epithelioid rhabdomyosarcoma" was given considering the concurrent lymph node biopsy morphology and immunoprofile. A diagnosis of rhabdomyosarcoma, though rare and challenging, should not be overlooked when considering malignant cells with an epithelioid morphology in cytology specimens.

KEYWORDS
cytopathology, effusion, rhabdomyo, sarcoma, sarcoma, soft tissue

1 | INTRODUCTION

Rhabdomyosarcomas (RMS) are malignant skeletal muscle tumors that are more common in pediatric populations. The WHO currently recognizes four classifications of RMS, embryonal, alveolar, pleomorphic, and spindle cell/sclerosing variants.[1] Other subclassifications have also been described in the literature. All RMS subtypes demonstrate morphologic and immunophenotypic features of rhabdomyoblastic differentiation with varying clinicopathologic and histological features. Epithelioid rhabdomyosarcoma (EpiRMS)[2] is a recently described, distinct variant of RMS. According to published cases, EpiRMS primarily affects older patients, median age of 70.5 years (age range 14 to 78), with a male predilection (2:1 M:F).[2] The clinical course is rapidly progressive with frequent regional metastasis to lymph nodes and distant metastasis, often to the lungs.[2] EpiRMS has been reported to arise intramuscularly or subcutaneously in the upper and lower extremities, head and neck, and trunk regions.[2]

Morphologically, the diagnosis of EpiRMS can be elusive, as it closely mimics poorly differentiated carcinoma or melanoma, demonstrating discohesive large epithelioid cells with abundant eosinophilic

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cytoplasm, frequent glassy cytoplasmic inclusions, vesicular nuclei, and prominent nucleoli.

Renshaw, et al. previously reported an EpiRMS diagnosed in a pleural effusion cytological specimen.[3] We present this challenging case of RMS with a similar epithelioid morphology that highlights the diagnostic difficulty that may arise in making the cytologic diagnosis of RMS.

2 | CASE REPORT

A 71-year-old male presented to the emergency department with an enlarging rectal mass, night sweats, weight loss and progressive shortness of breath over 1 month. CT and MRI pelvis with and without contrast showed a rapidly enlarging ill-defined pelvic soft tissue mass, expanding from 3.0 × 4.5 cm to 11.5 × 8.1 cm in 20 days. Enlarged contralateral inguinal lymph nodes were also noted on imaging. CT chest with intravenous contrast showed bilateral pleural effusions with atelectasis and multiple pulmonary nodules bilaterally, consistent with metastatic disease. Thoracocentesis and lymph node biopsies were performed, however, the patient died 5 days later.

3 | MATERIALS AND METHODS

Thoracocentesis was performed and the obtained pleural fluid was prepared for cytological analysis by the ThinPrep® method and a formalin-fixed paraffin embedded cell block. Immunohistochemical staining for cytokeratin AE1/AE3, desmin, MyoD1, myogenin, S100, SOX10, calretinin and INI-1/SMARCB1 was performed on separate unstained slides from the cell block.

A subsequent ultrasound-guided inguinal lymph node biopsy was performed 1 day later. The lymph node tissue was suspended in formalin to prepare a paraffin-embedded block for histology. Sections were stained with hematoxylin and eosin and immunohistochemical examination was performed, with a broader panel, including antibodies towards cytokeratin AE1/AE3, cytokeratin 20, cytokeratin 7, cytokeratin 5/6, INI-1/SMARCB1, NKX3.1, CDX2, TTF-1, PAX8, GATA3, PSA, myogenin, MyoD1, desmin, caldesmon, MIB1/KI67, synaptophysin, chromogranin, CD56, WT-1, and calretinin.

4 | RESULTS

Pleural fluid cytomorphologic and cell block evaluation revealed sheets of uniformly large, discohesive, malignant-appearing epithelioid cells (Figure 1A,B). Tumor cells had abundant eosinophilic, globular cytoplasm, eccentrically placed vesicular nuclei, irregular nuclear contours, and prominent nucleoli. Most cells displayed prominent rhabdoid cytoplasmic inclusions (Figure 1C). No cytoplasmic cross striations or strap cells were noted. By immunohistochemistry, the tumor cells were diffusely positive for desmin (Figure 1D) and negative for cytokeratin AE1/AE3, MyoD1, myogenin, calretinin, S100 and SOX10. Tumor cells retained INI-1/SMARCB1 expression.[4]

The lymph node biopsy was concurrently assessed with the cytological specimen and demonstrated an identical population of large malignant cells with epithelioid morphology, eccentrically placed nuclei, abundant pale eosinophilic cytoplasm, and prominent glassy cytoplasmic inclusions (Figure 2A-C). Tumor cells were diffusely positive for desmin, and in contrast to the cytological specimen, were strongly positive for myogenin (Figure 2D) and MyoD1 (consistent with rhabdomyoblastic differentiation). MIB1/Ki-67 revealed a high proliferation index (up to 50%). Tumor cells were nonreactive for keratins (cytokeratin AE1/AE3, cytokeratin 7, cytokeratin 20, cytokeratin 5/6), GATA3, PAX8, TTF-1, CDX2, NKX3.1 and PSA, calretinin, WT-1, CK5/6, caldesmon, synaptophysin, chromogranin, with weak membranous positivity for CD56. Tumor cells retained INI-1/SMARCB1 expression. Given the morphology of the tumor cells in both the cytology and biopsy specimens, and immunopositivity for desmin, MyoD1 and myogenin in the biopsy tissue, a cytological diagnosis of "metastatic rhabdomyosarcoma, favor epithelioid rhabdomyosarcoma" was given.

5 | DISCUSSION

The limited tissue and rapid clinical course of the patient's disease precluded definitive classification of this rhabdomyosarcoma. The unusual epithelioid morphology of this tumor was morphologically reminiscent of recently described EpiRMS.[2] On cytology, EpiRMS exhibits features of a high-grade malignancy characterized by sheets to clusters of malignant epithelioid rhabdoid cells with abundant eosinophilic, homogeneous cytoplasm, and large vesicular nuclei with irregular nuclear contours.[2,4] Rhabdoid inclusions, glassy eosinophilic round cytoplasmic inclusions, with eccentrically placed nuclei may be seen. Nucleoli are prominent, similar to those seen in melanoma. Increased mitotic figures and tumor necrosis are common.[2]

EpiRMS may be difficult to distinguish from other high-grade entities, however, there are clues to this diagnosis. EpiRMS lacks the striking pleomorphism and large multinucleated polygonal rhabdomyoblasts with dense cytoplasm and cross striations seen in pleomorphic RMS, and instead demonstrates cells with more size uniformity.

Embryonal RMS can demonstrate primitive mesenchymal cells in various phases of myogenesis, and typically have alternating cellular and myxoid areas, none of which were seen in this specimen. Differentiation of rhabdomyoblasts can become more prominent in a posttherapy setting, however, our patient had not undergone any previous therapy.[1]

Alveolar RMS (ARMS), in cytology specimens, typically present with discohesive monomorphic small round blue cells with scant cytoplasm, unlike what we find in this case. To definitely rule out ARMS, specific molecular testing for PAX3-FOXO1 and PAX7-FOXO1 may be performed.[1] Given these considerations, a diagnosis of RMS with epithelioid features was favored over the WHO described subtypes.

Immunohistochemical staining of EpiRMS, according to previous literature, exhibits focal to diffuse desmin staining and retained INI-1 expression.[2] Furthermore, Jo, et al., reported negative S100-protein reactivity in all cases, and rare cytokeratin positivity in a subset (4 of 16 cases). There is variability in the literature regarding staining for

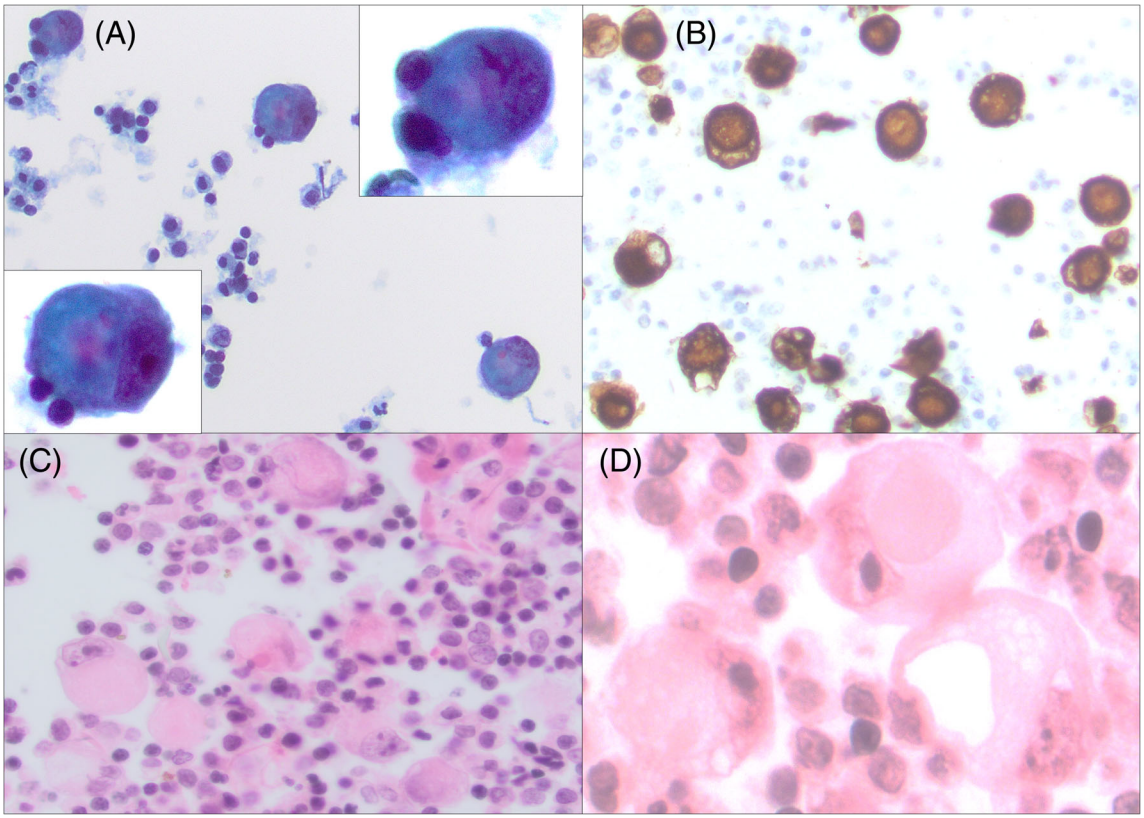
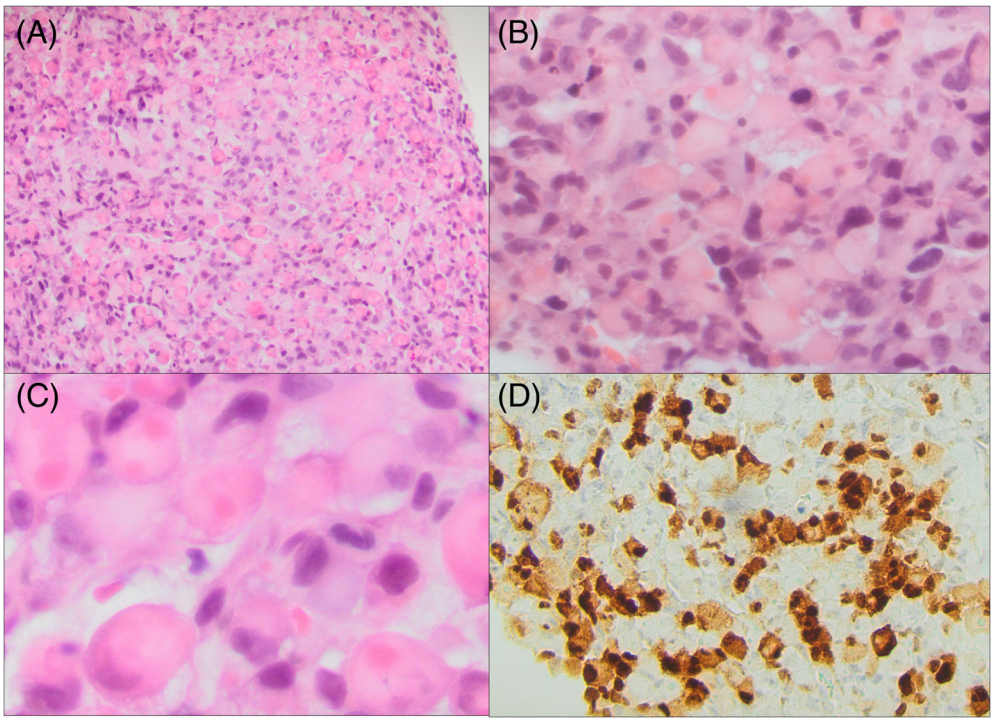


FIGURE 1 A, 400×- (inset Figures 600×) magnification Diff-Quik-stained cytological smear shows rhabdomyoblastic cells with eccentric nuclei and a central eosinophilic cytoplasmic globule. B, 400×- Immunohistochemical staining of the cell block by desmin shows diffuse positivity in rhabdomyoblastic cells. C, 400×- and D, 600×- H&E-stained section of the cell block shows discohesive large cells with abundant eosinophilic cytoplasm, eccentric, pleomorphic nuclei, and prominent nucleoli

FIGURE 2 A, 200×- B, 400×- and C, 600×- H&E-stained section of the lymph node biopsy demonstrates sheets of large epithelioid cells with eccentrically placed nuclei, abundant pale eosinophilic cytoplasm with prominent glassy cytoplasmic inclusions, and prominent nucleoli. D, 200×- Immunohistochemical staining for myogenin is seen within the rhabdomyoblastic cells



rhabdomyoblastic differentiation (myogenin and MyoD1)[5] from negative to multifocal to diffusely positive immunostaining for myogenin and MyoD1.[2,3,6] In broader terms, variability of staining of MyoD1 and Myogenin amongst the four different subtypes of RMS is described in the WHO.[1] Overall, in a limited cytological specimen with cells with rhabdoid morphology, it is important not to rule out RMS given inconsistent myogenin/myoD1 staining.

The uncommon morphology of this case illustrates the importance of considering rhabdomyosarcoma in a cytology specimen with malignant epithelioid cells.

Other tumors which can exhibit a similar morphologic phenotype include sarcomatoid carcinoma, melanoma, and malignant peripheral nerve sheath tumor (MPNST). In this case, immunohistochemistry revealed no evidence of epithelial differentiation (negative for cytokeratin AE1/AE3, cytokeratin 7, cytokeratin 20 and cytokeratin 5/6), melanocytic differentiation (negative for S100 and SOX10) or neural differentiation (negative for SOX10 and S100) and retained INI-1/SMARCB1 expression. While MPNST can have heterologous differentiation (ie, Malignant Triton Tumor), the tumor tissue in our case did not exhibit a high grade spindle cell component typically seen in such cases. Tumor cells retained INI-1/SMARCB1 expression, arguing against other tumors, such as MPNST, proximal type epithelioid sarcoma, and malignant extrarenal rhabdoid tumor.[7,8]

Careful morphologic evaluation and the pragmatic use of immunohistochemical stains are important for accurate diagnosis of rhabdomyosarcoma with epithelioid features in a cytology specimen with limited tissue. Also, pathologists should be aware of potential inconsistent staining pattern of MyoD1 and myogenin in limited specimens. When expanding an immunohistochemistry panel of epithelioid tumors of unknown primary, we advise including desmin, myogenin and MyoD1. Requesting additional tissue in order to perform a more extensive immunostain panel should also be considered.

CONFLICT OF INTEREST

No conflicts of interest declared.

AUTHOR CONTRIBUTIONS

Shannon Rodgers, Lagnajita Datta and Chad H. Stone contributed to report conception, data acquisition, data analysis and interpretation and manuscript writing and editing. Kyle D. Perry contributed to report conception, data analysis and manuscript editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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