Received: 22 November 2022 | Revised: 8 March 2023 | Accepted: 23 March 2023

DOI: 10.1111/cup.14433

CASE STUDY

JCP JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Cutaneous myoepithelioma with *EWSR1* gene rearrangement and its differentials: A diagnostic challenge

Chiamaka L. Okorie BSc[1] | Shaofeng Yan MD, PhD[1,2] | Darcy A. Kerr MD[1,2] | Laura J. Tafe MD[1,2] | Aravindhan Sriharan MD[1,2]

[1]Geisel School of Medicine at Dartmouth College, Lebanon, New Hampshire, USA

[2]Department of Pathology and Laboratory Medicine, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, USA

Correspondence
Chiamaka L. Okorie, Geisel School of Medicine at Dartmouth College, Lebanon, NH 03756, USA.
Email: chiamaka.l.okorie.med@dartmouth.edu

Abstract

Cutaneous myoepithelioma is a rare benign soft tissue neoplasm of myoepithelial cells involving the skin and subcutis. These tumors can be diagnostically challenging. The plasticity of myoepithelial cells leads to wide variability in the cytomorphology, immunophenotype, and genetic features of myoepithelioma. Their protean presentations may mimic malignant neoplasms. Therefore, distinction from malignancy is essential. Herein, we report a case of cutaneous myoepithelioma presenting similarly to Ewing sarcoma, with small round blue cells and an *EWSR1* rearrangement. Our case highlights the important morphologic, immunohistochemical, and cytogenetic features of this benign basaloid cutaneous tumor.

KEYWORDS

cutaneous, Ewing sarcoma, EWSR1, myoepithelial neoplasm, myoepithelioma, skin, soft tissue

1 | INTRODUCTION

Benign and malignant neoplasms of myoepithelial cells constitute a rare group of tumors. Involvement of the salivary gland is the best known, but extra-salivary myoepithelial neoplasms, such as those arising in the skin and soft tissue, are becoming increasingly characterized.[1–4] Myoepithelial neoplasms are classified as mixed tumors, myoepithelioma, or myoepithelial carcinoma.[1,3] Cutaneous myoepithelioma is a benign soft tissue neoplasm with predominant myoepithelial differentiation mainly involving the skin and subcutis.[3] Myoepitheliomas can be diagnostically challenging, given their variable cytomorphology, immunophenotype, and genetic features.[2,3] The variable cell morphology and stromal features make for a challenging histopathologic diagnosis. While cutaneous myoepithelioma is benign,[2,3] as a result of these variable presentations, it can mimic malignant neoplasms.

Our patient's cutaneous myoepithelioma showed an Ewing sarcoma RNA-binding protein 1 gene (*EWSR1*) rearrangement detected using fluorescence in situ hybridization (FISH). *EWSR1* rearrangement, while first described in malignant small round cell Ewing sarcoma, is known to play a role in a wide range of neoplasms.[2,5,6] That myoepithelioma is associated with translocation of EWSR1 has been well established,[7] with studies reporting it as present in up to 45% of cases.[1,2,8,9] Not only did our patient's cutaneous myoepithelioma share this *EWSR1* rearrangement with Ewing sarcoma but it also was composed of small round blue cells. Here, we discuss the distinct clinical, histopathologic, immunohistochemical, and genetic features enabling the distinction of myoepithelioma from other mostly malignant neoplasms that may prove helpful in future cases.

2 | CASE REPORT

A 59-year-old female with Fitzpatrick Type II skin was seen at a referring clinic for a routine full-body skin examination. During the visit, she reported a lesion on her right distal lateral thigh that had been enlarging for several years. She reported no accompanying pain or systemic symptoms. The patient noted, and her record confirmed, that the lesion grew on a previously biopsied area 20 years ago. The previous biopsy revealed extensive necrosis of a hyperkeratotic lesion per clinical documentation only, as the full report and biopsy slides were not accessible. Examination revealed a 1 cm pink-purple nodule just above the knee (Figure 1). A shave biopsy of only a portion of the lesion was performed, with a clinical differential of dermatofibroma versus other. Histopathologically, the biopsy specimen showed a diffuse dermal proliferation of

basaloid cells with scant cytoplasm in nodules, small islands, and cords (Figure 2A–D). Marked nuclear pleomorphism was not seen, and rare mitotic figures were identified (1 mitotic figure per 10 HPF). By immunohistochemistry, tumor cells showed diffuse and robust expression of S100 protein and SOX10 (Figure 3A,B), partial membranous staining for CD99, and focal expression of GFAP, EMA, and CEA. The cells were negative for INSM1, CKAE1/3, CK5, Melan-A, calponin, p63, actin, MITF, and PAX7. FISH, by break-apart probe, was positive for *EWSR1* gene rearrangement. FISH interrogation of potential fusion partner genes was not performed.

A diagnosis of myoepithelial neoplasm was made. Because the lesion was transected at the base, the tumor growth pattern at the deep portion of the lesion could not be evaluated; thus, it was not possible to entirely rule out myoepithelial carcinoma. Complete excision was recommended for comprehensive evaluation and treatment. The completely excised lesion showed no infiltrative growth and no perineural or lymphovascular invasion, confirming the diagnosis of myoepithelioma. With clear margins on excision, the lesion required no further treatment.

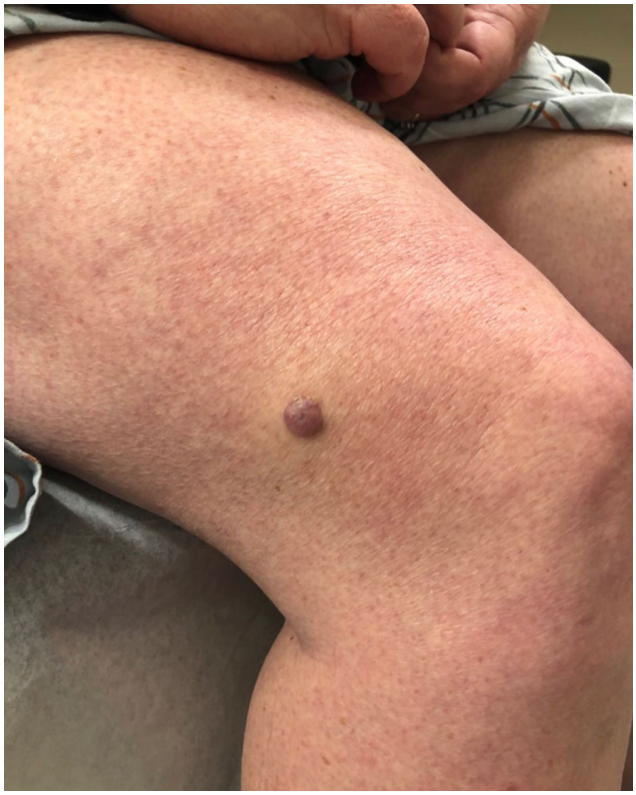

FIGURE 1 Single 1 cm pink-purple nodule on the right distal and lateral thigh, just above the knee.

3 | DISCUSSION

While cutaneous myoepithelioma commonly occurs in the second to fourth decade of life, there are documented cases in later stages, such as in this case.[1–4] The lesion arose in the dermis of the thigh, a commonly described location for cutaneous myoepithelioma. Other common sites include the calf, arms, and head/neck.[3,4] Eighteen percent of cutaneous myoepithelioma recur locally.[2,3] The diagnosis of cutaneous myoepithelioma has become more recognized and better characterized in recent decades.

Cutaneous myoepithelioma grossly presents as a well-circumscribed, glistening nodule with a myoid cut surface. Though well-circumscribed, myoepitheliomas are not encapsulated and show clusters of cells infiltrating surrounding soft tissue. As a result of myoepithelial cell plasticity, myoepithelioma has a wide array of cytologic features and growth patterns.[1–3,8,10] The neoplastic cell cytoplasm ranges from eosinophilic to clear.[2,3] The cell morphology can be epithelioid, ovoid, spindled, polygonal, clear cell, or plasmacytoid; architectural arrangements of these cells range from linear, chains and cords, nested, solid to trabecular growth patterns. The stroma is also variable, appearing most commonly as myxoid or hyalinized but also rarely showing adipocytic, chondroid, or osseous metaplasia.[2–4] These polymorphous histopathologic presentations can lead to diagnostic challenges as the differential becomes broad, depending on the predominant cell type and stroma.

In addition, the degree of expression of immunohistochemical markers can vary in myoepithelioma, adding to the diagnostic challenge. But expression of S100 protein and an epithelial marker may be common to most myoepithelial neoplasms.[2,3] SOX10 has also become a marker for myoepithelioma because more than 80% of cases have this finding.[11] The support for myoepithelial differentiation, in this case, rests in the combination of myoepithelial (S100, SOX10, GFAP) and epithelial (EMA) markers. Not all myoepithelial markers were expressed (p63, calponin), as may be expected from the reported variability.

There are several differentials worth consideration. It can be challenging to distinguish myoepithelioma from benign mixed tumors. Mixed tumors show true ductal differentiation and are usually smaller with a clear cutaneous origin. Because both are benign, a distinction may not be of critical importance in all cases. However, differentiation from myoepithelial carcinoma is essential. Histopathologically, most myoepitheliomas show mild nuclear atypia and few if any mitotic figures (0–6 per 10 high-power fields),[3] unlike myoepithelial carcinomas, which exhibit overt features of malignancy such as prominent cytologic atypia, high mitotic rate (mean, 8 mitotic figures/10 high-power fields),[4] deep extension, and tumor necrosis.[3] Other differentials for cutaneous myoepithelial lesions are extraskeletal myxoid chondrosarcomas, which are S100 negative, as well as extra-axial chordomas, which are brachyury positive, and ossifying fibromyxoid tumor, which typically shows a surrounding shell of bone.[2,3]

In our patient's cutaneous myoepithelioma, the predominant myoepithelial cell type was basaloid. There was also evidence of *EWSR1* gene rearrangement by FISH, as seen in 45% of myoepithelioma cases.[1,2,8] *EWSR1* encodes a ubiquitous protein essential in cell housekeeping functions, with the propensity to rearrange and fuse with numerous genes.[2,6] *EWSR1* rearrangement is characteristically

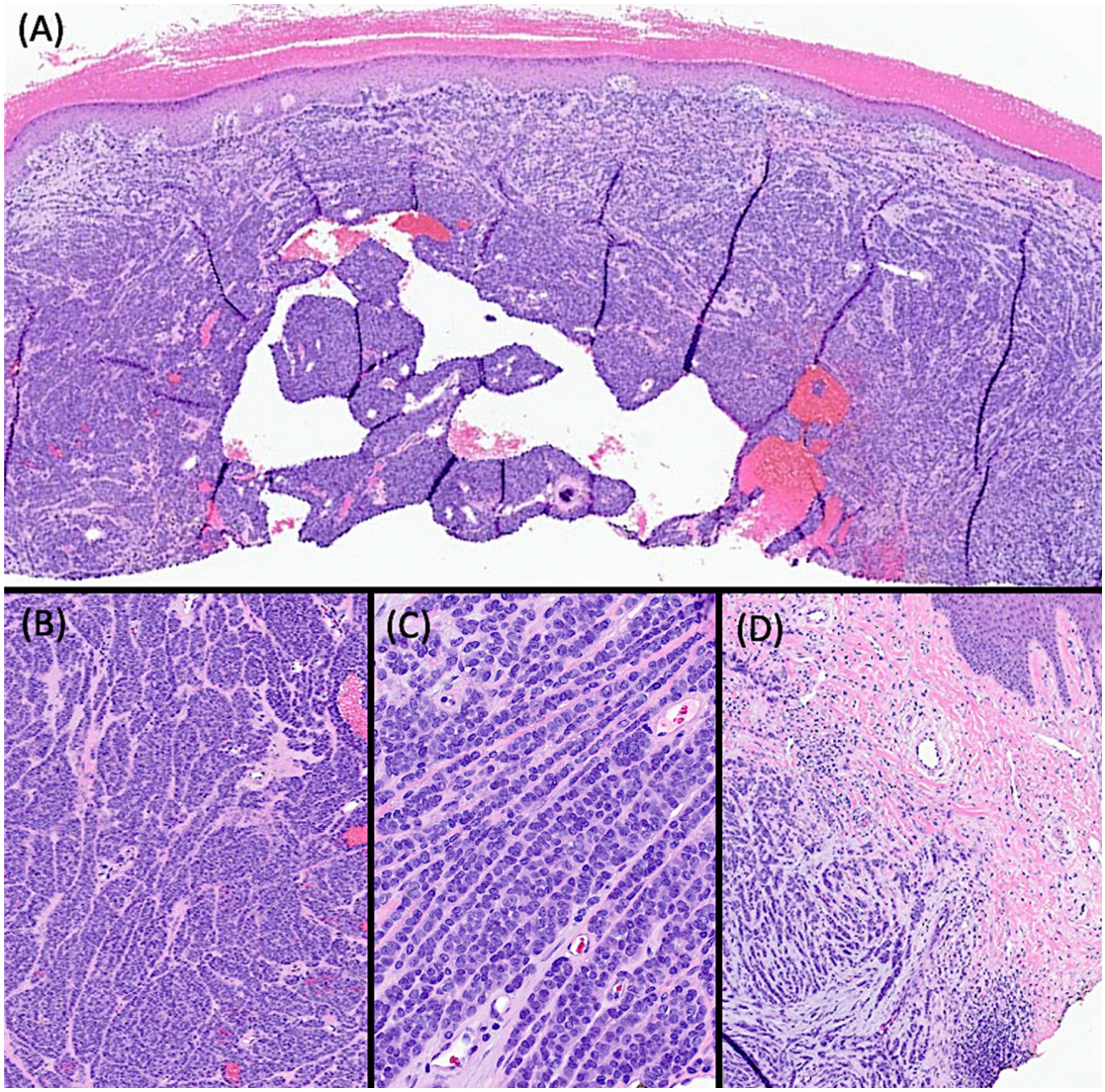

FIGURE 2 Cutaneous myoepithelioma. (A) Low-power image of a relatively grossly circumscribed highly cellular tumor involving the dermis and subcutis (H&E, ×10). (B) Diffuse dermal proliferation of basaloid cells in nodules, small islands, and cords in a myxoid matrix (H&E, ×40). (C) High-power magnification showing spindled and epithelioid basaloid cells in a linear arrangement with scant cytoplasm and no nuclear pleomorphism (H&E, ×200). (D) Subtle infiltrative growth identified at the periphery (H&E, ×40).

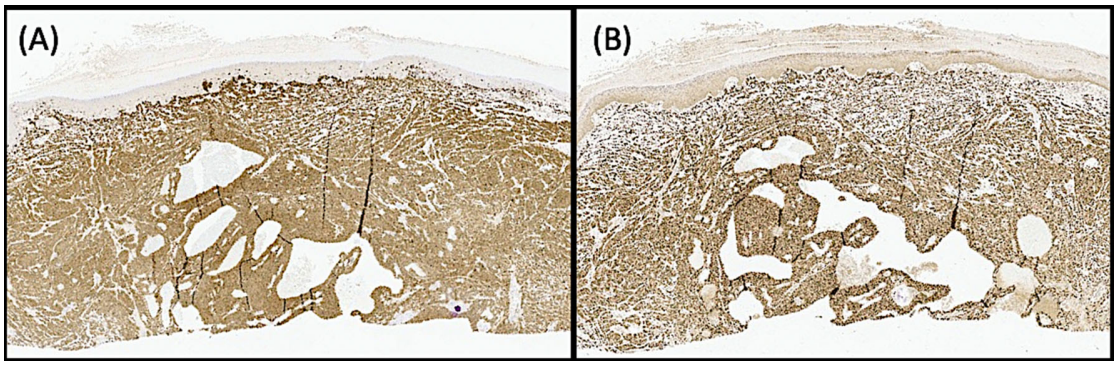

FIGURE 3 The neoplastic cells express (A) S-100 protein (×10) and (B) SOX10 (×10) strongly and diffusely.

TABLE 1 Table showing the common clinical features, histopathology, immunohistochemistry, and genetic findings in cutaneous myoepithelioma and cutaneous Ewing sarcoma.

Summary of common clinical features, pathology, immunohistochemistry, and genetic findings in cutaneous myoepithelioma of soft tissue vs. cutaneous Ewing sarcoma, with common differentials.

	Clinical features	Pathology	Immunophenotype	Genetics	Differential diagnosis
Cutaneous myoepithelioma	*Common demographic*: Adults in the second to fourth decades of life. *Common site of involvement*: Subcutis or deep soft tissues of the thigh, calf, arms, and head/neck. *Size*: 3–7 cm. Clinically benign. Local recurrences reported.	*Gross*: Well-circumscribed masses with a glistening, myxoid cut surface. *Microscopic*: Periphery contains small nests of predominantly spindled, glomoid, or vacuolated cells separated from the primary tumor, trailing into surrounding soft tissue. Similar histologic features as salivary gland counterparts: chains and cords of epithelioid, ovoid, or spindled cells deposited in a variably collagenous or chondromyxoid stroma. Children more often show atypical features.	Co-express epithelial markers (low-molecular-weight cytokeratins and/or EMA) and S-100 protein. *Note*: Limited cytokeratin expression. Limited expression of other myoepithelial markers, including muscle actins, GFAP, calponin, and p63. In malignant myoepitheliomas—loss of SMARCB1 (INI1) expression.	*EWSR1* rearrangements, with fusion partners (*PBX1*, *ZNF444*, *POU5F1*, and *ATF1*). *EWSR1::POU5F1* fusion is most common. Rarely show *FUS* rearrangement.	Broad depending on predominant cell type and stromal component. *Rule out*: • Mixed tumor variant • Ossifying fibromyxoid tumors • Extra-axial chordomas • Extraskeletal myxoid chondrosarcomas
Cutaneous Ewing sarcoma	*Common demographic*: Women and in teenagers and young adults. *Common site of involvement*: Localized to dermis/subcutis in extremities, trunk, head, and neck region. *Size*: <2.5 cm.	*Gross*: Superficial single mass, soft, mobile, and sometime painful with an average evolution time of 5 months. *Microscopic*: Dermal nodule showing uniform sheet-like small round monomorphic cells with clear to pale eosinophilic cytoplasm, dispersed chromatin, and small nucleoli.	Strong membranous staining for CD99. FLI-1 and ERG proteins staining sometimes positive. Uncommon but reported PAX7 staining.[12] Uncommon to show neuroectodermal or neuroendocrine markers such as S100[a] protein, synaptophysin, chromogranin, and CD56.	*EWSR1* rearrangements, with fusion partners (*FLI1*, *ERG*, *ETV1*, *ETV4*, *E1AF*). Classically *EWSR1::FLI1* fusion. Extremely rare cases of *FUS::ERG* fusion.	Radiographic studies needed to rule out metastasis. *Rule out*: • Lymphoblastic lymphoma • Small cell carcinoma • Merkel cell carcinoma • Small cell melanoma • Poorly differentiated synovial sarcoma • Rhabdomyosarcoma

Note: All reported information concisely referenced from Boland and Folpe,[2] except (a) Parra et al[12] and (b) Evangelou et al.[5]
[a]Cutaneous Ewing sarcoma showing strongly diffuse S100 staining has been reported in a handful of cases.[5,12]

associated with the pathogenesis of Ewing sarcoma, another tumor with basaloid cells, but has been reported in a range of other soft tissue tumors such as angiomatoid fibrous histiocytoma (AFH) and clear cell sarcoma, as well as a clinicopathologically diverse range of tumor types.[2,3,6] As our patient's lesion revealed *EWSR1* rearrangement and round blue cells on histopathology, further differentiation of myoepithelioma from the more malignant Ewing sarcoma was needed. Histopathologically, the case revealed corded growth peripherally, which would be unusual for Ewing sarcoma. Immunophenotypically, Ewing sarcoma typically shows diffuse, strong membranous staining for CD99 and diffuse nuclear reactivity for PAX7. However, the tumor cells in the current case showed only partial membranous CD99

staining and were negative for PAX7. Furthermore, diffuse reactivity for S100 made the diagnosis of Ewing sarcoma less likely (Table 1) although, very rarely, cutaneous Ewing sarcoma has been reported to show strong, diffuse SOX10 and/or S100 protein reactivity.[5,12] Regarding other cutaneous neoplasms exhibiting *EWSR1* gene rearrangements: AFH shows a peripheral rim of lymphocytic infiltrate without typical lymph node structures, and clear cell sarcoma shows melanocytic differentiation.[1–3] None of these features are typical of a myoepithelioma.

Our case highlights the diagnostic challenges of cutaneous myoepithelioma with its protean presentations. The morphology and clinical picture, in addition to a strong S100 protein/SOX10 expression, *EWSR1* gene rearrangement, and other negative immunohistochemical results, support the diagnosis. Given the similarity between this cutaneous myoepithelioma and Ewing sarcoma, misdiagnosis can constitute a significant pitfall. Therefore, diagnostic caution is required, as misdiagnosis can have significant clinical repercussions. The current treatment for cutaneous Ewing sarcoma comprises neoadjuvant chemotherapy, surgery, with or without radiation, and close follow-up, compared to excision alone in myoepithelioma.[5] Furthermore, while we ruled out other cutaneous lesions with *EWSR1* rearrangements, we emphasize that these lesions should be included in the differential for cutaneous myoepithelioma, especially when this molecular alteration is found, as their varying manifestations can lead to misdiagnosis.[2] As we continue to characterize these lesions, we emphasize the importance of using supportive cytogenetics and immunohistochemical results in diagnosing myoepitheliomas and differentiating them from their malignant counterparts.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Shaofeng Yan https://orcid.org/0000-0001-9654-2100

REFERENCES

1. Jo VY, Fletcher CDM. Myoepithelial neoplasms of soft tissue: an updated review of the clinicopathologic, immunophenotypic, and genetic features. *Head Neck Pathol*. 2015;9(1):32-38. doi:10.1007/S12105-015-0618-0
2. Boland JM, Folpe AL. Cutaneous neoplasms showing *EWSR1* rearrangement. *Adv Anat Pathol*. 2013;20(2):75-85. doi:10.1097/PAP.0B013E31828625BF
3. Hornick JL, Fletcher CDM. Cutaneous myoepithelioma: a clinicopathologic and immunohistochemical study of 14 cases. *Hum Pathol*. 2004;35(1):14-24. doi:10.1016/j.humpath.2003.08.016
4. Mentzel T, Requena L, Kaddu S, Soares de Aleida LM, Sangueza OP, Kutzner H. Cutaneous myoepithelial neoplasms: clinicopathologic and immunohistochemical study of 20 cases suggesting a continuous spectrum ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and myoepithelial carcinoma. *J Cutan Pathol*. 2003;30(5):294-302. doi:10.1034/j.1600-0560.2003.00063.x
5. Evangelou Z, Zhang L, Tafe LJ, Azzouz L, Grada Z, Linos K. Primary cutaneous Ewing sarcoma with diffuse S100/SOX10 positivity and pseudoalveolar pattern: an extraordinarily rare case highlighting a potential pitfall with significant repercussions. *J Cutan Pathol*. 2021;48(2):302-308. doi:10.1111/CUP.13788
6. Jo VY. *EWSR1* fusions: Ewing sarcoma and beyond. *Cancer Cytopathol*. 2020;128(4):229-231. doi:10.1002/CNCY.22239
7. Brandal P, Panagopoulos I, Bjerkehagen B, et al. Detection of a t(1;22)(q23;q12) translocation leading to an *EWSR1-PBX1* fusion gene in a myoepithelioma. *Genes Chromosomes Cancer*. 2008;47(7):558-564. doi:10.1002/gcc.20559
8. Fisher C. The diversity of soft tissue tumours with *EWSR1* gene rearrangements: a review. *Histopathology*. 2014;64(1):134-150. doi:10.1111/his.12269
9. Flucke U, Palmedo G, Blankenhorn N, Slootweg PJ, Kutzner H, Mentzel T. *EWSR1* gene rearrangement occurs in a subset of cutaneous myoepithelial tumors: a study of 18 cases. *Mod Pathol*. 2011;24(11):1444-1450. doi:10.1038/modpathol.2011.108
10. Jo VY. Myoepithelial tumors: an update. *Surg Pathol Clin*. 2015;8(3):445-466. doi:10.1016/j.path.2015.05.005
11. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. SOX10—a marker for not only schwannian and melanocytic neoplasms but also myoepithelial cell tumors of soft tissue: a systematic analysis of 5134 tumors. *Am J Surg Pathol*. 2015;39(6):826-835. doi:10.1097/PAS.0000000000000398
12. Parra O, Thuraisingam R, Baker ML, Kerr DA, Linos K. Adding perplexity to rarity: diffuse S100-protein and SOX10 expression in a molecularly confirmed PAX7-positive primary cutaneous Ewing sarcoma. *Am J Dermatopathol*. 2021;43(12):984-989. doi:10.1097/DAD.0000000000002000

How to cite this article: Okorie CL, Yan S, Kerr DA, Tafe LJ, Sriharan A. Cutaneous myoepithelioma with *EWSR1* gene rearrangement and its differentials: A diagnostic challenge. *J Cutan Pathol*. 2023;50(7):632-636. doi:10.1111/cup.14433