Myoepithelioma-like tumor of the vulvar region: a case report in China and review of the literature

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Abstract

Background: Myoepithelioma-like tumor of the vulvar region (MELTVR) is a recently described mesenchymal neoplasm which typically arising in vulvar regions of adult women.

Case presentation: Here we report a case of a 65-year-old woman who presented with a 6-year history of subcutaneous mass in the vulvar region. The mass had recently increased in size continuously. Histologically, the tumor cells had an epithelioid to spindled shape. Epithelioid tumor cells proliferated singly or in a loosely cohesive manner with myxoid areas, while spindled tumor cells grew in diffuse sheets or storiform arrangements mainly in nonmyxoid areas. Immunohistochemically, the tumor cells were positive for vimentin, epithelial membrane antigen, calponin, and were partially mild to moderate positive for estrogen receptor, but completely negative for S100 protein, glial fibrillary acidic protein, CD34, desmin, SMA and cytokeratin. INI1/SMARCB1 expression was deficient. EWSR1 and FUS genes were intact tested by fluorescence in situ hybridization analysis. Based on these findings, we diagnose this case as MELTVR. The patient remained relapse-free after the lesion was widely excised during 8 months follow-up.

Conclusions: This disease should be included in the differential diagnostic list of vulvar tumors with epithelioid to spindled morphology. Recognition of its histopathological features and immunohistochemical reactivity will help to understand the tumor better.

Keywords: Myoepithelioma-like tumor of the vulvar region, MELTVR, vulva, INI1/SMARCB1

Background

Myoepithelioma-like tumor of the vulvar region (MELTVR) is a soft-tissue neoplasm that is rarely observed in clinical practice; however, its typical characteristics have been described in the literature, including the histological, immunohistochemical and molecular signatures. MELTVR was first described by Yoshida et al. in 2015 [1], who reported nine cases arising from the vulvar region with a uniform INI1/SMARCB1-deficient immunohistochemical reactivity. In our report, we present a case of MELTVR that arose in the vulva of a middle-age woman, which was initially suspected to be a leiomyoma.

Case presentation

A 65-year-old woman presented with 6-year history of subcutaneous nodule in the vulvar region and recently the mass obviously increased creating personal discomfort. She was then admitted to our hospital for treatment. Computed tomography (CT) of the pelvis showed a cystic solid mass (diameter 50 mm) in the perianal region, suggesting a benign leiomyoma. The patient had no prior history of malignancy. Then, the patient underwent wide excision. On surgery, one nodule was found to be located in the vulvar muscle space, measuring approximately 45 mm in maximum diameter. The tumor was well-defined without obvious capsule. No sign of local recurrence or metastatic disease was observed after the initial excision during an eight-months follow-up.

Grossly, the lesion was a well-circumscribed (Fig. 1a), solid mass, with areas of translucent quality. On cut section, there was a solid white to gray lobulated nodule,
measuring 5.5 × 4.0 × 3.5 cm in size. Histologically, at low magnification, the tumor was well circumscribed, focally encapsulated, and lobulated. The tumor stroma was relatively hypervascular and comprised a mixture of myxoid and nonmyxoid components, myxoid areas accounted for 20% of the tumor volume. At high magnification, the lesion was composed of spindle-shaped to epithelioid cells with abundant amphophilic cytoplasm, consisting of vesicular nuclei and small nucleoli. In nonmyxoid area, the tumors cells arranged in storiform pattern (Fig. 1b, c) and some areas of tumor stroma was predominantly hyalinized or fibrous (Fig. 1d). In myxoid areas, tumors cells grew singly or in a loosely cohesive manner with abundant eosinophilic cytoplasm resembling rhabdomyoblasts (Fig. 1e, f). Rhabdomyoblasts-like cells accounted for approximately 80% of the total cells in the myxoid areas. The nuclear atypia was mild to moderate and mitotic figures were low (up to five mitosis per 50 high-power fields).

Immunohistochemically, the tumor cells were diffusely positive for Vimentin, and partially positive for epithelial membrane antigen (EMA) with at least moderate intensity, which was mainly expressed in epithelioid cells (Fig. 2a). Estrogen receptor (ER) was weakly expressed in some tumor cells (Fig. 2b). Calponin (clone: CALP and EP63) was positive for both the nucleus and the cytoplasm of the tumor cells (Fig. 2c). Focal expression for Bcl-2 and CD99 was observed. The tumor was negative for S100 protein (Fig. 2d), cytokeratin (CK), glial fibrillary acidic protein (GFAP), CK7, SOX10, CD31, CD34 (Fig. 2e), desmin, MyoD1, myogenin, smooth muscle actin (SMA), CD117, β-catenin and MUC4. Loss of INI1 protein expression was also confirmed (Fig. 2f). The Ki67 index was about 10%. The results of immunochemical staining were summarized in Table 1.

Using formalin-fixed, paraffin-embedded 4-mm-thick tumor samples, dual-color break-apart fluorescence in situ hybridization (FISH) was used to investigate EWSR1
and FUS1 gene rearrangements. Break-apart probes for EWSR1 (Abbott Molecular Inc., USA) and FUS1 (Abbott Molecular Inc., USA) were used, and no split signals were observed with either probe (Fig. 3a, b).

Discussion
MELTVR is a rare neoplasm. Up to present, eleven cases of MELTVR have been reported in the literature [1–3]. The tumor is not classified according to the 4th edition of WHO classification of Soft Tissue and Bone Tumors [4]. MELTVR represents one of SMARCB1-deficient vulvar neoplasms [5]. Although it is difficult to diagnose the disease due to its rarity, it can be confirmed by the combination of histological and immunohistochemical features. In addition, molecular is also an important tool for differential diagnosis of MELTVRs and other tumors. Based on the literatures, the clinical manifestation of MELTVR was not specific. Most patients presented with a painless mass or had occasional pain. The clinical diagnosis embraced a wide variety of disease, including solitary fibrous tumor, aggressive angiomyxoma, angio-myofibroblastoma, lipoma, hemangioma, and schwannoma [1, 2]. In our case, the lesion was originally considered leiomyoma or fibroma. At histology level, broad differential diagnoses need to be considered, including several tumors with loosely cohesive growths of epithelioid or spindle cells in a variable myxoid or hyalized background. The morphology of this tumor resembles soft tissue myoepitheliomas, particularly those tumors with a myxoid pattern, but the neoplastic cells are negative for S100, GFAP and myogenic markers such as SMA, desmin. At molecular level, most of soft tissue myoepitheliomas harbor EWSR1 gene translocation with a variety of different fusion partners, including EWSR1-POU5F1, EWSR1-PBX1, and EWSR1-ZNF444 [6–8]. FUS gene rearrangements have also been reported in some myoepitheliomas [6, 9]. However, EWSR1 and FUS rearrangements were absent in this tumor. The
differential diagnosis of MELTVR also includes extraskeletal myxoid chondrosarcoma (EMC) due to its uniform, loosely cohesive tumor cells in a myxoid matrix. EMC is an extremely rare subtype of vulvar sarcoma that is consistently positive for vimentin, variable positivity for S100 protein, neuron-specific enolase and synaptophysin, completely negative for CK [10–16], and harbor EWSR1–NR4A3 fusion in about 65% of cases [17]. However, the present case showed S100 negativity, EMA, ER positivity, and EWSR1 was intact showed by FISH assay. Nevertheless, INI1/SMARCB1 expression has been retained in most EMC cases [18, 19], while the loss of INI1/SMARCB1 gene has also been reported in EMCs without major fusion gene transcript [18].

Due to the loss of expression of the INI1/SMARCB1, MELTVR need to be differentiated from INI1/SMARCB1-deficient vulvar neoplasms, including epithelioid sarcoma and extrarenal malignant rhabdoid tumor (E-MRT) [20–24]. Epithelioid sarcoma is a malignant tumor, which is divided into classical type of epithelioid sarcoma and proximal type of epithelioid sarcoma. The classical type of epithelioid sarcoma is often located in dermis. The tumor cells are relatively bland epithelioid cells, often showing a "granuloma-like" pattern of necrosis, which is easily misdiagnosed as rheumatoid nodules or annular granulomas [25]. The proximal type of epithelioid sarcoma typically shows a much greater degree of nuclear pleomorphism, more frequent rhabdoid cytology, and geographic necrosis [26], in contrast to the uniform nuclei and amphophilic cytoplasm of MELTVRs. Both forms of epithelioid sarcoma typically coexpress CAM5.2, AE1/AE3, EMA, CK19, vimentin and are CD34 positive in 50 to 70% of cases [27, 28]. However, AE1/AE3 and CD34 were completely negative in our case. E-MRT is a highly malignant small round cell tumor that occurs in infants and children. Cellular atypia was easily observed, and mitotic activity was high. E-MRT is extremely aggressive tumor, patients with this tumor often have a short survival [29, 30]. Unlike E-MRT, most MELTVRs occur in adult women, and the majority of MELTVRs showed an indolent clinical

| Table 1 Immunohistochemical results of myoepithelioma-like tumor of the vulvar region |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Antibody | Clone | Dilution | Source | Result |
| CK | AE1/AE3 | 1:100 | Zhongshan China | – |
| CD34 | 10C9 | 1:100 | Zhongshan China | – |
| S-100 | 4C4.9 Ready-to-use | Maixin China | – |
| GFAP | UMA129 | 1:100 | Zhongshan China | – |
| SMA | 1A4 Ready-to-use | Maixin China | – |
| MyOD1 | MX049 Ready-to-use | Maixin China | – |
| Myogenin | FSD Ready-to-use | Maixin China | – |
| INI1 | 25 | 1:20 | Zhongshan China | – |
| ER | SP1 | 1:300 | Gene | + |
| Calponin | CALP Ready-to-use | Maixin China | + |
| Calponin | EP63 Ready-to-use | Zhongshan China | + |
| vimentin | UMA159 | 1:100 | Zhongshan China | + |
| Bcl2 | MX022 Ready-to-use | Maixin China | + |
| CD99 | HO36-1.1 | 1:50 | Zhongshan China | + |
| EMA | E29 Ready-to-use | Maixin China | + |
| CD3 | UMA830 | 1:100 | Zhongshan china | – |
| Ki-67 | UMA107 | 1:100 | Zhongshan china | 10% |
| DESMIN | EP15 | 1:100 | Zhongshan china | – |
| MUC4 | 8G7 | 1:100 | Zhongshan china | – |
| SOX10 | EP268 | 1:100 | Zhongshan china | – |
| B-catenin | UMA15 | 1:100 | Zhongshan china | – |
| CK7 | OV-TL12/30 Ready-to-use | Maixin China | – |
| CD117 | YR145 Ready-to-use | Maixin China | – |

Fig. 3 FISH results of present case. The tumor cells exhibited two pairs of fused signals by (a) EWSR1 and (b) FUS1 probes, no split signals were identified.
course. Immunohistochemically, E-MRT expressed AE1/AE3, CAM5.2, EMA and vimentin. Vimentin exhibited paranuclear globular staining, which was not observed in MELTVRs. In the present case, epithelioid cells with rhabdomyoblasts-like features in myxoid area was observed, which is needed to be differentiated from embryonal rhabdomyosarcoma (ERMS). However, ERMS is a highly malignant tumor with cellular atypia and a number of mitotic figures. Immunohistochemically, ERMS expresses SMA, desmin, MyoD1 and Myogenin, which are absent in MELTVRs.

The clinical and immunohistochemical features of the reported 11 cases and our case are summarized in Table 2. There is limited information regarding the incidence rate of MELTVRs due to its rarity. Immunohistochemically, there are no specific markers for this neoplasm, but the tumor cells are consistently positive for EMA and ER. All reported cases showed loss of INI1/SMARCB1 expression, which appears to be a key factor to define the classification of this disease. In the present case, calponin was expressed both in the cytoplasm and in the nucleus of the tumor cells. We analyzed the phenomenon using two different clonal antibodies and the results are consistent. FISH analyses were negative for the presence of a rearrangement of the FUS1 and EWSR1 gene in our case. Biologically, all patients of reported cases survive, which is needed to be differentiated from embryonal rhabdomyosarcoma (ERMS). However, ERMS is a highly malignant tumor with cellular atypia and a number of mitotic figures. Immunohistochemically, ERMS expresses SMA, desmin, MyoD1 and Myogenin, which are absent in MELTVRs.

### Table 2 Summary of clinical and immunohistochemical findings of previously reported and present cases of MELTVRs

| Author | Age | Size (mm) | Immunohistochemical findings | R | M | Prognosis (month) |
|--------|-----|-----------|-------------------------------|---|---|------------------|
| Yoshida [1] | 24–65 | 20–77 | ER + EMA + GFAP – S-100 – CD34 – INI1 – AE1/AE3 – SMA + Desmin + | 2/9* | 5/8* | NA 3/9 – 11m alive |
| Kaku [2] | 31 | 20 | + + – – – – +** – NA – 12m alive |
| Kojima [3] | 70 | 36 | +** + – – – – – – + + – – 8m alive |
| Present | 65 | 55 | + + – – – – – – – – – 8m alive |

NA: data not available; *Rare (< 1%); **Focal (1 to 30%).

### Conclusion

Based on previous reports and our observation, these tumors with low-grade malignant features and no metastases, wide excision and tumor-free margins seem to be an appropriate treatment. In summary, we have reported a rare case of MELTVR. Further investigation is required to clearly determine the pathological, immunohistochemical and molecular features of this tumor.

### Abbreviations

- CK: Cytokeratin
- CT: Computed tomography
- EMA: Epithelial membrane antigen
- EMC: Extraskeletal myxoid chondrosarcoma
- E-MRT: Extrarenal malignant rhabdoid tumor
- ER: Estrogen receptor
- ERMS: Embryonal rhabdomyosarcoma
- FISH: Fluorescence in situ hybridization
- MELTVR: Myoepithelioma-like tumor of the vulvar region
- NSE: Neuron-specific enolase
- Syn: Synaptophysin
- SMA: Smooth muscle actin
- WHO: World Health Organization

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None.

### Authors’ contributions

XY performed the histological and immunohistochemical evaluation as well as collected clinical data and drafted the manuscript. GH carried out the molecular genetic studies. GJL read and approved the final manuscript.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Ethics approval and consent to participate

This case study was approved by the Institutional Review Board for ethical committee of Tongji University Shanghai East Hospital.

### Consent for publication

The patient gave his written consent for image and data publication.

### Competing interests

The authors declare that they have no competing interests.

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