

Case Report

Histopathological Characterization of a Rare Case of Soft Tissue Malignant Myoepithelioma: A Diagnostic Challenge

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Abstract

Background: Soft tissue myoepitheliomas are rare and exhibit a wide spectrum of benignity and low- to high-grade malignancy with histopathological heterogeneity, including cell morphology, nuclear atypia, proliferation patterns, and background matrices, often making pathological diagnosis very challenging. Although recent molecular and genetic studies of the genetic abnormalities, particularly unique gene fusions, have determined associations with the clinicopathological features, they have not been sufficiently elucidated.

Case Presentation: We present a rare case of malignant myoepithelioma that developed in the soft tissue of the groin in an elderly man, along with its macroscopic, histological, immunohistochemical and fluorescence in situ hybridization (FISH) findings. The tumor invaded the adjacent fatty tissue, but no lymph node metastasis was observed locally. Histologically, the tumor cells exhibited severe nuclear atypia, pathological nuclear mitosis, myxoid background, and rhabdoid cells. INI1/SMARCB1 nuclear loss and frequent Ki-67 and p53 positivity indicated a malignancy. Hence, we considered soft tis-

sue malignancies with similar or overlapping histology, such as extra skeletal myxoid chondrosarcoma, proximal epithelioid sarcoma, extrarenal rhabdoid tumor, myxoepithelioid tumor with chordoid features, and malignant myoepithelioma for the differential diagnosis. We used a panel of antibodies, including epithelial membrane antigen (EMA) and cytokeratin's (CKs) as epithelial markers; vimentin, CD34, desmin and brachyury as mesenchymal markers; synaptophysin, CD56 and insulinoma-associated protein 1 as neuroendocrine markers; and p63, S-100, CD10, alpha-smooth muscle actin, caldesmon and calponin as myoepithelial markers. The tumor was positive for EMA, CK, vimentin, S-100 and CD10, but not for the other markers, and a pathological diagnosis of malignant myoepithelioma was established. The Ewing sarcoma RNA-binding protein 1 (EWSR1) and fused in sarcoma (FUS)-related fusion genes, which have been detected in half of the soft tissue myoepithelioma cases, were not detected upon split FISH. Therefore, a certain fusion gene that is distinct from the EWSR1 or FUS-related genes could be present in the present tumor.

Conclusion: Malignant myoepithelioma diagnosis is very challenging owing to its rarity and clinicopathological diversity. Thus, the possibility of malignant myoepithelioma should always be considered when encountering a soft tissue malignancy that is pathologically questionable, such as the present tumor, which served as a valuable and instructive case.

Keywords: Differential diagnoses; Fusion gene; Immunohistochemistry; Malignant myoepithelioma; Soft tissue

Introduction

Myoepitheliomas are uncommon tumors that develop in the salivary glands, mammary glands, lacrimal glands, sweat glands, and various glands of the respiratory tract, where myoepithelial cells exist in the ducts and acini. However, myoepitheliomas also arise in the soft tissues, bones and various organs without myoepithelial cells [1-11]. Myoepitheliomas occurring in the soft tissues are extremely rare. Soft tissue myoepitheliomas occur clinically in a wide range of ages, from infants to the elderly, and they exhibit a wide spectrum of benign, low malignant, and high malignant potentials. Furthermore, histologically, the tumor cells are oval to spindle-shaped, with nuclear atypia ranging from mild to severe. Therefore, pathological diagnosis is often challenging owing to the diverse clinicopathological characteristics [9,10].

Recently, we encountered an exceedingly challenging case of soft tissue malignancy that developed in the groin of an elderly male patient. For the pathological diagnosis of the present tumor, we considered tumors, such as extra-skeletal myxoid chondrosarcoma (EMC) [12], proximal epithelioid sarcoma (ES) [13], extrarenal rhabdoid tumor (RT) [14,15], myxoepithelioid tumor of chordoid features (METC) [16], and malignant myoepithelioma [9], that mimic the clinical and/or histopathological characteristics. Thus, we were able to diagnose this challenging tumor as a malignant myoepithelioma, using a panel of antibodies as epithelial, mesenchymal and neuroendocrine markers. Although we checked for a EWSR1 or FUS related fusion gene in the present tumor

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using split fluorescence in situ hybridization (FISH) [17], no fusion gene was detected. Therefore, another type of fusion gene could be present in this case. In soft tissue myoepitheliomas, although associations between genetically and molecular abnormalities, including fusion genes, and clinicopathological findings are being determined, they have not been sufficiently elucidated yet. Further studies and the accumulation of the data are required.

Case Presentation

A male patient in his mid-sixties has visited the urology department of our hospital for a painless mass in his left groin for two months. His family and medical history were unremarkable. A computed tomography (CT) scan revealed a deep soft tissue lesion with a maximum diameter of 37 mm (Figure 1), showing an unclear border with the spermatic cord. The lesion was weakly mobile upon ultrasound examination. The clinical diagnosis of spermatic cord tumor was suspected based on these findings. However, surgery revealed that the lesion was unrelated to the inguinal canal, and no regional or distant metastases were observed. Before surgery, the titers of C-reactive protein (CRP) and tumor markers including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and carbohydrate antigen 19-9 (CA19-9) were within normal ranges. Fifteen months after surgery, no signs of recurrence, lymph node metastasis or distant metastasis were observed, and follow-up is being continued currently.

Macroscopically, the cut-surfaces of the lesion were solid, grayish-white and relatively well-defined with lobulated patterns (Figure 2). Histologically, polygonal to short spindle-shaped tumor cells harbored highly atypical oval nuclei containing distinct nucleoli, and displayed irregular cord-like, reticular and nest-like patterns by tumor cells against a background of myxoid or fibrous stroma of varying degrees in the lesion. Rhabdoid cells were mixed in various proportions. Nuclear mitotic figures including pathological mitotic figures were sporadically observed. No hemorrhagic or necrotic foci were observed (Figures 3a-d). A solid and densely proliferating area of tumor cells was observed only in a small portion at the periphery of the lesion. In addition, the tumor cells partly invaded the fine fibrous capsule and adjacent fatty tissue (Figures 3e,f). Immunohistochemically, the tumor cells showed INI1/hSNF5/SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily B, member 1 (INI1/SMARCB1) nuclear loss, a Ki-67 index of 40 and a p53 positive rate of 20%, suggesting malignancy (Figures 3g-i).

Thus, EMC, proximal ES, extrarenal RT, METC and malignant myoepithelioma were considered for the differential diagnosis of the present tumor. We incorporated a panel of antibodies including epithelial membrane antigen (EMA), cytokeratin (CK)-AE1/AE3 (AE1/AE3) and CK-CK5/CK6 (CK5/CK6) as epithelial markers; vimentin, CD34, desmin and brachyury as mesenchymal markers; synaptophysin, CD56 and insulinoma-associated protein 1 (INSM1) as neuroendocrine markers; p63, S-100 protein (S-100), CD34, alpha-smooth muscle actin (SMA), calponin and h-caldesmon (caldesmon) as myoepithelial markers; and estrogen receptor (ER) as a hormonal marker. The tumor cells were practically positive for EMA, frequently positive for ER and sporadically positive for AE1/AE3, vimentin, S-100 and CD10, respectively, but not for p63, CK5/CK6, CD34, desmin, SMA, INSM1, synaptophysin, CD56 or brachyury (Figures 4a-i). Thus, the present tumor was pathologically diagnosed as malignant myoepithelioma. To detect a fusion gene in the tumor, Ewing sarcoma RNA-binding protein 1 (EWSR1) and fused in sarcoma (FUS) were

examined using the split fluorescence in situ hybridization (FISH) method; however, no split signals were observed (Figures 5a & b).



Figure 1: Computed tomography scan: A tumor, 37mm in maximum size, in the left inguinal deep soft tissue (red arrow).

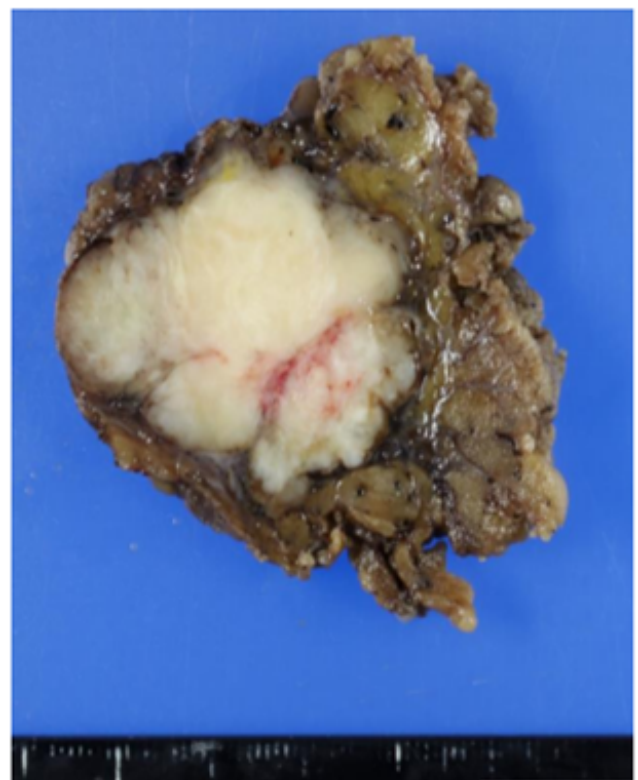


Figure 2: Macroscopic findings: A cut surface of grayish-white and solid tumor with a lobulated pattern and relatively clear borders.

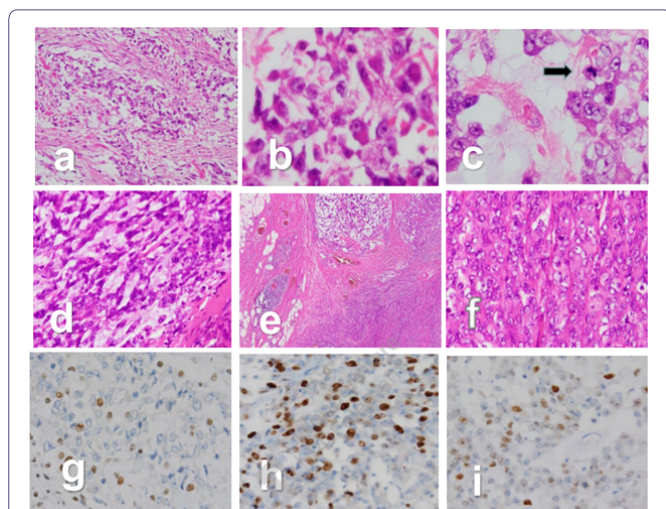


Figure 3: Microscopical and immunohistochemical findings: (a) Tumor cells proliferating in varying sized nests and with a background of fibrous and myxoid matrices 10x. (b) A cell nest consisting of polygonal to short spindle-shaped highly atypical cells with rhabdoid cells 40x. (c) A section showing a nuclear mitotic figure (black arrow) in a myxoid matrix 40x. (d) A section showing spindle-tumor cell proliferation with a myxoid background 20x. (e) A section of tumor cells invading the surrounding adipose tissue 4x. (f) A section showing solid proliferation of polygonal shaped tumor cells 20x. Immunohistochemically, the tumor cells showing (g) INI1 nuclear loss, and (h) Ki-67 index 40 and (i) 20% p53 positivity.

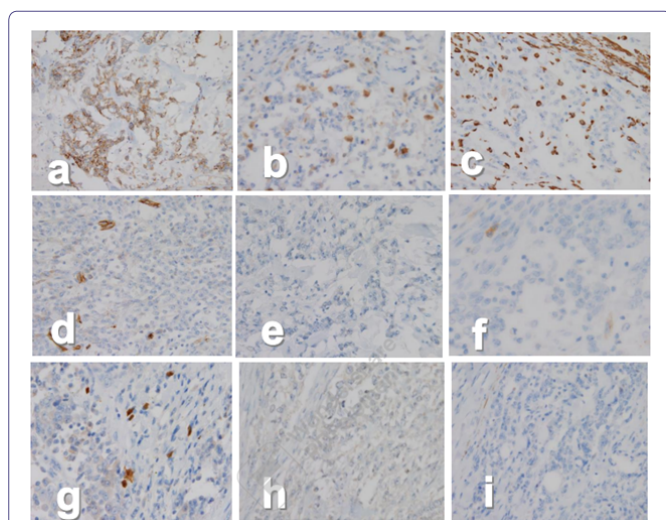


Figure 4: Immunohistochemical findings: The tumor cells being frequently positive for epithelial membrane antigen (EMA) (a), often positive for cytokeratin-AE1/AE3 (AE1/AE3) (b), vimentin (c), negative for CD34 (d) and insulinoma-associated protein 1 (INSM1) (e), occasionally positive for CD10 (f) and protein S-100 (S-100) (g), and negative for brachyury (h) and desmin (i).

Discussion

As already mentioned, the tumor in the present case developed in the deep soft tissue of the groin. Epithelioid to short-spindle cells with severe nuclear atypia and rhabdoid cells proliferated in various patterns on the background of the myxoid stroma. The tumor cells demonstrated INI1/SMARCB1 nuclear loss and a high incidence of Ki-67 and p53 positivity. Thus, we considered the following soft tissue malignancies for the differential diagnosis: EMC [12], proximal ES [13],

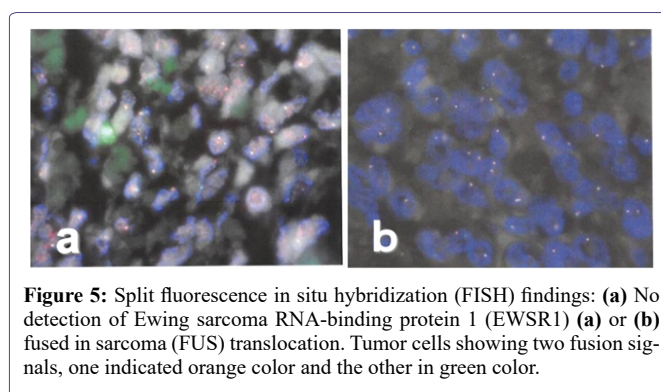


Figure 5: Split fluorescence in situ hybridization (FISH) findings: (a) No detection of Ewing sarcoma RNA-binding protein 1 (EWSR1) (a) or (b) fused in sarcoma (FUS) translocation. Tumor cells showing two fusion signals, one indicated orange color and the other in green color.

extrarenal RT [14,15], METC [16] and malignant myoepithelioma [9,10]. However, all the tumors are rare and exhibit similar or overlapping histological features; furthermore, their origin or line of differentiation is unknown. Therefore, their pathological diagnosis is often confusing or challenging.

Considering the clinical and pathological characteristics as well as the unique fusion genes in the tumors listed above, EMC typically reveals mild to moderate nuclear atypia and positivity for vimentin, S100, EMA and neuroendocrine markers such as synaptophysin, CD56 and INSM1 [12,18]. The rare solid and cellular variant of high-grade malignancy densely consists of atypical epithelioid cells and pleomorphic or rhabdoid cells that show INI1/SMARCB1 nuclear loss [19]. Nuclear receptor subfamily 4 group A member 3 (NR4A3)-related fusion genes lacking EWSR1 as a fusion partner have also been detected [20]. Proximal ES is characterized by a solid proliferation of highly atypical epithelioid cells with a number of rhabdoid cells [13] and seldom harbors a remarkable myxoid background [21]. Immunohistochemically, the tumor cells are diffusely and strongly positive for vimentin, CK and CD34, and moreover, INI1/SMARCB1 nuclear loss is observed in most cases [22]. No unique fusion genes have been described for this tumor. Extrarenal RT shows very similar histological features to proximal ES, but is more prevalent in children and the tumor cells are negative for CD34. Yoshida, et al. [23] in 2015 advocated myoepithelioid-like tumors of the vulvar region (METVR) as a new concept. This low-grade malignant tumor develops exclusively in women, and epithelial-like to spindle-shaped tumor cells with moderate nuclear atypia proliferate in cord-like, reticular and nest-like patterns against a background of abundant myxoid stroma. The tumor cells are positive for ER and SMA, and for CK in a minority, but not for S-100, GFAP and CD34 [23,24]. In 2021, Kinoshita, et al. [16] proposed the concept of myxoepithelioid tumor with chordoid features (METC) that encompasses METVR. It exhibits the same histological features as those of METVR and develops in both women and men. The tumor cells are positive for brachyury in METC. METVR and METC show rhabdoid cells and INI1/SMARCB1 nuclear loss upon immunostaining. No specific fusion gene is identified. METC and METVR recently proposed as a new entity are still not described in the World Health Organization (WHO) classification of soft tissue and bone tumors (5th edition) [25].

Since INI1/SMARCB1 nuclear loss of tumor cells and the appearance of rhabdoid cells may exist in the above-mentioned soft tissue tumors, these findings are not necessarily useful for differentiation among them. Moreover, EMC is positive for neuroendocrine markers, whereas the present tumor was negative. Proximal ES frequently

exhibits positivity for vimentin, CK, EMA and CD34 [13], and it seldom harbors a myxoid background [20]. Extrarenal RT displays similar histological findings and is frequently positive for vimentin and CK but not for CD34, and develops exclusively in children [14,15]. The present tumor occurred in an elderly patient and had an apparent myxoid background. Immunohistochemically, it showed only sporadic positivity for vimentin and CK, but not for CD34. Based on these findings, the present tumor does not correspond to proximal ES or extrarenal RT. Although METC appears histologically very similar to the present tumor, METC typically shows weaker nuclear atypia, and positivity for brachyury is essential for its diagnosis [16], while the present tumor showed severe nuclear atypia and negativity for brachyury. Therefore, the present tumor did not correspond to METC.

Myoepitheliomas present a broad clinicopathological spectrum ranging from benign and low-grade to high-grade malignancy, thereby making the diagnosis challenging in the cases being considered. Histologically, polygonal to spindle shaped tumor cells grow in sheet, nest and cord-like patterns, often in myxoid or fibrous to hyaline backgrounds. Tumor cells are positive for myoepithelial markers such as CD10, p63, calponin, caldesmon, GFAP and S100, as well as EMA, CKs and vimentin. The appearance of rhabdoid cells and INI1 nuclear loss of tumor cells have been found in a subset. The histological and immunohistochemical features as described above vary, reflecting the clinical variability between benign to malignant myoepitheliomas. The present tumor was positive for not only EMA, AE1/AE3 and vimentin but also CD10 and S100 as myoepithelial markers. Moreover, Ki67 and p53 were positively detected at high levels, indicating malignancy. Thus, in spite of the complicated case, the pathological diagnosis of the present tumor as a malignant myoepithelioma was finally established.

In recent years, molecular and genetic studies have been conducted on various soft tissue tumors, and tumor-related genetic abnormalities, especially unique fusion genes, have been identified [26-29]. These findings must strengthen or complement a conventional pathological diagnosis based on histological and immunohistochemical findings, anticipating further accumulation of the genetic and molecular findings. Concerning benign to malignant myoepitheliomas, EWSR1- and FUS-related fusion genes with various partner genes have been detected [30-33]. In 2020, Suurmeijer, et al. [17] reported that fusion genes involving EWSR1 and FUS were detected in 49 of 66 cases of benign to malignant myoepitheliomas. Among the 49 cases, EWSR1 was detected in 37, of which the partner genes were POU5F1, PBX3, PBX1, ZNF444, KLF15, and KLF17, whereas FUS was detected in 12 cases with KLF17 or POU5F1 as the partner gene. Of the 66 cases, 17 were malignant, of which 11 had EWSR1-POU5F1 and three possessed EWSR1-ZNF44. Three patients with FUS-KLF17 demonstrated myxoid backgrounds. The cases of EWSR1-PBX1/3 and FUS-PBX1/3 were benign with a fibrotic background. However, no fusion genes were detected in the remaining 17 cases, and therefore, other fusion genes unrelated to EWSR1 and FUS should be present. Actually, benign to malignant soft tissue myoepitheliomas with fusion genes unrelated to EWSR1 and FUS, such as ASCC2-GGNBP2, IRF2BP2-CDX2 and SRF-E2F1, have been reported previously [34-36]. In the present malignant myoepithelioma, EWSR1 and FUS were examined using split FISH; however, no fusion genes were identified.

Although myoepitheliomas arising from different sites exhibit similar histological features, salivary myoepitheliomas usually harbor fusion genes involving PLAG1 [37-40], which are distinct from those

of the soft tissue and cutaneous myoepitheliomas involving EWSR1 and FUS [17,41,42]. However, soft tissue myoepitheliomas with fusion genes related to PLAG1 have also been reported [39,43,44]. In addition, cutaneous syncytial myoepitheliomas were reportedly associated with fusion genes related to EWSR1 [41], whereas cutaneous myoepitheliomas with ductal differentiation were associated with PLAG1 related fusion genes [45]. Namely, some overlaps in fusion gene types exist among salivary, cutaneous and soft tissue myoepitheliomas. Hence, the fusion genes in myoepitheliomas have not been fully elucidated. To clarify the relationship between the clinicopathological findings of soft tissue myoepitheliomas and fusion genes in detail, further accumulation of cases of myoepitheliomas arising not only from the soft tissue but also other sites is warranted.

Conclusion

In conclusion, malignant myoepitheliomas of the soft tissue are often challenging to diagnose by histopathological characterization owing to their rarity and diversity in cell morphology, nuclear atypia, proliferation, and background matrices. The present malignant soft tissue myoepithelioma exhibited similar histomorphology to that of EMC, proximal ES, extrarenal RT, and METC. In the present case, a panel of antibodies composed of various makers, including myoepithelial markers, was considered a powerful weapon for establishing the pathological diagnosis. Moreover, the possibility of malignant myoepithelioma should always be considered when encountering a soft tissue malignancy that is pathologically questionable, such as the present tumor, which served as a valuable and instructive case.

List of Abbreviations

FISH: Fluorescence in situ hybridization; **EMC:** Extra skeletal myxoid chondrosarcoma; **ES:** Epithelioid sarcoma; **RT:** Rhabdoid tumor; **METC:** Myxoepithelioid tumor of choroid features; **CT:** Computed tomography; **CRP:** C-reactive protein; **CEA:** Carcinoembryonic antigen; **AFP:** Alpha-fetoprotein; **CA19-9:** Carbohydrate antigen 19-9; **EMA:** Epithelial membrane antigen; **CK:** Cytokeratin; **AE1/AE3:** Cytokeratin-AE1/AE3; **INSM1:** insulinoma-associated protein 1; **S-100:** S-100 protein; **ER:** Estrogen receptor; **SMA:** Alpha-smooth muscle actin; **Caldesmon:** h-caldesmon; **EWSR1:** Ewing sarcoma RNA-binding protein 1; **FUS:** fused in sarcoma; **GAFF:** Glial acidic fibrillary protein; **NR4A3:** Nuclear receptor subfamily 4 group A member 3; **METVR:** Myoepithelioid-like tumors of the vulvar region; **METC:** Myxoepithelioid tumor with choroid features.

Declarations

Source of support

None.

Ethics approval and consent to participate

All the procedures including the handling of personal information in this case report were conducted in accordance with the ethical standards of the Helsinki Declaration of 1964 and its later versions by the responsible committee at the NHO Fukuyama Medical Center.

Consent for publication

Written informed consent was obtained from the patient for publication of this article.

Availability of data and materials

All relevant data are within the paper and its supporting Information files.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Author's contribution

Hiroshi Sonobe was concerned with the conceptualization of the study, study design, data acquisition, data analysis, data interpretation, drafting the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

Hiroshi Sonobe, Rika Omote, Hiroyuki Yanai and Hidetaka Yamamoto discussed the pathological characterization of the present soft tissue tumor and subsequently, arrived at the diagnosis of malignant myoepithelioma.

Kazuma Yukihiro and Hiroshi Masumoto performed the clinical diagnosis based on the patient's history, symptoms and images, and conducted the surgery and follow-up.

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