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Soft Tissue Myoepitheliomas: A Discussion of Pathological Characteristics and Fusion Genes

Running Head: Pathology and Fusion Genes in Soft Tissue Myoepithelioma

Hiroshi Sonobe*, Rika Omote

Department of Diagnostic Pathology, National Hospital Organization（NHO）Fukuyama, Medical Center, Hiroshima, Japan.

***Corresponding Author:** Hiroshi Sonobe, Department of Diagnostic Pathology, National Hospital Organization（NHO）Fukuyama, Medical Center, Hiroshima, Japan.

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Abstract:
Owing to the diversity in cellular morphologies, nuclear atypia, proliferation patterns, and background matrices, rare soft tissue myoepitheliomas are often challenging to diagnose based solely on histopathological features. Benign tumors require differentiation from leiomyomas, neurogenic tumors, gastrointestinal stromal tumors, and solitary fibrous tumors. Due to histological similarities and overlaps, malignant myoepitheliomas should be differentiated from extraskeletal myxoid chondrosarcoma, proximal epithelioid sarcomas, extrarenal rhabdoid tumors, myoepithelioid tumor of the vulvar regions, and myoepithelioid tumor with chordoid features. Therefore, appropriate use of various markers, including myoepithelial cell markers and markers specific for other benign and malignant soft tissue tumors is essential.
To date, tumor-specific fusion genes have been identified in various soft tissue tumors, providing a useful complement to pathological diagnosis. Meanwhile, in soft tissue myoepithelioma, fusion genes composed of Ewing sarcoma breakpoint region 1 (EWSR1) or Fused in Sarcoma (FUS) gene with various partner genes and other fusion genes unrelated to EWSR1 or FUS have recently been identified. However, the relationship between these fusion genes and clinicopathological features has not been fully elucidated. Furthermore, therapeutic applications based on these findings have not yet been developed. Therefore, further research is needed to clarify them.

Keywords: Soft tissue myoepitheliomas; differential diagnosis; soft tissue tumors; fusion genes

Introduction:

Anatomically, myoepithelial cells are found in the ducts and acini of various glands, including the salivary, mammary, lacrimal, and sweat glands, and glands in the respiratory system. Myoepitheliomas usually arise in these organs and tissues [1-5], and rarely also occurring in soft tissues, bones, and viscera where myoepithelial cells are generally absent [6-9]. Such myoepitheliomas occur in a wide range of age groups, from infants to the elderly, and clinically exhibit a range of benign to low- to high-grade malignancies. Histologically, tumor cells exhibit oval to spindle shapes, mildly to severely atypical or pleomorphic nuclei, and a variety of growth patterns, including irregular fascicular, lobular, or glandular, often with diverse backgrounds such as fibrous, hyalinized, myxoid, or chondroid stroma. This heterogeneity and diversity in the histopathology [6-9] results in these histopathological similarities and overlaps with various other benign and malignant soft tissue tumors, making the pathological diagnosis extremely challenging. Therefore, to confirm the diagnosis of such soft tissue myoepithelioma, various myoepithelial markers, as well as markers specifically expressed in other soft tissue tumors require evaluation in addition to histological features.
In recent years, molecular and genetical studies, particularly of myoepithelioma arising in soft tissue and bone have revealed fusion genes related to Ewing sarcoma breakpoint region 1 (EWSR1) and Fused in Sarcoma (FUS), as well as several unrelated fusion genes [9-12]. However, the relationship between these fusion gene patterns and the clinicopathological features of rare soft myoepithelioma has not yet been fully elucidated. Additionally, therapeutic applications based on the fusion genes have not been developed. To resolve them, further accumulation of genetic data on this type of tumors is considered necessary.

Discussion

1. Pathological characteristics of soft tissue myoepitheliomas

Soft tissue myoepitheliomas display a wide clinical spectrum, ranging from benign to malignant. Histologically, similarities and overlaps with various benign and malignant soft tissue tumors are often observed, making a definitive diagnosis difficult. Benign tumors exhibit spindle-to-epithelioid cells and resemble benign soft tissue tumors, including leiomyomas, neurogenic tumors, gastrointestinal stromal tumors, and solitary fibrous tumors. In malignant cases, tumors exhibit more complex histopathological features, with tumor cells exhibiting diverse morphologies, including eosinophilic, amphophilic, or clear cytoplasm, moderate-to-severe nuclear atypia, pleomorphism, multinuclear structures, pathological mitotic figures, and even rhabdoid cells. Tumor cell nuclear loss of integrase interacting factor 1/switch/sucrose nonfermentable complex (SWI/SNF)-associated, matrix-associated, actin-dependent chromatin regulator subfamily b, member 1 (INI1/SMARCB1), and frequent positivity for marker of proliferation Kiel 67 (Ki-67) and tumor protein p53 (p53) suggest a high-grade malignant myoepithelioma [13,14]. Additionally, the stroma of the background exhibits diverse appearances, including myxomatous, chondroid, fibrous, and hyalinized features. Regardless of benign or malignant form soft tissue myoepitheliomas are often positive tumor protein p63 (p63), S-100 protein (S-100), CD10, α-smooth muscle actin (SMA), caldesmon, calponin, and glial fibrillary acidic protein (GFAP). Use of these markers as well as various specific markers found in other benign and malignant soft tissue tumors complements and strengthens the pathological diagnosis of soft tissue myoepithelioma.

2.Differentiation between malignant soft tissue myoepitheliomas and soft tissue sarcomas

Complex features of malignant soft tissue myoepitheliomas suggest similarities and overlaps with various other malignant soft tissue tumors. Extraskeletal myxoid chondrosarcoma (EMC) usually shows mild to moderate nuclear atypia and is positive for vimentin, S100, epithelial membrane antigen (EMA), and neuroendocrine markers such as synaptophysin, cluster of

differentiation (CD) 56, and nuclear insulinoma-associated protein 1 (INSM1) [15, 16]. The rare, highly malignant cellular EMC consists of densely packed atypical epithelioid cells often with pleomorphic cells and rhabdoid cells often with nuclear loss of INI1/SMARCB1 [17]. Proximal epithelioid sarcoma (ES) is characterized by the cellular proliferation of highly atypical epithelial cells with numerous rhabdoid cells, usually without a myxoid background. The tumor cells were diffusely and strongly positive for vimentin, cytokeratin (CK), and CD34. In addition, tumor cell nuclear loss of INI1/SMARCB1 was observed in most cases [18]. Extrarenal rhabdoid tumor shows histological features very similar to those of proximal ES but are found in children, and the tumor cells are CD34-negative [19]. Recently, myoepithelioid tumor of the vulval region (METVR) [20] has been proposed as a low-grade malignant tumor that occurs in women in which epithelioid and spindle-shaped tumor cells with moderate nuclear atypia grow in a cord-like, reticular, or nest-like pattern against abundant myxoid stroma. This tumor occasionally harbors rhabdoid cells that show nuclear loss of INI1/SMARCB1. In addition, the tumor cells are estrogen receptor- and SMA-positive with a minority being CK-positive, but S-100, GFAP, and CD34-negative. Subsequently, myoepithelioid tumor with chordoid features [21] was described. This tumor shows histological features similar to those of METVR. However, unlike METVR, it occurs in both men and women with notochordal histological features with brachyury-positive tumor cells. Hence, to confirm the pathological diagnosis of malignant soft tissue myoepitheliomas, it is important to understand the histological and immunohistochemical characteristics of not only myoepitheliomas but also various other soft tissue tumors mentioned above.

3.Fusion genes in soft tissue mesotheliomas and salivary gland myoepitheliomas

In recent years, molecular and genetic studies have been conducted on various soft tissue tumors, and tumor-associated genetic abnormalities, particularly specific fusion genes, have been identified [22-24]. These findings may strengthen or complement the pathological diagnoses based on histological and immunohistochemical findings. In soft tissue myoepitheliomas, EWSR1 or FUS-related fusion genes have been detected individually with various partner genes [25-28]. In a notable study [9], EWSR1 and FUS fusion genes were examined in 66 cases of benign and malignant myoepitheliomas using fluorescent in situ hybridization (FISH), targeted RNA sequencing, and cytogenetics. EWSR1 was present in 54 cases (81.8%), and EUS was present in 12 cases (18.2%). The partner genes of EWSR1 were POU domain, class 5, transcript factor I (POU5F1) in 15 cases, Pre-B-cell leukemia transcription factor 3 (PBX3) in 10 cases, Pre-B-cell leukemia transcription factor 3 PBX1 in 6, Zinc finger protein 444 (ZNF444) in 3, Krueppel-like factor 15 (KLF15) in 2, and KLF17 in 1, but the partner gene was unknown in 17 cases. The partner genes of FUS were KLF17 in eight cases, POU5F1 in two cases, and unknown in 2. Of the 66 cases with EWSR1 and FUS rearrangements, 17 cases (25.8%) were malignant, consisting of EWSR1-POU5F1 (11/15, 73.3%), EWSR1-ZNF44 (3/3, 100%), and FUS-KLF17 (3/8, 37.5%). Additionally, EWSR1-POU5F1 malignant cases were mostly found in children and young adults, and histologically, they showed focal proliferation of clear epithelioid cells. EWSR1/FUS-PBX 1/3 of the cases were associated with benign with sclerosing spindle cell proliferation. Furthermore, various fusion genes unrelated to EWSRI and FUS has been with the recent introduction of next generation sequencing (NGS). Fusion genes such as EWSRI-Vestigial-like family member 1 (VGLL1), Activating signal cointegrator 1 complex subunit 2 (ASCC2)-Nuclear factor erythroid 2 related factor1 (NBP2), Interferon regulatory factor 2 binding protein 2 "(IRF2BP2)-Caudal type homeobox2 (CDX2), and Serum response factor (SRF)-E2F1 transcription factor 1 (E2F1), have been reported in soft tissue myoepitheliomas, ranging from benign to malignant [28-31]. However, the relationship between the fusion gene patterns and clinicopathological findings is not fully elucidated, requiring further studies including accumulation of the data.

Myoepitheliomas arising from the salivary glands, sweat glands, glands in the respiratory tract, soft tissues, and other sites share common histopathological features. However, salivary gland myoepitheliomas usually harbor pleomorphic adenoma gene 1 (PLAG1)-related fusion genes [32-33]. These differ from the fusion genes found in soft tissue and cutaneous myoepitheliomas, including EWSR1 and FUS [9, 34], although some soft tissue myoepitheliomas harbor PLAG1-related fusion genes [35]. Furthermore, cutaneous syncytial myoepitheliomas harboring EWSR1-related fusion genes have been reported [34], and cutaneous myoepitheliomas with ductal differentiation have been associated with PLAG1-related fusion genes [36]. Indeed, there are overlaps in the fusion genes of salivary gland, skin, and soft tissue myoepitheliomas. Therefore, to clarify the relationship between clinicopathological findings and fusion gene patterns in soft tissue myoepitheliomas, detailed large-scale studies, including not only soft tissue myoepitheliomas but also myoepitheliomas occurring in other tissues and organs are necessary. However, to date, no treatments for myoepitheliomas have been developed based on the detected fusion genes [37].

4.Treatment of soft tissue myoepithelioma based on fusion genes

Owing to its rarity of soft tissue myoepithelioma, there has been no consensus regarding chemotherapy or other systemic therapies for this tumor, so far. Meanwhile, a recent report showed that a combination of mitogen-protein kinase kinase (MEK) inhibitors and cobimetinib was effective for this tumor harboring Acylglycerol kinase (AGK)-B-Raf proto-oncogene, serine/threonine kinase (BRAF) fusion gene, based on the results of NGS [38]. Like this case, in the soft tissue myoepithelioma, it is expected to lead to the development of new treatments using NGS.

Conclusion

Rare soft tissue myoepitheliomas exhibit a wide spectrum of benignity and low- to high-grade malignancy with clinicopathological diversity, including biological behavior, cell morphology, nuclear atypia, proliferation patterns, and background matrices, often making pathological diagnosis challenging. Recent molecular and genetic studies in genetic abnormalities in soft tissue myoepitheliomas have detected fusion genes related to EWSR1 and FUS as well as a variety of unrelated fusion genes. However, the relationship between these fusion gene patterns and clinicopathological features has not been sufficiently elucidated. Therefore, large-scale studies are required to investigate these associations. Furthermore, later, it is necessary to aim to develop new treatments based on the findings from genetical research of this tumor.

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Conflict of Interest

The author declares no conflict of interest.

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