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Case Report

A SMARCB1-deficient vulvar neoplasm with prominent myxoid stroma: report of a case showing ERG and FLI1 expression

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Abstract: In the vulvar region, epithelioid sarcoma (ES) is the most frequent SMARCB1-deficient neoplasm, followed by myoepithelial carcinoma (MC). Previous studies have demonstrated that some SMARCB1-deficient vulvar neoplasms cannot be classified as either ES or MC. Herein, we report of a 42-year-old woman with a SMARCB1-deficient neoplasm with prominent myxoid stroma in the vulva. It contained both epithelioid and spindled tumor cells, both of which showed vimentin and EMA expression. Although other markers useful for the differential diagnosis among SMARCB1-deficient tumors were negative, this tumor displayed characteristic expression of ERG and FLI1. As there are no reliable data regarding expression of ERG and FLI1 in MC, which are demonstrated to be often expressed in ES, further classification of cases such as the one reported here requires reliable data regarding their expression status in MC.

Keywords: SMARCB1/INI1, vulva, neoplasm, myxoid stroma, ERG, FLI1

Introduction

Genetic abnormalities including deletions and mutations in the *SMARCB1/INI1* gene have been found to be closely associated with atypical teratoid/rhabdoid tumors of the central nervous system and renal and extrarenal rhabdoid tumors [1, 2]. Since then, *SMARCB1/INI1* alterations have been demonstrated in other malignant neoplasms such as epithelioid sarcoma (ES), myoepithelial carcinoma (MC), epithelioid malignant peripheral nerve sheath tumor, extraskeletal myxoid chondrosarcoma, and renal medullary carcinoma [1]. All these neoplasms exhibit variable loss of SMARCB1/INI1 expression on immunohistochemistry (IHC); its loss has been found in approximately 90% of ES, 40% of pediatric MC, and 10% of adult MC [1].

The abovementioned mesenchymal tumors with *SMARCB1/INI1* alterations could acquire an epithelioid cellular morphology. Although differential diagnosis is difficult, it has recently been shown that ES is the most frequent SMARCB1-deficient neoplasm in the vulvar region, followed by MC [3]. As ES is extremely rare in the vulva and only a limited number of MC of the vulva have been documented [3], further studies to confirm these data are needed. In the same study, one SMARCB1-deficient vulvar neoplasm could not be classified as either ES or MC [3]. Such cases were designated as SMARCB1-deficient vulvar sarcoma, not otherwise specified [3].

For the diagnosis of ES, the usefulness of IHC for ERG and FLI1 has recently been described [4]. ERG and FLI1 are expressed in some mesenchymal tumors [5]. To our knowledge, there are no published studies examining ERG or FLI1 expression in MC.

Herein, we report of a 42-year-old woman with a SMARCB1-deficient neoplasm with prominent myxoid stroma in the vulva. It contained both

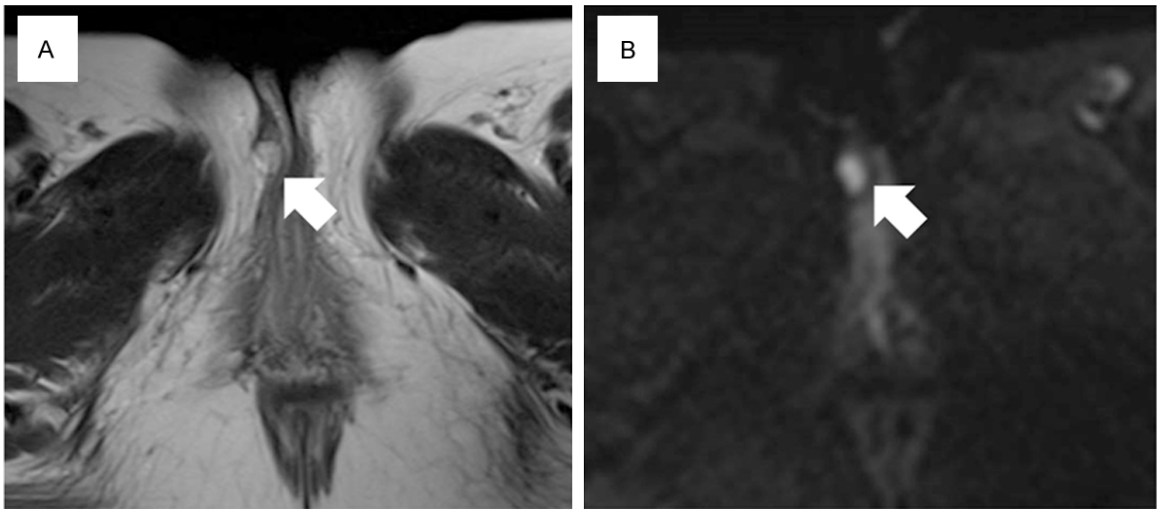

Figure 1. Magnetic resonance imaging findings. A. T2-weighted images showing a tumor with signal intensity similar to fat tissue (arrow). B. Diffusion-weighted images showing a tumor with high signal intensity (arrow).

epithelioid and spindled tumor cells, both of which showed vimentin and EMA expression. Although other markers used for the differential diagnosis of SMARCB1-deficient neoplasms were negative, this tumor expressed ERG and FLI1.

Clinical summary

A 42-year-old woman presented with a mass smaller than 1 cm at the vulva. She had a previous history of surgical resection of a mass at almost the same site 14 months previously, the diagnosis for which was indefinite suspecting low-grade malignancy. The size of the mass continued to increase, and magnetic resonance imaging was conducted. On T2-weighted images, a tumor with signal intensity similar to fat tissue was identified (**Figure 1A**); on diffusion-weighted images, a tumor with high signal intensity was apparent (**Figure 1B**). Plain computed tomography demonstrated no evidence of distant metastasis. Subsequently, a second tumorectomy for the mass, which was probably a recurrent lesion, was performed. The tumor was 1.5 × 1 × 1 cm in size, and complete resection was achieved. The postoperative course was uneventful, and the patient has been recurrence-free for 5 months.

Pathological findings

The surgically resected specimen showed physical artifacts, making marcoscopic observation difficult. However, palpation of the cut surface of the specimen indicated the tumor was myxoid in nature.

On histopathological examination, the lesion was multinodular in appearance. Each nodule contained variable degrees of myxoid stroma, which occupied approximately 80% of the volume of intranodular stroma; an internodular septum resulted in the tumor having a multinodular appearance, which was largely composed of collagenous stroma. Each nodule had a different proportion of tumor cells and myxoid stroma (**Figure 2A**). Each nodule was composed of epithelioid and spindle cells proliferating within a background of myxoid stroma. Nuclear atypia was slightly higher in epithelioid cells than in spindle cells considering the degree of enlargement of nuclei with coarse chromatin and small but distinct nucleoli. Both epithelioid cells and spindle cells had eosinophilic to amphophilic cytoplasm. Epithelioid cells and spindle cells were localized to both ends, and transitional cells showing short spindle morphology were also present. Within each nodule, the morphology of constituent cells and the amount of myxoid stroma was relatively homogenous in contrast to differences between each nodule. The most cellular type of nodule consisted of predominantly epithelioid cells showing some cohesiveness, accompanied with a lesser amount of myxoid stroma; however, in some areas of this type of nodule, myxoid matrix accumulated to form a kind of 'lake' (**Figure 2B**). As cellularity decreased, spindle cells became more numerous than epithelioid

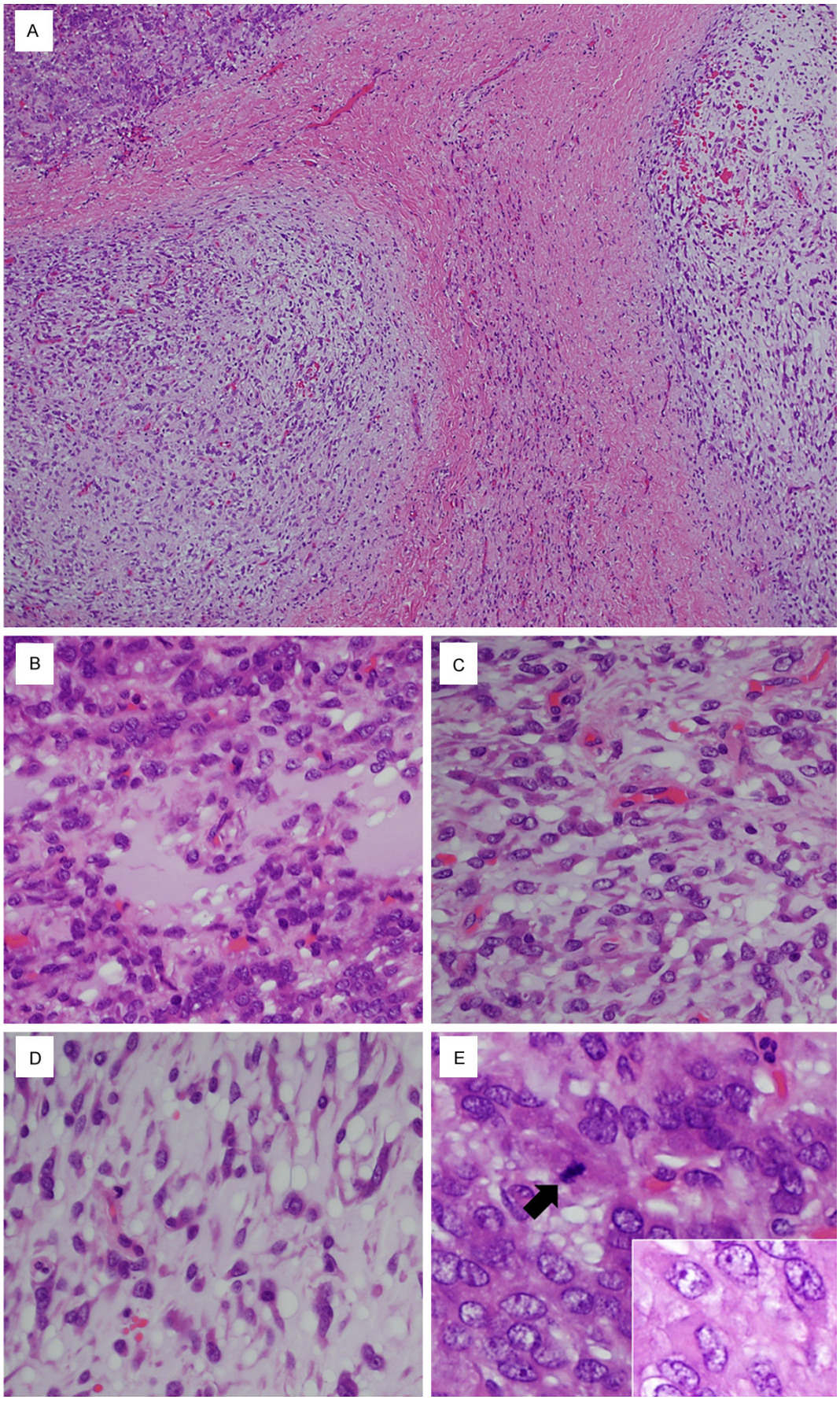
A
B
C
D
E

Figure 2. Microscopic findings. A. The lesion is multinodular in appearance. Each nodule shows variable degree of myxoid stroma, occupying approximately 30% of the volume of tumor stroma with the remainder being collagenous stroma constituting internodular septum and providing a multinodular appearance to the tumor. Each nodule has a different proportion of tumor cells and myxoid stroma (×20). B. The most cellular type of nodule consists of predominantly epithelioid cells showing some cohesiveness, accompanied with the least amount of myxoid stroma. In some areas of this type of nodule, myxoid matrix is accumulated to form a kind of 'lake' (×200). C. In another nodule of decreased cellularity, spindle cells became more numerous than epithelioid cells, accompanied by more abundant myxoid stroma than the most cellular type of nodule (×200). D. In the least cellular type of nodule, epithelioid cells almost disappeared and spindle cells proliferated in the most abundant myxoid stroma (×200). E. Epithelioid cells showing a mitotic figure (arrow) (×400). Inset: Rhabdoid cells are occasionally present intermingled with epithelioid cells (×600).

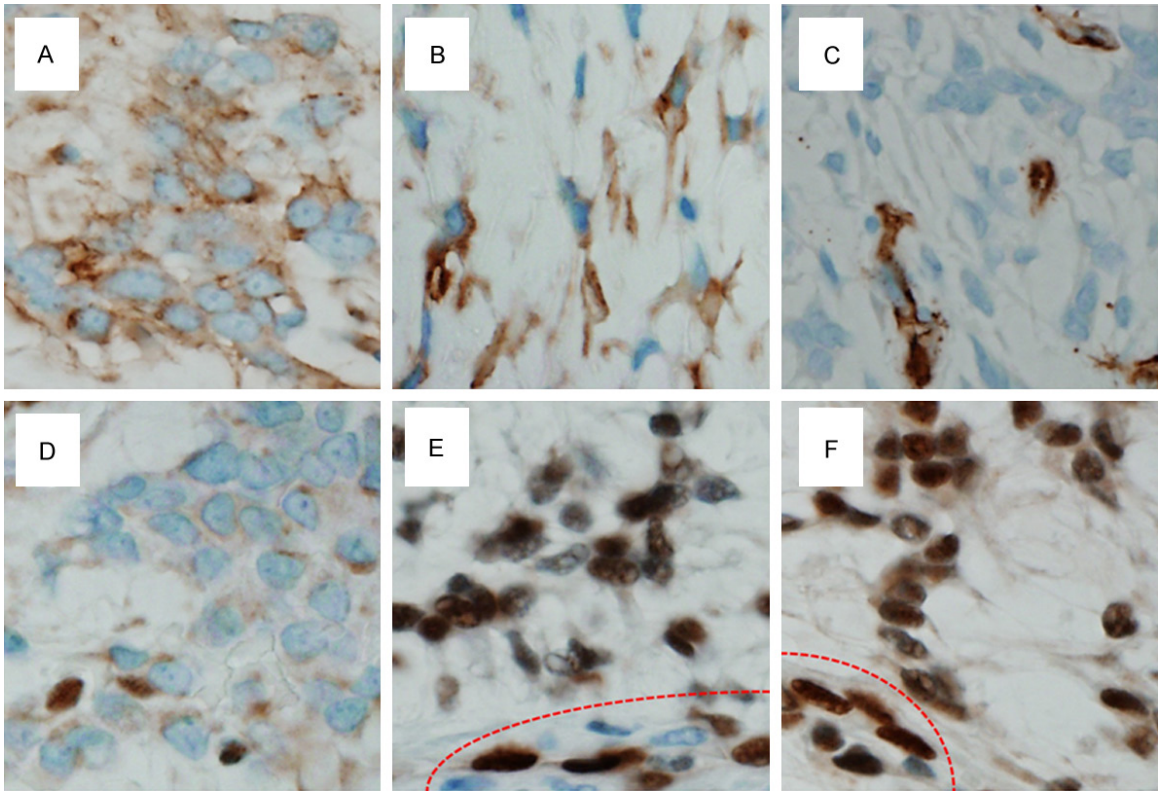

Figure 3. Immunohistochemistry findings. A. Epithelioid cells showing EMA positivity (×400). B. Spindle cells showing EMA positivity (×400). C. Complete CD34 negativity of tumor cells. Of note, small blood vessels are positive for it (×400). D. Nuclear expression of SMARCB1/INI1 is lost entirely in tumor cells. Of note, lymphocytes showing nuclear expression (×400). E. ERG expression in the nuclei of almost all tumor cells. Of note, the expression is comparable to that in vascular endothelial cells (dotted curvilinear line) (×400). F. FLI1 expression in the nuclei of almost all tumor cells. Of note, the expression is comparable to that in vascular endothelial cells (dotted curvilinear line) (×400).

cells, accompanied by more abundant myxoid stroma (**Figure 2C**). In the least cellular type of nodule, epithelioid cells almost disappeared and spindle cells proliferated in the more abundant myxoid stroma (**Figure 2D**). In the most cellular type of nodule, epithelioid cells showed 6 mitoses per 10 high-power fields (HPFs) (**Figure 2E**). Spindle cells exhibited less frequent mitoses, having less than 1 per 10 HPFs in the least cellular type of nodule. Rhabdoid cells were occasionally present and intermingled with epithelioid cells (**Figure 2E**, inset). Necrosis was absent. The surgical margin was free of tumor cells.

IHC analysis revealed that both epithelioid cells and spindle cells were positive for vimentin (V9, 1:100; Dako) and EMA (E29, 1:100; Dako, Glostrup, Denmark) (**Figure 3A**, **3B**), but negative for pan-cytokeratin (AE1/AE3, 1:100; Dako). Both cell types were negative for CD34 (QBEnd 10, 1:100; Dako) (**Figure 3C**), S-100

protein (polyclonal, 1:1000; Dako), αSMA (1A4, 1:100; Dako), desmin (D33, 1:100; Dako), calponin (CALP, 1:100; Dako), GFAP (6F2, 1:100; Dako), and p63 (4A4, 1:100; Dako). Nuclear expression of SMARCB1/INI1 (BAF47, 1:100; BD Bioscience, Oxford, UK) was lost entirely in tumor cells (**Figure 3D**). The nuclei of almost all tumor cells showed immunopositivity for N-terminus of ERG (EPR3863, 1:100; Epitomics, Burlingame, CA) (**Figure 3E**) and FLI1 (G146-222, 1:50; BD Pharmingen, San Diego, CA) (**Figure 3F**).

Considering the results of morphological analysis and IHC, ES and MC were included in the differential diagnosis. Although SMARCB1 negativity is observed in both ES and MC, EMA positivity alone other than ERG and FLI1 positivity was not sufficient to make a definitive diagnosis. However, ERG and FLI1 positivity might indicate that the tumor was an ES. Nevertheless, the positivity of these markers has not been sufficiently examined to exclude the possibility of MC or other unestablished tumor entities. Thus, we believe that the designation of this tumor as a SMARCB1-deficient vulvar sarcoma with prominent myxoid stroma is appropriate.

Discussion

It has recently been suggested that ES represents many of the SMARCB1-deficient neoplasms in the vulva, and that some cases of unclassifiable SMARCB1-deficient neoplasms, including SMARCB1-deficient vulvar sarcoma, not otherwise specified, would be included in the family of ES [3]. ES consists of two entities, the proximal type and the distal type. The distal type of ES, established by Enzinger in 1970 [6], most often originates in the distal extremities of young patients and characteristically consists of relatively bland epithelioid cells, often displaying a granuloma-like pattern of growth around central necrosis. The proximal type of ES, established by Guillou et al. in 1997 [7], is usually observed as a large mass of proximal soft tissues and exhibits a more pleomorphic appearance and more frequent rhabdoid cytology than the distal type and geographic necrosis. Both the distal and proximal ES typically express pan-cytokeratin and EMA, and CD34 expression is seen in 50% to 60% of cases [8, 9]. Nuclear staining for the N-terminus of ERG and FLI1 was seen in 68% (19 out of 28) and 93% (28 out of 30) cases of distal and proximal ES, respectively [4]. Considering the presence of epithelioid cells and rhabdoid cells and the expression of EMA, ERG, and FLI1 in our case, it is possible that our case is ES; however, negativity for both pan-cytokeratin and CD34 is not typical for ES.

In SMARCB1-deficient vulvar neoplasms, MC is the second most common neoplasm, following ES. The diagnosis of MC in soft tissues is difficult from the morphological examination alone, as it could display a broad morphological spectrum, ranging from spindled morphology to epithelioid and rhabdoid morphology [10, 11]. IHC is often helpful in the diagnosis of morphologically benign soft tissue myoepithelial tumors, which frequently coexpress epithelial markers and S-100 protein in addition to the expression of myoepithelial markers, such as αSMA, calponin, GFAP, and p63, in up to 50% of cases [10, 12, 13]; however, IHC is less helpful in diagnosing MC, as expression of epithelial markers and S-100 protein expression may be only focal or even absent [11, 14]. In this setting of equivocal immunophenotype, it is possible that the expression of muscle markers along with sufficient morphological features is suggestive of MC [3]. MC is not strongly suspected in our case despite its morphology being interpreted as existing in the spectrum of MC, as our case showed negativity for pan-cytokeratin, S-100 protein, and myoepithelial markers. In addition, the expression of ERG and FLI1 has not been closely examined in MC; thus, it is hard to definitively diagnose our case as MC.

Prominent myxoid stroma, which is one of the features sometimes encountered in myoepithelial tumors, could also be identified in ES in rare instances [10, 15, 16]. In one study of myxoid ES, the percentage of stroma described as prominent myxoid ranged from 50% to 90% [16]. If the present tumor represents an ES, it would be valid to define myxoid ES according to the percentage of myxoid stroma documented in the study, as the present tumor showed 80% myxoid stroma. At present, however, we believe this tumor would be better designated as a SMARCB1-deficient vulvar sarcoma with prominent myxoid stroma. We feel that one reported case of vulvar myxoid ES, which the authors mentioned as an extremely rare case [17], might be closely related to our case owing to its

morphology and immunophenotype, although CD34 expression of their case might suggest a diagnosis of ES. CD34 expression was observed in 2 out of 3 cases of SMARCB1-deficient vulvar sarcoma, not otherwise specified [3], and the authors stated that one of these cases would represent ES. However, the remaining CD34-expressing case in that study was not defined as representing ES or not [3]. Thus, CD34 expression status is not sufficient to discriminate between ES and MC, although MC is usually CD34-negative [18].

In conclusion, few cases of SMARCB1-deficient neoplasms, such as ES and MC, in the vulva have been reported. In addition, unclassifiable SMARCB1-deficient cases do exist. Moreover, prominent myxoid stroma is less frequently encountered in ES than in MC, although there are several reported cases of ES with prominent myxoid stroma. Although ES is probably more frequent than MC in the vulva, it is difficult to designate our case of SMARCB1-deficient vulvar neoplasm with prominent myxoid stroma characteristically expressing ERG and FLI1 as ES. As there are no reliable data regarding expression of ERG and FLI1 in MC, which are demonstrated to be often expressed in ES, further classification of cases such as the one reported here requires reliable data regarding their expression status in MC.

Disclosure of conflict of interest

None.

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