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Original contribution

Molecular characterization of a population-based series of endometrial stromal sarcomas in Kuwait☆,☆☆

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Summary Endometrial stromal sarcomas (ESSs) frequently harbor genetic fusions, including *JAZF1-SUZ12* and equivalent fusions in low-grade ESS (LGESS) and *YWHAE-NUTM2* in high-grade ESS (HGESS). This study aims to classify a population-based series of ESSs in Kuwait based on the 2014 World Health Organization classification system and to assess the diagnostic use of interferon-induced transmembrane protein 1 (IFITM1) immunomarker for ESSs. Twenty ESSs including 19 LGESSs and 1 HGESS treated during the period between 2002 and 2013 were identified, and the cases were reviewed and characterized using fluorescence in situ hybridization and immunohistochemical studies. Thirteen (81.3%) of 16 LGESSs with interpretable results showed *JAZF1* and/or *PHF1* genetic rearrangements by fluorescence in situ hybridization, and the only HGESS in the series showed *YWHAE* genetic rearrangement. All LGESSs with interpretable results showed positive immunostaining for CD10 compared with 11 (61%) of 18 that showed positive immunostaining for IFITM1; 4 of 7 IFITM1-negative LGESSs showed *JAZF1* and/or *PHF1* rearrangements. A series of uterine leiomyomas, leiomyosarcomas, adenosarcomas, and carcinosarcomas were included for comparison, and positive IFITM1 staining was found in 1 of 10 leiomyomas, 3 of 13 leiomyosarcomas, 3 of 4 adenosarcomas, and 3 of 8 carcinosarcomas, compared to 0 of 10 leiomyomas, 9 of 13 leiomyosarcomas, 3 of 4 adenosarcomas, and 5 of 8 carcinosarcomas that were positive for CD10. Our results demonstrated characteristic genetic rearrangements in a high percentage of LGESSs in this Middle Eastern population, and IFITM1 antibody appears to be less sensitive than CD10 for LGESS.

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1. Introduction

Endometrial stromal sarcoma (ESS) is the second most common type of uterine sarcoma, and it affects women predominantly in the perimenopausal age group. The previous version (2003) of the World Health Organization (WHO) tumor classification system recognized only the low-grade form of ESS (LGESS) [1–3]. Most LGESSs harbor chromosomal rearrangements, with t(7;17)(p15; q21) being the most common resulting in *JAZF1-SUZ12* genetic fusion [4–7]. Less common types of genetic fusions—*JAZF1-PHF1* [8,9], *EPC1-PHF1* [8], *MEAF6-PHF1* [10,11], *ZC3H7B-BCOR* [12] and *MBTD1-CXorf67* [13]—were also described in LGESSs. Recent genetic insights also offered support for the existence of HGESSs that are characterized by *YWHAE-NUTM2A/B* (formerly known as *YWHAE-FAM22A/B*) genetic fusion [14,15]. *YWHAE-NUTM2A/B* HGESS has a more aggressive clinical course than LGESS. The latest WHO tumor classification system (2014) [16] thus introduced the diagnostic category of HGESS in addition to LGESS, while uterine sarcomas that are undifferentiated and lacking known HGESS genetic rearrangement are referred to as undifferentiated uterinesarcomas.

Although most LGESSs exhibit classic morphologic features that closely resemble proliferative phase endometrial stroma, there are several well-recognized histologic variants [2,17–19]. Immunohistochemical analysis is sometimes used to differentiate these variant LGESSs from histologic mimics such as smooth muscle tumors of the uterus [20]. While CD10 has been regarded as a marker for endometrial stromal differentiation, it is not specific and can be positive in many other tumor types that are considered in the differential diagnosis of LGESS, including uterine smooth muscle tumors and undifferentiated uterine sarcoma [20,21]. Parra-Herran et al [22] recently described interferon-induced transmembrane protein 1 (IFITM1) as a novel diagnostic immunomarker that is highly sensitive and specific for endometrial stromal differentiation. They found that IFITM1 was particularly useful in the distinction between LGESS and uterine leiomyoma. About half of *YWHAE-NUTM2A/B* HGESSs contain an admixed low-grade component that is fibroblastic/fibromyxoid LGESS-like, and this low-grade component is positive for CD10 as well as hormone receptors. The high-grade areas of *YWHAE-NUTM2A/B* HGESS, however, lack CD10 staining in contrast to the low-grade area. Diffuse strong nuclear staining for cyclin D1 and cytoplasmic/membranous c-Kit staining is consistently seen in the high-grade areas of *YWHAE-NUTM2A/B* HGESS [23,24].

In this study, we applied the most recent WHO classification system and molecularly characterized a Middle Eastern population-based series of ESSs from Kuwait. We also evaluated the diagnostic use of IFITM1 in this cohort of ESS in comparison with potential histologic mimics.

2. Materials and methods

2.1. Case selection and tissue samples

This study was approved by the Joint Committee for Protection of Human Subjects in Research at the Health

Table 1 Primary antibodies used for immunohistochemistry

Antibody	Clonality	Clone	Source	Dilution	Antigen retrieval	Cutoffs used for scoring
IFITM1	Rabbit polyclonal	Polyclonal	Sigma-Aldrich, St. Louis, MO, USA	1:200	MW-20 min	Positive is intensity score >1 and distribution score > 1 [a]; negative is intensity and distribution ≤ 1
CD10	Mouse monoclonal	55C6	Novocastra, Wetzlar, Germany	1:50	MW-20 min	Diffuse positive is positivity in ≥75% of tumor cells; focal positive is positivity in <75% of tumor cells; negative is complete lack of staining of tumor cells
ER	Mouse monoclonal	1D5	Dako, CA, USA	1:50	MW-20 min	As above
SMA	Mouse monoclonal	1A4	Dako, CA, USA	1:100	MW-10 min	As above
Desmin	Mouse monoclonal	D33	Dako, CA, USA	1:100	MW-10 min	As above
h-Caldesmon	Mouse monoclonal	h-CD	Dako, CA, USA	1:50	MW-10 min	As above
c-Kit (CD117)	Rabbit polyclonal	Polyclonal	Dako, CA, USA	1:50	MW-10 min	As above
Cyclin D1	Mouse monoclonal	DCS-6	Dako, CA, USA	1:50	MW-20 min	Diffuse positive is nuclear positivity in ≥75% of tumor cells; nondiffuse is the presence of nuclear positivity in <75% of tumor cells or complete lack of nuclear staining of tumor cells

Abbreviation: MW, microwave.

[a] According to the original article, intensity scores were 0 (no staining), 1 (weak); 2 (moderate), and 3 (strong), and distribution scores were 0 (absent, 0-5% of cells), 1 (patchy, 6%-25% of cells), 2 (multifocal, 26%-75% of cells), and 3 (diffuse ≥75% of cells) [22].