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Endometrial stromal sarcomas and related neoplasms: new developments and diagnostic considerations

LIEN HOANG[1], SARAH CHIANG[2] AND CHENG-HAN LEE[3]

[1]*Department of Anatomical Pathology, Vancouver General Hospital, Vancouver, BC, Canada;* [2]*Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States; and* [3]*Department of Pathology, BC Cancer Agency, Vancouver, BC, Canada*

Summary

Our understanding of endometrial stromal sarcomas has evolved dramatically since their earliest descriptions from over a century ago. Initial studies focused on establishing the relationship between histological appearances of endometrial stromal sarcomas and their clinical outcomes. Studies performed in the last decade have uncovered several recurrent cytogenetic aberrations occurring in low- and high-grade endometrial stromal sarcomas. Low-grade endometrial stromal sarcomas bear close histopathological resemblance to proliferative-type endometrial stroma, and approximately half harbour t(7;17)(p15;q21) resulting in *JAZF1-SUZ12* gene fusion. Less common *JAZF1-PHF1*, *EPC1-PHF1*, *MEAF6-PHF1*, and *MBTD1-CXorf67* fusions have also been reported. The term 'high-grade endometrial stromal sarcoma' was recently re-introduced in the classification of endometrial stromal tumours after the discovery of t(10;17)(q22;p13) resulting in *YWHAE-NUTM2A/B* fusion and is associated with distinct morphological characteristics. This review highlights the evolution of endometrial stromal sarcoma classification schemes over time and describes the salient clinicopathological and molecular features of endometrial stromal nodule, low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma, and undifferentiated uterine sarcoma. It also describes the recent characterisation of endometrial stromal sarcoma with t(X;22)(p11;q13) resulting in *ZC3H7B-BCOR* fusion, a noteworthy entity due to its close histological resemblance to myxoid leiomyosarcoma. We also provide insights into common challenging scenarios encountered when assessing endometrial stromal lesions in daily surgical pathology practice.

Key words: Endometrial stromal sarcoma; low-grade endometrial stromal sarcoma; high-grade endometrial stromal sarcoma; undifferentiated uterine sarcoma; uterine sarcoma classification; molecular; *JAZF1*; *YWHAE*; *BCOR*.

INTRODUCTION

With the exclusion of carcinosarcomas, that are now considered an epithelial malignancy, endometrial stromal sarcomas (ESS) account for 7–25% of all uterine mesenchymal tumours and less than 1% of all malignancies arising in the uterus.[1–4] The incidence of uterine sarcomas is 1.5–1.7/100,000 females, with a slight increase over time.[3–6] ESS is the second most common type of uterine mesenchymal neoplasm after leiomyosarcoma.[3,5]

In the most recent 2014 World Health Organization (WHO) classification of gynecological malignancies, endometrial stromal tumours (EST) are divided into four categories: (1) endometrial stromal nodule (ESN), (2) low-grade endometrial stromal sarcoma (LGESS), (3) high-grade endometrial stromal sarcoma (HGESS), and (4) undifferentiated uterine sarcoma (UUS). To avoid confusion in this review, the abbreviations LGESS and HGESS will only be used in reference to the 2014 WHO definition of these tumours.

THE HISTORY AND EVOLUTION OF ENDOMETRIAL STROMAL SARCOMA CLASSIFICATION

Classification of uterine sarcomas has evolved considerably over the last half century, driven by several landmark studies that have improved our understanding of these rare neoplasms (Fig. 1). The first popularised classification scheme for uterine sarcomas was put forth in 1959 by W. B. Ober who adopted the philosophy of F. A. Zenker from almost a century prior. Ober proposed nomenclature based on histogenesis, thereby dividing uterine sarcomas into homologous types (bearing mesenchymal tissues native to the uterus) and heterologous types (exhibiting tissue types that did not normally reside in the uterus).[7–9] This classification was later modified by Kempson and Bari in 1970 to include three categories: (1) pure sarcomas, (2) mixed sarcomas, and (3) malignant mixed Müllerian tumours.[10] Both Ober's and Kempson/Bari's early classification schemes categorised ESTs under two main designations: (1) endolymphatic stromal myosis, and (2) endometrial stromal sarcoma.[7,10]

In the preceding two decades, tumours comprising cells resembling endometrial stroma were assigned a wide variety of names, including stromal adenomyosis,[11] stromal endometriosis,[12,13] stromatosis,[14] endometriosis interstitiale,[15] endolymphatic stromal myosis,[16] stromal sarcoma,[17,18] angioblastomatosis,[19] and even haemangiopericytoma.[20] This diversity in nomenclature highlights the ongoing uncertainties regarding the pathogenesis of these lesions and their biological behaviour at that time.[21] In 1949, Park *et al.* studied 43 tumours termed stromatosis endometriosis and noted that seven had metastasised, providing one of the earliest clues to the malignant nature of these neoplasms.[22]

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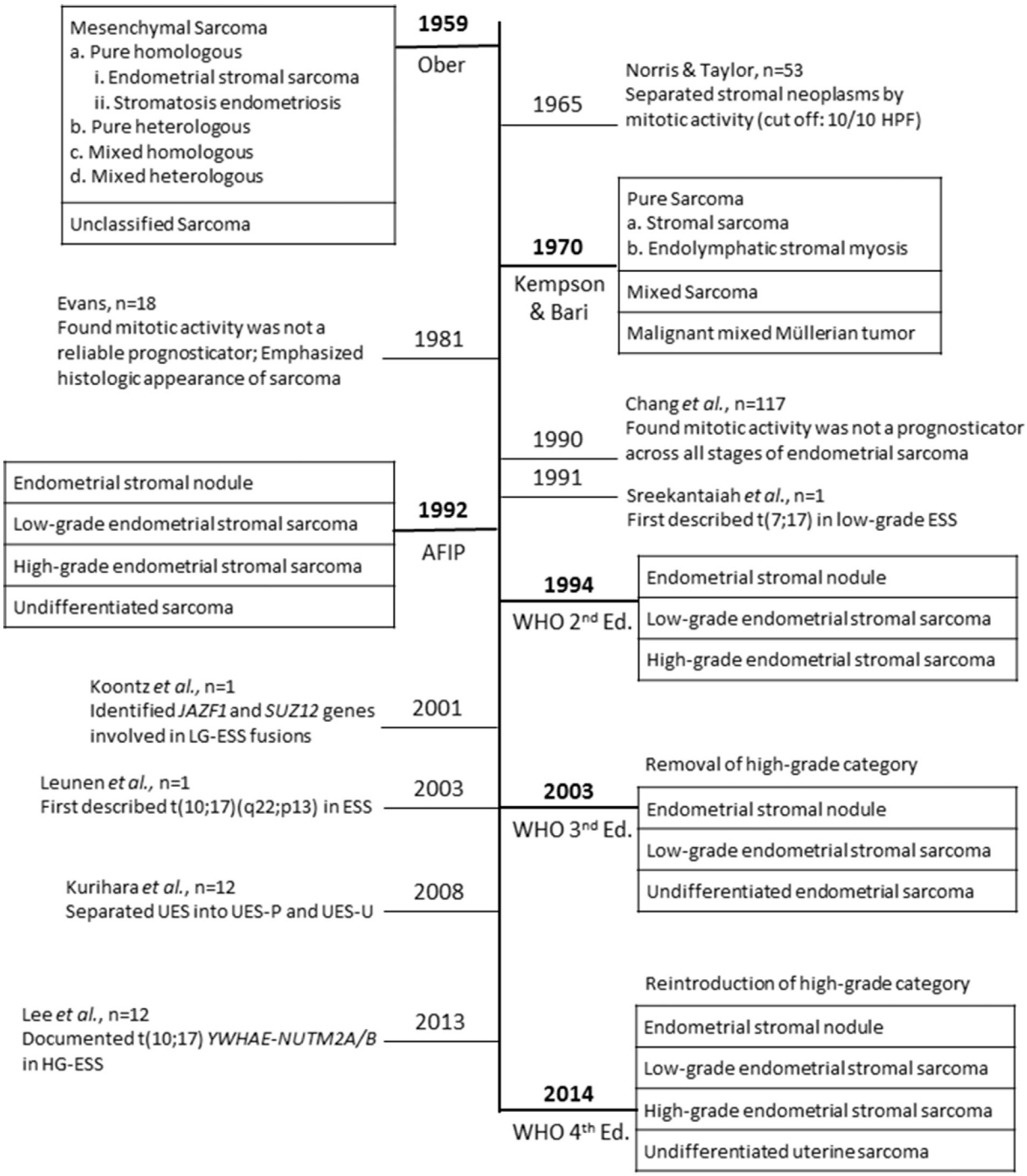

Fig. 1 Evolution of endometrial stromal sarcoma classification over time.

In 1965, Norris and Taylor were the first to propose objective criteria to distinguish between benign and malignant ESTs. In their study of 53 ESTs, 18 had pushing borders and lacked lymphovascular invasion; none of these tumours recurred. The authors hence designated these lesions as 'stromal nodules' to emphasise their benign nature. The remaining 35 tumours exhibited infiltrative borders where the cells extended irregularly between muscle bundles or into vascular spaces. Among patients with available clinical follow-up, 17 tumours had a mitotic index of <10/10 high power fields (HPF) and were associated with a 100% 5-year survival, while 14 had a mitotic index of ≥10/10 HPF and had a 55% 5-year survival. Given the contrast in prognosis between the two groups, the former was designated as 'endolymphatic stromal myosis' and the latter as 'stromal sarcoma'.[21]

These findings were subsequently reiterated by several other groups. Kempson *et al.* studied 17 infiltrating ESTs and found that those with mitotic counts of >20/10 HPF had all metastasised, while tumours with mitotic activity of <5/10 HPF did not recur.[10] Yoonessi and Hart in two reports, evaluated nine patients with endometrial stromatosis and

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