Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 463–471

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

Uterine sarcoma Part I—Uterine leiomyosarcoma: The Topic Advisory Group systematic review

Kuo-Chang Wen [a, b, 1], Huann-Cheng Horng [a, b, 1], Peng-Hui Wang [a, b, c, *], Yi-Jen Chen [a, b], Ming-Shyen Yen [a, b], Heung-Tat Ng [b, d], the Taiwan Association of Gynecology Systematic Review Group [e, 2]

[a] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Obstetrics and Gynecology, National Yang-Ming University School of Medicine, Taipei, Taiwan
[c] Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[d] Foundation of Female Cancer, Taipei, Taiwan
[e] The Taiwan Society of Gynecology Systematic Review Group at the Taipei Veterans General Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:
Accepted 8 April 2016

Keywords:
diagnosis
leiomyosarcoma
treatment

ABSTRACT

Uterine sarcomas account for 3–7% of all uterine cancers. Because of their rarity, unknown etiology, and highly divergent genetic aberration, there is a lack of consensus on risk factors for occurrence and predictive poor outcomes as well as optimal therapeutic choices. Tumor types according to the World Health Organization classification include leiomyosarcoma, endometrial stroma sarcoma, and undifferentiated sarcoma. Staging is done using the 2014 Federation International Gynecology and Obstetrics and 2010 American Joint Committee on Cancer tumor, lymph node, and metastases systems. Tumor grade can be classified based on the French Federation of Cancer Centers Sarcoma Group system or the Broder's system that incorporates tumor differentiation, mitotic count, and tumor necrosis. This review is a series

* Corresponding author. Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei, Taiwan.
E-mail addresses: phwang@vghtpe.gov.tw, phwang@ym.edu.tw, pongpongwang@gmail.com (P.-H. Wang).

[1] K.-C.W. and H.-C.H. contributed equally.

[2] The Taiwan Society of Gynecology Systematic Review Group includes the following members: Yen-Hou Chang, Yi Chang, Hsiang-Tai Chao, Kuan-Chong Chao, Chi-Mu Chuang, Chi-Hong Ho, Chen-Yu Huang, Zhi-Chen Hung, Ling-Yu Jiang, Hei-Yu Lau, Hsin-Yang Li, Chi-Yao Lin, Chia-Hao Liu, Pi-Lin Sun, Nae-Fang Twu, Hua-Hsi Wu, Hann-Chin Yu (Department of Obstetrics and Gynecology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan); Fong-Yuan Ju (Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan); Chih-Ping Tsai (Emergency Department, Taipei Veterans General Hospital, Taipei, Taiwan); Wen-Hsun Chang, Yen-Mei Hsu, Na-Rong Lee (Department of Obstetrics and Gynecology, and Department of Nursing, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan); Chih-Yao Chen (Dianthus MFM Center Minquan, Dianthus MFM Group, and National Yang-Ming University, Taipei, Taiwan); Ting-Chen Chang, Wen-Chun Chang, Chii-Hou Chen, Ruey-Jian Chen, Song-Nan Chow, Yih-Ron Lien, Bor-Ching Sheu, Pao-Ling Torng, Men-Luh Yen (Department of Obstetrics and Gynecology, National Taiwan University Hospital and National Taiwan University, Taipei, Taiwan); Wen-Ling Lee (Department of Medicine, Cheng-Hsin General Hospital, Taipei and Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan); Kuan-Chin Wang (Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan); Chih-Long Chang, Chih-Ping Chen, Jen-Ruei Chen, Tze-Chien Chen, Jian-Pei Huang, Ming-Chao Huang, Yeou-Lih Wang (Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan); Cheng-Chang Chang, Jah-Yao Liu, Her-Young Su, Yu-Chi Wang, Mu-Hsien Yu (Department of Obstetrics and Gynecology, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan); Lee-Wen Huang, Kok-Min Seow (Department of Obstetrics and Gynecology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan); Tsung-Hsuan Lai, Fa-Kung Lee (Department of Obstetrics and Gynecology, Cathay General Hospital, Taipei, Taiwan); Ching-Hui Chen (Department of Obstetrics and Gynecology, Taipei Medical University Hospital and Taipei Medical University, Taipei, Taiwan); Ben-Shian Huang (Department of Obstetrics and Gynecology, National Yang-Ming University Hospital, Ilan, Taiwan); Sheng-Mou Hsiao, Hsu-Dong Sun, Wen-Yih Wu (Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, New Taipei City, Taiwan); Sen-Wen Teng (Department of Obstetrics and Gynecology, Cardinal Tien Hospital-Hsintien and Fu Jen Catholic University, New Taipei City, Taiwan); Kuo-Hu Chen, Jeng-Hsiu Hung (Department of Obstetrics and Gynecology, Taipei Buddhist Tzu Chi General Hospital, New Taipei City, Taiwan); Hung-Cheng Lai, Chiou-Chung Yuan (Department of Obstetrics and Gynecology, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan); Ching-Hung Hsieh (Department of Obstetrics and Gynecology, Clinic of Fu Jen Catholic University, New Taipei City, Taiwan); Chin-Jung Wang (Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, and Chang Gung University, Taoyuan, Taiwan); Shing-Jyh Chang (Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Hsinchu, Taiwan); Man-Jung Hung, Shih-Tien Hsu, Yu-Min Ke, Chien-Hsing Lu, Lou Sun (Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, Taichung, Taiwan); Wei-Chun Chang, Yao-Ching Hung, Wu-Chou Lin (Department of Obstetrics and Gynecology, China Medical University Hospital and China Medical University, Taichung, Taiwan); Po-Hui Wang (Department of Obstetrics and Gynecology, Chung-Shang General Hospital and Chung-Shang Medical University, Taichung, Taiwan); Tze-Ho Chen (Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, Taiwan); Yiu-Tai Li (Department of Obstetrics and Gynecology, Kuo General Hospital, Tainan, Taiwan); Meng-Hsing Wu (Department of Obstetrics and Gynecology, National Cheng Kung University Hospital and National Cheng Kung University, Tainan, Taiwan); Kuo-Feng Huang (Department of Obstetrics and Gynecology, Chi-Mei Medical Center, Tainan, Taiwan); Hung-Chun Fu (Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, and Chang Gung University, Taoyuan, Taiwan); San-Nung Chen, An-Jen Chiang, Ju-Yueh Li, Li-Te Lin, Hsiao-Wen Tsai, Kuan-Hao Tsui (Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan).

http://dx.doi.org/10.1016/j.tjog.2016.04.033

uterine sarcoma
uterus

of articles discussing uterine sarcoma, and this is Part I, which focuses on one of the subtypes of uterine sarcomas—uterine leiomyosarcoma. The clinical characteristics, diagnosis, outcome, and recent advances are summarized in this article.

Overview of uterine sarcomas

Uterine sarcomas are rare tumors, accounting for 3–7% of uterine malignancies and less than 1% of all malignancies from female genital organs [1–5]. Because of their rarity, unknown etiology, and highly divergent genetic aberration, there is a lack of consensus on risk factors for their occurrence and predictive poor outcomes as well as optimal therapeutic choices. The diversity of uterine sarcoma can be classified according to the World Health Organization (WHO) classification, which includes the most common uterine leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine sarcoma [3,4]. Based on the WHO classification of soft-tissue sarcomas [4], other rare malignant mesenchymal tumors include adenosarcoma, rhabdomyosarcoma, perivascular epithelioid cell tumor, malignant type (PEComa), angiosarcoma, neurogenic sarcoma, osteosarcoma, chondrosarcoma, liposarcoma, primitive neuroectodermal tumor, myxofibrosarcoma, alveolar soft-tissue sarcoma, and epithelioid sarcoma.

Carcinosarcomas [malignant mixed mesodermal tumors or malignant mixed müllerian tumors (MMMTs)] are no longer considered as sarcoma due to their different spreading pattern. Carcinosarcomas spread as a dedifferentiated or metaplastic form of endometrial cancer (EC) [6,7], in which the mesenchymal part retains epithelial features (i.e., "conversion theory," which is supported by various molecular studies reporting similar chromosomal aberrations, cytogenetic aspects, concordant loss of heterozygosity, identical *p*53 and *K-ras* mutations, and matching X-inactivation patterns in both histological components of the majority of MMMT cases) [8]. However, because MMMT behaves more aggressively than the usual type of EC, even for Type II EC [9,10], it is still included in most retrospective studies of uterine sarcomas, and in the separate section of "mixed epithelial and mesenchymal tumors" of the 2014 WHO classification [4,11]. Besides MMMT, there are also some arguments for including ESSs because of the significant difference in their tumor behaviors. ESS is divided into (1) ESS, low-grade; (2) ESS, high grade; and (3) undifferentiated uterine sarcoma (UUS) [1,11].

Two staging systems are used for uterine sarcomas, including the 2014 Federation International Gynecology and Obstetrics (FIGO) and 2010 American Joint Committee on Cancer tumor, lymph node, and metastases systems (Table 1). The FIGO staging is more frequently applied in clinical practice. Tumor grade can be classified based on the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system or the Broder's system that incorporates tumor differentiation, mitotic count, and tumor necrosis (Grade 1, mild cytologic atypia; Grade 2, more nuclear irregularity; Grade 3, between Grades 2 and 4; and Grade 4, presence of bizarre cells) [11]. Evaluation of cytologic atypia is often subjective, but Oliva et al [11] provided the key components, which can help in such investigations (Table 2). Because MMMT might be better classified as mixed epithelial and mesenchymal tumors, we excluded the category of MMMT, and only focused on pure uterine sarcoma, mainly on uLMS and ESS. The series of documents attempted to provide updated information for this unusual uterine pathology, and we present by the order of clinical characteristics, diagnosis, pathology, treatment, and future perspectives.

Clinical characteristics and diagnosis

The median onset of uterine sarcomas is 50–70 years depending on the histological subtypes, but most women are of postmenopausal age. Identified risk factors, although uncertain, include previous pelvic irradiation and prior treatment with tamoxifen [12]. Clinical characteristics of uterine sarcoma vary greatly, and are also different by the histological subtypes [13]. Most symptoms and/or signs are nonspecific, including abdominal pain, enlarged abdominal circumference, enlarged uterine size, abnormal vaginal bleeding, and rapid uterine growth in perimenopausal or postmenopausal women with low estrogen levels. However, one study argued the relationship between rapid uterine growth and normal control, because there was no statistically significant difference in the diagnosed sarcoma between rapid uterine growth and normal control (0.27% vs. 0.23%) [14]. In addition, the absence of specific symptoms or signs made the diagnosis of many patients either incidental (when examining the resected specimen after myomectomy or hysterectomy) or by the appearance of accompanied

Table 1
2014 FIGO and 2010 American Joint Committee on Cancer TNM system for staging uterine sarcomas (leiomyosarcoma and endometrial stromal sarcoma).

FIGO	TNM	Definition
I[a]		Tumor limited to uterus
IA	T1aN0M0	<5 cm
IB	T1bN0M0	>5 cm
II		Tumor extends beyond the uterus but limited within the pelvic cavity
IIA	T2aN0M0	Adnexal involvement
IIB	T2bN0M0	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdominal cavity)
IIIA	T3aN0M0	1 site
IIIB	T3bN0M0	>1 site
IIIC	T3bN1M0	Pelvic and/or para-aortic lymph node metastases
IV		
IVA	T4NxM0	Tumor invades bladder and/or rectum
IVB	T4NxM1	Distant metastasis

FIGO = Federation International Gynecology and Obstetrics; TNM = tumor, lymph node, and metastases staging system.
[a] I is not applied for adenosarcoma ($x = 0$ or 1).

Table 2
Key factors for evaluation of cytologic atypia.

The following three key factors should be kept in mind:
1. Evaluate atypia at medium power magnification (10×)
2. Compare cytologic features of tumor with surrounding myometrium if possible
3. Look for background nuclear atypia not atypia of bizarre type that often is confined to groups of cells in an otherwise banal-appearing leiomyoma

Cytologic atypia includes more than one of the following features:
1. High nuclear size (high nuclear to cytoplasmic ratio)
2. Irregular nuclear membranes
3. Nuclear pleomorphism
4. Hyperchromatism
5. Prominent nucleoli or more than one nucleoli