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Microcystic, elongated, and fragmented pattern invasion is mainly associated with isolated tumor cell pattern metastases in International Federation of Gynecology and Obstetrics grade I endometrioid endometrial cancer☆

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Summary Although many studies have evaluated the impact of mismatch repair protein loss of expression (MMR LOE) or microcystic, elongated, and fragmented (MELF) pattern of myometrial invasion as individual factors in endometrial cancer, we analyzed the combined impact of both. We reviewed every case of International Federation of Gynecology and Obstetrics (FIGO) grade 1 endometrioid endometrial cancers (EECs) from our institution, between 2011 and 2015, that had a sentinel lymph node biopsy and/or a lymphadenectomy, and examined the following data: age, myometrial infiltration, MELF infiltration, lymphovascular space invasion, and lymph node status. These cases were then grouped according to the absence of lymph node metastases, the presence of isolated tumor cell (ITC) lymph node metastases, or the presence of non-ITC metastases. Among the 127 cases that were in our study, 105 patients did not have nodal metastases, whereas 22 patients showed metastases, of which 11 were ITC. MMR LOE was only significantly associated with a higher odds ratio (OR) of metastases (OR, 7.44; $P < .001$). MELF was only associated with a higher OR of ITC-pattern metastases (OR, 32.3; $P < .001$). This study distinguished the effects of MELF and MMR LOE on the risk of metastases in FIGO grade 1 EEC. Further

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research on the clinical impact of MELF and ITC-pattern metastases is warranted to better guide clinicians on the management of patients with FIGO grade 1 EEC harboring such characteristics, which are still considered low-risk cancer.

1. Introduction

International Federation of Gynecology and Obstetrics (FIGO) grade I endometrioid endometrial cancers (EECs) are generally associated with a good prognosis and low frequency of lymph node metastasis. However, the presence of microcystic, elongated, and fragmented (MELF) myometrial invasion in EEC has been previously been associated with poor prognosis [1]. On the other hand, hereditary nonpolyposis colorectal cancer/Lynch syndrome is associated with endometrial cancer, with 50% of affected female patients developing endometrial carcinoma before colorectal cancer [2]. Indeed, Lynch syndrome is defined by microsatellite instability (MSI) through the loss of expression (LOE) of DNA mismatch repair (MMR) proteins. Previous studies have also determined that LOE of MMR proteins is another independent factor of bad prognosis for EEC and is associated with nodal metastasis [3,4].

LOE of MMR proteins has been associated with macrometastases and micrometastases. The association between MELF and isolated tumor cells (ITCs) has been well studied, although its association to all types of lymph nodes is still controversial. A recent study by Han et al [1] has demonstrated an association between MELF and various types of positive lymph nodes, but did not take into account LOE of MMR proteins. The distinction between ITC and other types of metastases is particularly important because the prognostic value of ITC has not been well studied.

Because most studies have focused on the association of MELF or LOE of MMR proteins on EEC individually, our goal was to examine the combined impact of both predicting factors of lymph node metastasis in FIGO grade I EEC through a large retrospective cohort study.

2. Materials and methods

Patients who underwent hysterectomy that resulted in FIGO grade I EEC, with either sentinel lymph node or lymphadenectomy, were extracted from our Department of Pathology database at the Centre Hospitalier de l'Université de Montréal from June 2011 until June 2015. The study was limited to FIGO grade I EEC because their lymph node status has a stronger clinical impact when compared with higher-grade cancers. The ethics committee gave approval for experimentation with human subjects, and privacy rights were observed throughout the study.

The following features were noted from the pathology report and/or reviewed in histopathology slides: age, presence of villoglandular architecture, depth of myometrial invasion, MELF myometrial invasion pattern (Fig. 1A-C), lymphovascular space invasion (LVSI), lymph node status, and morphology of lymph node metastases when present (non-ITC versus ITC). MELF-type invasion was evaluated using hematoxylin-phloxine-saffron (HPS)–stained slides only, according to previously established morphologic criteria by Murray et al [5]. The presence of ITC (Fig. 2A and B) was evaluated by using criteria defined by the sixth edition of the *AJCC Cancer Staging Manual*, which consists in single cell or small clusters of cells less than 0.2 mm in largest dimension [6]. Lymph node slides were reviewed by 2 pathologists, one of whom is an expert in the field of gynecologic pathology, to determine exact lymph node status.

Tissue sections were stained with HPS, according to standard protocol for diagnostic purposes. Cytokeratin immunoperoxidase staining with AE1/AE3 antibody (Clone AE1/AE3, cat. #M351501; Dako, Mississauga, Ontario, Canada) was used to confirm the epithelial nature of suspect cells in lymph nodes. CD31 (Clone JC70A, cat. #M082301; Dako), and D2-40 (Clone D2-40, cat. #M361901; Dako) antibodies were used in one case to confirm the presence of LVSI. Staining was performed on an automated immunostainer (Benchmark ULTRA; Ventana Medical Systems, Tucson, AZ). All cases were tested for LOE of MMR proteins by immunohistochemistry (IHC), using commercially available antibodies from Ventana Medical Systems/Roche against the following MMR proteins: MLH1 (Clone M1, cat. #06472966001), MSH2 (Clone G219-1129, cat. #05269270001), MSH6 (Clone 44, cat. #05929911001), and PMS2 (Clone EPR3947, cat. #06419216001). Using MMR protein, LOE as a correlate for MSI has been widely accepted in previous studies [7].

Cases were grouped by the absence or presence of lymph node metastases and according to metastasis type (ITC or non-ITC). One case presented both types of metastases and was removed from the study to reduce confounding. Odds ratios (ORs), 95% confidence intervals (95% CIs) and *P* values were calculated in SPSS Statistics software version 20 (IBM, Armonk, NY). Univariate tests were performed using Fisher exact test for binomial analyses, Mann-Whitney *U* test for age differences, and binomial and ordinal regression for myometrial invasion. Multivariable analyses were performed using multinomial logistic regression.

3. Results

Table 1 shows the tumor characteristics among the 127 cases of FIGO grade 1 EEC in patients that fulfilled the inclusion criteria of the study. The median age of patients was