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The association of microcystic, elongated, and fragmented (MELF) invasion pattern in endometrial carcinomas with prognostic factors

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Summary

Purpose: One of the most important prognostic factors for endometrial carcinoma (EC) is myometrial invasion. Microcystic, elongated, and fragmented (MELF) myometrial invasion (MI) pattern is also important in terms of diversity of the invasion. To the best the present authors' knowledge, there is limited data about the significance of MELF type MI pattern, and lymph node (LN) involvement and therefore, the authors aimed to evaluate the frequency and association of MELF invasion pattern with other known prognostic factors in patients with EC. *Materials and Methods:* The authors reviewed the records of 102 patients who underwent staging surgery and had a result of EC in postoperative pathology in the present university clinic. Tissue specimens were re-evaluated according MI pattern (MELF positive or negative) by the same pathologist and the relation between the MELF pattern invasion and other prognostic factors were evaluated. *Results:* Stage Ia, Ib, II, IIIa, IIIb, and IIIc were observed 48 (47%), 29 (28%), 7 (7%), 11(11%), 1 (1%), and 6 (6%) in patients with EC respectively. Of the patients, MELF MI pattern was observed in 28 (27%) patients. When stage, grade, and MI patterns were compared, higher stage and grade were more frequently detected in patients with MELF pattern of MI. ($p < 0.001$) Moreover, none of the patients with grade 1 EC presented a MELF pattern MI. Patients with positive MELF MI pattern presented more lymphovascular space invasion (LVSI) ($p < 0.001$), LN metastasis ($p < 0.05$), and deeper MI ($p < 0.001$). *Conclusion:* Patients with MELF pattern of MI have more common LVSI and LN involvement.

Key words: Endometrial carcinoma; MELF; Myometrial invasion; Lymph node involvement.

Introduction

Despite good clinical outcome, a small but significant number of patients who has endometrial carcinoma (EC) may experience recurrence, and it has not been always exactly possible to predict which patients are at increased risk. Although the primary treatment is staging surgery in EC, it is an ongoing debate whether to perform or omit pelvic lymphadenectomy. There is limited retrospective data that suggest a therapeutic benefit to lymphadenectomy [1]. Therefore, Mayo criteria is commonly used including tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node (LN) involvement in EC [2]**.** In addition, sentinel LN evaluation is also introduced to decrease the morbidity of in patients undergoing lymphadenectomy [3].

Prognostic factors of EC are patient age, tumor grade, stage, histological subtype, depth of myometrial invasion (MI), extra uterine extension, and LN metastasis. MI, is one of the most important parameter for staging and LN involvement. Furthermore, there are some studies regarding myometrial invasion pattern (MIP) [4-6]. In recent years, the MIP has been proposed as a potential prognosis predictor. Microcystic, elongated, and fragmented (MELF) MIP is also important in terms of diversity of the invasion [4, 6-8].

To the best the present authors' knowledge, there is limited data about the significance of MELF type myometrial invasion pattern and LN involvement and therefore, the authors aimed to evaluate the frequency and association of MELF invasion pattern with other known prognostic factors in patients with EC.

Materials and Methods

For this retrospective study, the authors reviewed the records of 102 patients who underwent staging surgery and had a result of EC in postoperative pathology in this university clinic between May 2014- October 2015. The ethics committee of the university approved the study. Patients whose endometrial sampling result was EC underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, cytological sampling, and the specimens were sent to frozen examination during the operation. MAYO Criteria were used for pelvic and para-aortic lymphadenectomy [2]. All cases were classified according to 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system [9].

Tissue specimens were formalin fixed, paraffin embedded and subsequently sectioned at 4-µm thickness. The im-

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Table 1. — *Characteristics of 102 patients with endometrial carcinoma.*

Variable	n. (%)
Mean age (years)	57.47
FIGO Stage	
Ia	48 (47.05%)
Ib	29 (28.43%)
II	7 (6.86%)
IIIa	11 (10.78%)
IIIb	1 (0.98%)
IIIc 6 (5.88%)	
IV	0 (0%)
Grade	
G1	9 (8.82%)
G2	73 (71.56%)
G3	20 (19.6%)
Lymph node metastases	
Absent	96 (94.11%)
Present	6 (6.86%)
Myometrial invasion	
<50%	48 (47.05%)
≥50%	54 (52.94%)
Differentiation pattern	
Squamous differentiation	24 (23.52%)
Mucinous differentiation	7 (6.86%)
Endometroid differentation	1 (0.98%)
Neuroendocrine differentiation	1 (0.98%)

FIGO: International Federation of Gynecology and Obstetrics.

munohistochemical studies were performed using a standard procedure on an automated immunostainer. The sections counter stained with Mayer's hematoxylin and the sections were dehydrated, cleared, and mounted. Those specimens with histopathologic examination grade, MI depth, MIP (MELF positive or negative), the presence of lymphovascular space involvement (LVSI), and extrauterine extension and differentiation patterns were determined by the same pathologist (S.K.). The pathological results of the patients were also recorded.

All statistical analyses were performed using SPSS version 21. Data were analysed according to Pearson Chi–square, Shapiro Wilk normality test, ANOVA, and Tamhane test. Probability values less than 0.05% were considered statistically significant.

Results

In total, 102 consecutive cases of uterine EC were identified and mean age was 57.4 ± 9.32 years. Fifty-four patients went underwent pelvic-para-aortic lymphadenectomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Stages Ia, Ib, II, IIIa, IIIb, and IIIc were observed in 48 (47%), 29 (28%), 7 (7%), 11 (11%), 1 (1%), and 6 (6%) patients, respectively. As mentioned, stage distribution of patients was statistically significant, although perhaps to Stage IIIa, IIIb, and IIIc are taken together as Stage III (18 patients, 17%). Grades 1, 2, and 3 were observed in 9(9%), 73(72%), 20(%19) respectively (Table 1).

Of the 102 patients with EC, MELF MI pattern was observed in 28(27%) patients. Diagnostic criteria for MELF pattern of myoinvasion were microcystic, elongated, and/or slit-like glands, with clusters or individual tumor cells, which often appeared squamoid or eosinophilic. Frequently, there was an accompanying loose myxoid and mixed inflammatory reaction.

When stage, grade, and MI patterns were compared, higher stage and grade were more frequently detected in patients with MELF pattern of myoinvasion ($p < 0.001$). Moreover, none of the patients with grade 1 EC presented MELF pattern MI. Patients with positive MELF MI pattern presented more LVSI ($p < 0.001$), LN metastasis ($p < 0.05$), and deeper MI ($p < 0.001$). Histopathologic differentiation pattern of the specimens did not differ with MI pattern ($p > 0.05$). Detailed description of patient's characteristics and MI pattern are presented in Table 2.

Discussion

In thus study, the authors aimed to evaluate the frequency and association of MELF invasion pattern with other known prognostic factors in patients with EC. MELF pattern of MI was frequently observed in patients with high grade and stage of EC. Moreover, MI, LVSI, and LN metastasis were more frequent in MELF pattern of MI.

Although this study gives information that may be important for the clinical management, it still inherits biases. First, the method in this study was retrospective; therefore there was some information bias. Moreover, the authors did not perform systemic lymphadenectomy to all patients. They selected the patients according to tumor size, depth of MI, and grade of the tumor for requirement of systemic pelvic and para-aortic lymphadenectomy. However, the study also has strong points. First, staging surgery was performed in the present clinic by gynecologic oncology department with the same surgeons (S.O., O.T.Y., and T.O) and specimens were evaluated with the same pathologist (S.K) to standardize the procedures and evaluation. Second, sample size was appropriately powered.

There are limited studies about MI pattern detecting prognosis in EC. Murray *et al.* [4] first described MELF type MIP. They investigated 115 cases with EC, which had MI with or without MELF pattern. In cases of LVSI, commonly MELF pattern associated with, including fibromyxoid reaction, death, and recurrence was more followed. Stewart *et al.* [6] examined 133 cases of EC and 27 of them were MELF positive. MELF-positive patients often have focal mucinous differentiation, and LVSI was observed. Pavlakis *et al.* [8] searched 351 patients and LN-positive patients, positive for MELF 53.84% was observed. MELF negative of positive LNs were seen in 6.97% and it was statistically significant. In a study in which 513 patients par-

Table 2. — *Clinicopathological features of MELF-positive and MELF-negative cases.*

	MELF (+) (n:28)		MELF (-) (n:74)		*p* value
	n	(%)	n	(%)	
Age (years)(mean± SD)	59.28 ± 9.28		56.98 ± 9.60		0.997†
FIGO Grade					0.016*‡
Grade 1	0	0	9 100		
Grade 2	18	24.7	55	75.3	
Grade 3	10	50	10	50	
FIGO Stage					<0.001*‡
Stage IA	3	6.3	45	93.8	
Stage IB	11	37.9	18	62.1	
Stage II	2	28.6	5	71.4	
Stage IIIA	7	63.6	4	36.4	
Stage IIIB	1	100	0	0	
Stage IIIC	4	66.7	2	33.3	
Stage IVA	0	0	0	0	
Stage IVB	0	0	0	0	
Lymphovascular space invasion					<0.001*§
Absent	0	0	26	100	
Present	28	35.1	48	64.9	
Lymph node metastasis					0.048*§
Absent	24	25.3	72	74.7	
Present	4	66.7	2	33.3	
Depth of myometrial invasion					<0.001*§
< %50	3	6.3	45	93.8	
≥ %50	25	46.3	29	53.7	
Differentiation pattern					0.737‡
Squamous differentiation	8	33.3	16	66.7	
Mucinous differentiation	2	28.6	5	71.4	
Endometrioid differentiation	1	100	0	0	
Neuroendocrine differentiation	0	0	1	100	

**p<0.05, † Student's t-test. ‡ Fisher's exact test. §X^2-test. MELF: microcystic, elongated and fragmented; FIGO: International Federation of Gynecology and Obstetrics.*

ticipated Nofech-Moses *et al.* [10], showed that LVSI is an important predictor parameter for distant recurrence in early-stage EC. Guntupalli *et al.* [11] performed a study in 628 patients who had systematic lymphadenectomy, 196 of patients had LVSI, and 66 of them had nodal metastases which was found to be statistically significant. Quick *et al.* [12] reported a compilation about the importance of measuring the depth of MI and MIP. MELF pattern was seen in LVSI were reported more frequently. It also supports the study of Hertel *et al.* [7].

Clinical significance of MELF pattern of invasion seems important, and it is reported to be associated with distinct changes in the invasive glandular tissues and a high frequency of LVSI and LN metastasis. Based on these effects of the MELF pattern, further studies are needed to conclude LN involvement. However, this information may be important if pathologists not only evaluate depth of MI, but also MI pattern to frozen analysis of patients with EC.

To conclude, patients with MELF pattern of MI have more common LVSI and LN involvement. MIP may add additional information during frozen section analysis to differ the patients that may benefit from systemic lymphadenectomy or unnecessary extensive surgery.

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