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Histopathologic Features of Endometrial Carcinoma with Fallopian Tube İnvolvement

Kabukcuoglu S and Yildirim GD*

Department of Pathology, University of Osmangazi School of Medicine, Eskisehir, Turkey

Abstract

Objectives: Endometrial Carcinoma (EC) is the most common invasive neoplasm in female genital tract. Endometrial cancer occurs in both premenopausal and postmenopausal women. In the large series, 4% to 6% of the cases have diagnosed with the Stage III and Stage IV disease. The reccurences are seen at the same frequency with endometrial cancer cases. Sampling of fallopian tube according to Sectioning and Extensively Examining the Fimbrial End Protocol (SEE-FIM) and examination of dissected lymph nodes and peritoneal washing fluid cytology are necessary for appropriate histopathologic classification of patients. Recent reports indicate that up to 25% of patients with clinically Staged Stage I disease have positive lymph nodes and these cases have microcystic, elongated, and fragmanted glands (MELF). The aim of this study is to document the histopathologic features of endometrial cancer cases with tubal involvement.

Methods: Endometrial cancer cases were retrieved from the files of the Pathology Department of Osmangazi University Hospital between the November 2013 and February 2017.

Results: A total of 13 endometrial cancer cases with tubal involvement were identified. Positive or suspicious peritoneal washing fluid was observed in three cases. There were three cases that are under 60 years old with superficial myometrial invasion and these cases were associated with endometriosis. In all those cases that are above 60 years old there were deep myometrial invasion and 5 cases had cervical involvement. A total of 7 cases with cervical involvement had not been associated with endometriosis. There was a significant inverse correlation between cervical involvement and endometriosis in the EC cases ($P<0.05$). Endometriosis was associated with the cases under 60 years old. This correlation was found to be significantly important ($P<0.05$). The patients having immunohistochemical features of T cell factor/APC/β-cathenin pathway were mostly under 60 years old and this finding was also statistically significant ($P<0.05$). Among this group two patients had additional abnormalities, which are dual loss of MLH1 and PMS2, and strong p53 positivity. In cases above 60 years old, PTEN inactivation, aging and loss of PAX8 were detected by immunohistochemistry.

Conclusion: There is no specific immunohistochemical marker for discrimination of the spilling tubal cells in tubal lumina or peritoneum with the low grade endometrial cancer cells. In this study CK19, P16, WT-1, PAX-8 and calretinin immunohistochemistry were found as useful markers for true classification.

Keywords: Senescence of fallopian tube; Calretinin signature; Endometrial carcinoma; Stage III; Myoinvasion pattern; Immunohistochemistry

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Correspondence:
Kabukcuoglu S, Department of Pathology, University of Osmangazi School of Medicine, Eskisehir, Turkey, E-mail: sarekabukcuoglu@gmail.com

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Introduction

There is no single accepted follow-up strategy for patients with Endometrioid Endometrial Cancer (EEC). Early tumor reccurence may be observed at all stages of endometrial cancer [1]. Joehlin-Price et al. [2] reported 16 cases of lymph node metastases in 464 consecutive case of FIGO grade 1 EEC. After an average of 26 months follow-up 20 patients showed reccurences. In this group 45% of cases had isolated vaginal reccurences and 55% had extravaginal reccurences. In recent years, studies about myoinvasion patterns of EEC have pointed that lymphovascular space involvement mostly occurs in the Microcystic Elongated Fragmented pattern (MELF) [3-6]. Havrilesky et al. [7] reported 24 cases of Stage IIIA1, non-serous and FIGO grade 1-2 endometrial carcinoma. There were no reccurences among 12 cases receiving adjuvant treatment. Among the other 12 cases receiving no adjuvant therapy, one patient had experienced an extranodal abdominal recurrence at 6 years postoperatively. Hu et al. [8] demonstrated increased actin bundling protein fascin expression

Table 1: Tumor grades and Stages and follow-up of patients.

Patients	Age	Histopathologic type	Grade	Cervix involvement	Stage	Follow-up
1	58	ECC with squamous differentiaton	2	Stromal involvement	$3C_2$	*
2	61	ECC	2	-	3C	*
3	57	ECC	1	-	3A	*
4	85	EC	2	Stromal involvement	IV	**
5	67	Dedifferentiated EC	3	Stromal involvement	$3C_1$	**
6	50	ECC with squamous differentiation	2	Stromal involvement	IV	Reccurence after 16 months Metastasis in cervical LN
7	75	EC with squamous differentiation	2	-	3A	No reccurence after 36 months
8	60	EEC with mucinous differentiation, Granulosa cell tumor	2	-	3A, 1C	**
9	47	EEC	2	-	3A	*
10	52	ECC	3	-	3A	**
11	70	EC with squamous differentiation	2	Stromal involvement	IV	Reccurence after 11 months in urinary bladder
12	74	High grade EC arising in adenofibroma	3	Cervical epithelial involvement	IV	**
13	63	MMMT, heterolog type	3	Stromal involvement	3C	DOD***

* Recently operated cases; **No data of follow-up, *** DOD, indicates died of disease.

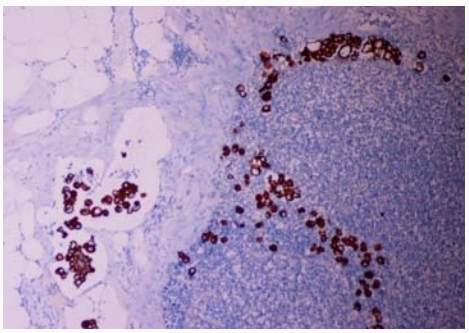

Figure 1A: Endometrioid carcinoma, cytokeratin positive histiocyte-like tumor cells are seen in the lymph node sinus (Case 2).

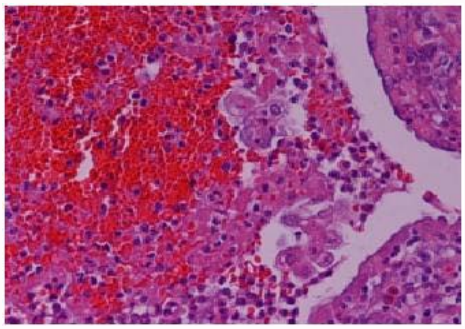

Figure 1B: The same tumor cells are seen among the inflammatory exudate in the tubal lumina.

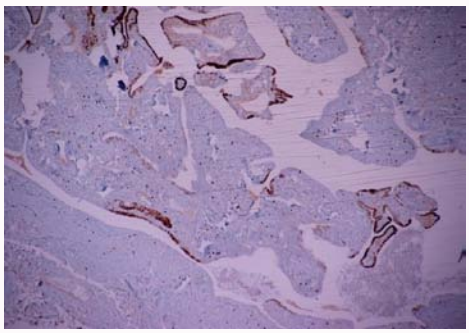

Figure 1C: Focal calretinin signature in tubal epitelium. Inflammatory exudate did not stain with calretinin.

in tissue samples and cell cultures derived from ovarian cancer and in tissues of borderline and carcinomatous ovarian neoplasms and suggested that fascin could serve as an important prognostic factor for abnormal ovarian epithelial pathology. Prognostic role of fascin was also shown in EEC with MELF pattern [4]. In tumors, differentiated epithelial cells mostly retain the keratin patterns of their epithelial origin. Caspases cleave cytokeratins during apoptosis. As a result, apoptotic bodies and soluble keratin fragments enter into the lymphovascular space [9,10]. Malignant cells in peritoneal washings fluid may be the result of trans-tubal dissemination of the primary tumor. Stewart et al. [11] conducted a study with 226 high grade and 36 low grade endometrial cancer patients who underwent surgical staging. Among these cases 26% of high grade and 3% of low grade endometrial cancer cases had intraluminal tumor cells. The presence of fallopian tube metastases and intra-luminal tumor cells was strongly correlated with positive peritoneal fluid cytology, peritoneal metastases and lymph node metastases in high grade tumor subtypes. Positive peritoneal cytology is an independent risk-factor in Stage I/II endometrial cancer [12]. Positive peritoneal cytology is also highly predictive of prognosis and relapse patterns in Stage III endometrial cancer, and is correlated with higher reccurence rates in the paraaortic nodes and peritoneum [13]. Serous endometrial carcinomas may rarely be detected by peritoneal washing cytology [14]. Differential diagnosis of cancer cells in peritoneal cytology by using immunohistochemistry may not be possible in most of the FIGO grade I cancers. Most of the immunohistochemical markers such as p^{16}, cytokeratins, estrogen receptor, progesteron receptor, p53, PAX8, p^{16} may stain both EEC cells and fallopian tube epithelium. The aim of the study is to detect fallopian tube metastasis and intraluminal tumor cells in endometrial cancer patients who underwent surgical staging by using SEE-FIM protocol and immunohistochemistry.

Materials and Methods

Patients who underwent total abdominal histerectomy, bilateral salpingo-oophorectomy, bilateral pelvic paraaortic lymph node dissection and infracolic omentectomy because of endometrial

Table 2: Histopathologic features of the same patients with fallopian tube involvement.

Case	Age	Histopathologic type	Immunohistochemical features	Grade	MI degree & pattern	Fallopian tube involvement	Serosal involvement/ peritoneal fluid washing serology	Ovarian involvement	Metastatic LN/ reactive LN	Endometriosis	Extra uterine extension
1	58	EEC with squamous differentiation	Beta-catenin, CDX-2, P63	2	>1/2, MELF	Right fimbrial end	-/-	-	5/55	-	-
2	61	ECC	E-cadherine loss, chromogranin (50%)	2	>1/2, MELF	Right tubal lumina, histiocyte like cells with inflammation	-/-	-	2/25	-	-
3	57	ECC	E-cadherin loss, chromogranin (70%)	1	<1/2, PL	Fimbrial end of right tube, histiocyte-like cells without inflammation	Suspicious serology by Giemsa stain	-	0/17	Tumor arising in the base of adenomyomatous polip and had obstructed of right tubal passage	-
4	85	EC	PAX8 down regulated, ER positive, P16 focal positive, WT1 negative and p53 (5%)	2	>1/2	Left tube muscular layer and vascular space	-/-	-	0/28	-	Extra cervical fat
5	67	Dedifferentiated EC	P53 weak positive, PTEN inactivaton	3	>1/2	Left tubal lumina, inflammatory cells positive	-/-	-	3/21, tumor in the extracapsular fat tissue	-	-
6	50	ECC with squamous differentiation	B-Cathenin, CDX-2 Lynch syndrome (PMS2 and MLH 1 loss) Calretinin signature positive in tubal epithelium	2	>1/2, MELF	Right and left tubal lumina and left ampullary region,among exudate	-/-		27/43	-	-
7	75	EC with squamous differentiation	P16 neg, CDX2 neg, p53 (10%), ER (50%), PR (15%), PAX-8 focal, CK19 (75%) positive	2	>1/2, DI**	Three lymphovascular space involvement in right tube	-/-	-/-	ND	-	-
8	60	EEC with mucinous differantiation (EIN with complex hiperplasia two years ago)	Focal beta cathenin loss, (Endometriosis epithelium showed focal calretinin positivity and PAX-2 expression loss)	2	<1/2, A***	Right tubal isthmus	-/-	Granulosa cell tumor in the left ovary, Stage IC	ND	Left tube	-
9	47		E-cadherin loss, p53 negative, chromogranin positive (calretinin positive in endometriosis and tuba epithelium)	2	<1/2, PI*	Left intramural tubal segment	-/-		ND	Right tube,	-
10	52	ECC	E-cadherin loss, beta-cathenin inactivation, strong p53 positive	3	>1/2, MELF	Left tubal fimbrial end and lumina	Serosal surface involvement/ negative serology (Omental vascular trombosis)	-	0/15	Right and left ovaries, right tube	-
11	70	EC with squamous differentiation	Beta cathenin, E-cadherin inactivation, 80% CDX2 positive	2	>1/2, MELF	Right fimbrial end and mucosa	Serosal involvement/-	-	0/2 (omental)	-	Pelvic peritoneum
12	74	High grade EC arising in adenofibroma	CD10 positive, P16 positive, estrogen and progesteron receptors were negative	3	>1/2	Serosal surfaces right and left tube	Serosal surface involvement/ positive serology in ascites fluid	Lymphovascular space involvement in ovarian hilus	ND	-	Omentum
13	63	MMMT, heterolog type (Rhabdomyoblastic differentiation)	PAX-8, myogenin, desmin		>1/2	Intramural involvement of right tube and serosal surfaces	Serosal surface involvement/ positive serology	Bilateral ovaries	ND	-	Vaginal cuff

*PL indicates, Properly Limited pattern of myoinvasion; **DI indicates, diffusely infiltrated myoinvasion, *** A indicates, Adenomyotic focus involvement.

carcinoma were examined by light microscopy. Patients' age, tumor type, tumor grade, tumor localization, depth of tumor invasion, cervical involvement, fallopian tube involvement, numbers of reactive and metastatic lymph nodes and extrauterin or omental histopathologic features and peritoneal washing fluid cytology results, type of the surgical procedure were taken from computer based patients' pathology reports at the Osmangazi University Hospital between November 2014 to February 2016. A total of 13 Stage III and Stage IV EC patients with fallopian tube involvement were found from the surgical pathology files. All of the tubes were examined according the SEE-FIM protocol including intramural tuba portion. All of the lesions of fallopian tubes and operation specimens had been recorded in the reports.

Immunohistochemistry

All of the immunohistochemical stainings which were applied to the EC cases had been recorded in computer based patients' pathology reports. The immunohistochemical studies were performed using a standart procedure on an automated immunostainer. Liquid rabbit monoclonal CK19, P53, CDX2, β-cathenin, E-cadherin, estrogen receptor, progesteron receptor, PAX-8, chromogranin were used as primary antigen. WT-1, p^{16}, calretinin, MLH1, PMS2, MSH2, MSH6 were also used as primary antigens if they were necessary for differential diagnosis. The primary antibody was replaced PBS as a negative control. Diaminobenzidine was used as chromogen. Finally, the sections counter stained with Mayer's hematoxylin, and the sections were dehydrated, cleared and mounted. According to the records MLH1, PMS2, MSH2, MSH6 applied to five cases (Case no: 1, 2, 3, 4, 6) at the (Table 1).

Statistical analysis

Pearson chi square statistic was used for data analysis.

Results

Clinical and histopathologic features of endometrial cancer patients

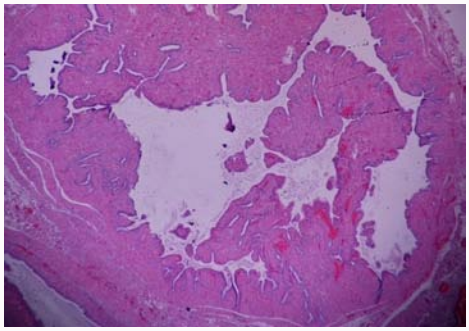

Figure 2A: Histiocyte-like intra-luminal tumor cell groups in the fimbrial end of the tuba. Duct-like appearance of tubal epithelium and muscle layer (Case 3).

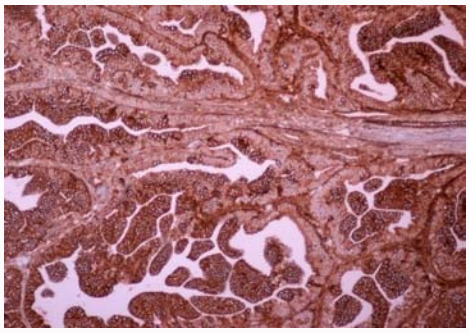

Figure 2B: Loss of E-cadherin expression in the adherrence junctions of tumor cells in Grade 1 ECC.

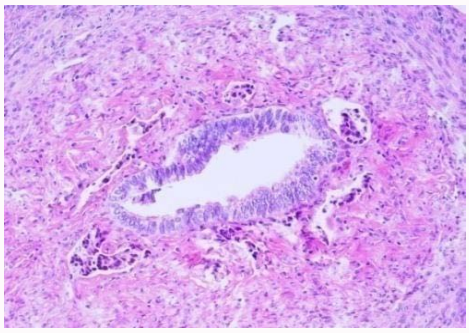

Figure 3: Proliferative glandular type tumor embolies in lympovascular space around the intramural tuba segment (Case 4).

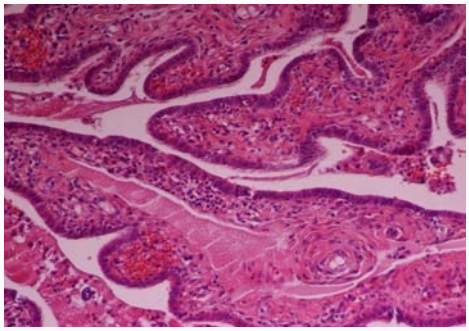

Figure 4: Endometrial carcinoma, dedifferentiated type. A few pleomorphic tumor cells among inflammatory exudate in the tubal lumina (Case 5).

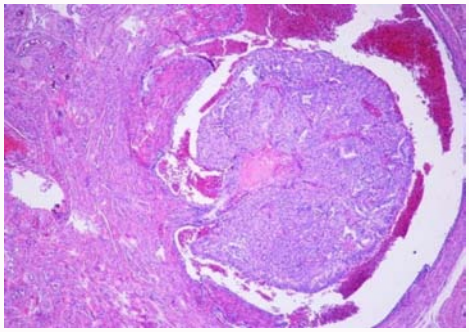

Figure 5: ECC with squamous differentiaton tubal metastases in the lumina (Case 6).

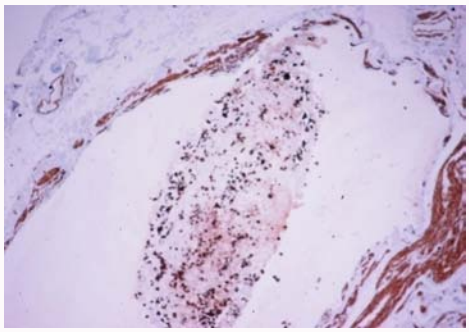

Figure 6: EEC with squamous differentiation, tumoral emboli is seen in tubal vascular lumina. (CK19 immunohistochemistry, case 7).

The patients' ages ranged from 47 to 85 years (mean, 63 y). Table 1 briefly describes the patients' age, histopathologic type of the tumor, surgical Stage's, cervical involvement, and follow-up of the patients. Table 2 briefly shows histopathologic type, specific immunohistochemical features of the case, myoinvasion degree and pattern, tubal, serosal and ovarian involvement, peritoneal fluid cytology, metastatic and reactive lymph nodes. Eight patients were grade 2. There was one dedifferentiated EC, one EC arising adenofibroma, one MMMT, one EC with squamous differentiaton and one EEC among the five grade 3 cases. One EC case with mucinous differrentiation associated with granulosa cell tumor of ovary and tubal endometriosis (Case 8). In 10 cases there were deep myometrial invasions, in 3 cases there were superficial myometrial invasions. Four cases were associated with endometriosis (patient 3, 8, 9, 10), among these cases three cases had superficial myometrial invasion. There were 7 cases with cervical involvement and all of these cases had deep myometrial invasions. There were no cases associated with endometriosis among them. Above 60 years old all of the patients' had deep myometrial invasion. There was no omental involvement among the surgically Staged cases.

Immunohistochemistry results

Immunohistochemistry showed T cell factor/APC/β-cathenin (wnt) pathway involvement in 8 cases. In these cases CDX2 or p^{63} positive squamous differentiation areas showed decreased estrogen receptor, progesteron receptor and CK19 expression and this features were compatible with β-cathenin mutation (Case 1, 6, 8, 11). Of these cases one patient at Stage IV had dual MLH1 and PMS2 loss and was associated with 27 metastatic lymph nodes (Case 6).

Focal or complete E-cadherin loss associated with decreased estrogen receptor, progesteron receptor and CK19 expression were compatible with E-cadherin gen (*CDH1*) mutation and were associated with T cell/APC/β-cathenin pathway (Case 2, 3, 9, 10). One of these cases had strong p^{53} positivity and associated with endometriosis

and omental vascular trombosis (Case 10). A 85 years old patient had complete PAX-8 loss (Case 4). Dedifferentiated EC case showed PTEN inactivation and weak p^{53} positivity (Case 5). Patient 7 was 75 years old and wild type p^{53} was observed. Decreased estrogen receptor and progesteron receptor expressions were associated with negative CDX2 and p^{16}. CD10 and p^{16} expression were observed in endometrial carcinoma arising adenofibroma (Case 12). MMMT was stained with PAX8, desmin, myogenin (Case 13). There was a significant inverse correlation between cervical involvement and endometriosis in EC cases ($P<0.05$). Endometriosis was associated with the cases under 60 years old. This correlation was significantly important ($P<0.05$). The patients having immunohistochemical features of T cell factor/APC/β-cathenin pathway were mostly under 60 years old and this finding was statistically significant ($P<0.05$).

Discussion

Endometrioid endometrial carcinoma has a good clinical outcome with low reccurence rate and metastasis. Prognostic factors for EEC are patient age, tumor grade, histological subtype, depth of myoinvasion, myoinvasion pattern, extrauterine extension and Lymph Node (LN) metastasis [6]. The patient's age is closely related to tumor types and histotypes. Endometrial carcinomas are divided into two types. Type I tumors are low grade endometrial carcinoma. Histopathologic prototype of type 2 tumors is serous carcinoma. Uterine serous carcinomas (USC) are extensively associated with p^{53} mutations and the often loss of the expression of the estrogen receptor [15]. In type I tumors mutations of *PTEN, KRAS, PIK3CA* and *CTNNBI* genes were frequently found and microsatellite instability coexisted in some cases. Loss of heterozygosity in cell cycle genes were also found in EEC [16]. Mixed and dedifferentiated endometrial carcinomas, clear cell carcinoma, malign mixed mullerian tumors and carcinomas arising from atypical polypoid adenomyomas, adenofibroma and endometrial polyps might be present in advanced stages and age [17]. In this study, T cell factor/APC/β-cathenin pathway associated immunohistochemical expression abnormality were detected in the 8 of 15 EEC patients. One of these cases coexisted with strong p^{53} expression (Case 10). Dual loss of *MLH1* and *PMS2* were detected in one patient of ECC who had defective T cell factor/APC/β-cathenin pathway. In this case calretinin signature was observed in tubal epithelium (Case 6, Figure 5). *PTEN* inactivation with weak p53 expression and the loss of PAX8 expression coexisting with strong p^{16} staining were detected in two cases diagnosed as dedifferentiated EC and MMMT, respectively. Kommoss et al. [18] detected 32 cases of fallopian tube metastases associated with 161 USC cases by using WT-1 and p^{53} immunohistochemistry. In their series, 17 of 30 mucosal metastases resembled STIC-like features. Twelve cases of STIC-like features were accepted as USC metastases. Two cases were probably metastatic USC and one case had uncertain origin. Two cases were considered to be of primary tubal origin. Giordano et al. [14] detected one USC that involved an endometrial polyp which was associated with positive peritoneal washing cytology and with simultaneous carcinoma of tubal fimbria. P^{16} is a tumor supressor gene. Horre et al. [19] showed that p^{16} immunostaining was seen in endometrial tubal metaplasia. Simon et al. [20] suggested that the presence of typical and atypical tubal metaplasia did not increase the risk of developing endometrial hyperplasia and endometrial cancer in the long term follow-up by using Ki-67, p^{53} and TERT immunohistochemical staining. Similarly, I observed a patient p^{53} who had become negative when she underwent histerectomy because of simple atypical hyperplasia whereas there were 40% positive p^{53} staining in preoperative endometrial biopsy. Acute stress results in apoptosis and, while chronic stress results in DNA damage and aging [21, 22]. CD95 is a transmembrane glycoprotein which belongs to the nerve growth factor/tumor necrosis factor (TNF/NGF) receptor superfamily. When fascin was downregulated CD95 shows tumorigenic activity by a pathway involving JNK and c-JUN. CD95 promotes tumor growth [4,23-25]. Lu et al. [26] had made a model serine phosphorilation of p^{16} which resulted in arginine methylation by H_20_2 for modulating cellular apoptosis and senescence. Doxorubicin induces apoptosis in cancer cells by similar mechanisms [27]. In this study, p^{16} expression in high grade endometrial cancer was observed in carcinoma arising in an adenofibroma (Case 12). Fallopian tube is an important passage for EEC and high grade endometrial cancer cells to peritoneum. Most of the immunohistochemical markers stain both EEC and tubal epithelium. When there are inflammatory exudates or the spilling tubal cells into the tubal lumina or peritoneum, it may not be possible to define tumoral cells by light microscopic examination. In the case it is neccesary to use immunohistochemical markers highlighting senescence of tubal epithelial cells. In cases of ageing and photoageing some common features such as enhancing p^{53} mutations, oxidative stress, malignant transformation and immortalization may be detected [28]. Similarly, it is recognised that 1,25D also exerts non-genomic actions by the activation of signalling molecules, such as phospolipase C and phospholipase $A_{2,}$ phosphatidylinositol-3 kinase (PI3K) and p^{21} RAS, and rapid generation of second messengers (Ca^{2+}, cyclic AMP, fatty acids and 3-phosphoinositides such as phosphatidylinositol 3,4,5 triphosphate). The activation of these molecules is associated with the activation of protein kinases, such as protein kinase A, src oncoprotein, mitogen activated protein kinases, protein kinase C and Ca^{2+} calmoduline kinase II. The non-genomic actions also include the opening of Ca^{2+} and Cl^{-} channels [29]. Sakaguchi et al. [30] showed steroid receptor coactivator (SRC)-3 mRNA expression correlated poor prognosis in endometrial cancer. The other studies had demonstrated that SRC-3 (CBP-interacting protein) had important role on carcinogenesis and metabolic pathways [31,32] One alpha, 25 dihydroxyvitamin D3 upregulates calcium binding proteins (CBP). Ovarian surface epithelium, stromal and thecal cells, follicular cysts, corpora lutea and rete ovary and endometrial stromal cells, histiocytes and fibroblasts show strong calretinin expression. Normal fallopian tube epithelium does not express calretinin [33]. Calretinin expression (calretinin signature) of fallopian tube epithelium may be associated with some endometriosis cases [34] and/or endometriosis associated with benign and malign neoplasms including endometrial carcinoma. As a result, calretinin is also a useful marker for differentiating intra-luminal or peritoneal tumor cells from transformed tubal cells. Eucher et al. [6] reported a case who had no myometrial invasion but had a focus of metastatic carcinoma in the fallopian tube. Han et al. [35] reported that reduced E-cadherin expression was associated with MELF pattern of MI, and these cases may have occult lymph node metastasis even when they were at Stage I. Hertel et al. [36] had made differential diagnosis between histiocyte-like cancer cells and histiocytes in the lymph nodes of ECC patients by using CD68, calretinin, cytokeratin and epithelial membrane antigen immunohistochemistry. Despite of the differences in MI patterns and degree of MI, the first three cases in the study group had E-cadherin loss or β-cathenin mutation and they had Stage III disease at the operation time (Table 2, Figure 1A, 1B, 1C and Figure 2A, 2B). The histopathologic differences among three cases are the presence of inflammatory exudate in the tubal lumina and calretinin signature in tubal epithelium and p^{16} staining of tumor

cells. Further studies are necessary to better clarify the effect of MI pattern on the Stage of ECC and its relation with calretinin signature of fallopian tube [37]. Our study showed that p^{16}, CK19, PAX-8, WT-1 and Calretinin immunohistochemistry are useful for discrimination of tumor cells among the spilling tubal or peritoneal fluid cells.

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