

Aberrant nuclear beta-catenin expression in the spindle or corded cells in so-called corded and hyalinized endometrioid carcinomas. Another critical role of the unique morphological feature

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Summary. Corded and hyalinized endometrioid carcinoma (CHEC), showing spindle and/or corded (SPICO) cells often in the background of hyalinized stroma, is a rare variant of uterine endometrioid carcinomas. The aim of our study was to explore the status of cell-adhesion molecules (beta-catenin, E-cadherin) in CHECs and to survey whether immunostains for beta-catenin and p53 can help to distinguish CHECs from their morphological mimics: malignant mixed mullerian tumors (MMMTs) and uterine tumors resembling ovarian sex-cord tumors (UTROSCTs). Immunohistochemistry was performed and scored for each element as follows: 0: negative, 1+: <10% positive cells, 2+: 10-30%, 3+: >30%. The SPICO patterns were classified as spindle/fusiform; 3, corded; 1, and both; 2. SPICO components consisted of <10%: 4, 10-30%: 1, >30%: 1. Five contained squamous components. In SPICO elements of all CHECs, nuclear beta-catenin expression (score: 1+; 1, 2+; 2, 3+; 3) and complete loss of membranous expression of E-cadherin was observed. In contrast, comparable components (sarcomatous ones for eight MMMTs or sex-cord-like ones for six UTROSCTs) showed no nuclear positivity for beta-catenin. p53 expression was observed in SPICO (64.7%), sarcomatous (87.5%), and sex-cord-like (50%) components, and sarcomatous areas of most MMMTs notably showed diffuse and intense staining. Sequence analysis of PCR amplification products of exon 3 of the beta-catenin gene revealed mutation in all cases, except two lacking SPICO components represented on microdissected areas. Our results suggest that alterations in beta-catenin/E-cadherin complex play a critical role in SPICO features. Immunostain for beta-catenin and p53 is a promising approach for distinguishing CHECs from

MMMTs and UTROSCTs.

Key words: Endometrioid carcinoma, Sarcomatoid, Cord-like, Beta-catenin, Immunohistochemistry

Introduction

Endometrioid carcinomas (ECs) with spindled epithelial cells and/or corded cells showing sarcomatoid biphasic appearance are a rare morphological variation of ECs in the endometrium. This variation has only been explained in detail in a review article authored by Clement and Young (2002). Subsequently, Murray et al. (2005) employed the term *corded and hyalinized endometrioid carcinoma (CHEC)* for this variation, and again the authors clearly defined it as ECs characterized by one or more of the following features: the presence of cords of epithelioid cells, spindle cells, fusiform cells, and a striking hyalinized stroma that sometimes forms osteoids. CHEC, as they named it, not only shows a unique morphology but also calls on pathologists to distinguish it from malignant mixed Mullerian tumor (MMMT). However, they did not refer to the etiology or the mechanism of these corded and hyalinized patterns. Unfortunately, these “sarcomatoid” *spindle and/or corded* (SPICO) cells in ECs have rarely been studied before.

These authors referred to a relationship between squamous differentiation and the corded and hyalinized patterns peculiar to CHECs (Murray et al., 2005). In other words, squamous foci that frequently exhibited keratinization were identified in 70% of the CHECs. They also described that, in some instances, sharply circumscribed foci of squamous differentiation with keratin pearl formation were present within a background of stromal hyalinization and cords, and that

in some cases, keratinized squamous elements abutted foci of spindle cells. In squamous foci of endometrioid carcinomas (ECs), nuclear accumulation of beta-catenin is frequently observed because of the mutation of the beta-catenin gene (Fukuchi et al., 1998; Kobayashi et al., 1999; Saegusa and Okayasu, 2001). Beta-catenin, a multifunctional protein, was originally identified as one of the E-cadherin-related cell-to-cell adhesion molecules and is also an important transducer of the Wnt-signaling pathways. Given this evidence, we hypothesized that the SPICO patterns of CHECs are related to alterations in the beta-catenin/E-cadherin system, mainly due to the gene mutation of beta-catenin. To confirm this hypothesis, the primary aim of our study was to perform immunostaining for beta-catenin and E-cadherin; in addition, we examined the exon 3 mutation of beta-catenin gene, focusing on the SPICO areas.

The SPICO morphology can be mimicked by the sarcomatous areas of MMMTs and sex-cord-like elements of uterine tumor resembling ovarian sex-cord tumors (UTROSCTs) (Murray et al., 2005). In this regard, a very low frequency of p53 expression in CHECs, in contrast to that reported for MMMTs, has also been described. The secondary aim of our study was to survey whether immunohistochemistry for beta-catenin and p53 (a cell cycle marker) can help to distinguish CHECs from their morphological mimics: MMMTs and UTROSCTs.

Materials and methods

From the files of Kurashiki Central Hospital, we retrieved six cases of CHECs. Anti-beta-catenin antibody (17C2, 1:50, Novocastra), p53 (DO7, 1:25, Novocastra), and E-cadherin (NCH-38, 1:50, DAKO) were applied to formalin-fixed, paraffin-embedded sections after heat-induced antigen retrieval using citrate buffer (pH 6.0) for 20 minutes or EDTA buffer for 15 minutes in a microwave oven. All cases were immunostained with the Envision Plus detection system (Dako, Japan). Diaminobenzidine was employed as the chromogen. The nuclear staining of beta-catenin and the membranous staining of E-cadherin, respectively, were scored (by Y.W.) for each glandular and SPICO element as follows: 0: negative, 1+: <10% positive cells, 2+: 10-30%, 3+: >30%. Furthermore, with comparable components (sarcomatous ones for eight MMMTs or sex-cord-like ones for six UTROSCTs), beta-catenin and p53 staining was scored in the same way as described above. For differential diagnosis, the intensity of the immunostaining (weak or intense) was also noted.

Genomic DNA was extracted from 10- μ m thick paraffin sections using microdissections of SPICO and glandular areas, respectively, and purified by proteinase K/phenol-chloroform treatment. Exon 3 of the beta-catenin gene was amplified in semi-nested polymerase chain reactions (PCR) and sequenced as described previously (Saegusa and Okayasu, 2001). In one case, the mutational analysis was performed in only SPICO

areas. Furthermore, with two cases, only the glandular areas were examined due to disappearance of the targeted SPICO areas.

Results

The six patients with CHEC ranged in age from 38 to 57 (mean: 46.0). The characteristic SPICO patterns of the CHECs were classified as spindle/fusiform (n=3), corded (n=1), and both (n=2) (Fig. 1.1A, 2A, 3A; Fig. 2, 1A). It consisted of <10%: 4, 10-30%: 1, >30%: 1 in the whole lesion. The ratios of the glandular elements ranged from 60% to more than 95%. Squamous differentiation was observed in 5 CHECs (keratinizing type; n=4, morular type; n=1). In all cases with squamous differentiation, keratinized or morular squamous elements abutted foci of SPICO areas. Notably, one case (case 4), lacking squamous differentiation in the biopsy specimen of the endometrial tumors, contained florid keratinizing squamous components in a metastatic tumor of the ovary. In this case, a hysterectomy was not performed. Distinctive stromal hyalinization and osteoid formation were only seen in one case (case 1) (Fig. 1.1A). Nuclear expression of beta-catenin was noted not only in the glandular or squamous foci (score: 0; none, 1+; 3 cases, 2+; 2 cases, 3+; 1 case), but also in the SPICO areas (score: 0; none, 1+; 1 case, 2+; 2 cases, 3+; 3 cases) of all six CHECs (Fig. 1.1B, 2B, 3B; Fig. 2. 1B). Complete loss of membranous expression of E-cadherin was seen in SPICO areas (score: 0; 6 cases), whereas it was well preserved in glandular and squamous elements (score: 3+; 6 cases) (Fig. 1.1C, 2C, 3C). p53 immunostaining was seen both in the glandular foci (score: 0; 1 case, 1+; 1 case, 2+; 3 cases, 3+; 1 case) and in the SPICO areas (score: 0; 2 cases, 1+; 3 cases, 2+; none, 3+; 1 case) (Fig. 1.1D, 2D, 3D; Fig. 2.1C). Three cases showed weakly positive staining with p53, whereas intense staining in the SPICO areas was identified in 1 case (case 3) (Fig. 2.1C).

With sarcomatous areas of eight MMMTs, there was no nuclear staining with beta-catenin, and p53 scores were as follows: 0, 1 case; 1+, none; 2+, 1 case; 3+, 6 cases (Fig. 2.2A-2C). All positive cases but one showed intense staining. With sex-cord areas of six UTROSCTs, nuclear beta-catenin staining was not noted in any cases, whereas p53 staining varied in scores (0; 3 cases, 1+; 1 case, 2+; 1 case, 3+; 1 case) and in intensity (weak; 2 cases, intense; 1 case) (Fig. 2.3A-3C).

Sequence analysis of PCR amplification products of exon 3 of the beta-catenin gene revealed a deleted codon 45 (Ser) in SPICO areas (Case 2), and a common mutation in glandular and SPICO areas, including a deleted codon 42 (Thr) (Fig. 1.1E), a TCT to TGT (Ser to Cys) change at codon 33 (Fig. 1.2E), and a GGA to AGA (Gly to Arg) change at codon 34 (Fig. 1.3E) (Table 1). Although in 2 cases (case 4, 6) the mutational status of beta-catenin in the target areas was not analyzed, analysis of a random sample of glandular areas showed

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Table 1. Results of morphological, immunohistochemical and mutational analyses for CHECs.

Case	Age	components			beta-catenin (nuclei)		p53		E-cadherin		beta-catenin (exon 3)	
		SPICO	squamous type	ratio of glands (%)	SPICO	GL	SPICO	GL	SPICO	GL	SPICO	GL
Case 1	55	both	keratinizing	80	2	2	0	2	0	3	42 deletion	42 deletion
Case 2	57	spindle	keratinizing	>95	2	1	1	2	0	3	42 deletion	NA
Case 3	38	spindle	morular	60	3	3	1	2	0	3	GGA34AGA	GGA34AGA
Case 4	44	corded	none	90	3	1	3	3	0	3	NA	wild
Case 5	38	both	keratinizing	80	1	2	1	1	0	3	TCT33TGT	TCT33TGT+45 deletion
Case 6	44	spindle	keratinizing	>95	3	1	0	0	0	3	NA	wild

CHEC: *corded and hyalinized endometrioid carcinoma*; SPICO: spindle and/or corded components; GL: glandular components; NA: not assessable. Definition of each score is mentioned in the Material and methods section.

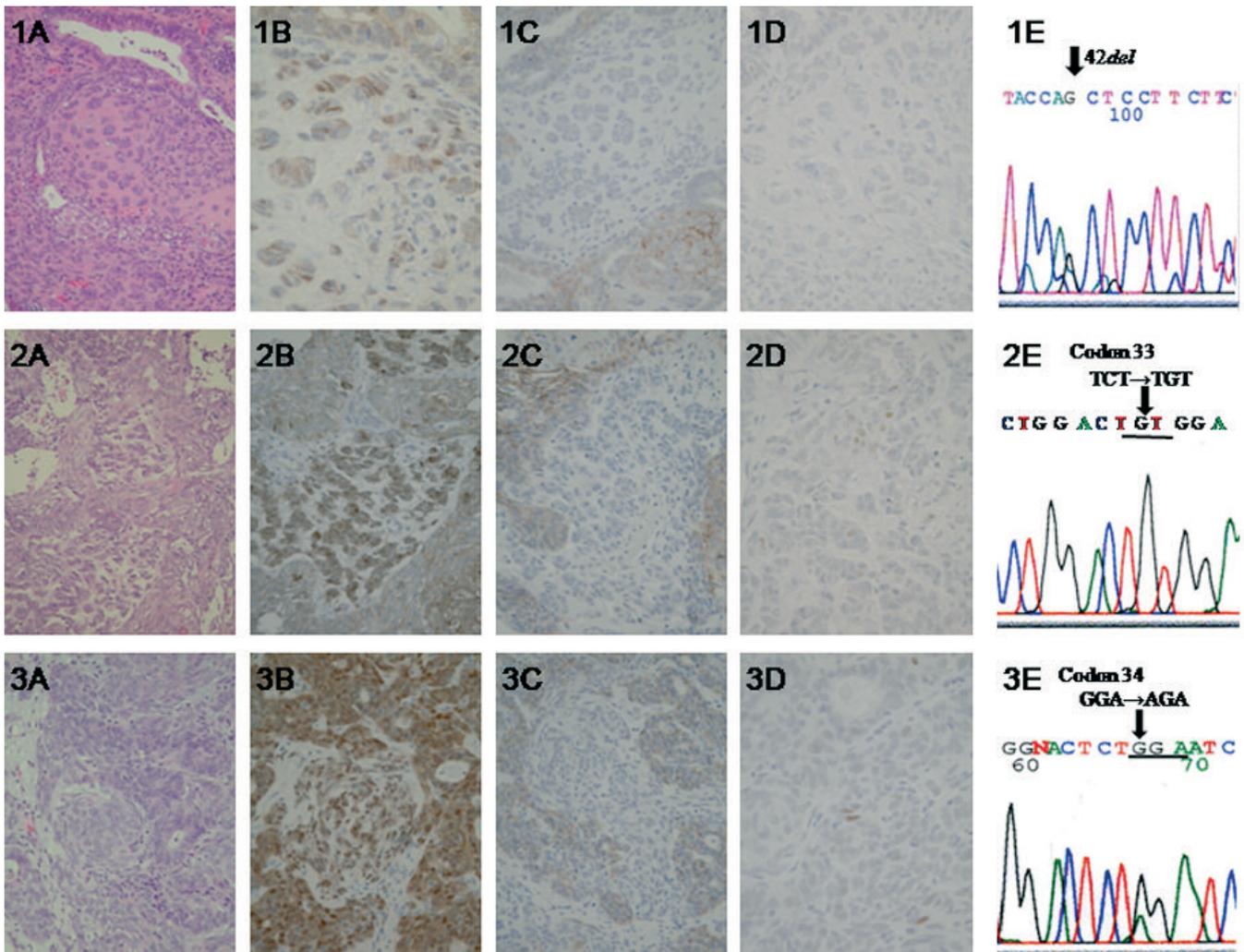


Fig. 1. Corded pattern with hyalinization (**1A**, x100) and without hyalinization (**2A**, x100) and the spindled/fusiform pattern (**3A**, x200) in CHECs. Note the aberrant nuclear expression of beta-catenin in these SPICO patterns (Score; **1B**: 2+, **2B**: 1+, **3B**: 3+) (**1B**, x 400, **2B**, x 200, **3B**, x 200). Complete loss of E-cadherin expression was shown in the SPICO patterns (**1C**, x 200, **2C**, x 200, **3C**, x 200). No or few p53-positive cells were noted in the same fields (**1D**, x 400, **2D**, x 400, **3D**, x 400). Analysis of exon 3 of the beta-catenin gene in these foci revealed mutation including a deleted codon 42 (**1E**), a GGA to AGA (Gly to Arg) change at codon 34, (**2E**), and a TCT to TGT (Ser to Cys) change at codon 33 (**3E**).

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Table 2. Summaries of immunohistochemistry for beta-catenin and p53 in CHEC, MMMT and UTROSCT.

	comparable components	beta-catenin (nuclei)	p53	
		positive (%)	positive (%)	major pattern
<i>CHEC</i>	(spindle and/or corded) n=6	6 (100)	4/6 (66.7)	focal (weak)
<i>MMMT</i>	(sarcomatous) n=8	0 (0)	7/8 (87.5)	diffuse (intense)
<i>UTROSCT</i>	(sex-cord like) n=6	0 (0)	3/6 (50)	variable (variable)

CHEC: corded and hyalinized endometrioid carcinoma; *MMMT*: malignant mixed mullerian tumor; *UTROSCT*: uterine tumor resembling ovarian sex-cord tumor.

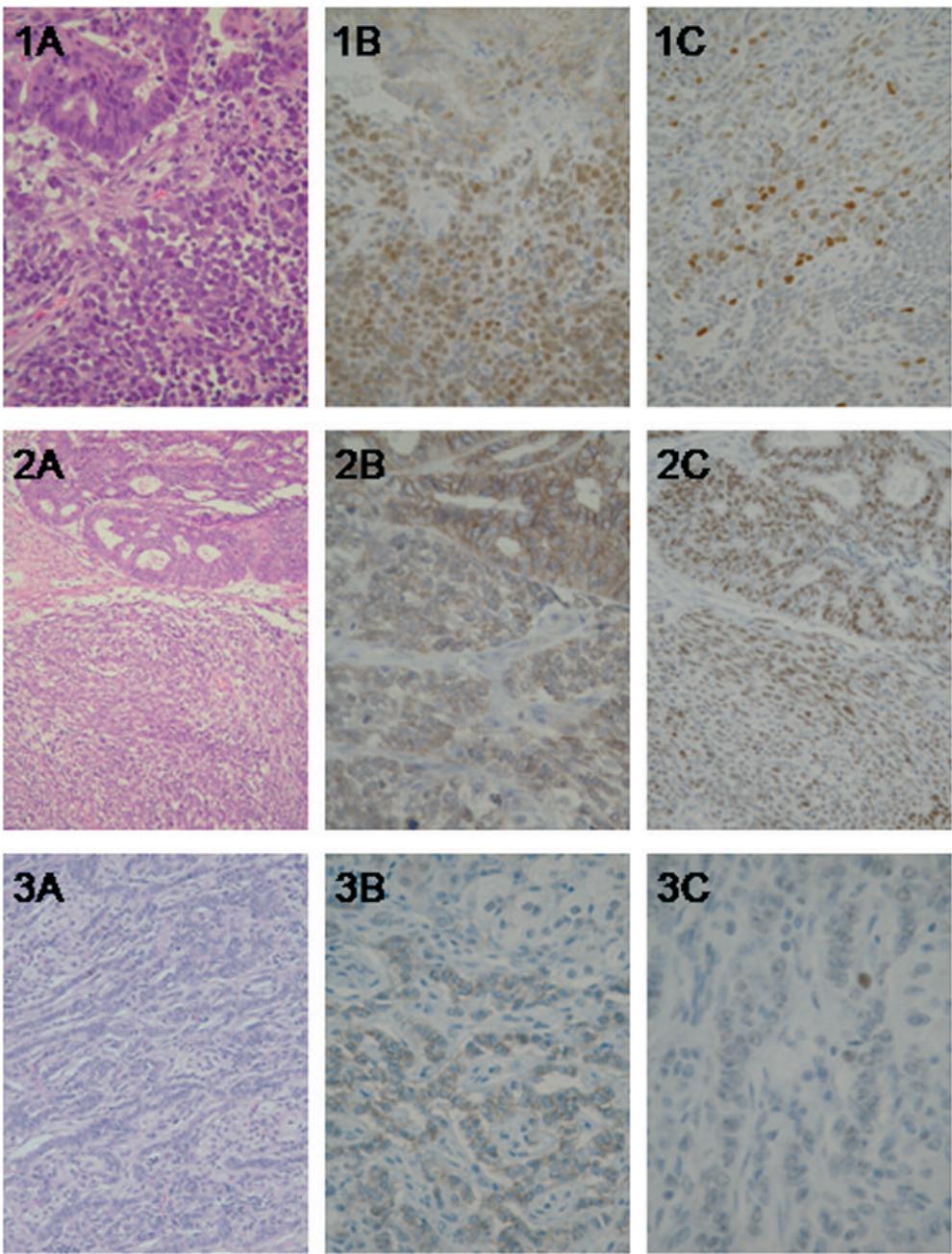


Fig. 2. Comparison of immunohistochemistry for beta-catenin (**1B**, **2B**, **3B**; x 400) and p53 (**1C**, x 400, **2C**, x 200, **3C**, x 400) between SPICO areas of CHEC (**1A**, x 400), sarcomatous areas of MMMT (**2A**, x 100) and sex cord-like components of UTROSCT (**3A**, x 200). Diffuse and intense p53 staining was detected in Case 3 (**1C**), an exceptional case, as well as in most of the MMMTs (**2C**), whereas this case showed nuclear staining for beta-catenin (**1B**) in contrast to only membranous staining in MMMTs (**2B**). In UTROSCTs, no nuclear stain for beta-catenin was identified (**3B**). In this example case, a few p53 positive cells were seen in this field (**3C**), although UTROSCTs exhibited variable scores and intensity for p53 staining.

no presence of the gene mutation.

Discussion

MMMTs are the best-known biphasic tumors; it is notable, however, that pure ECs of various types showing foci of spindle, fusiform, or corded cells may descriptively be biphasic. ECs with spindle cells have been described in the ovary (Tornos et al., 1995) and fallopian tube (Daya et al., 1992; Navani et al., 1996). In the endometrium, such tumors have especially been detailed in a review article authored by Clement and Young, 2002. Subsequently, Murray et al., 2005 employed the term *corded and hyalinized endometrioid carcinoma* (CHEC) for this variation, and again the authors clearly defined it as ECs characterized by one or more of the following features: the presence of cords of epithelioid cells, spindle cells, fusiform cells, and a striking hyalinized stroma that sometimes forms osteoids.

Indeed, the hyalinized stroma is an eye-catching feature of CHECs, but hyalinization in itself does not seem to be substantial. In fact, most of our cases lacked a hyalinized pattern, even if SPICO patterns were obvious. In our experience, hyalinized stroma seems to frequently occur in ECs with squamous differentiation. We assume that Murray et al. may have noticed these facts and therefore included three cases without hyalinization in their study, despite their use of the term CHEC.

Nuclear expression of beta-catenin in the SPICO patterns of CHECs was clearly evident in the present study and associated with the mutation of exon 3. Beta-catenin is a well-known marker that shows aberrant nuclear accumulation in squamous foci of ECs. The nuclear accumulation of beta-catenin is attributable to mutations at phosphorylation sites in exon 3 of the beta-catenin gene (Fukuchi et al., 1998; Kobayashi et al., 1999; Saegusa and Okayasu, 2001). The incidence of the beta-catenin mutation in our CHEC cases seems to be higher than generally expected in ECs and that may represent the high incidence of squamous components (5 of 6 cases). In these cases, squamous elements were observed abutting the foci of SPICO areas. Our results regarding beta-catenin indicate that the relationship between CHEC and squamous differentiation is not merely coincidental, as Murray et al., 2005 described in their article. Keratinizing-type CHECs were more often observed than morular-type ones by both Murray et al. and ourselves. Indeed, the incidence of nuclear beta-catenin expression and the gene mutation is less frequent in keratinizing-type squamous foci than morular-type ones, but conversely the lower frequency in keratinizing-type ECs might explain the rarity of the SPICO morphology.

When phosphorylation of beta-catenin due to the gene mutation occurs, it prevents binding to E-cadherin, thereby deranging the molecular composition of cell-cell complexes and favoring cell dissociation (Guarino et al.,

2007). Nuclear beta-catenin has been found to be associated with a loss of membranous staining for E-cadherin, indicating an inverse correlation (Schlosshauer et al., 2002; Shih et al., 2004). Our results suggest that alterations in the beta-catenin/E-cadherin complex are attributable to the formation of SPICO features in CHECs. Namely, the loss of cell adhesion among carcinoma cells may induce these characteristic features. This change in tumor tissue architecture takes place through a peculiar phenotype modulation known as epithelial-mesenchymal transition (EMT) (Guarino et al., 2007). The essential features of EMT are the disruption of intercellular contacts and the enhancement of cell motility, thereby leading to the release of cells from the parent epithelial tissue. Although the molecular bases of EMT have not been completely elucidated, several interconnected transduction pathways and a number of signaling molecules that are potentially involved have been identified. These include growth factors and their surface receptor (tyrosine or serine-threonine kinase receptor), Extracellular matrix (ECM)-related molecules (integrins, collagens, matrix degrading protease), and signal transduction pathways (Ras, Src, beta-catenin). As mentioned above, alterations in beta-catenin molecules cause a down-regulation of E-cadherin, which plays a major role in EMT (Brabletz et al., 2005; Guarino et al., 2007). Our two cases, which were negative for the mutation of beta-catenin, might not have been truly negative because the areas of interest were not represented on the microdissected areas. Even if these cases were truly devoid of the gene alteration, the involvement of transcription factors like Snail, which is a strong repressor of E-cadherin transcription and a well-known inducer of EMT, could also be hypothesized (Guarino et al., 2007; Saegusa et al., 2007). Hence, we consider that CHECs may be one of prominent tumors representing EMT-like features. In comparison with well-documented EMTs of colorectal carcinomas (CRCs), these EMT-like features of CHECs were frequently located in the superficial areas, not in deeply invasive fronts. The nuclear expression of beta-catenin is commonly observed in the EMT features in CHECs and CRCs; however, the latter frequently show APC mutations and are far less associated with the beta-catenin mutation. In addition, considering that ECs with the beta-catenin mutation tend to be more differentiated and show better prognosis (Fukuchi et al., 1998; Kobayashi et al., 1999; Wright et al., 1999; Saegusa et al., 2001), these EMT-like features of CHECs are not presumed to lead to poorer prognosis for the tumors. The identical mutation between both glandular and SPICO areas does not mean that an intra-tumoral alteration of the beta-catenin gene itself straightforwardly causes the SPICO features. Carcinoma cells with a nuclear accumulation of beta-catenin in some cases (e.g. loss of E-cadherin expression) might be vulnerable to different morphological change in the SPICO pattern from squamous differentiation (morules) with E-cadherin expression.

We would also like to refer to p53 expression in the SPICO foci in CHECs. Murray et al., 2005 have reported a very low frequency of p53 expression in CHECs in contrast to that reported for MMMTs. In contrast, our results showed p53 expression in 66.7 % of CHECs, whereas the scores were lower and the intensity was generally weaker than those of MMMTs. As previously described, p53 over-expression for MMMTs is related mainly to mutation of the p53 gene (Costa et al., 1994; Szukala et al., 1995; Kounelis et al., 1998). Nuclear beta-catenin expression of MMMTs was not observed in our research. On the other hand, nuclear accumulation of beta-catenin induces activation of the p53-p21WAF-1 pathway with squamous foci in ECs (Saegusa et al., 2004). Considering the high incidence of squamous differentiation in CHECs, we speculated that the p53 expression in some CHECs, even in SPICO areas, is partly due to this mechanism, not the gene mutation itself. Based on our observations, we agree with the opinion of Murray et al. that CHECs are a morphological variation of ECs, not a form of low-grade MMMTs.

In practice, the “sarcomatoid” appearance in CHECs may sometimes cause difficulties in interpretation, especially in the setting of biopsy or curettage. We should not consider these patterns as high-grade components of ECs. That is, the SPICO patterns, as well as squamous components, should not be considered to be part of the components that increase the grade of an EC, due to their bland morphology and their close association with squamous components. The main differential diagnosis of CHECs includes MMMTs and UTROSCTs. MMMTs show “biphasic” carcinomatous and sarcomatous patterns. The sarcomatous components contain heterologous elements (chondrosarcoma, rhabdomyosarcoma, osteosarcoma, etc.) and consist of spindle and/or cord-like cells with increased nuclear atypia and mitosis. Although UTROSCTs also contain cord-like patterns and spindled cells, they lack a typical component of ECs and are devoid of squamous differentiation, and characteristically contain clusters of luteinized-like cells with abundant foamy or eosinophilic cytoplasm. Pathologists should pay close attention to interpretation of the p53 stain. A diffuse and distinct stain for p53 was noted in some of the CHECs and UTROSCTs, as well as in most of the MMMTs, while no or fewer positive cells were identified in our two MMMT cases. The high-grade appearance and diffuse and intense p53 staining in “sarcomatoid cells” can directly lead to the common diagnosis of MMMT or carcinosarcoma. Nevertheless, in a worrisome case with low-grade “sarcomatoid” SPICO cells, the finding of nuclear beta-catenin expression may be indicative of a diagnosis of CHECs rather than MMMTs or UTROSCTs, even if p53 shows a diffuse and intense stain. Further results are necessary, however, to confirm this hypothesis due to the small number of our cases.

In summary, we have reported nuclear beta-catenin expression and a complete loss of membranous expression of E-cadherin in SPICO elements of all

CHECs. Aberrant beta-catenin expression in the SPICO cells as well as in the glandular cells was mainly due to exon 3 mutation of the gene. Our results also indicated that immunostaining for beta-catenin and p53 can be a promising approach to distinguishing CHECs from their mimics, MMMTs and UTROSCTs.

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