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Corded and hyalinized endometrioid carcinoma: Summary of clinical, histological, immunohistochemical and molecular data

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ABSTRACT

Corded and hyalinized endometrioid carcinoma (CHEC) represents a potential pitfall for pathologists. This study aimed to provide a complete overview of all clinicopathological and molecular features of CHEC.

Electronic databases were searched for all published series of CHEC. Clinical, histological, immunohistochemical and molecular data about CHEC were extracted and pooled.

Six studies with 62 patients were identified; mean age was 49.8 years (range 19–83). Most cases showed FIGO stage I (68%), low grade (87.5%), and a favorable outcome (78.4%), with "no specific molecular profile" (NSMP). A subset of cases showed high-grade features (12.5%), p53 abnormalities (11.1%) or mismatch repair (MMR) deficiency (20%) and occurred at an older age (mean age>60 years). Common features of CHEC were: superficial localization of the corded component (88.6%), squamous/morular differentiation (82.5%), nuclear β-catenin accumulation (92%), partial/total loss of CKAE1/AE3 (88.9%), estrogen receptor (95.7%) and e-cadherin (100%), stromal changes such as myxoid (38.5%), osteoid (24%) and chondroid (4.5%), *CTNNB1* mutations (57.9%), and POLE-wild-type (100%); 24.4% of cases showed lymphovascular space invasion. A minority of cases (16.2%) showed poor outcome despite a low-grade, NSMP phenotype; the molecular basis for the aggressiveness of these cases is still undefined. Further studies are necessary in this field.

1. Introduction

Endometrial carcinoma (EC) is the most common gynecological malignancy in the western countries [1]. Risk stratification is crucial in EC, as its biological behavior significantly vary among different risk groups [2,3]. According to the ESGO-ESTRO-ESP guidelines, the risk stratification of EC should be based on a combination of newly introduced immunohistochemical/molecular factors and traditional histopathological factors [2]. Immunohistochemical and molecular prognostic factors allow categorizing EC into four TCGA-based prognostic groups: *POLE*-mutated, mismatch repair (MMR)-deficient, p53-abnormal, and "no specific molecular profile" (NSMP). Histopathological features include histotype, FIGO grade and stage, lymphovascular space invasion (LVSI), and myometrial invasion. Defining the pathological subtype of EC, with histotype and FIGO grade, remains crucial for the risk stratificaion. In fact, among FIGO IA EC of the NSMP group, low-grade endometrioid ECs need no adjuvant treatment, while non-endometrioid carcinomas require chemoradiotherapy [2,3]. However, assignment of grade and histotype may be challenging. In fact, there are morphological features of low-grade endometrioid ECs (such

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as squamous/morular metaplasia and cytoplasmic clarification) that may mimic high-grade endometrioid or even non-endometrioid ECs [4,5]. On the other hand, some non-endometrioid EC (such as mesonephric-like carcinoma and gastrointestinal-type carcinoma) may mimic low-grade endometrioid carcinoma [6,7].

One of the most interesting diagnostic pitfall is given by the so-called corded and hyalinized endometrioid carcinoma (CHEC), a variant of endometrioid carcinoma which shows corded and spindled cells embedded in a hyaline stroma. Such pattern may raise the concern of a highly aggressive carcinosarcoma [8]. In this study, we reviewed all the

Table 1
Clinicopathological characteristics of the previously published series of CHEC.

	Murray 2005	Wani 2009	Sun 2016	Ladwig 2020	Safdar 2021	Travaglino 2022	TOTAL
Sample size (*n*)	31	6	5	7	7	6	62
Age, years mean (range)	52.3 (25–83)	46 (38–57)	33 (29–39)	48.4 (19–69)	48.9 (34–68)	57.5 (29–74)	49.8 (19–83)
Stage	20/27 (74.1%)	NA	3/5 (60%)	4/7 (57.1%)	2/5 (40%)	5/6 (83.3%)	34/50 (68%)
- I	5/27 (18.5%)		0/5 (0%)	2/7 (28.6%)	1/5 (20%)	0/6 (0%)	8/50 (16%)
- II	1/27 (3.7%)		2/5 (40%)	1/7 (14.3%)	2/5 (40%)	1/6 (16.7%)	7/50 (14%)
- III	1/27 (3.7%)		0/5 (0%)	0/7 (0%)	0/5 (0%)	0/6 (0%)	1/50 (2%)
- IV							
Last follow-up status	15/18 (83.3%)	NA	5/5 (100%)	2/6 (33.3%)	2/3 (66.7%)	5/5 (100%)	29/37 (78.4%)
- NED	1/18 (5.6%)		0/5 (0%)	2/6 (33.3%)	0/3 (0%)	0/5 (0%)	3/37 (8.1%)
- AWD	1/18 (5.6%)		0/5 (0%)	2/6 (33.3%)	0/3 (0%)	0/5 (0%)	3/37 (8.1%)
- DOD	1/18 (5.6%)		0/5 (0%)	0/6 (0%)	1/3 (33.3%)	0/5 (0%)	2/37 (5.4%)
- DOC							
% of the corded component Mean (range)	10–90	< 5–40	10–60	< 10 to > 90	15–80	15–50	< 5 to > 90
Deep Localization	1/31 (3.2%)	NA	NA	4/7 (57.1%)	NA	0/6 (0%)	5/44 (11.4%)
FIGO grade 3	0/31 (0%)	NA	0/5 (0%)	1/7 (14.3%)	1/7 (14.3%)	5/6 (83.3%)	7/56 (12.5%)
LVSI	7/27 (25.9%)	NA	NA	3/7 (42.9%)	1/5 (20%)	0/6 (0%)	11/45 (24.4%)
Squamous differentiation	22/31 (71%)	5/6 (83.3%)	NA	7/7 (100%)	7/7 (100%)	6/6 (100%)	47/57 (82.5%)
Stromal changes	8/31 (25.8%)	1/6 (16.7%)	NA	1/7 (14.3%)	NA	2/6 (33.3%)	12/50 (24%)
- osteoid	1/31 (3.2%)	NA		0/7 (0%)	NA	1/6 (16.7%)	2/44 (4.5%)
- chondroid	NA	NA		NA	3/7 (42.9%)	2/6 (33.3%)	5/13 (38.5%)
- myxoid	NA						
CKAE1/AE3	3/16 (18.7%)	NA	NA	3/7 (42.9%)	2/4 (50%)	0/6 (0%)	8/33 (24.2%)
- negative	1/16 (6.2%)			4/7 (57.1%)	1/4 (25%)	1/6 (16.7%)	7/33 (21.2%)
- positive < 10%	10/16 (62.5%)			0/7 (0%)	1/4 (25%)	4/6 (66.7%)	15/33 (45.5%)
- 10–50%	2/16 (12.5%)			0/7 (0%)	0/4 (0%)	1/6 (16.7%)	3/33 (9.1%)
- > 50%							
Vimentin	2/16 (12.5%)	NA	NA	NA	NA	NA	2/16 (12.5%)
- negative	1/16 (6.2%)						1/16 (6.2%)
- positive < 10%	4/16 (25%)						4/16 (25%)
- 10–50%	9/16 (56.2%)						9/16 (56.2%)
- > 50%							
ER	5/10 (50%)	NA	NA	2/7 (28.6%)	NA	2/6 (33.3%)	9/23 (39.1%)
- negative	2/10 (20%)			2/7 (28.6%)		3/6 (50%)	7/23 (30.4%)
- positive < 10%	2/10 (20%)			3/7 (42.9%)		1/6 (16.7%)	6/23 (26.1%)
- 10–50%	1/10 (10%)			0/7 (0%)		0/6 (0%)	1/23 (4.3%)
- > 50%							
e-cadherin	NA	0/6 (0%)	NA	1/7 (14.3%) focal	NA	6/6 (100%) focal, weak or heterogeneous	7/19 (36.8%) focal, weak or heterogeneous
Nuclear β-catenin	NA	6/6 (100%)	NA	7/7 (100%)	6/6 (100%)	4/6 (66.7%) one focal and one outside the corded component	23/25 (92%)
P53 mutation-pattern	0/10 (0%)[a]	0/6 (0%)[a]	NA	1/7 (14.3%)	1/7 (14.3%)	2/6 (33.3%)	4/36 (11.1%)
MMR loss	NA	NA	NA	1/7 (14.3%)	0/7 (0%)	3/6 (50%)	4/20 (20%)
POLE mutation	NA	NA	NA	NA	0/7 (0%)	0/6 (0%)	0/13 (0%)
CTNNB1 mutation	NA	4/6 (33.3%)	NA	7/7 (100%)	NA	0/6 (0%)	11/19 (57.9%)

[a] Data were interpreted from text and images as there were no standardized criteria to define a p53 aberrant expression at the time of publication.

published series of CHEC. We discussed in detail clinical, morphological, immunohistochemical and molecular features, trying to provide new insights in this uncommon entity.

2. Literature review

Three electronic databases (PubMed, Scopus, and Web of Science) were searched from their inception to November 2022 for all published series of CHEC. We identified six series of CHEC published from 2005 to 2022 [9–14]. The first one (Murray 2005 [9]) was from the USA and Canada and reported clinicopathological and immunohistochemical features of 31 CHECs. The second one (Wani 2009 [10]) was from Japan and performed a clinicopathological and immunohistochemical analysis of 6 cases of CHEC in addition to 8 carcinosarcomas and 6 uterine tumors resembling ovarian sex cord tumors (UTROSCT); data about tumor stage and follow-up were not reported. The third study (Sun et al., 2016 [11]) was from China reported 5 cases of CHEC; we were not able to retrieve the full-text article, and we also tried to contact the authors but received no response; therefore, we only considered data from the abstract in our analysis. The fourth and fifth studies (Ladwig et al., 2020 [12]; Safdar et al., 2021 [13]) were from the USA and performed a clinicopathological, immunohistochemical and molecular data of 7 cases each; Safdar et al. also included 2 cases of endometrioid carcinoma with spindle cells. The sixth study (Travaglino et al., 2022) was from our group and included 6 CHECs, out of which 5 were high-grade and one showed focal bizarre cells [14]. Characteristics of the reviewed studies are summarized in Table 1.

2.1. Histological data

CHEC is characterized by the presence of epithelioid and/or spindled cells arranged in cords, small clusters, or as single elements, immersed in a hyaline stroma. These cells merge imperceptibly with a conventional endometrioid component [9–13]. It is worthy to remark that a corded and hyalinized component may also be observed in non-endometrioid ECs, where its clinical significance is undefined [15]. The percentage of the corded and hyalinized component in CHEC was highly variable among the published cases (from <5% to >90%); in one case, no overt endometrioid component was observed, but the tumors showed foci of keratinization suggestive of endometrioid lineage [12]. Squamous/morular differentiation appears as a typical features of CHEC as it was present in most cases (82.5%); squamous/keratinizing features was also observed in the corded and hyalinized component [9,14]. The corded component often showed stromal changes, which were most commonly of myxoid type (38.5%); a discrete percentage of cases showed osteoid matrix (24.2%), while chondroid matrix was observed in a small subset (4.5%).

In the vast majority of cases (87.5%), the endometrioid component showed low-grade features, and the corded/spindled cells showed a bland appearance and low mitotic index. These features can be crucial to differentiate CHEC from carcinosarcoma, which typically shows a high-grade epithelial component and a high-grade mesenchymal component [2,8,16]. However, a minor subset of CHEC (12.5%) showed either a high-grade endometrioid component or a corded component with increased nuclear atypia. These may be difficult to differentiate from high-grade biphasic ECs such as carcinosarcoma and dedifferentiated carcinoma [14,16]. Our series of high-grade CHEC consistently showed anastomosing cords of epithelioid cells merging with an endometrioid component with prominent squamous/morular differentiation [14]; these features are typical of CHEC and might allow differentiating these cases from other biphasic ECs. Other features that favor CHEC are (i) a superficial localization of the corded/spindled component and (ii) a lower mitotic index in the corded/spindled component compared to the endometrioid component [9,14]. In our series, we also included a case of CHEC with only focal bizarre cells; we speculated that the presence of focal bizarre cells with no increased mitotic index may have no prognostic significance (as it occurs in leiomyoma with bizarre nuclei) [14].

A minority of cases showed LVSI (24.4%).

2.2. Immunohistochemical features

The corded/spindled component of CHEC typically shows decreased expression of epithelial markers. A diffuse expression of cytokeratin AE1/AE3 was only found in 9.1% of cases, while E-cadherin was negative in all but one case, which showed focal expression. As observed in carcinosarcoma, these data suggest that CHEC undergoes a process of epithelial-to-mesenchymal transition [17]. Similarly, estrogen receptor showed decreased expression, with a diffuse positivity in only 4.3% of cases; it is unclear if this finding is accompanied by a lower responsiveness to hormone therapy. Vimentin showed diffuse positivity in most cases (56.2%); this is not necessarily a sign of mesenchymal differentiation as vimentin is also expressed in conventional endometrioid carcinoma [18]. Ladwig et al. also assessed PAX8 and p16, which showed variable expression, while PTEN and ARID1A were lost in 4/7 and 1/6 cases [12], respectively, consistently with the endometrioid nature of CHEC.

Interestingly, an aberrant nuclear expression of β-catenin was reported in 92% of cases and was advocated as a marker to differentiate CHEC from carcinosarcoma [11]. As the Wnt/ β-catenin pathway is involved in tissue differentiation [19], we may speculate that β-catenin alterations are involved in the formation of the corded and hyalinized component. In fact, nuclear β-catenin expression is also observed in EC with morular metaplasia [4] and, in our experience, in sertoliform EC. However, we observed several cases of CHEC that showed membranous β-catenin expression at our institution, including both low-grade and high-grade CHEC [14]. Moreover, we also observed dedifferentiated carcinomas with squamous differentiation in the endometrioid component and a corded arrangement of the undifferentiated component, which showed diffuse nuclear β-catenin expression and might mimic CHEC. We are therefore unconvinced of the accuracy of β-catenin as a diagnostic marker of CHEC.

A mutant p53 pattern and a loss of mismatch repair (MMR) proteins was observed in a minority of cases (11.1% and 20%, respectively). However, out of 7 reported cases of high-grade CHECs, all but one showed either p53 abnormalities (3/7) or MMR deficiency (3/7) [12–14]. These data suggest that the p53-abnormal and MMR-deficient signatures could be typical of high-grade CHECs.

2.3. Molecular data

Ladwig et al. found that CHEC harbor several mutations that are typical of endometrioid carcinoma, such as *CTNNB1 (7/7), PIK3CA* (6/7), *PIK3R1* (1/7), *PTEN* (6/7), and *ARID1A* (2/7) mutations, while *TP53* mutation was identified in the only case showing aberrant p53 expression [12]. These findings support the similarities between CHEC and classical endometrioid carcinoma [20]. Interestingly, CHEC shows a high frequency of *CTNNB1* exon 3 mutations (57.9%), which is associated with the nuclear expression of β-catenin. In fact, nuclear β-catenin accumulation has been proposed as specific surrogate marker of *CTNNB1* exon 3 mutations in EC. Since the sensitivity of β-catenin immunohistochemistry as a surrogate test of *CTNNB1* sequencing in suboptimal [20], we cannot exclude that cases of CHEC with membranous β-catenin expression still harbor *CTNNB1* mutations. In our recent series, no cases showed *CTNNB1* exon 3 mutations, also including 4 cases with focal-to-diffuse nuclear β-catenin expression; however, only hotspots were evaluated [14]. Further studies are necessary in this regard.

In the series by Safdar et al., none of the 7 analyzed cases showed *POLE* mutation. Since all but one cases showed neither p53 abnormalities nor MMR deficiency [13], they concluded that most CHEC fall into the NSMP group, similar to classical low-grade endometrioid carcinoma

[3,20]. As discussed above, high-grade CHECs often show either p53 abnormalities of MMR deficiency; since these signatures are associated with high somatic copy-number alternation and high mutational burden, respectively [21], they may be the genomic cause for the high-grade features in CHEC.

2.4. Clinical considerations

Mean age of CHEC from literature data was 49.8 years; this is by far lower than carcinosarcoma (70 years [22]) but also lower than classical endometrioid carcinoma (62 years [23]). In our series of 5 high-grade CHEC, which were either p53-abnormal or MMR-deficient, mean age was 63.2 years [14], resulting intermediate between classical CHEC and carcinosarcoma and similar to endometrioid carcinoma. Interestingly, the previously published CHECs with p53 abnormal pattern ($n = 2$) or MMR deficiency ($n = 1$) were 64-, 66-, and 69-years-old, respectively [12,13]. This suggest that p53-abnormal and MMR-deficient CHECs occur at an older age compared to classical NSMP CHEC.

The majority of the CHECs reported in the Literature showed a favorable outcome: 68% were at FIGO stage I, 84% were uterine-confined, and 70% were alive with no evidence of disease at the last follow-up. This is the reason why CHEC has been considered as a variant of low-grade endometrioid carcinoma [8,9]. A subset showed a more aggressive behavior, with advanced stage at presentation (16%) and/or unfavorable outcome (16.2%), including persistence/recurrence of disease on follow-up (8.1%) or death of disease (8.1%). Interestingly, such subset did not overlap with MMR-deficient or p53-abnormal tumors [12,13]. In our series, among 5 MMR-deficient/p53-abnormal CHECs, four cases were uterine-confined and showed no evidence of disease at the last follow-up [14]. In the series by Ladwig et al., two MMR-deficient/p53-abnormal CHECs had a favorable outcome, while four classical low-grade CHECs showed aggressive behavior, with persistence/recurrence of disease or death of disease [12]. Reasons for an aggressive behavior in NSMP, low-grade CHECs are unclear. In recent years, *CTNNB1* exon 3 mutation has been studied as a prognostic marker in EC; in fact, early-stage, low-grade ECs with a NSMP phenotype and *CTNNB1* mutations have shown increased risk of recurrence [3,24]. In CHEC, the significance of *CTNNB1* mutations is difficult to assess because of the rarity of this entity. However, given the similarities between CHEC and classical endometrioid carcinoma, it is reasonable to think that the clinical significance of *CTNNB1* mutations is also similar. According to this view, CHEC may have a higher baseline risk of recurrence than *CTNNB1* wild-type low-grade EC. In a recent study, Momeni-Boroujeni et al. found that NSMP ECs could be stratified into three prognostic groups based on the status of PTEN, PI3KCA, PI3KR1, and chromosome 1q gain. The authors also included two CHECs, which clustered into the groups at intermediate and poor prognosis [25]. Further studies are warranted in this field.

3. Conclusions

CHEC is an uncommon variant of EC, characterized by a tumor component with morphological and immunohistochemical signs of epithelial-to-mesenchymal transition. Nuclear accumulation of β-catenin might have a role in the development of CHEC and might serve as an adjunctive diagnostic marker in the differential diagnosis, although its accuracy has not yet been defined.

CHEC appears clinically and molecularly similar to classical endometrioid carcinoma and mostly shows low-grade features and a NSMP phenotype. A subset CHEC displays high-grade features, typically accompanied by p53 abnormalities or MMR deficiency, and seems to occur at an older age compared to low-grade CHEC. Remarkably, a minority of cases shows an aggressive behavior even in the presence of a low-grade, NSMP phenotype; this might be due to genetic alterations that are still under evaluation. We hope that further multicentric studies may help clarifying these points.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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