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Case report

High-grade corded and hyalinized endometrioid carcinoma of "no specific molecular profile": report of two cases

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Summary

High-grade corded and hyalinized endometrioid carcinoma (CHEC) is an uncommon endometrial carcinoma variant which may mimic carcinosarcoma or dedifferentiated carcinoma and has shown association with mismatch repair deficiency (MMRd) and p53 abnormalities. Herein, we expand the spectrum of high-grade CHEC by presenting two cases showing a "no specific molecular profile" (NSMP). Case #1 was a 6-cm endometrial mass in a 25-year-old woman, infiltrating the deep myometrium and cervical stroma, with diffuse lymphovascular space invasion. Case #2 was an advanced, unresectable endometrial carcinoma involving the lower third of the vagina in an 81-year-old woman. On the endometrial biopsy specimen, both cases showed a markedly atypical and mitotically active corded component merging with a FIGO G3 endometrioid component and accompanied by squamous/morular differentiation. Both tumors showed nuclear β-catenin accumulation, retained MMR protein expression, wild-type p53 pattern, and no *POLE* mutations.

The corded component was absent in the hysterectomy specimen of case #1 and in the vaginal biopsy specimen of case #2. The present cases confirm the clinical and molecular heterogeneity of high-grade CHEC, including a wide age range at presentation, variable prognosis, and variable molecular background. Nonetheless, these cases retain unique features that support their distinction from carcinosarcoma and dedifferentiated carcinoma. We suggest to consider them as a variant of FIGO G3 endometrioid carcinoma. Further studies are necessary in this field.

Key words: corded and hyalinized, endometrioid carcinoma, no specific molecular profile, NSMP, histotype, mismatch repair

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Introduction

Corded and hyalinized endometrioid carcinoma (CHEC) is an uncommon morphological variant of endometrioid carcinoma with a biphasic appearance. In detail, CHEC is characterized by corded and spindled cells immersed in a hyaline stroma, which merge imperceptibly with a conventional endometrioid component. Prototypical CHEC is a low-grade tumor in which the corded and spindled cells are bland and show low mitotic activity; these features allow differentiating CHEC from carcinosarcoma [1-4]. However, in a minority of cases CHEC can be of high

grade and represent a serious diagnostic issue [5,6].
In our recently published study, we found that, unlike prototypical low-grade CHECs, high-grade CHECs were either mismatch repair-deficient (MMRd) or p53-abnormal. We therefore speculated that MMRd or p53 alterations could be the basis for the high-grade features [6].
Herein, we would expand the spectrum of high-grade CHEC by presenting two cases not showing MMRd or p53 alterations and hence fall into the "no specific molecular profile" (NSMP) group.

Case presentation

Case #1 was a 25-year-old woman with a 6 cm endometrial mass. Histological examination of an endometrial biopsy specimen showed a FIGO G3 endometrioid carcinoma with prominent squamous differentiation merging with a corded component immersed in a hyaline stroma; the stroma was highly dense, resembling osteoid matrix. The corded component was composed of epithelioid cells with high-grade atypia and evident mitotic activity. The tumor showed positivity for estrogen and progesterone receptors in 20% and 10% of cells, respectively, with diffuse nuclear accumulation of β-catenin, retained MMR expression, and wild-type p53 expression. No *POLE* mutations were detected. Therefore, the tumor was categorized as NSMP. On the hysterectomy specimen, the tumor infiltrated 90% of the myometrial thickness and the cervical stroma, with diffuse lymphovascular space invasion but no sentinel lymph node metastases. Interestingly, the corded component was only found on the biopsy specimen, indicating that it was superficial.
Case #2 was an 81-year-old woman with an advanced endometrial carcinoma involving the lower third of the vagina. Endometrial and vaginal biopsies were obtained. Endometrial biopsy showed a FIGO G3 endometrioid carcinoma with prominent squamous differentiation merging with a highly atypical, corded component immersed in a hyaline stroma (similar to case #1). In some areas, the squamous areas and the corded cells were accompanied by ghost cell keratinization. Estrogen and progesterone receptors were positive in 40% and 60% of tumor cells, respectively. Multifocal β-catenin nuclear accumulation was observed. As in case #1, the tumor was categorized as NSMP as it showed no MMRd, p53 abnormalities or *POLE* mutation. Given the advanced stage and old age, the patient did not undergo hysterectomy and is currently being treated with palliative radiotherapy. Although we do not know if the corded component was superficial, we observed it in the endometrial biopsy specimen but not in the vaginal specimen.
Histological and immunohistochemical features of the two cases are shown in Figure 1.

Discussion

High-grade CHEC represents a diagnostic issue. Unlike its low-grade counterpart, high-grade CHEC shows marked nuclear atypia which may raise the concern of highly aggressive biphasic carcinoma, such as carcinosarcoma and dedifferentiated carcinoma [5,6]. In our recently published series of high-grade CHEC, one case mostly showed prototypical low-grade CHEC features (including a NSMP), with only focal high-grade atypia in the corded component. The remaining five cases showed diffuse high-grade features and a MMRd (n = 3) or p53-abnormal (n = 2) signature. We hypothesized that the genomic changes related to MMRd and p53 alterations (i.e., microsatellite instability with high mutational burden, and copy number-high status, respectively) may underlie the presence of high-grade atypia in CHEC [6].
In this study, we expanded the spectrum of high-grade CHEC by presenting two cases showing diffuse high-grade atypia but lacking MMRd or p53 abnormalities. The two tumors were categorized as NSMP since they harbored no *POLE* mutations. This finding suggests that high-grade CHEC is molecularly heterogeneous and not necessarily related to MMR or p53 alterations. Moreover, the current two cases occurred in a young woman (25 years, case #1) and in an elderly one (81 years, case #2), demonstrating a wide age range at presentation. Even the prognosis of high-grade CHEC has proven to be heterogeneous [5,6]. Such heterogeneity makes it difficult to define diagnostic criteria for high-grade CHEC, especially considering the existence of other high-grade biphasic tumors such as carcinosarcoma and dedifferentiated carcinoma [7].
However, high-grade CHEC shows peculiar features that support its distinction from other entities. The most striking is clearly the presence of anastomosing cords of epithelioid cells immersed in a hyaline stroma. This component is typically limited to the superficial portion of the tumor, merge imperceptibly with the endometrioid component, and is accompanied by diffuse squamous/morular differentiation. Squamoid features and keratinization are often observed within single cells or small cell clusters in the corded component. Myxoid, osteoid or chondroid changes can be observed in the hyaline stroma. Nuclear β-catenin expression is often found in the corded component [5,6].
The corded and hyalinized pattern is different from the solid sheets of monomorphic dyscohesive cells ob-

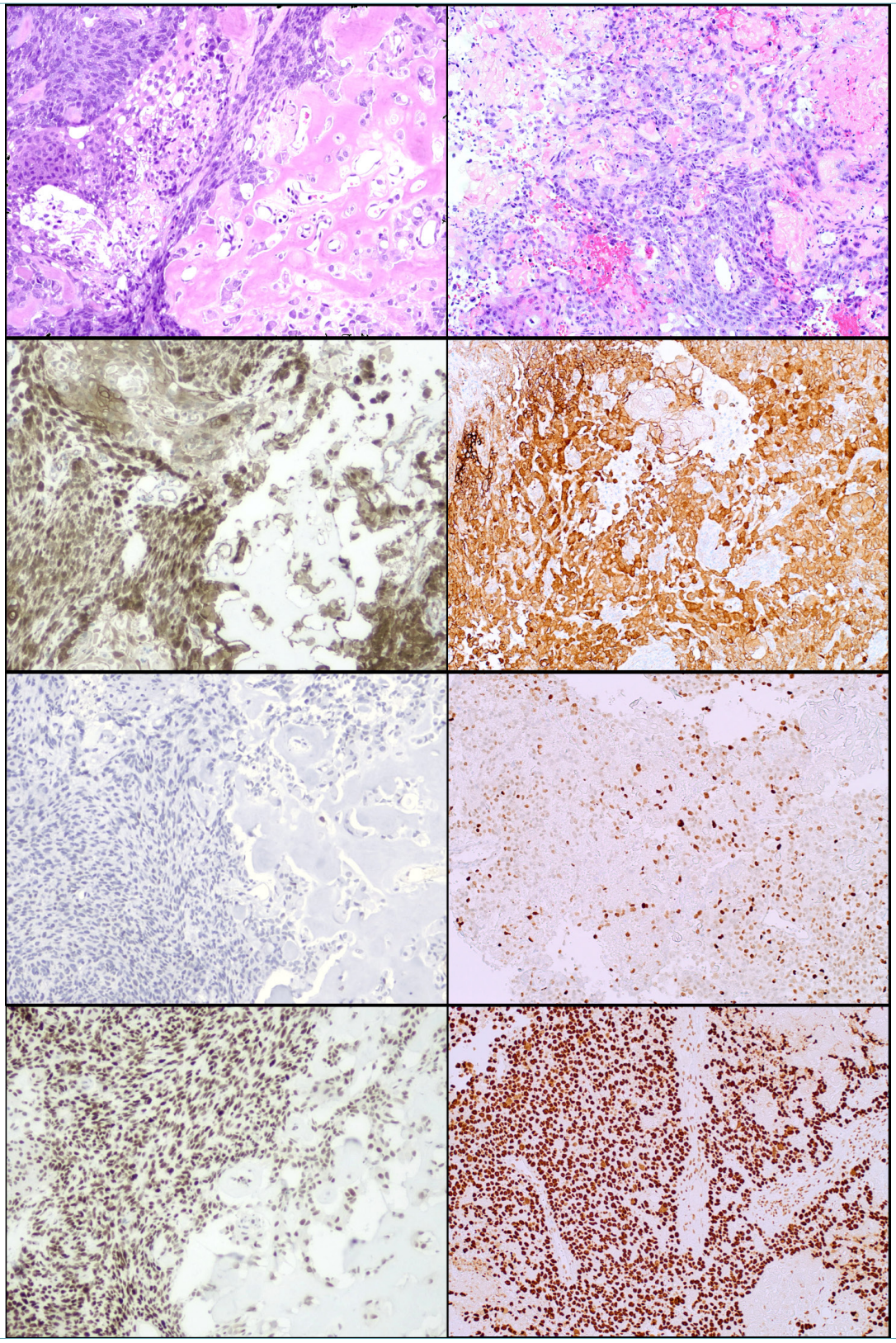


Figure 1. Histomorphological and immunohistochemical features of case #1 (left) and case #2 (right) (magnification X100). From top to bottom: - Cords of atypical cells immersed in a hyaline stroma and accompanied by squamous differentiation; - Nuclear β-catenin expression; - Wild-type p53 expression; - Retained MMR expression

served in dedifferentiated carcinoma, which typically show a sharp transition with a low-grade endometrioid component and are often characterized by loss of SWI/SNF protein expression [7-9]. It also differs from the prominent sarcomatous component of carcinosarcoma, which is usually accompanied by a serous or mixed carcinoma component and shows no nuclear β-catenin expression [2,7]; a recent study suggested that carcinosarcoma is almost exclusively of the p53-abnormal subtype [10]. Moreover, in both dedifferentiated carcinoma and carcinosarcoma, the non-epithelial component is often diffusely myoinvasive [7].

The heterogeneity of high-grade CHEC might reflect the heterogeneity of FIGO G3 endometrioid carcinoma. In fact, it is well-known that endometrioid carcinoma is highly diverse in terms of histomorphology, molecular features, and biological behavior [11-13]. This would be consistent with high-grade CHEC being a variant of FIGO G3 endometrioid carcinoma rather than of carcinosarcoma or dedifferentiated carcinoma. In a recent study, Hammer *et al.* showed that the prognosis of FIGO G3 endometrioid carcinomas with spindled growth was strongly associated with molecular classification [14]. We hypothesize that the same could be true for high-grade CHEC. In fact, it has been suggested that endometrioid carcinoma with spindled cells and CHEC are part of the same spectrum [4]. In the absence of additional evidence, we advocate that the prognostic stratification of high-grade CHEC should be based on molecular features analogous to FIGO G3 endometrioid carcinoma [15]. Further studies are necessary in this field.

Conclusion

The present cases, together with the previously published ones, confirm the clinical and molecular heterogeneity of high-grade CHEC, including a wide age range at presentation, variable prognosis, and variable molecular background. Such heterogeneity may reflect the heterogeneity observed in FIGO G3 endometrioid carcinoma, of which high-grade CHEC presumably represents a variant. These cases share unique features that support their distinction from carcinosarcoma and dedifferentiated carcinoma. Further studies are necessary in this field.

Conflict of interest statement

The authors declare no conflicts of interest.

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Authors contribution

Conception: AT, DA, AS AR; Data collection: GS, NN, FA, SR, BPU, NN, CF, EDL, JC; Histological assessment: AT, AS; DA, SR, GS, CF, EDL, SLR, GFZ; Interpretation: AT, AS, DA, AR, GFZ Writing (original draft): GS, SR, BPU, NN, CF, EDL; Writing (review and editing): AT, DA, AR, JC, SLR, GFZ; Supervision: AT, DA, SLR, AS, GFZ

Informed consent

The patients signed an informed consent for the use of their anonymized data and material.

Data availability

Additional data are available from the corresponding author upon reasonable request.

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