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Case report

Endometrial serous carcinoma with a corded and hyalinized pattern: a clinicopathological and molecular analysis

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Summary

A corded and hyalinized pattern has been described in endometrial endometrioid carcinoma. Herein, we describe a clinicopathological and molecular analysis of the first reported case of endometrial serous carcinoma with a corded and hyalinized pattern.

A 64-year-old woman underwent hysterectomy and bilateral salpingo-oophorectomy due to a 5.5 cm endometrial lesion. Histologically, the tumor was composed of a minor (20%) serous carcinoma component and a predominant corded component embedded in a hyaline-to-myxoid matrix. This component showed diffuse and strong p53 and p16 expression, heterogeneous positivity for epithelial markers and WT1, focal positivity for estrogen and progesterone receptors, retained MMR, SMARCA4/BRG1, and SMARCB1/INI1 expression, and negativity for smooth muscle, germ cell, sex cord, neuroendocrine, endothelial, and melanocytic markers and GATA3. Next-generation sequencing showed a mutation of uncertain significance in *APC* and no mutations in *MLH1, MSH2, MSH6, PMS2, MUTYH, POLE, POLD1, EPCAM*, or *CTNNB1*. The patient had a recurrence on the vaginal stump after 15 months.

In conclusion, endometrial serous carcinoma can show a corded and hyalinized pattern, which may represent a diagnostic challenge.

Key words: serous carcinoma, endometrial carcinoma, corded and hyalinized, immunohistochemical, molecular

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Introduction

Endometrial carcinoma includes several different entities with highly different prognosis, identified by clinicopathological and molecular features. Endometrial carcinoma may be morphologically heterogeneous, showing different growth patterns or even different tumor components with their own biological behavior. For instance, dedifferentiated carcinoma and carcinosarcoma exhibit a conventional carcinoma component (mostly endometrioid in the former and serous in the latter) and a component showing loss of epithelial differentiation. The presence of the non-epithelial component appears associated with aggressive

behavior [1,2]. In fact, the NCCN guidelines consider undifferentiated/dedifferentiated carcinoma and carcinosarcoma as the two most aggressive histotypes of endometrial carcinoma [3]. Interestingly, there are peculiar growth patterns in endometrial carcinoma that may mimic these aggressive entities. This is the case of the so-called "corded and hyalinized" pattern, which can be found in endometrioid carcinoma and does not seem to be associated with worsened prognosis [4-9]. Herein, we present the first case of endometrial serous carcinoma with a corded and hyalinized pattern, providing a clinicopathological, immunohistochemical, and molecular analysis.

Case presentation

A 64-year-old-woman underwent hysterectomy with bilateral salpingo-oophorectomy and sentinel lymph node resection due to a 5,5 cm endometrial mass. Histological examination revealed a biphasic neoplasm, composed of a minor serous carcinoma component (approximately 10% of the tumoral area) and a major corded component immersed in a hyalinized to myxoid component (Fig. 1A). The corded component showed a prominent exophytic growth and consisted of epithelioid cells with high nucleus-to-cytoplasm ratio and decreased pleomorphism compared to the

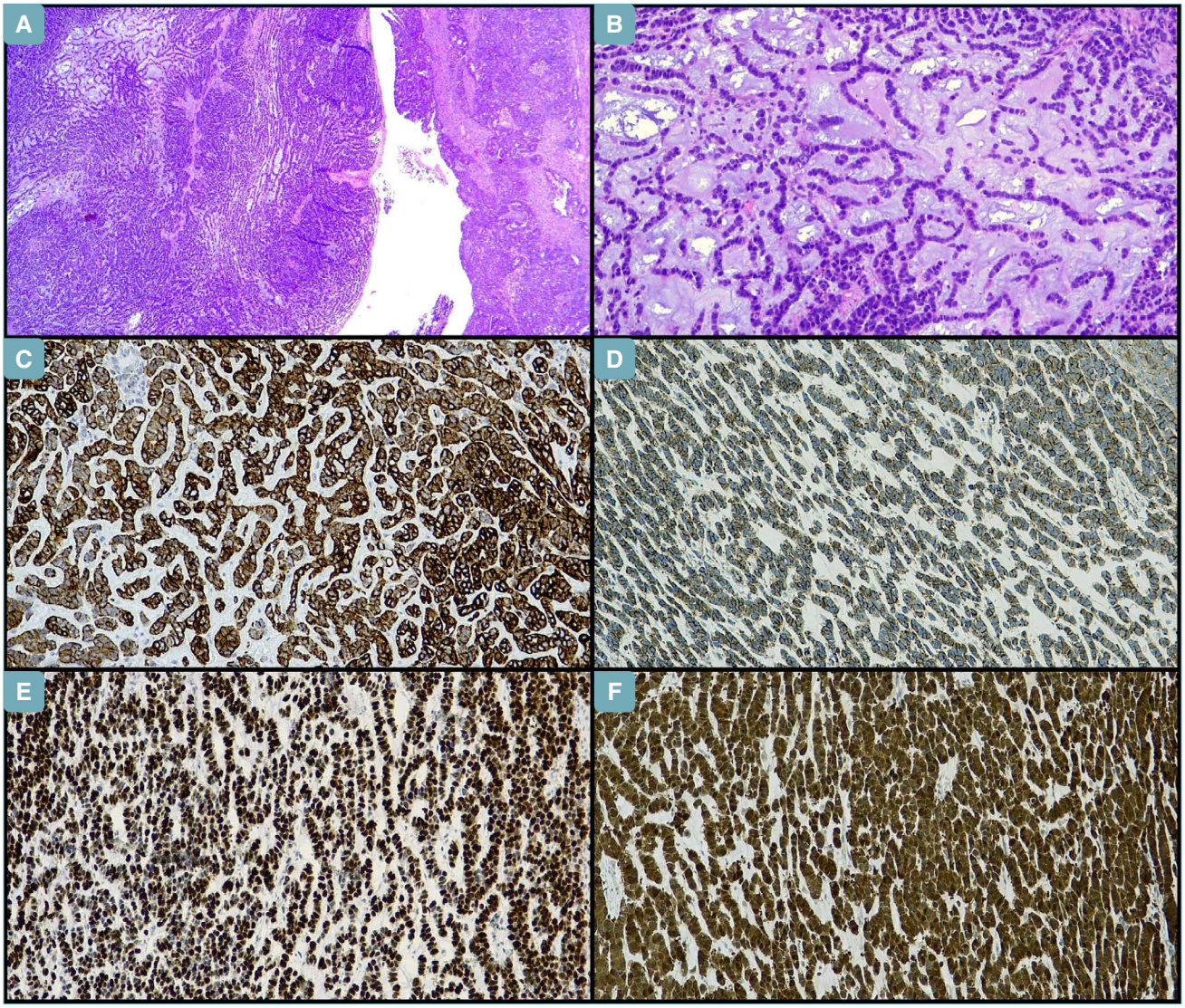

Figure 1. (A) Coexistence of serous component (left) and corded and hyalinized component (right). (B) Cords of relatively uniform atypical cells with a high nucleus-to-cytoplasm ratio, immersed in a hyaline-to-myxoid stroma. (C) Area of positivity for cytokeratin-AE1/AE3. (D) Membrane β-catenin expression with no cytoplasmic/nuclear accumulation. (E) Overexpression of p53 (mutation-type pattern). (F) Strong and diffuse p16 positivity (block-type pattern).

serous component (Fig. 1B). Both the serous and the corded component showed high mitotic index (79 and 81 mitoses/10 HPF, respectively) and infiltrated the myometrium for more than half of its thickness, with substantial lymphovascular space invasion. Extensive areas of serous intraepithelial carcinoma were observed in the adjacent endometrium. No sentinel lymph node metastases were detected. FIGO stage was IB.

The corded component showed positivity for BerEP4, heterogeneous expression of cytokeratin AE1/AE3 (Fig. 1C) and e-cadherin, zonal expression of WT1, focal expression of p63, estrogen and progesterone receptors, and complete negativity for chromogranin A, synaptophysin, S100, alpha-fetoprotein, cytokeratin-20, CDX2, melan A, inhibin, calretinin, GATA3, cyclin D1, desmin, CD31, CD34, Factor VIII, and PLAP. Occasional tumor cells were positive for CD10, CD56, and CD99. Beta-catenin showed membrane expression with no cytoplasmic/nuclear accumulation (Fig. 1D). The expression of mismatch repair proteins and of SWI/SNF proteins SMARCA4/BRG1 and SMARCB1/INI1 was retained; p53 showed overexpression (mutation-type pattern), accompanied by block-type p16 positivity (Fig. 1E-F). Next-generation sequencing analysis showed a mutation of unknown pathogenetic significance in *APC* (c.1441G>A, p.Val-481Met) and no mutations in *MUTYH, POLE, POLD1, MLH1, MSH2, MSH6, PMS2, EPCAM,* and *CTNNB1*. Based on the TCGA classifier, the tumor was classified as a p53-abnormal carcinoma. The patient was treated with carbotaxol and external beam radiation therapy and showed recurrence on the vaginal stump after 15 months.

Discussion

In this study, we performed a clinico-pathological and molecular analysis of the first reported case of endometrial serous carcinoma with a corded and hyalinized pattern.

Corded and hyalinized endometrioid carcinoma (CHEC) was first described by Murray et al in 1995 as a morphological variant of low-grade endometrioid carcinoma [4]. Subsequent studies have contributed to provide new clinicopathological and molecular insights in this entity [5-9]. The "corded and hyalinized" component consists of corded cells, small clusters or single cells with epithelioid to spindled morphology, immersed in a hyaline to myxoid stroma. Immunohistochemistry shows variably decreased expression of epithelial markers. Such a pattern may raise the concern of a carcinosarcoma, which is a highly aggressive entity. Unlike carcinosarcoma, CHEC typically shows bland cells with low mitotic activity; in addition, the corded component of CHEC is often superficial and non-myoinvasive [9]. However, there have been reports of endometrioid carcinomas exhibiting typical corded and hyalinized features in combination with high-grade features [6-9]. The corded and hyalinized pattern has also been described in non-endometrioid carcinomas, such as endometrial mesonephric-like carcinoma and ovarian low-grade serous carcinoma [19,11]. Another typical feature of CHEC is the prominent squamous/morular differentiation [4-9]. Immunohistochemically, CHEC shows nuclear β-catenin expression in most cases, which reflects *CTNNB1* exon 3 mutations [5-7,9]. Our case is the first described case of endometrial serous carcinoma with a corded and hyalinized component. Such a component showed several crucial differences from the typical CHEC. First of all, the corded cells in our case were highly atypical with a high mitotic index and showed myoinvasion. In addition, our case did not show overt squamous differentiation (despite the focal p63 positivity), nuclear β-catenin accumulation, or *CTNNB1* mutation. These features are indeed typically absent in serous carcinoma [12]. However, the corded component of our case did not resemble a sarcoma component. In fact, tumor cells were epithelioid and were arranged in cords, which were reminiscent of a sex cord tumor. Sex cord markers inhibin, calretinin, and SF1 were negative; occasional tumor cells were positive for CD10, CD56 and CD99 (which are often positive in sex cord tumors) [1]. Epithelial markers (cytokeratin-AE1/AE3, e-cadherin, BerEP4) were positive in the corded component, although their intensity was variable and sensibly decreased compared to the serous component. Such pattern raised the suspicion of a neuroendocrine carcinoma, but the neuroendocrine markers chromogranin and synaptophysin were negative. Other types of differentiation considered were neuroectodermal, endometrial stromal, germ cell, and melanocytic, but immunohistochemistry did not support these hypotheses. Smooth muscle markers were also negative.

Given the presence of relatively uniform epithelioid cells with high nucleus-to-cytoplasm ratio and the absence of a specific differentiation, our case should also be distinguished from a dedifferentiated endometrial carcinoma. The latter typically shows a low-grade endometrioid component, although cases with a serous component have been reported [1,2]. The positivity for epithelial markers did not support a diagnosis of dedifferentiated carcinoma [13]. Specific immunohistochemical markers of dedifferentiated carcinoma, such as SMARCA4/BRG1 loss and SARCB1/INI1 loss [2], were not observed. In the light of the described find-

ings, we labeled our tumor as a serous carcinoma with a corded and hyalinized pattern.

Regarding prognosis, we do not know if the corded component in our case should be interpreted as a peculiar growth pattern (like corded and hyalinized endometrioid carcinoma) or a distinct tumor component (like dedifferentiated carcinoma and carcinosarcoma). Since our case falls in the p53-abnormal group according to the TCGA classifier, it would be included in the high-risk ESGO-ESTRO-ESP category anyway, with no prognostic stratification issues [2]. In contrast, the NCCN guidelines consider undifferentiated/dedifferentiated carcinoma and carcinosarcoma as more aggressive than serous carcinoma, and the management may change between the former two and the latter one [3].

We hope our report may help pathologists to identify additional similar cases, in order to better define the biological significance of a corded and hyalinized pattern in serous carcinoma.

Conflicts of interest

The authors declare no conflict of interest.

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No funds were received for this study.

Authors' contributions

Conception: AT, AS, DA, GFZ; literature search: AT, GS, AR, MAE, LPA, data collection: AT, DA, GS, AP, LPA; histological assessment: AT, AS, DA, GS, GFZ; molecular analysis: AP, MAE, AM; data interpretation: AT, AS, DA, AR, MAE, AM, FF, GFZ; writing (original draft): AT, DA, GS, AR, AP, MAE, LPA; writing (review and editing): AT, AS, AR, AM, FF, GFZ; supervision: AT, AM, FF, GFZ

Ethical consideration

A written consent for the use of biological material for research purpose was obtained from the patient. All data were anonymized.

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