Corded and hyalinized endometrioid carcinoma: a rare case and review of the literature

Yan Li
Sun Yat-sen University First Affiliated Hospital https://orcid.org/0000-0003-4994-2034
Yuejiao Lang
Sun Yat-sen University First Affiliated Hospital
Kaitao Yuan
Sun Yat-sen University First Affiliated Hospital
Ying Tuo
Sun Yat-sen University First Affiliated Hospital
Pei Xiang
Sun Yat-sen University First Affiliated Hospital
Donghua Zheng
Sun Yat-sen University First Affiliated Hospital
Dawei Liu (liudwei@mail.sysu.edu.cn)
Sun Yat-sen University First Affiliated Hospital

Case Report

Keywords: Endometrioid carcinoma, corded and hyalinized endometrioid carcinoma, sex cord-like formations

Posted Date: September 22nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-71402/v1

Abstract

Background

Corded and hyalinized endometrioid carcinoma(CHEC) is a rare morphological variation of endometrioid carcinoma(EC) in the endometrium. Reports of CHEC were very limited. We represent the clinical and pathological findings of this rare endometrioid carcinoma in a 26-year-old woman and reviews the literatures updated on CHEC.

Case presentation:

A 26-year-old woman presented with abnormal vaginal bleeding for 3 months and the initial cervical biopsy revealed a mullerian mixed tumor in another clinic. Abdominopelvic computed tomography revealed a mass in the uterine cavity and cervix, suggesting a malignant tumor. Histologically, the tumor showed a biphasic pattern characterized by an appearance of 2 components, the conventional endometrioid carcinoma component and sex cord-like component with hyalinization. In the areas of sex cord-like elements, the epithelioid and spindle cells were usually seen around the glands, and mostly arranged in cords or trabeculaes, sometimes embedded within a richly hyalinized collagenous or sometimes myxoid matrix. Tumor cells in the sex cord-like region show a different immunohistochemical expression pattern from conventional adenocarcinoma. Cytokeratin(CK) and vimentin are positive in both components, and vimentin shows more diffuse positivity while CK is more restricted and focally expressed in tumor cells in the sex cord-like region. Complete loss of expression of E-cadherin and epithelial membrane antigen(EMA) was seen in tumor cells in the sex cord-like region whereas it was well preserved in the area of conventional adenocarcinoma. Nuclear expression of β-catenin was noted in tumor cells in the sex cord-like region. P53 was focally positive in both components. Based on histological and immunochemical examinations, the patient was diagnosed with CHEC.

Conclusions

CHEC is not uncommonly mistaken for a wide variety of diseases. It’s of great significance to raise the awareness of CHEC to avoid over-treatment caused by over-diagnosis, especially in young patients and in curettage. We report one case of CHEC in a 26-year-old woman which was misdiagnosed as a mullerian mixed tumor in the initial curettage specimen. The clinicopathologic, light microscopic, immunohistochemical features of this tumor are described and the differential diagnosis is discussed.

Background

Endometrioid carcinoma (EC) accounts for 70 ~ 80% of newly diagnosed uterine corpus cancer worldwide in recent years[1]. The recognition of its typical morphology and clinical significance are usually straightforward; however, EC may have a variety of unusual appearances that can pose a diagnostic

challenge and be associated with unique clinicopathological findings[2]. EC with sex cord-like formations and hyalinization is a rare morphological variation of EC in the endometrium which was first described in a review article in 2002[3]. In 2005, Murray et al. described the clinical and pathologic features of this distinct variant and referred to this subtype as “corded and hyalinized endometrioid carcinoma(CHEC)”[4]. Histologically, CHEC is characterized by the presence of cords, nests, or clusters of bland epithelioid and spindled cells, which merge with a conventional component of low-grade typical EC. Typically in between the cords and clusters, there is abundant hyalinized to myxoid stroma which compresses the neoplastic cells and imparts a sex-cord like appearance. Clinically, CHECs tend to arise in younger patients compared with typical ECs and are usually low stage with a generally favorable prognosis, so it is important to distinguish CHECs from other endometrial tumors[5]. However, CHEC is not uncommonly mistaken for a wide variety of diseases, in particular carcinosarcoma, which is often high grade and clinically aggressive. Therefore, increased awareness of this rare morphological variation is essential for both clinicians and pathologists to avoid misdiagnosis and over-treatment.

To our knowledge, reports of CHEC were very limited[4, 6]. In this study, we represent the clinical and pathological findings of this rare endometrioid carcinoma in a 26-year-old woman and reviews the literatures updated on the clinical, morphologic and immunohistochemical features of CHEC.

Materials And Methods

The tissue obtained via hysterectomy was processed using routine histological methods: 10% formalin fixed, paraffin embedded and haematoxylin-eosin stained. Immunohistochemical studies were carried out on formalin-fixed paraffin-embedded tissue. Appropriate positive and negative controls were applied simultaneously. The primary antibodies used for the immunohistochemical studies are listed in Table 1.

Table 1
Proteins explored in the present study

Targeted proteins	Clone	Dilution	Expression in typical endometrioid carcinoma component	Expression in the epithelial cells in the sex cord-like component
CK[a]	AE1 + AE3	Ready-to-use	Diffuse +	Focally +
Vimentin[a]	V9	Ready-to-use	Focally +	Diffuse +
E-cadherin[a]	Nch-38	Ready-to-use	Diffuse +	-
EMA[a]	E29	Ready-to-use	Diffuse +	-
CK7[a]	OV-TL	Ready-to-use	Diffuse +	Focally +
ER[b]	SP1	Ready-to-use	Diffuse +	Focally +
PR[b]	1E2	Ready-to-use	Diffuse +	Focally +
Pax-8uhe[c]	EP298	Ready-to-use	Diffuse +	Focally +
P53[a]	DO-7	Ready-to-use	Focally +	Focally +
β-catenin[c]	CAT-5H10	1;200	Nuclear -	Nuclear +
Actin[a]	1A4	Ready-to-use	-	Focally +
MLH1[a]	ES05	Ready-to-use	Diffuse +	Diffuse +
PMS2[a]	EP51	Ready-to-use	Diffuse +	Diffuse +
MSH2[a]	FE11	Ready-to-use	Diffuse +	Diffuse +
MSH6[a]	EP49	Ready-to-use	Diffuse +	Diffuse +
CD10[a]	56C6	Ready-to-use	-	-

[a]: DAKO; [b]: ROCHE; [c]: MAI XIN BIOTECHNOLOGY CO.,LTD.

Targeted proteins	Clone	Dilution	Expression in typical endometrioid carcinoma component	Expression in the epithelial cells in the sex cord-like component
Desmin[a]	D33	Ready-to-use	-	-
Inhibin-a[a]	R1	Ready-to-use	-	-
Melan-A[a]	A103	Ready-to-use	-	-
[a]: DAKO; [b]: ROCHE; [c]: MAI XIN BIOTECHNOLOGY CO.,LTD.				

Case Presentation

Clinical history

A 26-year-old woman visited another clinic because of abnormal vaginal bleeding for 3 months. The initial cervical biopsy revealed a mullerian mixed tumor, following which she was referred to our hospital for evaluation and treatment. Her familial history and past history was uneventful. Her body mass index was 28.6 kg/m^2. Abdominopelvic computed tomography revealed a mass in the uterine cavity and cervix, suggesting a malignant tumor (Fig. 1a-1b). Serum levels of the tumor markers carcinoembryonic antigen, cancer antigen 125 and carbohydrate antigen 19 – 9 were 0.66 ug/L, 10.6 U/mL, and 3.85 U/mL respectively. The patient received total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, intra-pelvic, para-aortic and presacral lymphadenectomy.

Pathological findings

Gross examination in the hysterectomy specimen revealed a 60 × 33 × 10 mm papillary mass with a grey-whitish cut surface in the uterine cavity that appeared to invade into the superficial myometrium and the surface of cervix (Fig. 1c).

Histologically, low-power magnification revealed the tumor invaded the superficial layer of myometrium and extended to the surface of cevix but did not invade the cervical stroma (FIGO stage IA), showing a biphasic pattern characterized by an appearance of 2 components, the conventional endometrioid carcinoma component and sex cord-like component with hyalinization (Fig. 2a). Sections of the tumor showed typical low-grade endometrioid carcinoma (FIGO grade 1) in a background of endometrial hyperplasia (Fig. 2b). In 60% of areas of the tumor, sex cord-like elements were found to blend with the conventional endometrioid carcinoma. This distinct component of sex cord-like formations was restricted to the superficial aspects (Fig. 2c). In the areas of sex cord-like elements, the epithelioid and spindle cells were usually seen around the glands, and mostly arranged in cords or trabeculaes (Fig. 2d). In some areas, the epithelioid and spindle cells were embedded within a richly hyalinized collagenous or

sometimes myxoid matrix, and the cells may formed small clusters or were individually disposed (Fig. 2e); but in some areas, a hyalinized matrix was absent and the cells were arranged in solid sheets (Fig. 2f). Squamous differentiation exhibiting keratinization was common (Fig. 2g). Cytologic atypia of the epithelioid and spindle cells was uniformly low grade. The cells had scant eosinophilic cytoplasm. Compared with the tumor cells within the glands of the typical EC component, the nuclei of the epithelioid, spindle and fusiform cells showed less atypia and only rare mitotic figures(Fig. 2h). Lymphovascular invasion was not identified. The right and left ovaries and fallopian tubes were negative for tumor.

A panel of immunohistochemical stains was performed. In the typical endometrioid carcinoma component, CK, E-cadherin, EMA, CK7, estrogen receptor(ER), progesterone receptor(PR) and Pax-8 was diffusely positive; Vimentin was focally positive; actin was negative. In the epithelial cells in the sex cord-like component, Vimentin was diffusely positive; CK, CK7, ER, PR, Pax-8, actin was focally weakly positive; E-cadherin, EMA was negative. Nuclear expression of β-catenin was noted in tumor cells in the sex cord-like region. P53 was focally positive in both components. MLH1, PMS2, MSH2 and MSH6 was postive in both components. CD10, desmin, inhibin-α, melan-A was negative in both components (Table 1, Fig. 3).

Based on histological and immunochemical examinations, the patient was diagnosed with CHEC.

Follow up

The patient had a disease-free follow-up 8 months after the surgery.

Discussion And Conclusions

EC may have a variety of unusual appearances which can cause difficulty in making correct diagnosis[2]. CHEC is a rare morphological variant of EC developing in the endometrium[4]. Lack of awareness of this entity may lead to misdiagnosis and unnecessary treatment.

Reports of CHEC are limited; updating to now, only 37 cases are described by two articles (written in English) retrieved from PubMed[4, 6]. From these studies, patient age ranged from 25 to 83 years, with a mean of 51 years. Among 27 patients with clinical staging data, 20 patients (74%) were at FIGO stage Ⅰ. Among 18 patients with follow-up information, 15 patients were alive with no evidence of disease, 1 patient was alive with disease, 1 patient died as a result of tumor, and 1 patient died of other causes. In the present case, the patient was only 26-year-old, at FIGO stage Ⅰand was alive with no evidence of disease for 8 months. We can conclude that CHEC tends to arise in younger patients compared with conventional endometrial EC, and usually develops at a lower stage with more favorable prognosis than conventional endometrial EC[7, 8]. However, CHEC is not uncommonly mistaken for a wide variety of diseases. In the present case, the patient was misdiagnosed as a mullerian mixed tumor in the curettage specimen. Accordingly, it's of great significance to raise the awareness of CHEC to avoid over-treatment caused by over-diagnosis, especially in young patients and in curettage.

Histologically, all cases that have been reported consist of a component of conventional grade or conventional EC that accounts for 10–90%. Endometrial hyperplasia can be identified in most cases. The definition of CHEC is the presence of cords of epithelioid cells, spindled cells, or fusiform cells with or without hyalinized stroma. This component is generally restricted to the superficial aspects and often embedded within a striking hyalinized collagenous matrix which in some cases formed osteid. Increased squamous differentiation is often found.

As for immunohistochemical staining, tumor cells in the sex cord-like region show a different expression pattern from conventional adenocarcinoma. CK and vimentin are positive in both components in most cases, and vimentin shows more diffuse positivity while CK is more restricted and focally expressed in tumor cells in the sex cord-like region. Complete loss of expression of E-cadherin and EMA was seen in tumor cells in the sex cord-like region whereas it was well preserved in the area of conventional adenocarcinoma. Nuclear expression of β-catenin was noted in tumor cells in the sex cord-like region. Both components show a positive immunoreactive for ER in about half of the cases and p53 overexpression was rarely observed. Desmin, inhibin and CD10 are negative in both components. Molecularly, sequence analysis showed mutations in the exon 3 of β-catenin gene in tumor cells in the corded and hylinized region.

The main pathological differential diagnoses of the present case include carcinosarcoma, dedifferentiated EC, sertoliform EC, low-grade endometrial stromal sarcomas (LGESS), i.e.

CHEC tends to be easily misdiagnosed as carcinosarcoma, because of its striking biphasic appearance exhibiting both epithelioid and mesenchymal elements, especially in the setting of biopsy or curretage. Unlike CHEC, carcinosarcoma often occurs in elderly women and has a high-stage clinical presentation and more aggressive clinical behavior[9]. Moreover, pathologically carcinosarcoma is mostly composed of high-grade adenocarcinomatous and sarcomatous components with increased nuclear atypia and mitosis[10]. Also, p53 is diffusely and strongly expressed in adenocarcinoma while it is scattered positive in CHEC[11].

Dedifferentiated EC contains a component of either FIGO grade 1 or 2 EC and a second component of undifferentiated carcinoma. The undifferentiated carcinoma is composed of dyshesive cells of uniform size arranged in sheets without any corded or trabecular architecture which is seen in CHEC. The nuclear chromatin is usually condensed and most cases have > 25 mitotic figure per 10 HPF while the nuclei of the epithelioid and spindle cells showed less atypia and only rare mitotic figures in CHEC[12, 13]. The undifferentiated component grows beneath the differentiated endometrioid component while the epithelioid and spindle cells are restricted to the superficial aspects in CHEC. The undifferentiated components display evidence of epithelial differentiation in only occasional tumor cells, with intense EMA and CK18 expression in the absence of staining with pan-cytokeratins[14]. Also, a proportion of dedifferentiated EC appear to be associated with microsatellite instability[15].

In sertoliform EC, tumor cells are arranged as small hollow tubules in the areas resembling Sertoli and Sertoli-Leydig cell tumors, but sometimes they can arranged as cord and trabeculaes, which can be

confused with CHEC. However, prominent stromal hyalinization and spindle cells are not a feature of the sertoliform EC of the endometrium and the sertoliform elements are always positive for EMA and CK, which helps us distinguish sertoliform EC with CHEC[16, 17].

LGESS can also show sex cord-like features and the tumor cells in this element are small and uniform without prominent nuclear atypia and mitotic activity[18]. However, typical EC is absent in LGESS. Immunohistochemically, the sex cord elements in LGESS show positive staining of endometrial stromal, smooth muscle markers. Sex cord markers including inhibin, CD99, calretinin and CD56 could also be positive[19, 20]. PHF1 rearrangement has been found to be predominant in the sex cord variant of LGESS[21].

Corded and hyalinized mesonephric-like adenocarcinoma can also mimick CHEC. Differentiating the tumor from CHEC is its heterogeneous architecture resembling mesonephric growth patterns, segments of attenuated epithelium, lack of squamous differentiation, essentially negative hormone receptor expression, considerable positivity for TTF1 and GATA3[22].

In summary, CHEC is not uncommonly mistaken for a wide variety of diseases. We report one case of CHEC in a 26-year-old woman. The

clinicopathologic, light microscopic, immunohistochemical fetaures of this tumor are described and the differential diagnosis is discussed. We hope that this report help to raise the awareness of CHEC and avoid misdiagnosis and mistreatment.

Abbreviations

CHEC: Corded and hyalinized endometrioid carcinoma; EC:Endometrioid carcinoma; Cytokeratin(CK); EMA:Epithelial membrane antigen; FIGO:International Federation of Gynecology and Obstetrics; ER:estrogen receptor; PR:progesterone receptor.

Declarations

Ethics approval and consent to participate

The patient provided informed consent. The study was approved by the Ethics Committee of Clinical Research and Experimental Animal of the First Affiliated Hospital, Sun Yat-sen University.

Consent for publication

Written informed consents for publication of clinical details and clinical images were obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

Please contact author for data requests.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Authors' contributions

Y Li, DZ and DL analysed and interpreted histological and immunohistochemistry examination. Y Li and Y Lang made major contributions in writing the manuscript. DL revised the manuscript. KY collected the patient’s clinical history. YT performed the immunohistochemical examination. PX performed the abdominopelvic computed tomography examination and wrote the coincident part of the report. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893–917.
2. Malpica A. How to approach the many faces of endometrioid carcinoma. Mod Pathol. 2016;29(Suppl 1):29–44.
3. Clement PB, Young RH. Endometrioid carcinoma of the uterine corpus: a review of its pathology with emphasis on recent advances and problematic aspects. Adv Anat Pathol. 2002;9(3):145–84.
4. Murray SK, Clement PB, Young RH. Endometrioid carcinomas of the uterine corpus with sex cord-like formations, hyalinization, and other unusual morphologic features: a report of 31 cases of a neoplasm that may be confused with carcinosarcoma and other uterine neoplasms. Am J Surg Pathol. 2005;29(2):157–66.
5. Jia M, Sun PL, Gao H. Uterine lesions with sex cord-like architectures: a systematic review. Diagn Pathol. 2019;14(1):129.

6. Wani Y, Saegusa M, Notohara K. 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. Histol Histopathol. 2009;24(2):149–55.
7. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY, Pecorelli S. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006;95 Suppl 1:S105-43.
8. Zaino RJ, Kurman RJ, Diana KL, Morrow CP. Pathologic models to predict outcome for women with endometrial adenocarcinoma: the importance of the distinction between surgical stage and clinical stage–a Gynecologic Oncology Group study. Cancer. 1996;77(6):1115–21.
9. Singh R. Review literature on uterine carcinosarcoma. J Cancer Res Ther. 2014;10(3):461–8.
10. Denschlag D, Ulrich UA. Uterine Carcinosarcomas - Diagnosis and Management. Oncol Res Treat. 2018;41(11):675–9.
11. Keeling L, Taraporewalla D, Perunovic B, Smith JH. Uterine carcinosarcoma with p53-positive intraepithelial component. Histopathology. 2011;59(6):1277–8.
12. Tafe LJ, Garg K, Chew I, Tornos C, Soslow RA. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently underrecognized neoplasms. Mod Pathol. 2010;23(6):781–9.
13. Silva EG, Deavers MT, Bodurka DC, Malpica A. Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? Int J Gynecol Pathol. 2006;25(1):52–8.
14. Altrabulsi B, Malpica A, Deavers MT, Bodurka DC, Broaddus R, Silva EG. Undifferentiated carcinoma of the endometrium. Am J Surg Pathol. 2005;29(10):1316–21.
15. Garg K, Leitao MJ, Kauff ND, Hansen J, Kosarin K, Shia J, Soslow RA. Selection of endometrial carcinomas for DNA mismatch repair protein immunohistochemistry using patient age and tumor morphology enhances detection of mismatch repair abnormalities. Am J Surg Pathol. 2009;33(6):925–33.
16. Eichhorn JH, Young RH, Clement PB. Sertoliform endometrial adenocarcinoma: a study of four cases. Int J Gynecol Pathol. 1996;15(2):119–26.
17. Liang SX, Patel K, Pearl M, Liu J, Zheng W, Tornos C. Sertoliform endometrioid carcinoma of the endometrium with dual immunophenotypes for epithelial membrane antigen and inhibin alpha: case report and literature review. Int J Gynecol Pathol. 2007;26(3):291–7.
18. Ohta Y, Suzuki T, Kojima M, Shiokawa A, Mitsuya T. Low-grade endometrial stromal sarcoma with an extensive epithelial-like element. Pathol Int. 2003;53(4):246–51.
19. Richmond AM, Rohrer AJ, Davidson SA, Post MD. Low-grade endometrial stromal sarcoma with extensive sex cord differentiation, heterologous elements, and complex atypical hyperplasia: Case report and review of literature. Gynecol Oncol Rep. 2017;19:34–8.
20. Baker RJ, Hildebrandt RH, Rouse RV, Hendrickson MR, Longacre TA. Inhibin and CD99 (MIC2) expression in uterine stromal neoplasms with sex-cord-like elements. Hum Pathol. 1999;30(6):671–9.

21. D'Angelo E, Ali RH, Espinosa I, Lee CH, Huntsman DG, Gilks B, Prat J. Endometrial stromal sarcomas with sex cord differentiation are associated with PHF1 rearrangement. Am J Surg Pathol. 2013;37(4):514–21.
22. Patel V, Kipp B, Schoolmeester JK. Corded and hyalinized mesonephric-like adenocarcinoma of the uterine corpus: report of a case mimicking endometrioid carcinoma. Hum Pathol. 2019;86:243–8.

Figures

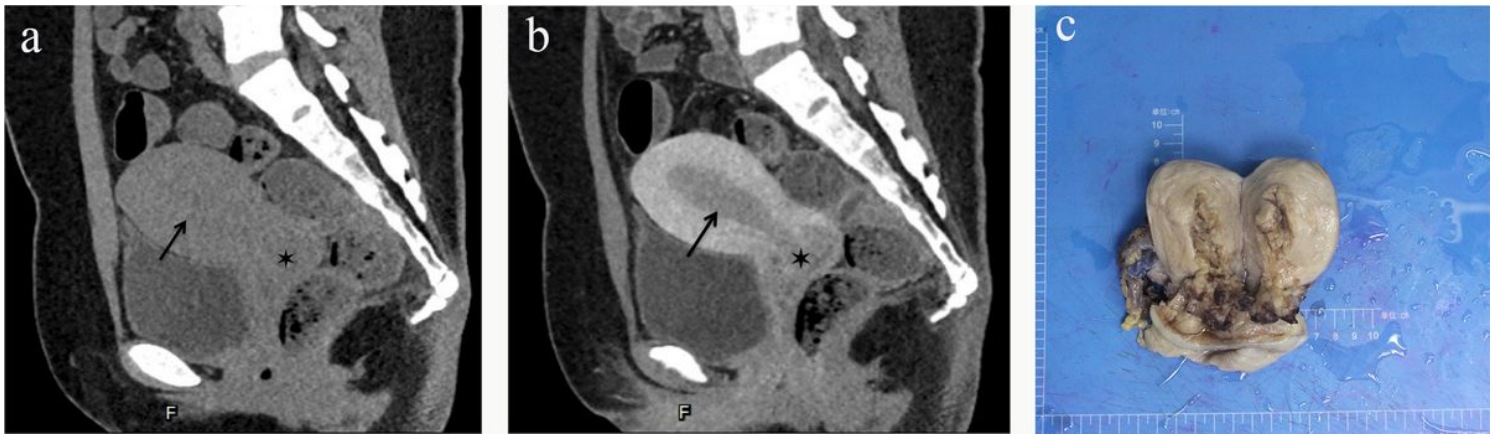

Figure 1

Computed tomography imaging and macroscopic analysis a. Reconstructed sagittal pre-contrast CT image: the presence of endometrial thickening (arrow) and cervical mass (star) is obscured in the pre-contrast CT image. b. Reconstructed sagittal post-contrast CT image endometrial thickening (arrow), enhancing mass (less enhanced than the myometrium) in the uterus cervix (star). c. Gross examination in the hysterectomy specimen revealed a 60 x 33 x 10 mm papillary mass with a grey-whitish cut surface in the uterine cavity that appeared to invade into the superficial myometrium and the surface of cervix.

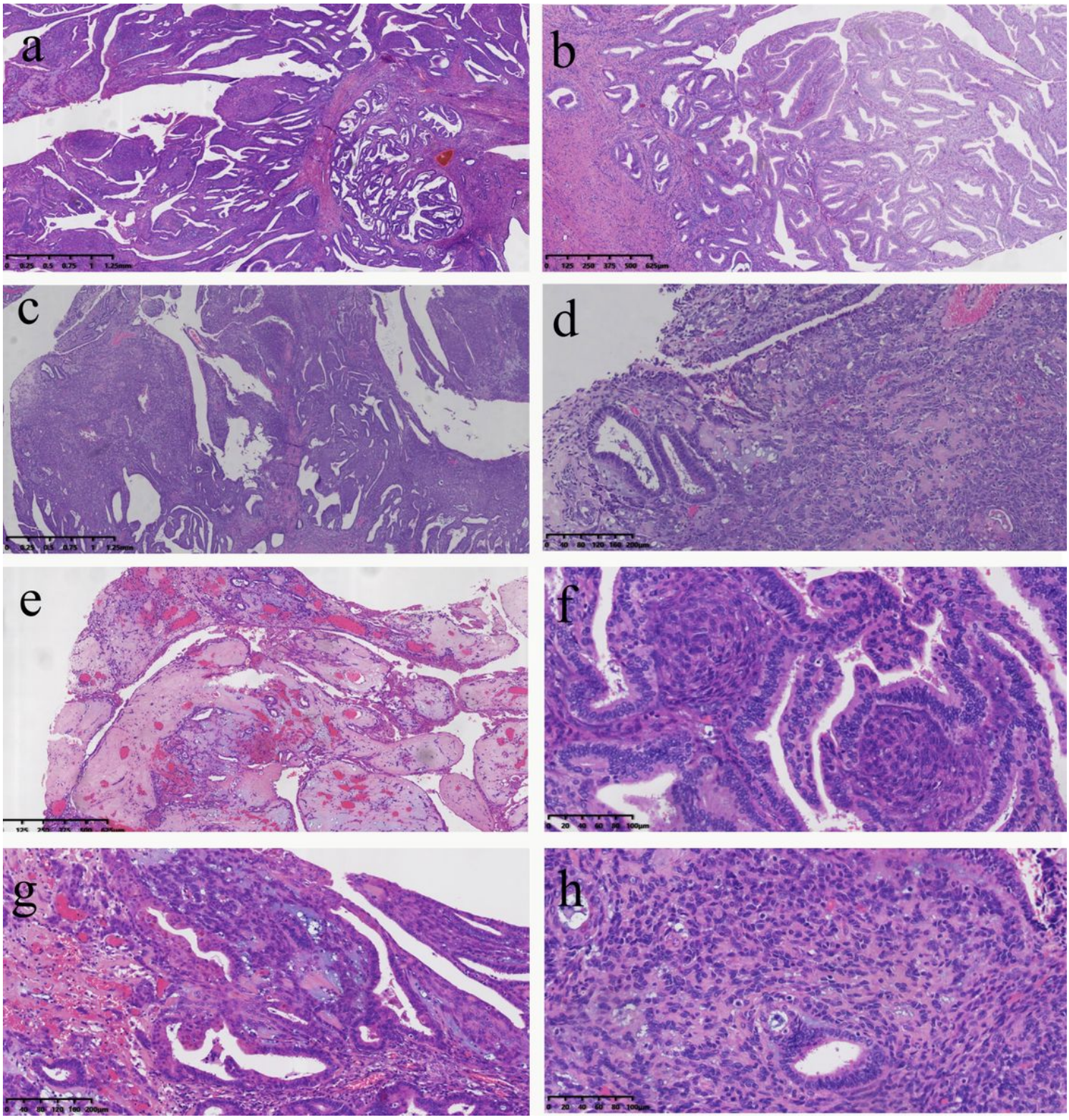

Figure 2

Histological findings of the tumor. a. Low-power magnification showed a biphasic pattern due to neoplastic endometrioid glands separated by a focally hyalinized stroma containing cords. Haematoxylin-eosin staining, 20x magnification. b. Typical endometrioid carcinoma (grade 1) in a background of endometrial hyperplasia. Haematoxylin-eosin staining, 40x magnification. c. The sex cord-like elements blended with the conventional endometrioid carcinoma. Haematoxylin-eosin staining, 20x

magnification. d. In the areas of sex cord-like elements, the epithelioid and spindle cells were around the glands, and mostly arranged in cords or trabeculaes. Haematoxylin-eosin staining, 100x magnification. e. In some areas, the epithelioid and spindle cells were embedded within a richly hyalinized collagenous or sometimes myxoid matrix, and the cells may formed small clusters or were individually disposed. Haematoxylin-eosin staining, 40x magnification. f. A hyalinized matrix was absent and the cells were arranged in solid sheets. Haematoxylin-eosin staining, 200x magnification. g. Squamous differentiation exhibiting keratinization was common. Haematoxylin-eosin staining, 100x magnification. h. The neoplastic cells display low-grade cytologic features. Haematoxylin-eosin staining, 200x magnification.

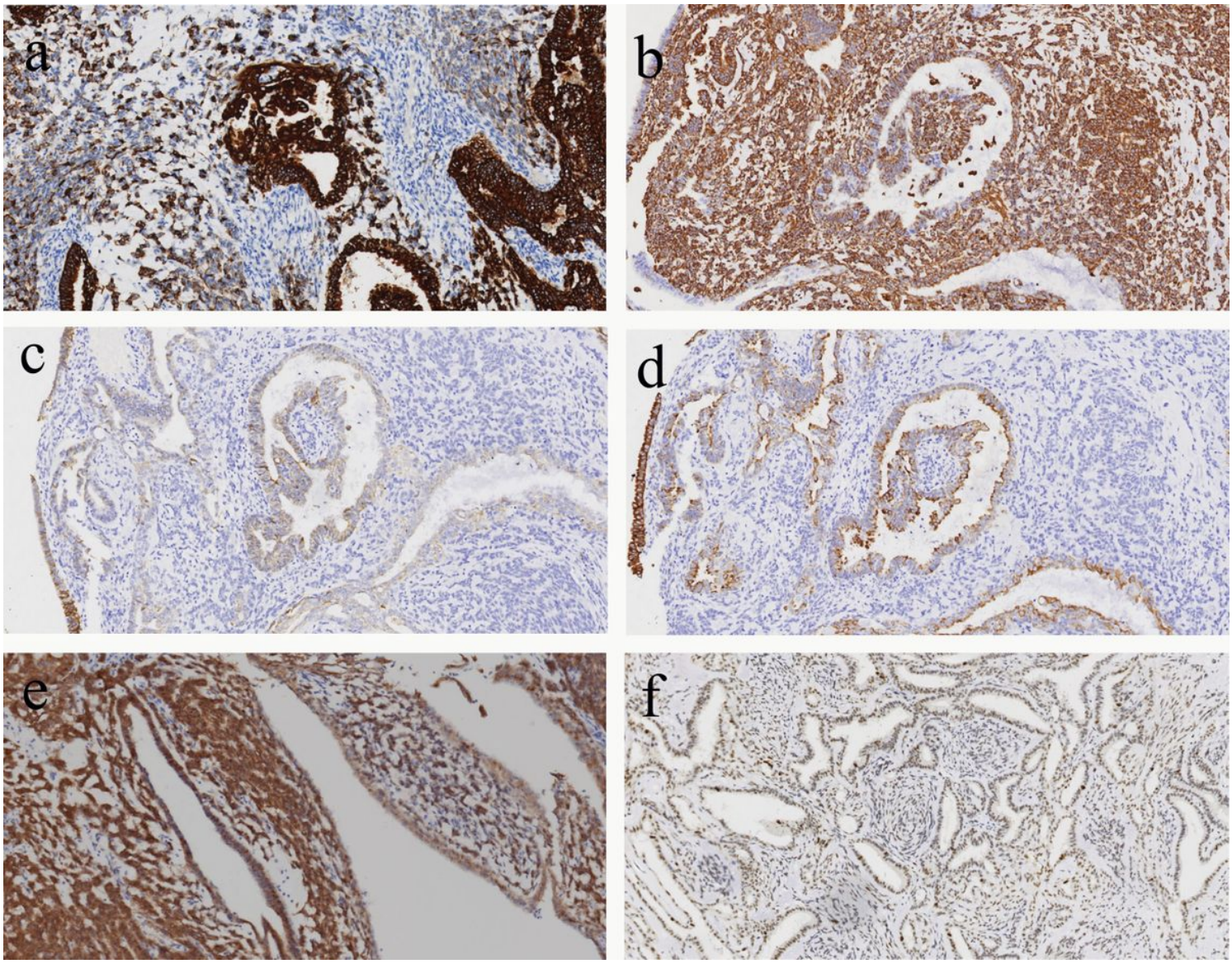

Figure 3

Immunohistochemical findings of the tumor. a. CK was diffusely positive in the typical endometrioid carcinoma component and was focally weakly positive in tumor cells in the sex cord-like region. b. Vimentin was focally positive in the typical endometrioid carcinoma component and was diffusely positive in tumor cells in the sex cord-like region. c. E-cadherin was diffusely positive in the typical endometrioid carcinoma component and was negative in tumor cells in the sex cord-like region. d. EMA

was diffusely positive in the typical endometrioid carcinoma component and was negative in tumor cells in the sex cord-like region. e. Nuclear expression of β-catenin was noted in tumor cells in the sex cord-like region. f. P53 was focally positive in both components.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklisnew.pdf