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Variants of in situ carcinoma of the endometrium: Clear cell and gastrointestinal types, with a review of the literature

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ABSTRACT

Two precursor lesions are commonly associated with endometrial carcinoma. Atypical endometrial hyperplasia/endometrial intraepithelial neoplasia is a known precursor lesion of endometrial endometrioid carcinoma, while endometrial intraepithelial carcinoma, is a recognized precursor lesion of endometrial high-grade serous carcinoma. Other than these two recognized entities, other rare precursor lesions for endometrial carcinoma do exist, although reported cases are relatively few and not universally recognized. This therefore poses diagnostic challenges in clinical practice. Here, we describe a series of rare precursor lesions of the endometrium identified at our institution, including clear cell and gastrointestinal variants, their morphologic and immunohistochemical characteristics, and review current literature regarding these variants. The information provided may guide the proper diagnosis and ultimately lead to effective clinical management in every-day practice.

1. Introduction:

Precursor lesions for the two most frequent types of endometrial cancers are commonly encountered in clinical practice. Atypical hyperplasia/Endometrial intraepithelial neoplasia (EIN), is a recognized precursor lesion of endometrial endometrioid carcinoma (EC) (Kurman et al., 1985). Additionally, endometrial intraepithelial carcinoma (EIC) is a known precursor lesion of high-grade endometrial serous carcinoma (SC) (Ambros et al., 1995).

Putative precursor lesions for endometrial clear cell carcinoma have been described (Fadare et al., 2006; Islam et al., 2020), however, reported cases are few and not currently standardized in the literature. Gastrointestinal differentiation in the female genitalia is most commonly described in the cervix, with only very few cases reported in the endometrium (Buell-Gutbrod et al., 2013; Hino et al., 2016; McCarthy et al., 2018). The reported cases showed mild to minimally aggressive histologic features, with one patient with follow-up data dying from disease within three years of diagnosis, due to deeply invasive tumors and positive regional lymph nodes (Hino et al., 2016). However, an in situ variant of endometrial gastrointestinal-type carcinoma has never been described in the literature.

Here, we present three cases with uncommon precursor lesions of the endometrium, two with endometrial intraepithelial clear cell adenocarcinoma and the third with endometrial adenocarcinoma in situ of gastrointestinal type. All these lesions were present in hysterectomy specimens from these patients. A discussion of the morphologic and immunohistochemical findings, the background of these lesions, and a summary of other cases in the literature will be reported. Our series will add to and expand the current literature about these uncommon, important precursor lesions in the endometrium.

2. Case Presentation:

Case 1.

The patient was a 61-year-old woman who presented with abnormal uterine bleeding. An endometrial biopsy was performed followed by a hysterectomy with bilateral salpingo-oophorectomy, and bilateral pelvic and *para*-aortic lymph node dissection.

Histopathologic findings:

The patient's preoperative endometrial biopsy showed invasive clear cell carcinoma. On hysterectomy, clear cell carcinoma in situ arising on the surface of an endometrial polyp was identified (Fig. 1A). Tufting, focal papillary architecture, nuclear atypia, and clear cytoplasm was evident (1B). A single small focus of invasive clear cell carcinoma with

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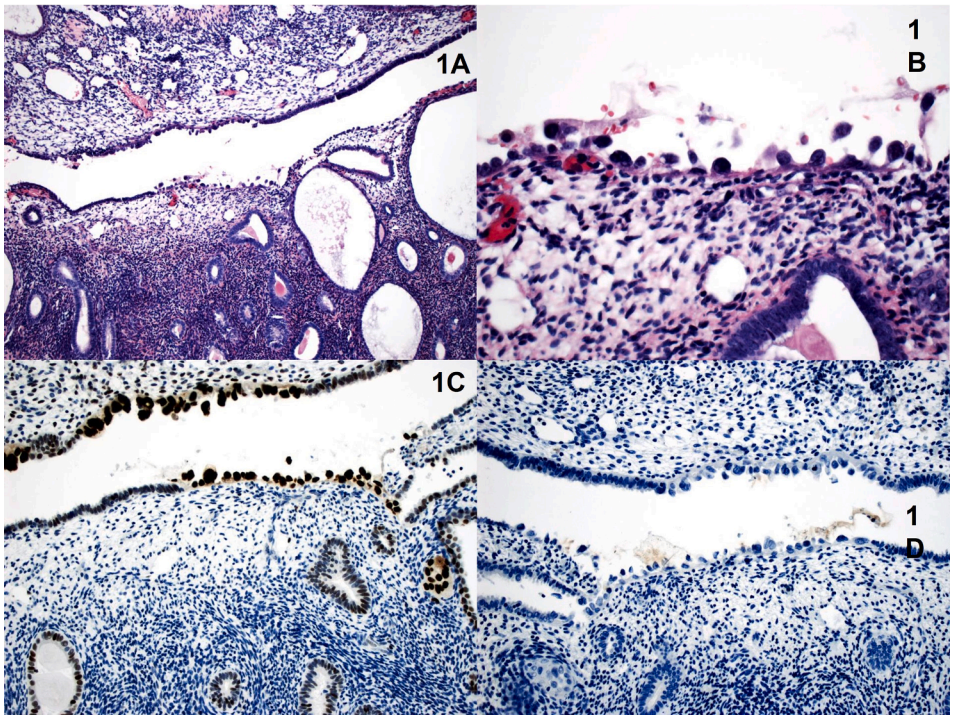

Fig. 1. Clear cell carcinoma in situ, arising on the surface of an endometrial polyp, also with underlying atrophic endometrium (1A). Tufting and focal papillary architecture are appreciated with nuclear atypia and clear cytoplasm (1B). p53 staining shows diffuse positivity (1C), No expression of Napsin-A (1D).

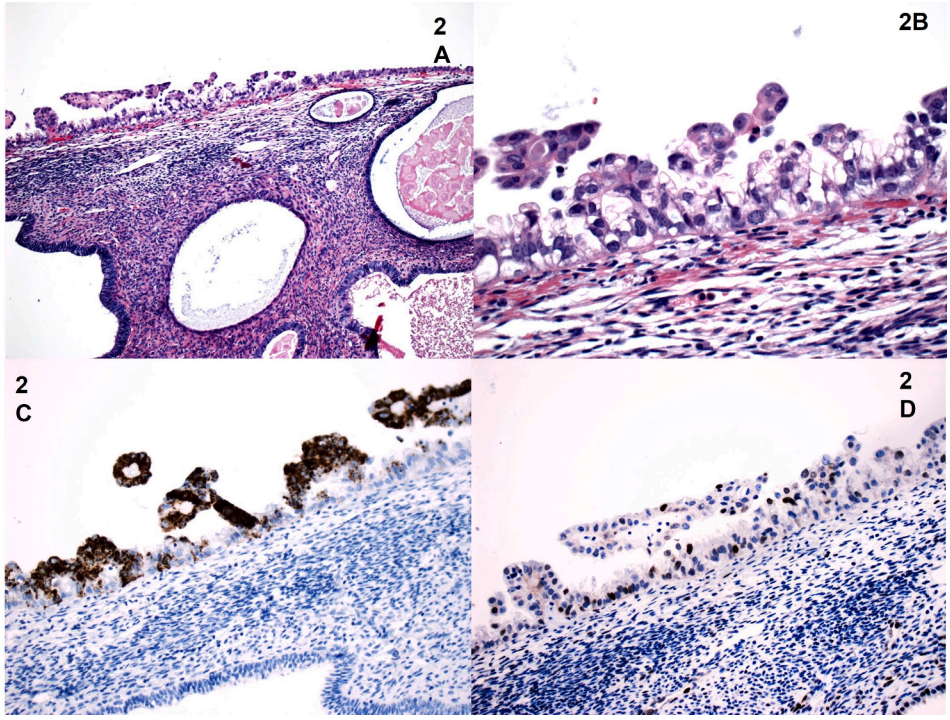

Fig. 2. Clear cell carcinoma in situ, arising on the surface of an endometrial polyp with underlying background atrophic endometrium (2A), showing marked nuclear pleomorphism and clear to eosinophilic cytoplasm (2B). Immunohistochemistry showed diffuse expression for p53 (2C) and Patchy expression of Napsin-A (2D).

the same cytologic features as the cells on the surface of the polyp was also identified. The underlying endometrium was atrophic. No other focus of invasive carcinoma was identified in the entirely submitted and embedded endometrium. By immunohistochemistry (IHC), p53 staining showed diffuse positivity (Fig. 1C), with patchy expression of Napsin-A (Fig. 1D). ki-67 was mildly elevated. The remainder of the endometrial tissue was benign. No follow-up on this patient was available.

Case 2.

The patient was a 69-year-old G2P2 woman who presented with abnormal uterine bleeding. An endometrial biopsy was performed followed by a hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic and *para*-aortic lymph node dissection.

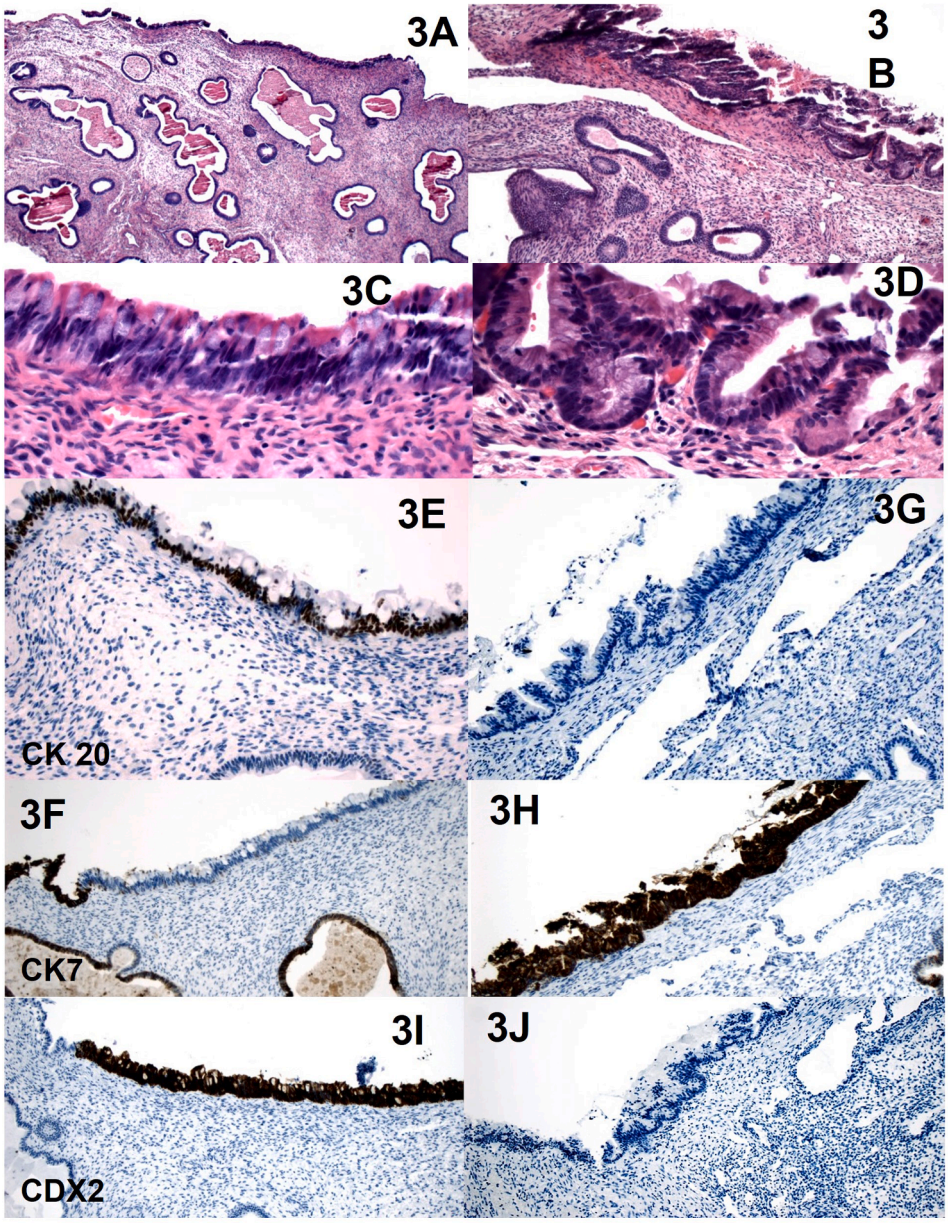

Fig. 3. Low-powered view shows carcinoma on the surface of an endometrial polyp, in two separate foci (3A) and (3B). Flat architecture is appreciated with overlapping, atypical nuclei showing goblet cell differentiation in the first area (3C), with tufting and glandular outlines noted with apical mucin and goblet cells in the second area (3D). Immunohistochemistry shows different findings in these two areas, with the first area showing diffuse expression of CK20 (3E), no expression of CK7 (3G), and positivity for CDX2 (I). The second area shows no staining for CK20 (3F), posiivity for CK7(3H), and lack of CDX2 staining (3J).

Histopathologic findings:

The endometrial biopsy specimen showed fragments of frankly invasive clear cell carcinoma. The hysterectomy specimen from this patient showed no residual invasive carcinoma. Instead, only clear cell carcinoma in situ arising on the surface of an endometrial polyp with underlying background atrophic endometrium (Fig. 2A), was identified. Cytologically, the cells showed marked nuclear pleomorphism with clear to eosinophilic cytoplasm (Fig. 2B). By IHC, the tumor cells showed diffuse expression for p53 (Fig. 2C) and no expression of Napsin-A (Fig. 2D). Nine years after hysterectomy, the patient is free of disease.

Case 3.

The patient was a 79-year-old woman who presented with post-menopausal bleeding. An endometrial biopsy was performed and subsequent hysterectomy with bilateral salpingo-oophorectomy was done.

Histopathologic findings:

The endometrial curettage specimen showed strips of adenocarcinoma with gastrointestinal differentiation. The differential diagnoses included metastatic disease versus carcinoma of the endocervix with gastrointestinal differentiation. Hysterectomy showed an endometrial polyp with non-atypical hyperplasia and adjacent adenocarcinoma in situ of the endometrial surface epithelium in 2 separate areas (Fig. 3A & B). A flat architecture with atypical overlapping nuclei and goblet cell differentiation was seen in the first focus (Fig. 3C), while glandular tufting with apical mucin and goblet cells was identified in the second focus (Fig. 3D). IHC showed different patterns of expression in both foci. The first focus was diffusely positive for CK20 (Fig. 3E), negative for CK7 (Fig. 3G), and showed reactivity with CDX2 (Fig. 3I). The second focus showed no immunoreactivity with CK20 (Fig. 3F), was positive for CK7 (Fig. 3H) and was negative for CDX2 (Fig. 3J). The remainder of the specimen was benign. No invasive carcinoma was identified in the entirely submitted endometrium. Extensive clinical and radiologic examinations revealed no evidence of cancer in any other parts of the body. No follow up data is available on this patient.

The Estrogen (ER) and progesterone receptors (PR) were negative in all three lesions.

3. Materials and Methods:

Tissue was fixed in 10 % buffered formalin and subjected to routine processing and paraffin embedding. Four micrometer sections of tissue were prepared and stained with hematoxylin and eosin. Immunohistochemical stains for Napsin-A (monoclonal; clone MRQ-60; Cell Marque, Rocklin, California), p53 (monoclonal; clone DO-7; Dako Corporation, Carpinteria, CA) were performed for Cases 1 and 2, while CK7 (monoclonal; OV-TL12/30; Dako Corporation, Carpinteria, CA), CK20 (monoclonal; clone Ks20.8; Dako Corporation, Carpinteria, CA), and CDX2 (monoclonal; clone DAK-CDX-2; Dako Corporation, Carpinteria, CA) were performed for case 3.

4. Pathologic Findings:

4.1. Discussion:

Precursor lesions for non-endometrioid carcinoma of the endometrium are less well described than their counterparts, due to their under-recognition and the fact that they are likely less common. The other possible explanation is that unlike in the breast where histologic subtypes and the percentages of in-situ lesions are considered in the management of patients with invasive carcinoma, the in-situ component of an endometrial carcinoma carries no additional treatment considerations. As a result, pathologists possibly underreport the presence of these entities.

Descriptions of precursor lesions of endometrial clear cell carcinoma (ECCC) are less robust, owing in large part to the relative rarity of ECCC when compared to other uterine carcinomas (Clement and Young, 2004; Islam et al., 2020). Two reports exist positing a precursor lesion for endometrial clear cell carcinoma like that of SEIC as noted in association with ESC. One utilizes the term "Endometrial Intraepithelial carcinoma, clear cell type," describing the lesion as markedly atypical glands overlying a basement membrane with clear cytoplasm, coarse chromatin, irregular nuclear membranes, and prominent nucleoli (Moid and Berezowski, 2004). Another coins the term "Clear cell Endometrial Intraepithelial carcinoma," a report which describes atrophic glands with large, atypical cells, large round to oval nuclei with size greater than three times that noted in adjacent, background endometrium, and clear cytoplasm (Ishida et al., 2014). Of note, in both of these reports, abnormal expression of p53 was noted by IHC, with "focal nuclear staining" (Moid and Berezowski, 2004) and diffuse staining noted (Ishida et al., 2014).

To further characterize the precursor lesions of ECCC, Fadare and colleagues examined 30 cases of endometrial carcinoma with pure or mixed components of ECCC. They then searched for "putative precursor lesions (PPL)", defined as single or small, clustered glands with clear or eosinophilic cytoplasm (Fadare et al., 2006). The nuclear features were graded on a three-point scale, with grade 3 nuclei being essentially equivalent to EIC, clear cell type, previously described. Overall, 27/30 cases had at least one PPL, with 18 grade 3 lesions being noted in all cases with PPLs. Higher p53 scores were noted in association with the grade 3 PPL, based on intensity, percentage, and heterogeneity of staining (Fadare et al., 2006).

Cases one and two in our series shows an in-situ lesion with marked nuclear atypia, prominent, eosinophilic nucleoli, clear to focally eosinophilic cytoplasm, and a single-file pattern which colonizes the surface of the patient's endometrium and focally involves the surface of an endometrial polyp. Case one additionally had a small focus of invasive clear cell carcinoma adjacent to the in-situ lesion also within the endometrial polyp. In case 2, the patient had undergone a prior biopsy which showed abundant clear cell carcinoma, which possibly supports our assertion as a possible precursor lesion. Important for diagnostic considerations are the mixed immunohistochemical findings, which can impact the ease of diagnosis of these lesions, especially in limited biopsy specimens. Findings from these 2 cases are in keeping with prior reports in the literature (Table 1A).

Table 1A
Cases with prior clear cell adenocarcinoma/ endometrial intraepithelial clear cell adenocarcinoma.

Paper	No. of Cases (N)	Findings	Ancillary studies
Fadare et al. (Fadare et al., 2006) [17122507]	30	27/30 cases of CCC or mixed carcinomas with > 10 % CCC showed "putative precursor lesions" in surrounding endometrium	Aberrant staining with p53 and ki-67, decreased ER ad PR staining compared to background endometrium
Moid et al. (Moid and Berezowski, 2004) [15504080]	1	Endometrial Intraepithelial Carcinoma, Clear Cell Type presenting in a hysterectomy specimen	Aberrant p53 staining with increased ki-67
Ishida et al. (Ishida et al., 2014) [24817975]	1	2 endometrial polyps with one case showing probable precursor lesion in surrounding endometrium	Diffuse p53 staining in precursor lesion, loss of ER and PR

Intestinal differentiation in endometrial epithelia is rarely found, with very few cases reported in the literature (Nieuwenhuizen et al., 2007; Boyd et al., 2010 Nicolae et al., 2011; Wong et al., 2020). Endometrial gastric (gastrointestinal)-type adenocarcinoma term has been proposed (Wong et al., 2020). Table 1B highlights reports with endometrial intestinal differentiation. In some cases, intestinal-type differentiation including presence of goblet cells was noted in otherwise conventional endometrioid adenocarcinoma (Buell-Gutbrod et al., 2013; Nieuwenhuizen et al., 2007). In one case, immunohistochemical analysis showed that the intestinal differentiated cells were positive for CDX2, CK7, and negative for CK20 (Buell-Gutbrod et al., 2013), while in other cases histochemical staining for PAS and Alcian Blue were performed to confirm the intestinal differentiation (Nieuwenhuizen et al., 2007). A separate type of intestinal differentiation toward gastric-type epithelium has also been described as a component of otherwise conventional endometrioid adenocarcinoma of the endometrium (Hino et al., 2016; McCarthy et al., 2018; Abiko et al., 2010). Some of these patients presented with advanced stage disease and had an aggressive clinical course (Buell-Gutbrod et al., 2013), while others failed to support this finding (Hino et al., 2016). In contrast to these cases, the third patient in our series only had an in situ gastrointestinal carcinoma with no other areas of invasive disease identified after examination of the hysterectomy specimen. We therefore hypothesize that our findings of her in situ disease which was detected early might have been a harbinger to an invasive carcinoma along the carcinomatous sequence later. However, being that our finding of an in situ endometrial gastrointestinal carcinoma is the first to be reported in literature, further research is needed to validate our findings. It is important to rule out a metastatic gastrointestinal tumor in the endometrium when such a scenario is encountered, which was however not identified in our index case.

Studying the underlying molecular changes would help understand the pathogenesis of this lesion. However, clinical management may not necessarily change. These lesions are incidental and, when found, should prompt the pathologist to examine the entire endometrium to rule out any grossly invisible invasive lesion.

In situ lesions of the endometrium can pose diagnostic challenges, especially when interpreted in limited specimens. However, the clinical implications can be myriad. It is important to account for less common lesions when evaluating patients, including clear cell lesions and those with gastrointestinal differentiation, as described above.

Informed consent and patient details.

This is an academic institution and all patients receiving medical care here sign a consent form agreeing that their material can be used for educational purposes without using any unique identifiers.

Table 1B
Cases with prior gastrointestinal metaplasia in situ and invasive carcinoma.

Paper	No. of Cases (N)	Findings	Ancillary studies
Buell-Gutbrod et al. (Buell-Gutbrod et al., 2013) [23915109]	1	Figo grade 1 endometrioid adenocarcinoma with endocervical and intestinal-type metaplasia	IHC: CK7, CDX2, and CEA positive, negative for CK20, Synaptophysin and chromogranin
Hino et al. (Hino et al., 2016) [27123265]	1	Mucinous carcinoma of the endometrium with features of adenoma malignum and gastric metaplasia	HIK1083 and/or MUC6 IHC positive
McCarthy et al. (McCarthy et al., 2018) [29281925]	2	Two cases of endometrial carcinoma with focal gastric differentiation	Case 1: IHC: MUC6, vimentin, and PR +, CEA and p16 – Case 2: IHC: MUC6+, Loss of MLH1 and PMS2
Nieuwenhuizen et al. (Nieuwenhuizen et al., 2007) [22593653]	2	Goblet cell metaplasia noted in 2 moderately differentiated endometrioid adenocarcinoma.	PAS and alcian blue special stains positive in metaplastic cells
Boyd et al. (Boyd et al., 2010) [20881852]	2	Endometrial cases with signet ring cell differentiation	Case 1: IHC positive for Ber-EP4, CK7, CA125, ER, CEA (focal), and negative for CDX2 Case 2: IHC positive AE1/3, CK7, ER, and negative for GCDFP15, CK20
Nicolae et al. (Nicolae et al., 2011) [21804398]	2	Intestinal metaplasia noted in endometrium in two patients, including an endometrial polyp.	Cells positive with CK20, CDX2, chromogranin, and villin by IHC
Wong et al. (Wong et al., 2020) [33170811]	9	Four adenocarcinoma and five benign lesions. Four adenocarcinoma showed gastric morphology and one goblet cells	Positive IHC: CK 7 (4/4), CEA (4/4), MUC6 (3/3), PAX8 (3/4), CK20 2/4), CDX2 (2/4), ER 1/4. p53 mutation (2/4), Napsin A (0/3), Block positive p16 (1/4). RB1 nonsense mutation in p16 block positive case. Aggressive behavior. Two patient dies of disease.
Abiko et al. (Abiko et al., 2010) [20055951]	1	Mucinous carcinoma of the endometrium with features of adenoma malignum and gastric metaplasia	HIK1083 and MUC6 IHC positive

CCC = Clear cell carcinoma; ER = Estrogen Receptor; PR = Progesterone Receptor; IHC = immunohistochemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abiko, K., Baba, T., Ogawa, M., Mikami, Y., Koyama, T., Mandai, M., Konishi, I., 2010. Minimal deviation mucinous adenocarcinoma ('adenoma malignum') of the uterine corpus. Pathol. Int. 60 (1), 42–47. https://doi.org/10.1111/j.1440-1827.2009.02473.x. PMID: 20055951.

Ambros, R.A., Sherman, M.E., Zahn, C.M., Bitterman, P., Kurman, R.J., 1995. Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. Hum. Pathol. 26, 1260–1267. https://doi.org/10.1016/0046-8177(95)90203-1. PMID: 7590702.

Boyd, C., Cameron, I., McCluggage, W.G., 2010. Endometrial adenocarcinoma with signet ring cells: report of two cases of an extremely rare phenomenon. Int. J. Gynecol. Pathol. 29 (6), 579–582. https://doi.org/10.1097/PGP.0b013e3181e20c66. PMID: 20881852.

Buell-Gutbrod, R., Sung, C.J., Lawrence, W.D., Quddus, M.R., 2013. Endometrioid adenocarcinoma with simultaneous endocervical and intestinal-type mucinous differentiation: report of a rare phenomenon and the immunohistochemical profile. Diagn. Pathol. 2;8:128, doi: 10.1186/1746-1596-8-128. PMID: 23915109; PMCID: PMC3849525.

Clement, P.B., Young, R.H., 2004. Non-endometrioid carcinomas of the uterine corpus: a review of their pathology with emphasis on recent advances and problematic aspects. Adv. Anat. Pathol. 11 (3), 117–142. https://doi.org/10.1097/00125480-200405000-00001. PMID: 15096727.

Fadare, O., Liang, S.X., Ulukus, E.C., Chambers, S.K., Zheng, W., 2006. Precursors of endometrial clear cell carcinoma. Am. J. Surg. Pathol. 30, 1519–1530. https://doi.org/10.1097/01.pas.0000213296. 88778.db. PMID: 17122507.

Hino, M., Yamaguchi, K., Abiko, K., Yoshioka, Y., Hamanishi, J., Kondoh, E., Koshiyama, M., Baba, T., Matsumura, N., Minamiguchi, S., Kido, A., Konishi, I., 2016. Magnetic resonance imaging findings and prognosis of gastric-type mucinous adenocarcinoma (minimal deviation adenocarcinoma or adenoma malignum) of the uterine corpus: Two case reports. Mol. Clin. Oncol. 4 (5), 699–704. doi: 10.3892/mco.2016.789. Epub 2016 Feb 23. PMID: 27123265; PMCID: PMC4840738.

Ishida, M., Iwai, M., Yoshida, K., Kagotani, A., Okabe, H., 2014. Clear cell adenocarcinoma present exclusively within endometrial polyp: report of two cases. Int. J. Clin. Exp. Pathol. 7 (4), 1757–1763. PMID: 24817975; PMCID: PMC4014259.

Islam, K.M.S., Lawrence, W.D., Quddus, M.R., 2020. Clear cell endometrial carcinoma in situ (CCEIC) exists. Int. J. Surg. Pathol. 28 (3), 290–291.

Kurman, R.J., Kaminski, P.F., Norris, H.J., 1985. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer 15 (56), 403–412. https://doi.org/10.1002/1097-0142(19850715)56:2<403::aid-cncr2820560233>3.0.co;2-x. PMID: 4005805.

McCarthy, W.A., Makhijani, R., Miller, K., Rojas, K., Beffa, L., Mathews, C., Robison, K., Quddus, M.R., 2018. Gastric-type endometrial adenocarcinoma: report of two cases in patients from the United States. Int J Surg Pathol. 26 (4), 377–381. https://doi.org/10.1177/1066896917743010. Epub 2017 Dec 27 PMID: 29281925.

Moid, F., Berezowski, K., 2004. Pathologic quiz case: a 70-year-old woman with postmenopausal bleeding. Endometrial intraepithelial carcinoma, clear cell type. Arch. Pathol. Lab. Med. 128 (11), e157–e158. https://doi.org/10.5858/2004-128-e157-PQCAYW. PMID: 15504080.

Nicolae, A., Goyenaga, P., McCluggage, W.G., Preda, O., Nogales, F.F., 2011. Endometrial intestinal metaplasia: a report of two cases, including one associated with cervical intestinal and pyloric metaplasia. Int. J. Gynecol. Pathol. 30 (5), 492–496. https://doi.org/10.1097/PGP.0b013e318211d586. PMID: 21804398.

Nieuwenhuizen, L., Khalil, M.K., Naik, V.R., Othman, N.H., 2007. Prevalence of goblet cell metaplasia in endocervical and endometrial adenocarcinoma: a histochemical study. Malays. J. Med. Sci. 14 (1), 56–61. PMID: 22593653; PMCID: PMC3351219.

Wong, R.-W.-C., Ralte, A., Gordin, K., Talia, K.L., McCluggage, W.G., 2020. Endometrial gastric (gastrointestinal)-type mucinous lesions. Report of a series illustrating the spectrum of benign and malignant lesions. Am. J. Surg. Pathol. 44, 1736–1737. https://doi.org/10.1097/PAS.0000000000001473. PMID: 33170811.