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Case report

# Low-grade endometrial endometrioid carcinoma of the p53-abnormal group: case presentation and diagnostic issues

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**Summary**

P53-abnormal endometrial carcinomas are high-grade and aggressive tumors which should be treated with chemo-/radiotherapy. In low-grade endometrioid carcinoma (LGEC), abnormal expression of p53 is an exceptional finding and is typically accompanied by patchy p16 positivity and diffuse hormone receptor expression.

Herein, we report a case of LGEC exhibiting both p53 and p16 overexpression, highlighting the diagnostic pitfalls related to such phenotype.

A 60-year-old woman underwent hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy due to a deeply myoinvasive endometrial mass. The tumor showed glandular architecture, low-grade nuclei and glandular differentiation. Focal lymphovascular space invasion and no lymph node metastases were observed. Immunohistochemically, the tumor showed p53 overexpression, p16 block-type positivity, diffuse hormone receptors positivity and retained mismatch repair proteins expression. No *POLE* mutations were identified. A diagnosis of p53-abnormal LGEC was eventually made.

A glandular neoplasm with p53 and/or p16-overexpression on endometrial biopsy specimens may raise the concern of other entities such as serous carcinoma, HPV-related endocervical adenocarcinoma, and gastric-type adenocarcinoma. An immunohistochemical panel including hormone receptors, p53, p16 and mismatch repair proteins appears necessary for an accurate diagnosis of uterine adenocarcinomas.

**Key words:** endometrioid, low-grade, p53, p16, TCGA

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## Introduction

The integration of molecular data into both the European guidelines and the 2023 FIGO staging has revolutionized the approach to endometrial carcinoma. In particular, the management has crucially changed for tumors exhibiting a *POLE*-mutant or p53-abnormal phenotypes [1-3].

In fact, *POLE*-mutant endometrial carcinomas limited to the uterus are now managed by follow-up alone with no adjuvant therapy, even in the case of high-grade, non-endometrioid type, cervical stromal invasion and/or lymphovascular space invasion. On the other hand, p53-abnormal carcinomas require chemo-/radiotherapy even in the case of superficial myometrial invasion, endometrioid-type and no lymphovascular space invasion [1,2].

As p53-abnormal carcinomas are almost exclusively of high-grade, issues have been raised regarding the management of low-grade endometrioid carcinomas (LGEC) with a p53-abnormal pattern. In fact, the latter ones are considered to be extremely rare, and some pathologists consider a p53-abnormal pattern inconsistent with a low-grade morphology. Some authors have suggested that treating LGEC on the basis of a p53-abnormal pattern would be an overtreatment, while other authors reported that LGECs tend to have a favorable prognosis regardless of the molecular subtype [4-7].

A recent study by Jamieson et al. presented the first series of LGEC exhibiting a p53-abnormal expression pattern. The authors identified 26 cases of p53-abnormal LGEC, in most of which there was disagreement among pathologists regarding diagnosis. The authors found that these cases were characterized by hormone receptors positivity, patchy p16 expression and a substantial risk of recurrence, supporting universal p53-testing in endometrial carcinoma [8].

Herein, we present a case of unequivocal LGEC showing a p53-abnormal pattern accompanied by a strong and diffuse (block-type) p16-expression. We then discuss the diagnostic issues related to this case.

## Case presentation

A 60-year-old woman underwent hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy due to a 2.5 cm endometrial mass. The mass had been diagnosed as LGEC with p53-abnormal expression on the hysteroscopic biopsy specimen. On the hysterectomy specimen, the tumor

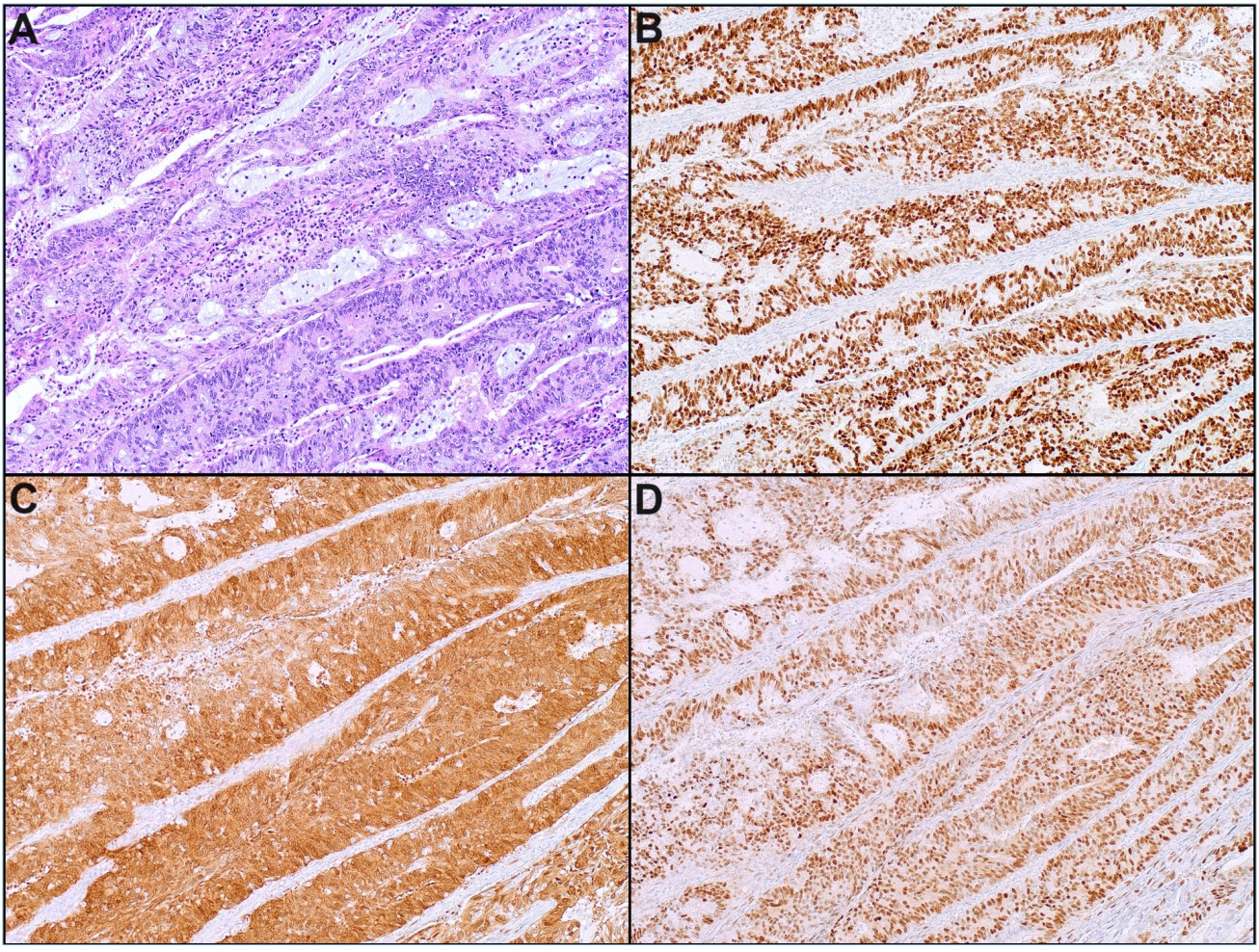


**Figure.** Histological and immunohistochemical features of the case. A) Glandular architecture with columnar cells and smooth luminal surface, mucinous differentiation, ovoidal pseudostratified nuclei with low-grade atypia, and low mitotic index, consistent with low-grade endometrioid carcinoma. B) p53 abnormal expression (strong expression in ≥80% of cells, consistent with *TP53* mutation). C) p16 strong and diffuse (block-type) expression. D) Strong and diffuse positivity for estrogen receptor.

showed glandular architecture with smooth luminal surface and mucinous differentiation. The tumor cells were columnar, with ovoidal pseudostratified nuclei mostly located in the basal half of the cells. No striking nuclear pleomorphism was observed, and the mitotic index was relatively low (1-5 mitotic figures/10HPF) (Fig. 1A). Solid areas with the same cytological features occupied about 10% of the tumoral area, yielding a G2 FIGO grade. The tumor infiltrated almost 90% of the myometrial thickness, with focal lymphovascular space invasion. No lymph node metastases were found.

Immunohistochemical analysis showed p53 overexpression (mutation-type pattern) and strong and diffuse (block-type) p16 expression (Fig. 1B-C). Estrogen and progesterone receptors were strongly and diffusely expressed (Fig. 1D). Mismatch repair (MMR) proteins expression was retained. Next-generation sequencing analysis showed absence of *POLE* mutations.

Based on these findings, the final diagnosis was p53-abnormal LGEC. We also reviewed the biopsy specimen, which showed the same features.

## Discussion

The current case and similar ones might represent a diagnostic pitfall, especially when found on endometrial hysteroscopic biopsy or dilation and curettage specimens. In fact, many pathology laboratories do not routinely perform the full characterization of endometrial tumors, including estrogen and progesterone receptors, p53 and MMR proteins, on preoperative specimens. The first pitfall might be to consider the tumor as a usual LGEC without performing p53 immunohistochemistry. This might impact the surgical procedure, as patients with high-risk tumors (as p53-abnormal carcinomas are) should undergo lymphadenectomy and omentectomy [1].

Another pitfall might be to misdiagnose the tumor as a serous carcinoma based on the coexistence of p53-abnormal expression and p16 block-type expression. In fact, these two markers have long since been used to differentiate between endometrioid and serous carcinoma [9,10]. Compared to LGEC, serous carcinoma usually shows a scalloped profile of tumor glands, striking pleomorphism, high mitotic index, loss of nuclear polarization and a "syncytial" appearance of tumor cells with no evident cell borders [3,9,10]. In some cases, these features can be attenuated, e.g. in the so-called "SET" (solid, endometrioid and transitional) pattern found in serous carcinomas harboring homologous recombination defects. These cases are more common in the tubo-ovarian setting and are typically accompanied by more conventional high-grade serous areas [9,11]. While LGEC diffusely exhibits ER and PR, serous carcinoma typically shows ER positivity associated with a negative or weak/focal PR positivity. Moreover, mucinous and squamous differentiations are common in LGEC, while they are exceptional in serous carcinoma [9,10].

The glandular architecture with a diffuse p16 expression might raise the concern of a HPV-related endocervical adenocarcinoma, which can also show mucinous differentiation. In fact, p16 is usually adopted in the differential diagnosis between LGEC and endocervical adenocarcinoma, as it shows a patchy expression in the former and a block-type expression in the latter. In our case, the diffuse hormone receptors expression would be against an endocervical adenocarcinoma, as the latter is typically negative for ER. Moreover, endocervical adenocarcinoma typically is p53-wild-type [9].

Another uncommon tumor which might be considered in the differential diagnosis is gastric-type adenocarcinoma (either endometrial or endocervical). In fact, gastric-type adenocarcinoma exhibits a glandular mucinous pattern and is commonly p53-abnormal; p16 is more often patchy, but it can be diffusely positive as well. Also in this case, the diffuse expression of ER and PR would exclude a gastric-type adenocarcinoma [3,9,12].

With regard to MMR proteins, they were retained in our case. However, MMR-deficiency may lead to a subsequent *TP53* mutation and p53-abnormal pattern. The presence of MMR-deficiency would support a diagnosis of LGEC against serous carcinoma, HPV-related endocervical adenocarcinoma or gastric-type adenocarcinoma [3,7,9,12].

In conclusion, p53-abnormal LGEC may show block-type p16 expression and represent a diagnostic pitfall due to partial overlap with other entities. We advocate the use of a full panel (including p53 and p16 but also ER, PR and MMR) in the diagnosis of uterine carcinomas with glandular architecture. Further studies are necessary in this field.

### Conflict of interest statement

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.

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### Ethical consideration

Our study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1975, revised in 2013). Ethical approval was not relevant to our paper, moreover the non-interventional, retrospective nature of our study did not require informed consent; however a written informed consent was obtained obtained from patient before surgical procedures. Patient' medical records and pathology reports were utilized to obtain clinical data. Patient' initials or other personal identifiers were not shown in images. All samples were anonymized and no further ethical approval was necessary to perform this retrospective study.

### Authors contribution

AT, SLR, GFZ, AS: study design; SR, EDL, CF, AR, CF: acquisition of pathological data. AT: writing of the manuscript. JC, CFu: acquisition of clinical data and surgical procedures. AT, SLR: performed the histological examination and revised the paper critically for important intellectual content. SLR, DA, GA: critical review of the manuscript. All authors have read and approved the manuscript.

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