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Case Report

# Papillary Endometrioid Carcinoma of Intermediate Grade with Infiltration in a Leiomyoma

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## Abstract

In endometrioid cancer cases, the depth of myometrial invasion, the lymphovascular space invasion (LVSI) and the microcystic, elongated, and fragmented (MELF) glands type of invasion are predictors for a metastasis. Although the intermediate grade papillary endometrioid adenocarcinoma of the endometrium is currently not included in the latest classification of the tumors in the female reproductive system, its existence provokes an interest due to the necessity to perform differential diagnosis against other endometrioid tumors. Hereby presented is a case of papillary endometrioid carcinoma of intermediate grade with invasion in leiomyoma, expressed via LVSI and MELF syndrome with intact myometrium. Morphological and immunohistochemical algorithms have been performed.

## Keywords

carcinoma, immunohistochemical, leiomyoma, uterus

## INTRODUCTION

Endometrial cancer is the most common gynecological disease in Europe and South America.[1] Endometrioid endometrial adenocarcinoma (EEA) has a favourable outlook. The total survival rate for 5 years is 93-94% for first and second grade tumors, according to International Federation of Gynecology and Obstetrics (FIGO).[2] Apart from the depth of the myometrical invasion, other invasion patterns pointing to a possible metastatic engagement of the lymph nodes and organs[3,4] have been proposed as prognosis factors for ectopics spread of the tumor. The microcystic, elongated and fragmented type is an example of myometrial invasion, characterized by an uncommon change in the neoplastic glands, described by Murray et al.[5] At first, it is presumed that this is a simple degenerative process, but with the identification of MELF invasion with highly differentiated carcinomas of the endometrioid type, those same changes begin to be regarded as an active cellular process and specific tumor - stromal interaction.[6] The papillary endometrioid carcinoma of intermediate grade is a rare challenge, despite its exclusion from the classification of tumors in the female reproductive system. It is often expressed with LVSI and MELF.

## CASE REPORT

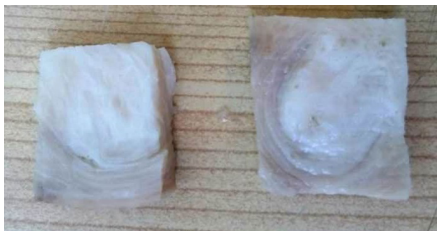
*A 56-year-old female with a 10-month history of light vaginal bleeding. Gynecological status: her cervix had an atrophic*

*porcio, no changes in the uterine body. Ultrasound transvaginal test: uterine body with intramural leiomyoma measuring 3 cm in diameter. Paraclinical tests: blood smear and biochemistry were within normal limits. Histological results from the sample abrasio: moderately differentiated papillary endometrioid adenocarcinoma of the endometrium. Lack of entailing diseases.*

*The next treatment was a total hysterectomy, salpingo-oophorectomy with a dissection of the pelvic lymph nodes and part of the omentum. No postsurgical complications were registered. The patient was referred to the oncological center for further treatment and monitoring.*

*Macroscopically: Cervix with a whitish porcio. The uterus* ***(Fig. 1)*** *- 7/5/5cm. Grey-whitish tumor formation in the uterine cavity infiltrated up to ½ of the myometrium. Intramural leiomyoma in the uterine fundus measuring 3 cm in diameter. The uterine tubes and ovaries were atrophic. There were five lymph nodes: three on the right 4×2 mm, 3×2 mm and 2×2.5 mm, and two on the left, 4×2 mm each.*

1a

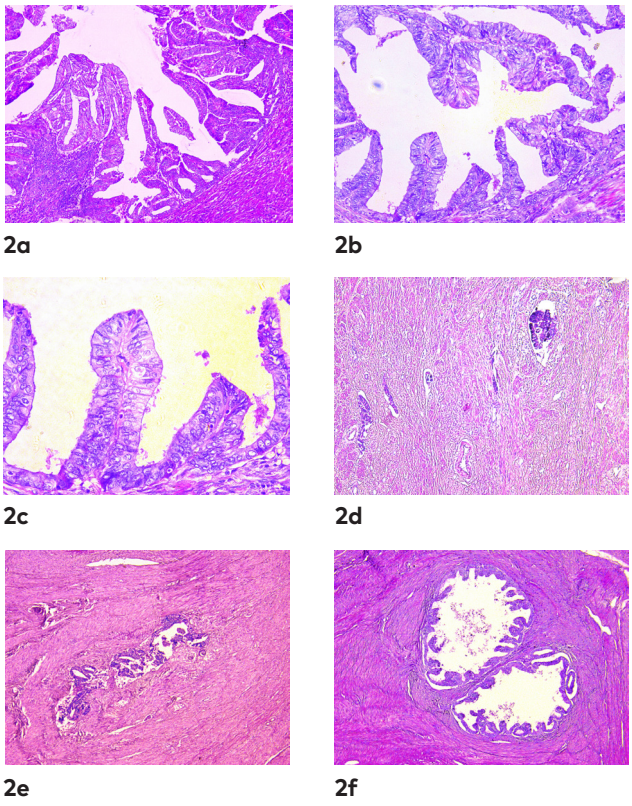


1b

**Figure 1.** General appearance of tumors in the uterine body (yellow arrow - papillary endometrioid carcinoma of intermediate grade, red arrows - leiomyoma): **a.** Uterine body with a tumor in the uterine cavity and intramural leiomyoma; **b.** Cut surfaces of leiomyoma.

*Histology (H&E)****(Fig. 2)****: Cervix – atrophic exocervical epithelium, subepithelial round cell inflammatory infiltration. Uterine body: endometrium – papillae and irregular glands with papillary expansions in parts of their lumens. The papillae had an uneven surface at several places, they were lined by cylindrical cells with vesicular nuclei, which were distributed in several rows at certain places, moderate cytological atypicality. Some of the cells had mucinous metaplasia and sporadic mitosis. The solid tumor areas were below 5%. Tumor infiltrates up to ½ of the myometrium. Myometrium – typical leiomyoma containing the remains of torn tumor glands and tumor cell emboli in the lymphatic vessels. LVSI and MELF are not present in the myometrium.*

*The fallopian tubes had fibrosis. The ovaries were with white bodies. Five lymph nodes with sinus histiocytosis.*



2a 2b 2c 2d 2e 2f

**Figure 2.** Histology (H&E): **a.** Papillary endometrioid carcinoma of intermediate grade (magnification ×100); **b.** Papillary endometrioid carcinoma of intermediate grade (magnification ×200); **c.** Papillary endometrioid carcinoma of intermediate grade (magnification ×400); **d.** infiltration in leiomyoma by papillary endometrioid carcinoma of intermediate grade with MELF and LVSI (enlargement ×100); **e.** infiltration into leiomyoma by Papillary endometrioid carcinoma of intermediate grade with MELF and LVSI (magnification ×50); **f.** infiltration into leiomyoma by papillary endometrioid carcinoma of intermediate grade with MELF (magnification ×50).

*Immunohistochemistry (Dako, Glostrup, Denmark)* ***(Fig. 3)****: Over 75% of the tumor nuclei were positive for ER in the tumor, and the tumor outbreak in the leiomyoma had a 50% nucleus signs for ER. The nucleus marker for p53 was extremely weak in the tumor and the tumor outbreak areas of the leiomyoma.*

*Diagnosis: Papillary endometrioid carcinoma of intermediate grade. Typical leiomyoma with tumor infiltration type LVSI and MELF.*

## DISCUSSION

Papillary endometrioid carcinoma of intermediate grade (Grade II) is not listed in the 2014 classification of WHO, for the tumors in the female reproductive system. However, more and more authors mention this variation of Endometrioid endometrial adenocarcinoma.[7] Presence of papillary structures with or without fibrovascular bundle, cells with moderate cytological atypia, papillae with



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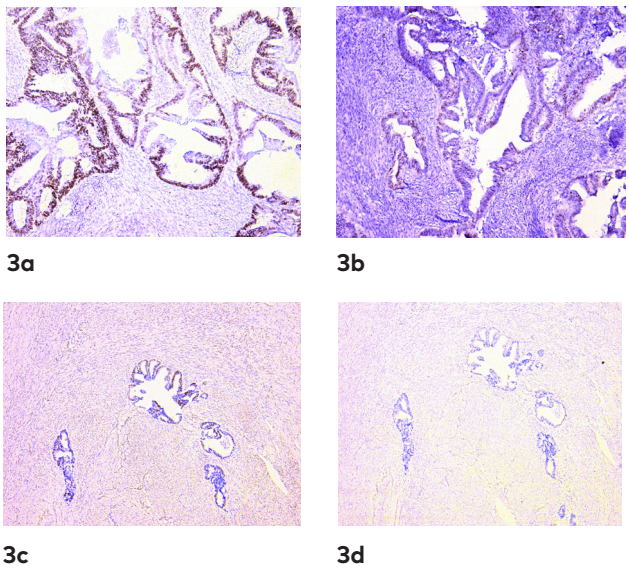

3a 3b

3c 3d

**Figure 3:** Immunohistochemistry: **a.** Papillary endometrioid carcinoma of intermediate grade, strong nuclear signal for ER (magnification ×100); **b.** Papillary endometrioid carcinoma of intermediate grade, weak nuclear signal for p53 (magnification ×100); **c.** Papillary endometrioid carcinoma of intermediate grade in collision with leiomyoma, a moderate nuclear signal for ER in papillary endometrioid carcinoma of intermediate grade (magnification ×100); **d.** Papillary endometrioid carcinoma of intermediate grade in collision with leiomyoma, very weak nuclear signal for p53 in papillary endometrioid carcinoma of intermediate grade (magnification ×50).

a smooth or slightly disturbed surface, at times mucinous metaplasia is a histological sign for papillary endometrioid carcinoma of intermediate grade. Insufficient awareness of its histological characteristics can lead to an error with a serous carcinoma of the endometrium, villoglandular and mucinous endometrial carcinoma. This similarity requires its full understanding and suggests performing a differential diagnosis with other types of endometrial carcinoma.[7] Papillary endometrioid carcinoma of intermediate grade is often connected with a MELF model of myometrium invasion, characterized with edgy and/or fragmented glands, occasionally also with a missing epithelium and areas of inflammatory cellular aggregations. In some cases sporadic small cell clusters with eosinophilic and vacuolated cytoplasm – resembling histiocytes can be spotted in a fibromyxoid stroma or in areas of inflammation and often go unnoticed. The biological significance of MELF is still under discussion. There has been researching associating it with LVSI, but with more benign outcomes for the patient.[5] Other authors state a resemblance between MELF and LVSI with metastasis in the lymph nodes.[3,4] In the case of papillary endometrioid carcinoma of intermediate grade described herein, apart from LVSI and MELF[7] there is also the rare occurrence of a collision between two tumors - papillary endometrioid carcinoma of intermediate grade and leiomyoma; with MELF and LVSI being present only in the leiomyoma. A number of series of examinations performed on the lymph nodes showed no tumor cells at a subcapsular level.

Differential diagnosis was performed between papillary endometrioid carcinoma of intermediate grade and serous carcinoma of the endometrium – due to their relative resemblance and a combination of papillary endometrioid carcinoma of intermediate grade with MELF and LVSI. Clinically intermediate grade papillary endometrioid adenocarcinoma of the endometrium can occur before or after menopause, whereas serous carcinoma of the endometrium tends to emerge in patients in menopause.[8] This papillary endometrioid carcinoma of intermediate grade exhibits moderate cytological atypia, not too intense mitotic activity and lack of numerous apoptotic bodies. In the cases of Serous carcinoma of the endometrium there is clear cytological atypia, clearly outlined fibrous bundle in the vessels, numerous mitotic figures, and apoptosis. Sometimes serous carcinoma of the endometrium can occur with a lack of marked cytological atypia, but the increased ratio between the nucleus and cytoplasm is always easy to spot. The serous carcinoma of the endometrium lacks a MELF model and mucinous metaplasia.[7] Immunohistochemically prudent measures for differentiation between papillary endometrioid carcinoma of intermediate grade and serous carcinoma of the endometrium are p53, p16, ER, PgR and Ki-67. Two markers were used p53 and ER. The wild type expression of p53 (namely the colouring of p53 in the scattered tumor cell nuclei) is typical for the papillary endometrioid carcinoma of intermediate grade, whereas serous carcinoma of the endometrium is characterized by abnormal p53 (meaning: 75% of the tumor nuclei show extremely positive for complete lack of colouring, zero response).[7,9] The papillary endometrioid carcinoma of intermediate grade with a model of MELF invasion is of interest because it can be connected with the concept for epithelial-mesenchymal transition, since they are prone to show bigger expression of cytokeratin 7 and 19, cyclin D1, p16 and a reduced expression of ER and PR, CD147, Ki-67 and beta-catenin compared to the usual type of endometrioid endometrial adenocarcinoma.[10] In the case we presented there was a lower nucleus expression of ER in the tumour areas in the leiomyoma as opposed to the intense nuclear expression in the tumor. There were no changes observed in the expression of p53 in the tumor and tumor areas in the leiomyoma.

Differentiation between papillary endometrioid carcinoma of intermediate grade and the villoglandular variant of endometrioid adenocarcinoma.

In the case of villoglandular variant of endometrioid adenocarcinoma, the papillae are gentler with finer surface and a smooth fibro-vascular bundle. The nuclei are elongated with preserved polarity, low cytological atypia; there are no signs of mucinous metaplasia.[7]

Differentiation between papillary endometrioid carcinoma of intermediate grade and mucinous carcinoma of the endometrium.

With mucinous carcinoma of the endometrium, there is a characteristic presence of a mucinous component at more than 50% of the tumor mass. There is the additional need to differentiate between cervical adenocarcinoma, where the nucleus expression to ER shows negative in most cases, while p16 shows positive. In the case presented herein, there is no tumor in the cervix, which together with the positive nucleus expression for ER in 75% of the tumor excludes the chances of endocervical adenocarcinoma.[7]

The remaining tumors of the endometrium exhibit distinctly different morphological architectonics compared to the papillary endometrioid carcinoma of intermediate grade, expressed in certain cases with solid growth, visible cytological atypia, and distinctly different immunohistochemical response.

In the cases of clear cell carcinoma uterus, there is a characteristic morphology of the large, clear to rarely eosinophilic cells with glycogen, enlarged angulated nuclei with enlarged irregular nucleoli. Immunohistochemically, the nuclear signal for ER is negative or slightly positive, and p53 is focally positive, which is in contrast with the case of papillary endometrioid carcinoma of intermediate grade presented herein.

## CONCLUSIONS

Presented herein is a rare tumor, still not included in the classification of tumors of the uterine body: papillary endometrioid carcinoma of intermediate grade with expressed MELF and LVSI in the leiomyoma. The main challenge in cases of papillary endometrioid carcinoma of intermediate grade is the diagnosis that requires a differential diagnosis in comparison with other variations of endometrial tumors, mainly with serous carcinoma uterus, villoglandular and mucinous carcinoma of the endometrium.

The aggregation of clinical and morphological observations would pave the way for a potential listing of the papillary endometrioid carcinoma of intermediate grade in the classification of tumors of the uterine body; while research into its connection with the microcystic, elongated and fragmented glands type of invasion and LVSI and any potential interaction between them with metastasis of the lymph node and internal organs will allow for various opportunities for diagnosing and curing it.

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# Папиллярная эндометриоидная карцинома средней степени тяжести с инфильтрацией лейомиопатии

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## Абстракт

В случаях эндометриоидного рака глубина инвазии миометрия, лимфоваскулярная инвазия (LVSI) и инвазия микроцистной, удлинённой и фрагментарной железы (MELF) являются предикторами метастазирования. Хотя папиллярная эндометриоидная аденокарцинома среднего класса в настоящее время не включена в последнюю классификацию опухолей женской репродуктивной системы, её существование вызывает интерес в связи с необходимостью поставить дифференциальный диагноз для других эндометриоидных опухолей. Здесь мы представляем случай папиллярной эндометриоидной карциномы средней степени тяжести с инвазией лейомиомы, выраженной с синдромом LVSI и MELF с интактным миометрием. Реализованы морфологические и иммуногистохимические алгоритмы.

## Ключевые слова

слова, матка, карцинома, лейомиома, иммуногистохимический