

## Case Report

# Well-differentiated mucinous uterine adenocarcinoma predominantly diagnosed as adenoma malignum: a case report with an immunohistochemical analysis

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Received March 17, 2015; Accepted May 17, 2015; Epub June 1, 2015; Published June 15, 2015

**Abstract:** Adenoma malignum (AM), also referred to as “minimal deviation adenocarcinoma”, is an extremely uncommon variant of highly-differentiated adenocarcinoma of the uterine cervix. The study presented herein describes a case of uterine AM found out after hysteroscopy. An early-stage, well-differentiated mucinous uterine adenocarcinoma was diagnosed post-operatively. A subsequent immunohistochemical assessment of a panel of antibodies was applied, in order to distinguish between female genital tract malignancies.

**Keywords:** Adenoma malignum, uterine cancer, immunohistochemistry

## Introduction

Adenoma malignum (AM), also referred to as “minimal deviation adenocarcinoma”, is an extremely uncommon variant of highly-differentiated adenocarcinoma of the uterine cervix [1-4]. This type of the female genital tract malignancy, first designated as “malignant adenoma of the cervix” by Gusserow in 1870, has ultimately been referred to as “minimal deviation adenocarcinoma” by Silverberg and Hurt [1]. It accounts for only 3% of all cervical adenocarcinomas, and due to its rarity, it is difficult to diagnose it before surgery [5-9]. Kojima et al. [10] have written that “mucinous adenocarcinoma of the uterine cervix with gastric immunophenotype can be a distinct morphologic variant showing an aggressive clinical course”. The clonal and neoplastic nature of adenoma malignum of the uterine cervix, in spite of its distinctive pattern of PCR-LOH analysis, has also been reported [11].

An unusual case of cervical AM, which proved difficult to preoperatively differentiate from uterine endometrial adenocarcinoma, was

recently presented by Japanese investigators [9]. Abiko along with *co-investigators* [6] reported on the case of a minimal deviation mucinous adenocarcinoma (“adenoma malignum”) of the uterine corpus, which was similar to cervical AM in terms of its morphology and gastric immunophenotype. There were significant differences in ER, MUC6/HIK1083, CEA, and vimentin immunoreactivity between their case and the usual reported cases of mucinous uterine adenocarcinoma [6].

The current study presented herein describes a case of uterine AM found out after hysteroscopy. An early-stage, mucinous G1 uterine adenocarcinoma was diagnosed post-operatively. A subsequent immunohistochemical (IHC) assessment of a panel of markers was then evaluated, in order to distinguish between female genital tract malignancies.

## Case report

A 50-year-old woman (gravida II, para II) was admitted in August 2014 to the IIND Department of Gynecology, Lublin Medical University, Lublin,

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**Table 1.** Immunohistochemical evaluation of primarily diagnosed uterine AM and well-differentiated mucinous endometrial adenocarcinoma

|                       | Uterine AM                   | Well-differentiated mucinous endometrial adenocarcinoma |
|-----------------------|------------------------------|---|
| Estrogen receptor     | positive, nuclear            | strong positive, nuclear                                |
| Progesterone receptor | weak positive, nuclear       | weak positive, nuclear                                  |
| Androgen receptor     | negative                     | negative  |
| cytokeratin           | strong positive, cytoplasmic | positive, cytoplasmic                                   |
| p53                   | positive, nuclear            | positive, nuclear                                       |
| vimentin              | weak positive, cytoplasmic   | weak positive, cytoplasmic                              |
| MIB-1 PI (%)          | 10.1%, nuclear               | 10.9%, nuclear  |
| CEA                   | only occasionally positive   | only occasionally positive                              |
| SMA                   | negative                     | negative  |

Poland. She had previously suffered from abnormal uterine bleeding, and a subsequent ultrasonographic scan revealed an endometrial polyp. Her last menstrual period had been a year before. Previously, her menstrual cycle had been normal, with periods lasting up to 5 days. Her medical history included cerebral ischemia at 40 years of age and depression 5 years earlier. Her family history was not contributory. A cytological evaluation performed two years before was normal. Gynecologic examination at the Department revealed a normal uterine cervix, and a normal-sized uterus with non-palpable ovaries. An ultrasonographic scan showed an endometrial thickness of 6 mm in greatest diameter with an endometrial polyp (12 mm in diameter) outgoing from the posterior uterine wall. The uterus measured 6.32×3.38 mm with both ovaries of normal size, and there was no fluid in the pouch of Douglas. The results of the completed blood count, urinalysis, serologic tests, electrocardiogram, and chest X-ray were within normal range. Written informed consent was obtained from the patient before surgery. Hysteroscopic resection of the endometrial polyp was performed, and the patient was discharged the next day in good condition. Adenoma malignum of the uterus (well-differentiated mucinous adenocarcinoma-minimal deviation) was diagnosed by pathology. Through immunohistochemistry, the tumor was found to be positive for cytokeratin and vimentin, and only occasionally positive for CEA; MIB-1 immunoreactivity was positive in 10.1% of the tumor cells. The patient was admitted for the second time to the IIND Department of Gynecological Surgery, Lublin Medical University, Lublin, Poland, where a

total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. The post-operative pathological assessment revealed a mucinous G1 uterine adenocarcinoma. The tumor did not invade either the myometrium or the cervix. Extension of the tubes and ovaries was not identified. Finally, the patient was staged IA, based on the newly established FIGO classification [12]. The postoperative course was

uneventful. The patient was discharged at day 6 and referred to the Outpatient Oncology Department, Lublin, Poland. There were no high-risk factors for the patient, and adjunctive therapy was not administered. At the last follow-up, 6 months after surgery, the patient was disease-free.

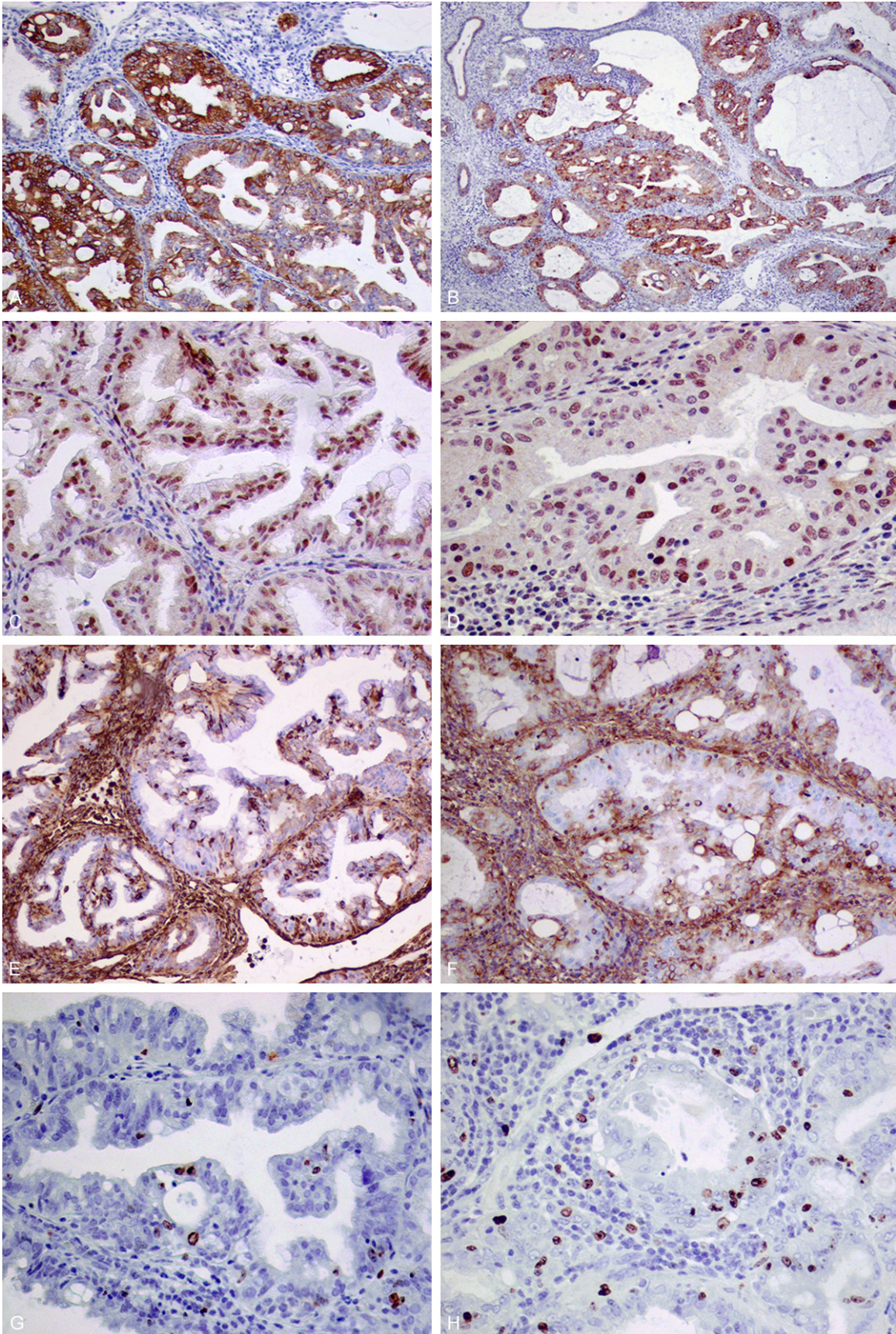
A panel of IHC markers has been applied thereafter in order to distinguish between female genital tract malignancies. Immunohistochemical results are depicted at **Table 1** and the examples of staining are shown at **Figure 1**. In general, most of the immunohistochemical markers, including MIB-1 Proliferative Index (PI), revealed almost identical immunoreactivity.

### Discussion

AM is an uncommon variant of adenocarcinoma, which comprises only 3% of all uterine cervical neoplasms [4, 8]. Variants of “minimal deviation adenocarcinomas” of the uterine corpus have been recently described [6, 9]. Uterine AM, displaying an elevated levels of serum CA 19-9, but with CEA and CA125 levels within the normal range, and which also exhibits highly infiltrating growth, as well as a gastric immunophenotype, has been characterized as a different entity compared to cervical AM [6]. In the present case, we reported well-differentiated mucinous adenocarcinoma of the uterine corpus that was preoperatively diagnosed as uterine AM.

A diagnosis of cervical/endometrial AM is based on the careful pathological examination of a biopsy of the cervix and/or material from

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**Figure 1.** Examples of the immunohistochemical reactivity of primarily diagnosed uterine AM and well-differentiated mucinous endometrial adenocarcinoma-cytokeratin (A and B), p53 (C and D), vimentin (E and F), and MIB-1 (G and H) (Original magnification  $\times 100$  and  $\times 200$ ).

cervical conization or from endometrial biopsy and curettage [4, 7, 8, 13]. In general, cytological examination of the uterine cervix as a diagnostic method is difficult, whereas there are some cytological features suggesting the existence of AM [5, 8, 14]. In general, a preoperative pathologic diagnosis is often difficult because AM exhibits an endophytic growth pattern [8]. Imaging analysis, including transvaginal ultrasonography or magnetic resonance imaging, may be more precise as a tool in evaluating tumor dissemination, rather than at diagnosis [15, 16]. However, Guo et al. [7] reported that "T2-weighted in particular, shows the characteristics of MDA in detail and exhibits a reliable correlation with histological findings". Applying USG with a Doppler examination may be more efficient and accurate in evaluating the increased intra-lesional AM vascularity [17].

IHC staining with valuable markers is commonly applied in gynecological pathology to distinguish various gynecologic malignancies, distinctive components from the same tumor or primary/metastatic neoplasms [18-20]. A more accurate and final diagnosis may also be complemented by careful IHC examination [21-23]. Based on various studies, HIK-1083 and MUC6 monoclonal antibodies have been proved to stain positively with cervical AM cells [5, 24]. Application of HIK-1083 has been argued to be a valuable marker for mucinous minimal deviation adenocarcinoma of the uterine cervix [24-27]. Moreover, other markers, CEA, MIB-1, p53 or alcian blue-periodic acid-Schiff, have been shown to play important roles in the IHC assessment of AM [7, 26-28]. In the literature, Guo et al. [7] summarized the data from 60 cases of uterine cervical AM that reported staining for various markers, including CEA, p53, CA125, Ki-67,  $\alpha$ SMA, CA19-9, MUC6, HIK-1083, CK7, CK19, CA19-9, SMA and vimentin. We applied a panel of IHC markers (**Table 1; Figure 1**) that showed almost identical immunoreactivity. Unfortunately, the HIK-1083 antibody, specific for cervical/uterine AM, was not yet available in our lab. Nevertheless, based on the clinicopathological data as well as our careful IHC analysis, well-differentiated mucinous uterine

adenocarcinoma, at early clinical stage of the disease, was finally diagnosed, and the patient was successfully managed.

### Acknowledgements

The authors would like to acknowledge the staff of the Department of Pathology for tumors assessment. We also would like to thank Mrs Mariola Bigas and Mrs Maria Nowak for performing excellent immunostaining analysis and Mr Robert Klepacz for high-quality photographs. This study was granted by Lublin Medical University, Lublin, Poland (grant number 326/15).

### Disclosure of conflict of interest

None.

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