



Difficulties in diagnosis of a minimal deviation adenocarcinoma of uterine cervix diagnosed postoperatively: brief communication and literature review

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Abstract

Purpose Rare minimal deviation adenocarcinoma (MDA) diagnosed postoperatively as incidental finding of a suspicious cervical lesion at laparoscopy, emphasizing it represents a diagnostic challenge mimicking both benign and malignant cervical lesions with often overlapping imaging characteristics—case report and literature review.

Case presentation 35-year-old Gravida with primary infertility presented with a suspicious cervical lesion and complained about menorrhagia, hyper-/dysmenorrhea. Clinical examination was unremarkable, transvaginal scan presented a 42 × 38 × 28 mm sized cervical lesion (i.e. fibroid) without hypervascularization. Unexpectedly, the diagnosis of minimal deviation adenocarcinoma in tissue sample taken from suspicious cervical lesion at laparoscopy was revealed in final pathological report. According to suspected early stage of MDA a radical abdominal hysterectomy (PIVER III/IV), bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy was scheduled. Final histology report confirmed: “MDA”, G2, FIGO pT1b1, pN0 (0/23 LN) L0 V0 Pn0 R0.

Results Ultrasonography may indicate MDA throughout the examination of vascularization/echogenicity with possibility of mimicking benign lesions with similar characteristics. Magnetic resonance imaging shows no pathognomonic signs for MDA. Subsequently, a review of literature was conducted and main factors affecting the prognosis of MDA considering diagnostic tools, clinical stage, histopathological results and surgical protocols were analyzed.

Conclusions Minimal deviation adenocarcinoma represents one of rare cervical adenocarcinomas without HPV-association. While it is crucial to differentiate benign from malignant lesions in this subtype, imaging characteristics often overlap and may not provide a specific diagnosis. Therefore, it should be considered in suspicious multicystic cervical lesions and inconclusive PAP-smear. Definitive diagnosis of this subtype should be based on cervical biopsy.

Keywords Adenoma malignum · Laparoscopy · Gastric-type adenocarcinoma · Overlapping imaging characteristics · Pathology

Abbreviations

AM	Adenoma malignum
MRI	Magnetic resonance imaging
DWI	Diffusion weighted imaging
GAS	Gastric-type adenocarcinoma
MDA	Minimal deviation adenocarcinoma

HPV	Human papilloma virus
PAP	Papanicolaou
WHO	World Health Organisation
IHC	Immunohistochemistry
CEA	Carcinoembryonic
MIB-1	Ki-67, Molecular Immunology Borstel
CK7	Cyto keratine 7
CK20	Cyto keratine 20
P16	Cyclin dependent kinase inhibitor 2A
P53	Transformation-related protein 53
CT	Computed tomography
HIK1083	Antibody
MUC6	Antibody
CA19.9	Carbohydrate-Antigen 19-9
PAX8	Paired-Box-Protein 8

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LEGH Lobular endocervical glandular hyperplasia
OS O7verall survival

Introduction

With approximately 1–3% of cervical adenocarcinomas gastric-type adenocarcinoma (GAS) or minimal deviation adenocarcinoma (MDA) is a very rare variant of highly-differentiated uterine cervical adenocarcinoma [1, 2]. Adenocarcinomas represent 25% of all cervical carcinomas [3]. MDA has no HPV-association and is the most frequent subtype of non-HPV associated cervical cancers [3]. It represents merely 0.15–0.45% of all cervical carcinomas [4]. Neither the clinical presentation nor the pathological findings are consistent. In particular due to tumors ability to mimic benign lesions finding definite diagnosis of MDA is rather difficult. Furthermore, there are numerous differential diagnoses such as adenomyoma, deep nabothian cysts and endocervical glandular hyperplasia, ranging from harmless benign lesions over to pre-malignant lesions through to malignant peculiarity [3]. Subsequently, a review of literature was conducted and main factors affecting the prognosis of MDA such as early diagnosis, clinical stage, pathology results and surgical protocols were described. Aim is to bring to light the challenge of diagnosis of this rare and postoperatively diagnosed incidental MDA case found at laparoscopy, emphasizing these lesions could mimic both benign and malignant cervical lesions with often overlapping imaging characteristics.

Brief report

A 35 year old nulliparous woman with primary infertility presented with a suspicious cervical lesion, a.e. cervical fibroid. The annual PAP-smear showed no salience and was rated as PAP I each time; categorized as NILM according to Bethesda system of classification [5]. She also complained about meno-/metrorrhagia, hyper- and dysmenorrhea as well as dyspareunia. The transvaginal scan revealed a 42 × 38 × 28 mm sized lesion in the anterior cervical wall without increased perfusion. It ranged from the inner side of uterine cervix to serosa and arched the isthmus part of uterus forward. The lesion appeared roundly and was smooth delimited and encapsulated, the suspected diagnosis was either an adenomyoma, myoma (WHO type 2–5) or a partly necrotic myoma [2, 6] (Figs. 1, 2).

The internal structure seemed spongy, with accentuated vascularization in the peripheral areas and with some smaller vessels in the center without the evidence of bladder infiltration. Clinical examination of uterine cervix was inconspicuous with normal appearance of cervical surface



Fig. 1 Transvaginal ultrasonographic findings of the cervical lesion showing an inhomogeneous multicystic mass (↑) (University Womens Hospital Tübingen)

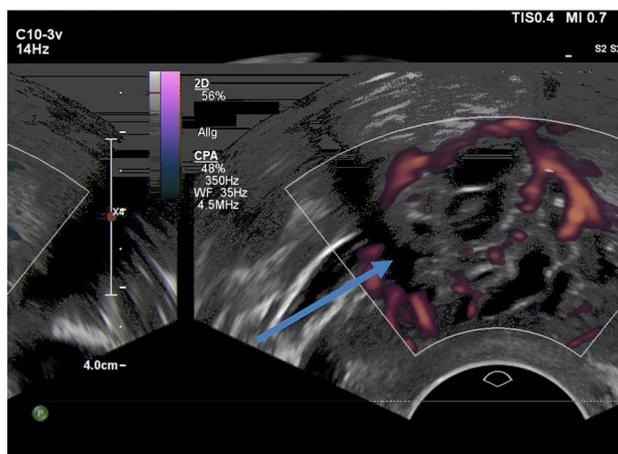


Fig. 2 Transvaginal ultrasonographic findings of the cervical lesion showing a peripheral accentuated vascularization (↑) (University Womens Hospital Tübingen)

as well. The patient was scheduled for hysteroscopy (unremarkable), chromopertubation (no patency for the left fallopian tube/normal patency for the right fallopian tube) and laparoscopy. At laparoscopy, the space-consuming lesion in the posterior cervical part showed a size of 30 × 30 mm with normal serosa; a biopsy of the lesion was performed to get a definitive diagnosis. The final pathology report unexpectedly revealed the diagnosis of infiltration of a highly differentiated invasive adenocarcinoma of gastric type (respective: MDA) (Fig. 3). By immunohistochemistry (IHC), tumor profile was negative for estrogen and progesterone receptors (Fig. 4), but slightly positive for carcinoembryonic antigen (CEA; Fig. 5). Tumor cells showed a very weak activity with MIB1-antibody, illustrating a very slow growing character (Fig. 6). The strong

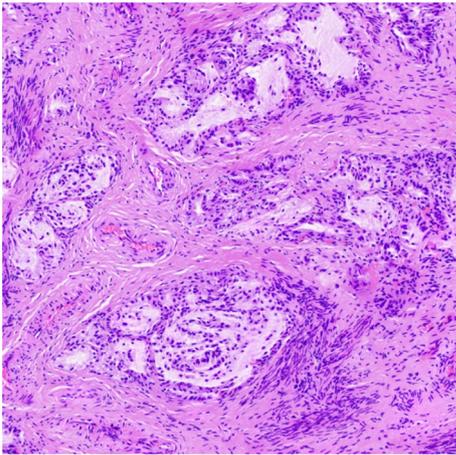


Fig. 3 Higher magnification of these bland looking glands with small nuclei, only the deep infiltrating character shows the neoplastic behavior. Hematoxylin and Eosin staining, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

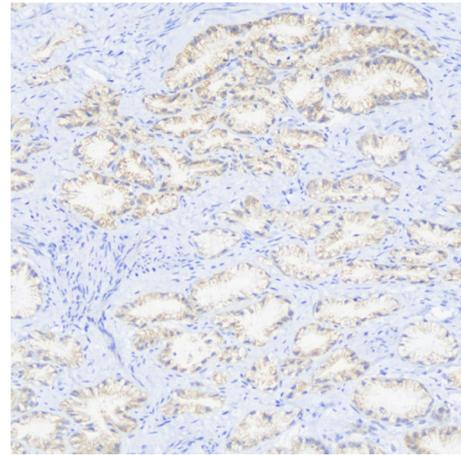


Fig. 5 The tumor cells show a weak cytoplasmic positivity for carcinoembryonic antigen (CEA), typically for this entity. CEA immunoperoxidase, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

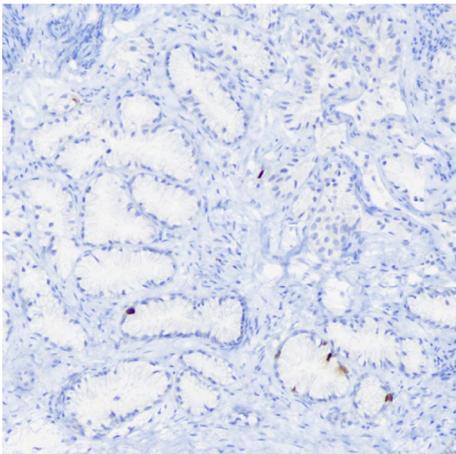


Fig. 4 The tumor cells show a very weak activity with the MIB1 antibody, illustrating a very slow growing character. Ki67 immunoperoxidase, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

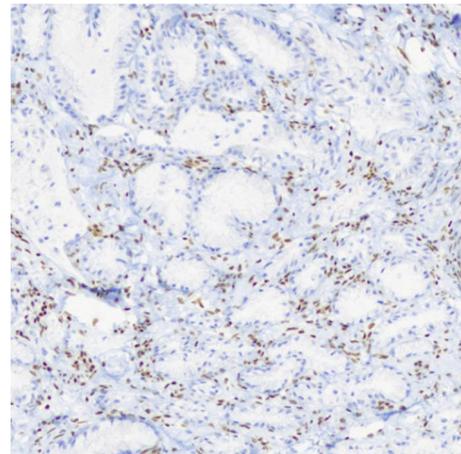


Fig. 6 The immunohistochemistry of the estrogen receptor show a diffuse positivity of the stroma cells, but a clear negativity of the tumor cells. Estrogen receptor immunoperoxidase, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

membranous and cytoplasmic positivity for CK7 together with negativity for CK20 show a gastric differentiation (Figs. 7, 8). Tumor cells show no aberrant expression of p16 and p53, demonstrating no HPV-association and no serous differentiation, respectively (Figs. 9, 10). The subsequently carried out colposcopy showed a coarse mosaic in the anterior cervical part with iodine yellow staining in this area. The taken samples revealed no malignancy. At that examination lots of vaginal mucoid discharge was found. A whole-body computed tomography (CT) was carried out and precluded any metastatic spread, inhomogenous contrast filling of the uterine cervix was detected. Based on underlying histology staging was completed with

a gastro- and colonoscopy. By gastroscopy angiodysplasia (Paris-classification type II: flat-elevated) and a polyp in gastric corpus were found, histological examination revealed no malignancy. Colonoscopy was unremarkable. Subsequently, a Peutz–Jeghers syndrome was excluded. According to the suspected early stage of MDA a radical abdominal hysterectomy (PIVER III/IV), bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy was scheduled. Final histology report confirmed: “MDA”, G2, FIGO pT1b1, pN0 (0/23 LN) L0 V0 Pn0 R0. Based on clinicopathological findings, as well as IHC findings, highly differentiated invasive cervical adenocarcinoma of gastric type, at early clinical stage of

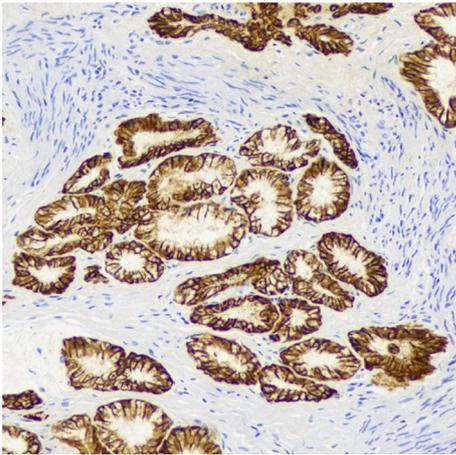


Fig. 7 The strong membranous and cytoplasmic positivity for CK7 together with the negativity for CK20 (on the right) show a gastric differentiation. CK7 and CK20 immunoperoxidase, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

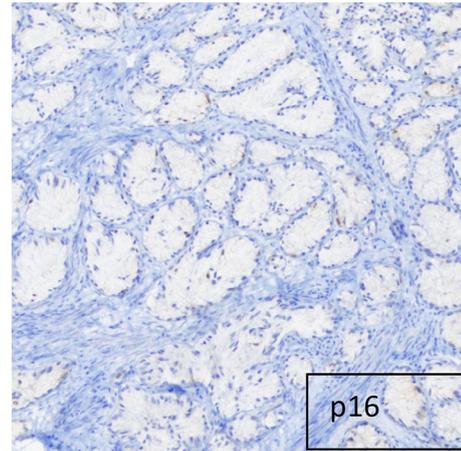


Fig. 9 The tumor cells show no aberrant expression of p16, demonstrating no HPV association and no serous differentiation, respectively. P16 and p53 immunoperoxidase, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

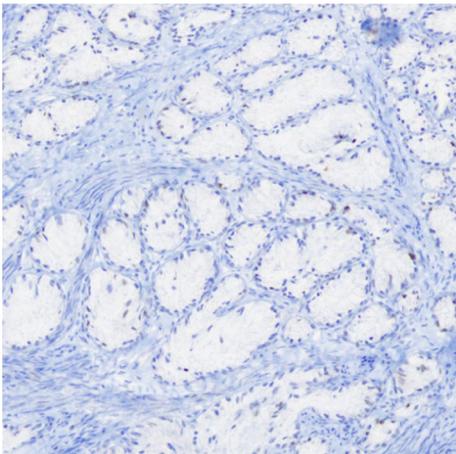


Fig. 8 Negativity for CK20 shows a gastric differentiation. CK7 and CK20 immunoperoxidase, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

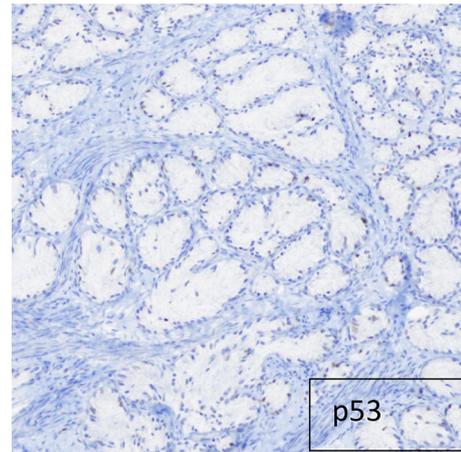


Fig. 10 The tumor cells show no aberrant expression of p53, demonstrating no HPV association and no serous differentiation, respectively. P16 and p53 immunoperoxidase, 400×original magnification. (Institute of Pathology, University Hospital Tübingen)

disease, was finally diagnosed and patient was successfully managed. A routine follow-up was recommended.

Discussion

As mentioned before neither clinical symptoms nor histo- and immunopathological findings are consistent, aggravating diagnosis of MDA. Most of previous cases prove, MDA is typically diagnosed postoperatively as an incidental finding after hysterectomy due to benign indications [7]. Furthermore, MDA tends to—due to its rather benign appearance in histologic specimens and missing malignant symptoms—mimic benign lesions such as Nabothian cysts. As

differential diagnoses adenomyoma, deep nabothian cysts or endocervical glandular hyperplasia should be considered [7]. Therefore, a careful examination is needed to prevent unnecessary therapeutic actions to be taken (e.g., hysterectomy). Nowadays, this includes use of imaging methods (ultrasonography/CT/MRI) [8]. An overview of literature is given (Table 1).

Clinical presentation

Owing to sparseness of documented cases and implemented analyses epidemiologic data of MDA is rare. In median the age of manifestation of MDA is about 45 years

Table 1 Overview and comparison of literature with respect to clinical course, diagnosis, therapy and prognosis

Reference	Year	Age	Gravida	Para	Clinical presentation	PAP cytology	Ultrasonography findings	Immunohistochemistry	FIGO	Neoadjuvant therapy	Therapy	Adjuvant therapy	Status (0=alive, 1=dead)	Status	
Stöhr et al.	2018	35	0	G/0	P	Meno-/metrorrhagia, hyper- and dysmenorrhea	I/1 negative	39 × 38 × 32 mm sized cystic-solid space-consuming lesion	CEA+, ER-, PR-, p16-, p53-, MIB+, CK7+, CK20-	Ib2	None	MRHE/BSO/PLND	None	0	NED
Koo et al. [38]	2010	30	n.a.	n.a.	Diffuse abdominal pain	n.a.	n.a.	Ki-67 (focal staining)	Ib2	CHT (PX, CP)	LRHE, P/PLND	CHT (PX,CP)	n.a.	n.a.	n.a.
Granter et al. [42]	1996	46	n.a.	n.a.	Irregular uterine bleeding with leiomyoma	5/5 negative	n.a.	n.a.	I	None	TAH/BSO	RX (pelvic)	0	NED	
	45	n.a.	n.a.	n.a.	Menorrhagia	I/1 negative	n.a.	n.a.	I	None	TAH/BSO	RX (pelvic)	0	NED	
	43	n.a.	n.a.	n.a.	Vaginal discharge	I/1 negative	n.a.	n.a.	I	None	TAH	None	0	NED	
Hino et al. [22]	37	n.a.	n.a.	n.a.	Irregular cervix noted on pelvic examination	I/3 ATY	n.a.	n.a.	I	None	TAH/BSO	None	0	NED	
	33	n.a.	n.a.	n.a.	Vaginal spotting, vaginal discharge at 35 weeks of gestation	I/1 negative	n.a.	n.a.	I	None	TAH/BSO	None	0	NED	
Hino et al. [22]	60	n.a.	n.a.	n.a.	None	3/5 negative, 1/5 SUS, 1/5 ATY, reactive changes	n.a.	n.a.	I	None	TAH/BSO	None	0	NED	
	48	n.a.	n.a.	n.a.	Cervical discharge	Negative	n.a.	n.a.	I	None	TAH/BSO	None	0	NED	
Hino et al. [22]	2016	72	IV	G/II	P	Abnormal genital bleeding	I/1 SUS	Walnut-sized tumor, irregular shape in the uterine cavity	IIIC2	None	LRHE/BSO/P/PLND	CHT (PX, CP)	1	DOD	

Table 1 (continued)

Reference	Year	Age	Gravida	Para	Clinical presentation	PAP cytology	Ultrasonography findings	Immunohistochemistry	FIGO	Neoadjuvant therapy	Therapy	Adjuvant therapy	Status (0=alive, 1=dead)	Status
		56	n.a		Abnormal genital bleeding + vaginal discharge	n.a	n.a	MUC6+, HIK1083+, CA19-9+, CEA+, MUC2-, ER-, p16-, vimentin-	n.a	none	TAH/BSO/P/PLND/OM	CHT (TS-1, CP)	1	DOD
Gotoh et al. [20]	2004		n.a		Atypical bleeding	n.a	n.a	HIK1083+	IA		TAH/BSO		0	NED
Abiko et al. [21]	2010		n.a		Vaginal discharge and abnormal genital bleeding	n.a	n.a	HIK1083+, MUC6+, CEA+, CA19-9+, p53+ (partially), MUC2-, p16-, vimentin-	IVB		TAH/BSO/P/PLND/OM	CHT (PX,CP)	1	DOD
Silverberg et al. [1]	1975	34	VIII	G	n.a	Not done	n.a	n.a	IIB	RX (external + internal)	None	None	1	DOD
		36	II	G	n.a	AM	n.a	n.a	IB	RX (external + internal)	RH/BSO/PLND	None	0	NED
		40	I	G	n.a	I/I negative	n.a	n.a	IB	RX (external + internal)	None	None	0	NED
		38	IX	G	n.a	I/I SUS	n.a	n.a	IB	RX (external + internal)	None	None	0	NED
		84	XII	G	n.a	I/I SUS	n.a	n.a	IIB	RX (external + internal)	None	None	0	NED
Hirai et al. [6]	1998	38	n.a		Vaginal bleeding and/or watery discharge	n.a	n.a	n.a	IIB	None	RH/PLND	None	0	NED

Table 1 (continued)

Reference	Year	Age	Gravida	Para	Clinical presentation	PAP cytology	Ultrasonography findings	Immunohistochemistry	FIGO	Neoadjuvant therapy	Therapy	Adjuvant therapy	Status (0=alive, 1=dead)	Status
Eun Young Ki et al. [13]	2013	39	n.a	n.a	Vaginal bleeding and/or watery discharge	n.a	n.a	n.a	IB	None	RH/PLND	None	0	NED
		65	n.a	n.a	Vaginal bleeding and/or watery discharge	n.a	n.a	n.a	IB	None	TAH	None	0	NED
		70	n.a	n.a	Vaginal bleeding and/or watery discharge	n.a	n.a	n.a	IB	None	RH/PLND	None	0	NED
		53	n.a	n.a	Vaginal bleeding and/or watery discharge	n.a	n.a	n.a	IB	None	RH/PLND	None	0	NED
Mowat et al. [43]	2014	54	n.a	n.a	Leukorrhoea, menorrhagia	n.a	Several small-intramural myomas and nabothian cysts	n.a	n.a	None	TAH/BSO	None	0	NED
		53	n.a	n.a	Vaginal bleeding	n.a	n.a	n.a	n.a	None	Stump resection	None	0	NED
		39	n.a	n.a	Vaginal discharge	n.a	No abnormal findings	n.a	n.a	None	TAH/PLND	None	0	NED
Mowat et al. [43]	2014	42	n.a	n.a	Vaginal discharge	n.a	n.a	n.a	n.a	None	TLH/P/PLND	None	0	NED
		45	n.a	n.a	Vaginal discharge for 11 years	I/1 negative	Bulky uterus, 4 cm nabothian cyst and adenomyosis uteri suspected	CEA+, ER-, PR-, PAX2-	IB1	None	TLH/P/PLND	None	0	NED

Table 1 (continued)

Reference	Year	Age	Gravida	Para	Clinical presentation	PAP cytology	Ultrasonography findings	Immunohistochemistry	FIGO	Neoadjuvant therapy	Therapy	Adjuvant therapy	Status (0=alive, 1=dead)	Status
Kamath et al. [44]	2017	35	I	G/1	P	Mucoid discharge	Balloned appearance of the cervix, well-defined complex cystic lesion within the stroma of the cervix with internal solid areas and inner vascularity	n.a	IB1	None	RH/PLND	RX	0	NED
Guo et al. [15]	2013	45	3	G/1	P	Vaginal discharge	Edematous cervix, multiple cysts with honeycomb appearance	n.a	IB2	None	TAH/BSO/PLND	RX	n.a	n.a
Peng et al. [45]	2015	33	0	G/0	P	Watery vaginal discharge	n.a	MUC6+, HIK1083+, p16+, CK7+, CK20+, CEA-, ER-, PR-, Ki67: 5%	IB	None	TAH/BSO/PLND	None	n.a	n.a
Ding et al. [46]	2016	58	5	G/3	P	Mucoid vaginal discharge	Intrauterine 33 × 16 × 31mm hypoechoic lesion with echogenic ring	CEA+, Vimentin+	IB	None	TAH/BSO/PLND	None	0	NED
Simionescu et al. [47]	2006	32	n.a	n.a	n.a	Atypical vaginal discharge	n.a	CEA+, PR-, ER-, CA125+, Ki67: 1%	n.a	None	None	CTX, RX	n.a	n.a
Steeper et al. [54]	1986	38	n.a	n.a	n.a	Vaginal discharge	n.a	CEA+	IIB	None	RH	n.a	n.a	n.a
		55	n.a	n.a	n.a	Vaginal bleeding	n.a	CEA+	IA	None	RH	n.a	n.a	n.a

Table 1 (continued)

Reference	Year	Age	Gravida	Para	Clinical presentation	PAP cytology	Ultrasonography findings	Immunohistochemistry	FIGO	Neoadjuvant therapy	Therapy	Adjuvant therapy	Status (0=alive, 1=dead)	Status
Castán Senar et al. [34]	2016	74	n.a		Vaginal bleeding	n.a	n.a	CEA+	IB	None	None	RX	n.a	n.a
		52	n.a		Vaginal bleeding	n.a	n.a	CEA+	IB	None	RH	n.a	n.a	n.a
		37	n.a		Vaginal bleeding	1/1 negative	Poorly vascularized and heterogeneous submucosal lesion in the cervix	CEA+	n.a	None	MRHE/BSO/PLND	CTX, RX	0	PRO
Hissong et al. [48]	2016	64	n.a		Vaginal spotting	4/4 negative	Thickened heterogeneous endometrium with cystic foci, measuring up to 1.8 cm	ER-, PR-, p16-, Ki67: 30%	n.a	None	RH/BSO/PLND	None	0	NED
Nishii et al. [49]	2014	65	II	G/0 P	Vaginal bleeding	n.a	Small amount of ascites and mildly thickened endometrium	n.a	IV	None	TAH/BSO/supraclavicular LNS	CTX	0	NED

with a wide range [range 30–85 years [9–12] (Table 1)]. Various previous case reports describe meno-metrorrhagia, vaginal discharge or postmenopausal vaginal bleeding as well as abdominal swelling as main symptoms of MDA [7, 11]. Nevertheless, there is also a considerable number of patients without specific symptoms leading to diagnosis of MDA [13], as seen in our patient. From the presented case reports in Table 1 merely two patients were asymptomatic at all; the other patients complained about vaginal bleeding/vaginal mucoid discharge and combined symptoms (bleeding/vaginal mucoid discharge) at the time of diagnosis of MDA (Table 1). A previous report described that in clinical examination the cervix tends to appear abnormal with firm, nodular or occasionally exophytic polypoid lesions as well as it may appear enlarged and indurated as a so-called “barrel cervix” [3], even if usually MDA tends to show endophytic growth due to the fact that the lesion is located deep in the endocervix [14]. In our patient clinically a hint to MDA was missing. Nassif et al. described that small-sized Nabothian cysts are usually clinically asymptomatic and require no treatment or intervention, but the diagnosis of larger Nabothian cysts can be mistaken with malignant tumors, including mucin producing carcinomas such as MDA [8]. Among MDA, approximately 10% are associated with Peutz–Jeghers syndrome according to histological subtype [3, 7]; subsequently, Peutz–Jeghers syndrome should be excluded, as done in the presented patient. Most often the diagnosis of MDA is an incidental finding; in 17 cases MDA was incidentally diagnosed following hysterectomy for benign conditions in 6 cases [12]. Table 1 demonstrates an overview about clinical presentation and ultrasound findings of pathologically confirmed MDA cases as well. This overview represents the wide-spread pattern of MDA and underlines the difficulty of preoperative diagnosis due to normal cervical surface, unremarkable PAP-smear and insufficient cytology results [7].

Ultrasonography findings

As an easy and harmless diagnostic tool, transvaginal ultrasonography is the first imaging tool which is carried out to describe space-consuming cervical lesions. In MDA, Park SB et al. demonstrated that the uterine cervix was seen to be enlarged in 8 out of 11 cases (73%), 45% (5/11 cases) of tumors grew intracervically and infiltrated the uterine cervix completely [13]. Most often the lesions have smooth margins; merely a minority had irregular margins [13]. The appearance differs between multilocular lesions with or without solid lesions, solid lesions and moderate to abundant vascularization, respectively [13]. In this series, most solid lesions (3 of 4) manifested with heterogeneous echogenicity [13]. In our presented case, the lesion appeared to have smooth margins with peripheral accentuated vascularization.

These findings might be a helpful tool to distinguish benign from malignant lesions. To differentiate the lesions from leiomyomas the echogenicity seems to be a possible tool. Mostly the leiomyomas show a rather homogenous hypoechoic structure, whereas in MDA some cases showed heterogeneous echogenicity [13, 15].

Another severity in diagnosing MDA by ultrasonography is the fact that it may mimic multiple Nabothian cysts [3]. Since hypervascularization is a characteristic of malignant tumors, the evaluation of vascularity renders useful information. Using Doppler ultrasound is described to be more efficient in the evaluation of multilocular cervical lesions; Park et al. described increased intralesional vascularization in MDA [13]. Ultrasonography findings underline the challenge diagnosing MDA, they differ a lot and most often it is difficult to classify a lesion as benign or malignant and misdiagnosis is possible due to various ways of its presentation. In our patient, the lesion was suspicious for adenomyoma or fibroid. Table 1 demonstrates the ultrasound findings in presented cases. Merely one case had no abnormal ultrasound finding; the ultrasound findings showed lesions from suspected nabothian cysts/well defined complex cystic lesion within the stroma of the uterine cervix through heterogeneous submucosal cervical lesions (Table 1). Additionally, most often no ultrasound was given in previous cases (Table 1).

Cytological findings and biopsy specimens

Diagnosing MDA is very difficult [16]. Analysis of Gilks et al. showed that three biopsies were required to diagnose MDA; in 25.0% (3/12 cases) even up to four biopsies were needed to establish diagnosis [11]. Further, in 53.8% (14/26 cases) diagnosis could be established only after a hysterectomy [11]. Guo et al. demonstrated that neither the cytological examination nor the punchbiopsy as well as cervical conization specimen could clarify the diagnosis of MDA in one case [17]. Reason of this diagnostic challenge seems to be through the subtle and often just focally seen stromal reaction of infiltrating glands which can easily be missed in small biopsy specimens [18]. It consists of predominantly highly differentiated neoplastic endocervical glands lined by mucin-rich columnar epithelial cells with basally located nuclei and profuse apical eosinophilic cytoplasm, resembling gastric foveolar and pyloric epithelium [3]. It often simulates benign endocervical epithelium [19]. For a cervical neoplasm to be considered MDA it should contain < 10% of ordinary adenocarcinoma [20]. The gastric-type cervical glandular lesions present a full spectrum of benign/premalignant and malignant lesions [3]. The rare benign lesions include simple gastric metaplasia and lobular endocervical glandular hyperplasia. The postulated premalignant lesions comprise atypical LEGH and gastric-type adenocarcinoma in situ (gAIS) [3]. Talia et al. described term ‘gastric-type’

derives from morphological resemblance of glandular epithelium to that seen in the stomach and pancreaticobiliary tree; intestinal metaplasia with goblet cells and neuroendocrine cells are present in some cases [3]. In these cases, gastroscopy and colonoscopy is necessary to exclude intestinal or gastric tumours, as done in the presented case. Nevertheless, the depth of stromal involvement and possible vascular or perineural infiltration are important hints for malignancy [11, 21, 22]. Vaginal PAP-smears are mostly unremarkable and most often not helpful [7, 16]. This diagnostic obstacle is probably caused by endophytic growth pattern and location of lesion deeply in the uterine cervix, so malignant cells could escape the smear [14, 23, 24]. One previous case demonstrated that endometrial biopsy results suggested a well-differentiated endometrioid adenocarcinoma and the subsequently performed MRI did not show typical images for MDA; the final histology report revealed MDA [25]. Kamath et al. described that a deep incision biopsy or conization is needed to make a preoperative definitive diagnosis and that obtaining a diagnosis of MDA by fine needle aspiration and cytology may be inconclusive [7].

IHC findings

CEA as a subset of glycoproteins involved in cell-adhesion and known for its positivity in adenocarcinomas of all kind also shows positivity in MDA and, therefore, it serves as a negative marker for clear cell differentiation. Progesterone (PR) as well as estrogen receptors (ER) are usually negative in MDA, consequently serving as a possibility to differentiate MDA from benign endocervical glands on an IHC basis [26] and as demonstrated in overview Table 1. Especially the combination of a positive staining for CEA [27] with a moderate-to-high proliferative-index measured by staining with MIB-1 (Ki-67) are features of malignant lesions rather than benign ones [28] (Table 1). A helpful tool to recognize MDA seems to be presentation of HIK1083 as well as MUC6 immunohistochemically [26, 29–31]. MUC6 was detected as positive in 81% of cases [32]. Carleton et al. found that gastric-type adenocarcinomas were generally positive for HIK1083 [32]. These markers are specific for pyloric gland mucin-expression and, therefore, a possible and effective way to describe the gastric-type adenocarcinomas in a further way. Nevertheless, there are some previous cases showing that these two markers have only focal or even negative staining and, therefore, need to be evaluated in more detail in future to further elucidate its role diagnosing MDA [33–35]. p16 as a cell cycle regulating protein (cyclin-dependent kinase-4 inhibitor) is most often negative or represents only mosaic-type staining [26]. This finding is consistent with result that MDA is one of HPV-negative cervical adenocarcinomas and p16 becomes overexpressed in the presence of integrated oncogenic HPV [2, 36, 37].

Table 1 demonstrates the unexpected rare case of a p16 positive MDA in a patient with Peutz–Jeghers syndrome [38] representing a synchronous MDA and a gastric type adenocarcinoma (GTA) [38]. Known is an association between gastric-type cervical lesions and Peutz–Jeghers syndrome [3]. The other presented cases in Table 1 had negative p16 tumour (Table 1). Talia and McCluggage described awareness of spectrum of gastric-type lesions is important, as the diagnostic features of both gAIS and GAS, particularly well differentiated examples, may be subtle, and additionally mentioned p16 immunohistochemistry is usually negative [3]. This is also shown in a study where seven out of 52 carcinomas were designated as gastric-type adenocarcinomas were negative for high-risk HPV-DNA and had negative staining in immunohistology with P16^{INK4a} [36]. p53, one of most important tumor suppressors, showed negative or only focal positive staining in six cases. The ones with focally positive staining were tested with polymerase chain reaction based DNA sequencing which failed to detect any p53 mutations in exons 5–8 [39]. But as p53-expression is only seen in endocervical neoplasms, it may help to distinguish between benign or malignant endocervical lesions [40]. CK20, as a type I cytokeratin, is specifically found in the gastric and intestinal mucosa and the stain is used to detect mature enterocytes and goblet cells. CK20 was negative in our case, but it is described that a subset of MDA cases is focally positive for CK20 in 49% [32]. CK 7 (type II cytokeratin family) is seen to be negative in a majority of all squamous cell carcinomas, except for cervical squamous cell carcinomas, therefore, serving as an additive marker to distinguish adenocarcinomas of the uterine cervix, where it showed a 100% of positive staining, from squamous cell carcinomas with other origin. CK7 also showed a 87% positive-staining for squamous cell cervical carcinomas. All different staining characteristics seem to be important for diagnosis [41]. Interestingly, Carleton et al. showed a 100% positive staining for CA19.9 presenting that in combination with other positive staining it is not easy to distinguish MDA from primary pancreatic or biliary adenocarcinomas while dealing with cancers of unknown primary [32]. Using PAX8-staining may be a good tool to differentiate the mostly positive MDA from other intestinal carcinomas [32].

Imaging findings (MRI)

Using only cervical cytology, endocervical curettage and two-dimensional ultrasonography as preoperative diagnostic tools seem to be a very insufficient way, since Umesaki et al. based their diagnosis on these three methods and could detect MDA in 30% (3/10 cases) [42]. Therefore, it seems to be necessary to establish more valid methods. In MRI, MDA is often described as a multicystic lesion with solid component invading cervical stroma and marked

hyperintensity on T2-weighted images [43] or as a solid, irregularly shaped mass and large masses may display cystic cavities [31]. MRI, as a further diagnostic tool, seems at least to help to differentiate between benign and malignant lesions, nevertheless there are no pathognomonic signs for MDA. Sometimes enhancement by contrast medium led to the suspicion of hypervascularity of cervical lesion, again another sign for malignancy [42]. Nevertheless, these findings are not pathognomonic and there is even no specific diffusion-weighted imaging (DWI) finding that indicates MDA but it may help to differentiate MDA from common cervical cancer [44]. Castan et al described that the utility of diffusion-weighted imaging in differential diagnosis of MDA and other multicystic cervical lesions was not evaluated [44]. They reported a case that did not show restriction on the apparent diffusion coefficient map and supposed this can be explained by the low cellularity of the tumor and might be consistent with the proper correlation between the diffusion imaging and histopathology of tumor [44]. Their analysis described MDA can present with high apparent diffusion coefficient values, as in benign cervical lesions. Therefore, the combination of a solid multicystic lesion that invades the cervical stroma on T2-weighted magnetic resonance images and the absence of restriction on the apparent diffusion coefficient map are very suggestive of MDA [44]. In contrast, Kamath et al [7] described MDA has characteristic radiological features: it is seen on MRI as a multicystic mass, with high-signal intensity on T2-weighted images and isointensity or moderate hyperintensity on T1-weighted images [7]. Oguri et al. showed that especially T2-weighted MRI can elucidate characteristics of MDA in detail and shows a reliable correlation with histologic findings as well [45]. Therefore, preoperative diagnosis of MDA is difficult and surgeries due to misdiagnosis should be avoided because this could lead to under- as well as overtreatment [3, 15, 46]. Otherwise, a retrospective analysis described three cases with preoperative suspected diagnosis of ovarian cancer, nabothian cysts and endometrial adenocarcinoma and final pathology report revealed diagnosis of advanced MDA [47]. This represents the difficulty of ultrasound and MRI. After histological confirmation of MDA, clinical and instrumental investigations are aimed at assessing the extent of disease and to perform the staging according to FIGO. After pathological examination treatment is adapted to the stage of disease and additionally prognostic risk is defined. Hereby, in MDA the FIGO-classification based on cervical cancers should be used [2, 6] (Fig. 1).

Therapeutic options

Besides, standard screening, diagnostic tools and treatments are not established in MDA [47]. Table 1 demonstrates an overview of type of surgeries, adjuvant/neoadjuvant

therapies performed in MDA cases and shows the widespread pattern of surgical radicality (\pm lymphadenectomy) and radio-/chemotherapy. Gastric type adenocarcinomas have much poorer prognosis than HPV-associated cervical cancers, with propensity of presentation at advanced stage and disseminated tumour spread, for example, in ovary/peritoneum/omentum [3]. Most results are from studies subsuming all kinds of cervical adenocarcinomas. An analysis evaluated 18 cases with MDA; thereof 88.8% were classified as early stage (FIGO IB1/IB2), rarely MDA was detected (2/18 cases; 11.1%) in advanced stages (FIGO III/IV). This suggests that even though making definite diagnosis appears to be difficult, most often diagnosis is made in early stages. Yet again, it suggests possibility of an early diagnosis due to early clinical symptoms such as vaginal discharge, abnormal vaginal bleeding and considering MDA [9]. A retrospective study showed a significantly better median OS comparing a group of patients with mucinous adenocarcinoma treated with a neoadjuvant chemotherapy compared to a group of patients undergoing only radical hysterectomy. Recurrence-free survival (RFS) did not show any significant differences. Another analysis demonstrated advanced stages of disease have a significant association with poor OS rates [12]. Additionally advanced stage disease and lymphovascular space invasion have a statistically significant association with poor OS rates [12].

Based on the rarity there is no established treatment for MDA and treatment is adapted to cervical adenocarcinomas; limitations of this study (retrospective, no differentiation between different types of mucinous adenocarcinoma) should be considered when deciding for a treatment option in MDA [48]. As shown in case reports of McKelvey et al. [16] and Koo et al. [49] neoadjuvant radiation or chemotherapy do not seem to have an effect in MDA. Due to low incidence of disease, no standardized therapy recommendations are available, but surgical treatment seems to be the most favorable in early stages [50]. Surgical therapy (hysterectomy) prior to administration of adjuvant radio- and/or chemotherapy seems to be treatment of choice. Nevertheless, preferred way of hysterectomy varies a lot. In 7% of all described cases (3/41) a simple abdominal hysterectomy was carried out. In 19.5% a hysterectomy with a bilateral salpingo-oophorectomy was implemented and 46.3% (19/41) got a pelvic lymphadenectomy (PLND) as well. Thereof 14.6% (6/41) of patients additionally got a para-aortic lymphadenectomy (Table 1). Lim et al. showed node involvement in 23% ($n = 3$) after pelvic lymphadenectomy [9].

Current recommendations are to treat MDA surgically such as cervical adenocarcinoma and adjuvant therapy to be considered in a similar manner as per pathological staging [7]. Adjuvant therapies (radiation \pm chemotherapy) are only used in high-grade tumors. Nevertheless, adjuvant chemotherapy with carbo-/cisplatin and paclitaxel has no

great prognostic impact in MDA [30, 31]. In previous cases prognosis of MDA seems to vary a lot. MDA shows a less favorable prognosis than common type of endocervical adenocarcinoma [26]. A firm conclusion seems to be difficult due to slight number of cases (Table 1). Early diagnosis seems to have a rather good prognosis. The retrospective analysis by Lim et al. showed a 5 year OS of 88.8% in 18 patients [9]. Cervical adenocarcinomas in total show an increase in incidence and approach around 20% of uterine carcinomas [51, 52]. Unfortunately, missing data and the fact that all cases can only be analyzed retrospectively aggravates prognostic statements. MDA has been for long considered to be a benign looking tumour with an aggressive clinical course. However, recent reports have suggested that if diagnosed early, the long-term outcome is comparable to conventional cervical cancer [7]. Therefore, it is decisive using all methods described previously to diagnose MDA as early as possible to improve prognosis [12]. The findings in Table 1 may be helpful regarding the fact that due to HPV-vaccination these kind of lesions such as MDA without HPV-association might be increasing in relative prevalence in upcoming years [3, 53]. Imaging and clinical history can only include MDA among diagnostic hypotheses. However, to date, tumour stage remains the most important prognostic factor for cervical cancer of each histological subtype. Regarding the histological subtype, there are no concordant data in literature concerning the prognostic impact, even if the histotype “adenocarcinoma” appears to be a pejorative independent prognostic factor [54]. This presented case underlines that any cervical lesion of uncertain significance should be subjected to biopsy especially if imaging, pap smear, clinical evaluation were inconclusive.

Conclusion

In MDA, screening, diagnostic tools and treatments are not established. Despite its rarity MDA should be considered in patients with watery vaginal discharge or suspicious multicystic cervical lesions. While it is crucial to differentiate benign from malignant lesions in this specific subtype, imaging characteristics often overlap and may not provide a specific diagnosis. Subsequently, there is a high risk of misdiagnosis due to different results in imaging techniques. Furthermore, MDA is one of the rare cervical adenocarcinomas without HPV-association and, therefore, should be considered in suspicious cervical lesions and inconclusive PAP-smear. HPV-related carcinomas are recognized earlier because of the wide-spread screening (PAP-smear) and generally nowadays decreasing occurrence due to HPV-vaccination itself. Further research is needed to elucidate best diagnostic and therapeutic options in cervical adenocarcinomas, to improve prognosis and further describe this

possibly upcoming increasing special subtype of cervical adenocarcinoma. Definitive diagnosis of this special subtype should be based on cervical biopsy.

Author contributions AS conception, data acquisition, data analysis, preparation and writing of the manuscript. DN analysis of tumor specimen, selection of specimens for this case, data acquisition and data analysis. AS: analysis of tumor specimen, selection of specimens for this case, data acquisition and data analysis. EO review and proofreading of the manuscript. SB: review and proofreading of the manuscript. CB: conception, review and proofreading of the manuscript, coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest All authors declare there is no conflict of interest. No competing financial interests exist.

Ethics approval This investigation has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed consent Written informed consent was obtained from the patient.

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