Difficult Diagnosis of Minimal-deviation Adenocarcinoma of the Uterine Cervix: a Case Report and Review of the Literature.

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Case Report

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Abstract

Background: Minimal-deviation adenocarcinoma (MDA) is a rare form of cervical adenocarcinoma. The clinical manifestations of MDA were not typical. Cervical cancer screening is not always effective at screening for MDA. Early clinical manifestations of MDA were lack of specificity and frequently regarded as cervicitis, the effect of treatment was usually poor. The cytological characteristics of MDA were similar to the normal cervical endometrial glands. It was difficult to distinguish between MDA and benign endometrial lesions. Therefore, early diagnosis difficulties often lead to delayed diagnosis.

Case presentation: A rare case of MDA of the uterine cervix undergoing a hard process to make a confirmed diagnosis is reported. This case, with an initial complaint of cervical contact bleeding, pelvic pain, and vaginal itching, was negative for Thinprep cytologic test (TCT), the human papillomavirus (HPV) genotyping test by Hybrid Capture 2 (HC2), and cervical biopsies. Finally, the MDA was diagnosed with the assistance of the Bard-Magnum Biopsy Instrument under computed tomographic (CT) guidance and staged as an IIIB tumor according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. The patient received concurrent chemoradiation as primary treatment and unfortunately died a few months later.

Conclusion: Thus, MDA should be considered in the differential diagnosis of a cervical space-occupying lesion with negative HPV, cervical cytology, and biopsy. With the assistance of the Bard-Magnum Biopsy Instrument, CT-guided biopsy of deep cervical tissues could improve the early diagnosis rate of MDA, which was helpful for clinicians in early diagnosis.

Background

Minimal-deviation adenocarcinoma of the cervix was initially alluded to as adenoma malignum by Gusserow [1], because its cytological features showed the resemblance of the glands to the common endocervical glands, later proposed by Hurt and Silverberg [2] who called it “Minimal deviation adenocarcinoma”. Following the World Health Organization 2014 classification, the neoplasm was classified as a novel entity: Gastric-type adenocarcinoma (GTA). Gastric-type adenocarcinoma of the uterine cervix included minimal-deviation adenocarcinoma of adenoma malignum. The World Health Organization (WHO) also described MDA as an extremely well-differentiated form of GTA [3].

Preoperative clarity diagnosis of MDA was a challenge to our gynecologist. Because of atypical symptoms, infiltration deep of the glands, endogenous growth performance, lack the positive results of HPV, the low positive rate of cytology and biopsy, deceptively benign appearance. In our case, we used a new type of diagnostic tool (Bard-Magnum Biopsy Instrument, USA) to assist us to take the depth of the lesion. The methods of diagnosis of MDA were analyzed and the key to improving the prognosis and the survival rate of the patient was discussed with a brief literature review.

Case Presentation

A 52-year-old, menopausal and multiparous female (gravida11, para2, G11P2) existed cervical contact bleeding in the past 6 years. The patient appeared pelvic pain, vaginal itching, sweating, fatigue, and mucoid vaginal discharge, no abnormalities in the local hospital for TCT, the HPV genotyping test by Hybrid Capture 2, and biopsies. From 2015, the patient made multiple visits to the hospital for TCT and HPV examination which reported the presence of benign squamous epithelium with reactive change and visible inflammatory cells and red blood cells. Multiple HPV genotyping tests by HC2 were negative. One cervical biopsy at the 3, 6, 9, and 12 o'clock positions of the cervical was diagnosed with condyloma acuminate, three cervical biopsies at the 3, 6, 9, and 12 o'clock positions of the cervical showed chronic cervical inflammation, but negative for intraepithelial lesions or malignancies. Transvaginal sonography revealed hydrops in the endometrial cavity and uterine myoma. She was diagnosed and treated with the only vaginitis and the effect was poor. A few months later, the cervical neoplasms were treated by hysteroscopic resection, pathology results confirmed the cervical polyps, chronic cervical inflammation, and squamous metaplasia of the cervical epithelium. Then the patient developed right flank pain symptoms. She went to the hospital and gave the cervical biopsy. The biopsy found chronic cervicitis, partial CIN 1, no HPV infection, loop electrosurgical excision procedures (LEEP) were performed to diagnose chronic cervicitis. At the same time, the patient was difficulty in defecating and oral laxatives could help, anorexia and lower abdominal pain intensified.

Subsequently, this patient was referred to our department. Through the gynecologic examination, a grossly enlarged, thickened, and hard cervix was discovered, and the hypertrophic cervix was like a barrel, gross appearance of the cervix was very contracture, the anterior vaginal fornix appeared partially obliterated, the enlargement of the right sacral ligament was discovered. We highly suspect that this was a case of cervical cancer. However, despite undergoing two conventional cervical biopsies, she was diagnosed with only chronic cervical inflammation and not with cervical malignancy. Two HPV tests by HC2 were negative and with normal liquid-based cytology (LCT) results. Later, our patient undergoing ureteroscope double-J stent insertion due to ureter compression and low back pain. Ultrasound suggests ovaries cyst. The pelvic magnetic resonance imaging (MRI) appeared cervical hypertrophy, morphological abnormalities, the Irregular lumps with long intensity on T1weighted images and high intensity on T2weighted images infiltrated deeply into the uterus, vaginal anterior fornix and the posterior wall of the bladder, the right lower ureter with its proximal ureteral dilatation, infiltration was evident on the right side of the uterine structure. The lumps were measured 51 mm × 33 mm × 41 mm, contrast-enhanced T1-weighted images showed a hyperintense mass. There was a cyst about 6 cm in diameter in the right ovary. No pelvic lymph node metastases. Tumor markers such as carcinoembryonic antigen (CEA), cancer antigen 125(CA125), cancer antigen 19 – 9 (CA19- 9), squamous cell carcinoma antigen (SCC), alpha-fetoprotein (AFP), cancer antigen 153(CA153), neuron-specific enolase (*NSE*), human epididymis secretory protein 4 (HE4), cancer antigen 72 – 4 (CA72-4), free beta-human chorionic gonadotropin (Free β-HCG), and cytokeratin 19 fragment (CYFRA21-1) were within the normal limits. To achieve a definitive diagnosis, a 22-mm-throw biopsy gun (Bard-Magnum Biopsy Instrument, USA) with an 18-gauge automated needle device was used for cervical biopsies under CT guidance. The biopsy was located at the 10, 11, and 12 o'clock positions of the cervical. The biopsy specimens were sent for histological

evaluation, which confirmed the diagnosis of a cervical MDA (Fig. 1a, Fig. 1b). Immunohistochemical staining showed positive staining for P53 and CEA, while ER, PR, and P16 were negative. This case was finally staged as IIIB MDA according to the FIGO staging system.

Our patient was subjected to concurrent chemoradiation. Two courses of paclitaxel 175-mg/m (2) plus nedaplatin 80-mg/m (2) were administered intravenously every 3 weeks. Subsequently, the Intensity Modulated Radiotherapy (IMRT) of cervical and pelvic lymph nodes was performed. Our patient was treated with 50.4 Gy in 28 fractions to the Planning Clinical Target Volume (PCTV) and another 56 Gy in 28 fractions to the Planning Gross Target Volume (PGTV). Intracavitary brachytherapy and interstitial brachytherapy were performed during this period. CT examination showed that the left pelvic cyst was enlarged, the cyst was punctured and catheterized under ultrasound guidance, infusion chemotherapy of paclitaxel and cisplatin for pelvic cyst was performed. After that, the patient felt the relief from pelvic pain. Two courses of chemotherapy containing paclitaxel 175-mg/m (2) and cisplatin 80-mg/m (2) were administered intravenously every 3 weeks. Interstitial brachytherapy was performed during this period. After that, there is a marked narrowing of the lesion, while our patient had recurrent grade 2 gastrointestinal reaction,grade 3 leukopenia and middle liver damage. The patient died a few months later.

Discussion And Conclusions

MDA is a rare form of cervical adenocarcinoma with an incidence of 1–3%, accounting for only 0.15–0.45% of all cervical cancer [4]. The clinical manifestations of MDA were not typical. Li et al. [5] reported a meta-analysis of 347 cases of patients with MDA, 69.4% of patients appeared to have profuse mucoid or watery vaginal discharge, 50.0% of patients had contact or abnormal vaginal bleeding, pelvic pain, or urination obstacle existed in 24.5% of the MDA patients. In our case, her predominant clinical symptoms were pelvic pain and a 6-year history of cervical contact bleeding, gynecological inspection revealed cervical abnormalities, we highly suspect that this was a case of cervical cancer. These symptoms and signs guided us for further examination to confirm the diagnosis.

The preoperative methods for the screening and diagnosis of MDA were liquid-based cytology test, cervical biopsy, imaging technology, and immunohistochemical staining of biopsy tissue. MDA was extremely well-differentiated and lack of malignant cytological characteristics, this tumor could easily be diagnosed with the benign disease in biopsy [6]. In our case, no malignant was identified in multiple cytological tests and 6 cervical biopsies, the positive rate of cytology and biopsy were very low. Hence, accurate diagnosis of MDA previous to treatment was a very intractable problem. The optimally reliable criterium for assessing the malignant nature of MDA is the haphazard array of the glands, beyond the normal range of the endometrial glands (depth > 7 mm), and occasional the glandular epithelium shows mitotic figures [7]. Due to the infiltration depth of the gland is an essential histological feature of MDA, it was difficult to diagnose by biopsy specimens. The majority of cases were diagnosed by conization or hysterectomy. Itoh K et al [8]. believed that the depth of cervical biopsy greater than 5mm or cervical conization was more conducive to the explicit diagnosis of MDA.

It was difficult to diagnose MDA with cross-sectional imaging techniques due to this neoplasm resemble a benign histological appearance. Itoh et al. [8] reported MRI could inspect MDA more effectively compared with CT and transvaginal sonography. By magnetic resonance imaging (MRI), MDA manifested as multiple cavities lesions with solid components extending from the cervical glands to the depth of the cervix. The imaging features of MRI were with intermediate or long signal intensity on T1weighted images and high signal intensity on T2weighted images. T2-weighted MRI images showed more detailed features and reliable correlation with the histological findings [9–12]. In this case, The Irregular lumps displayed long intensity on T1weighted images and high intensity on T2weighted images and have penetrated the surrounding tissues when our patient was referred to our hospital. The detailed features of MRI provided a solid foundation for clinical diagnosis.

Immunostaining of tumor markers and pathology could distinguish benign proliferating diseases of the glands from MDA. Alcian blue pH 2.5/ periodic acid-Schiff staining (AB / PAS), Ki67, carcinoembryonic antigen (CEA), HIK1083 [13, 14], and smooth muscle actin (SMA) [15] helped to confirm the diagnosis of MDA. Isamu Hayashi et al. [16] reported MDA cells produced neutral mucoproteins, the cytoplasm was stained diffusely red by AB-PAS; in contrast, all unremarkable cervical glands and glandular hyperplasias created both acid and neutral mucins, the cytoplasm was stained blue or purple by AB-PAS. HIK1083 is a monoclonal antibody directed bonding gastric mucin, Li et al. [5] reported that Immunostaining for all specimens of MDA was positive for HIK1083 and therefore were positive for gastric mucin, and also showed positive staining of vimentin and proliferating cell nuclei Antigen (PCNA) with 100% sensitivity. Bei lin suggested that the positive rates for p53 and Ki67 in > 50% of the cell nuclei (Ki67/50+) were 88% and 64% in MDA respectively and CA 125 was 18% in MDA [17].

HPV infection is not considered to be associated with MDA because high-risk HPV (types 16 and 18) have found positive in more than 80% of cervical mucinous adenocarcinomas (MACs), but negative in all lobular endocervical glandular hyperplasias (LEGHs) and MDAs examined [18, 19].

Radical hysterectomy with pelvic lymphadenectomy should be performed in the early stage of MDA unless there were contraindications to surgery, otherwise, radiotherapy or chemotherapy should be given. All patients with advanced disease ought to be treated with synchronized radiotherapy or chemotherapy. Surgery alone was usually insufficient in patients with MDA lesions because of the low diagnosis rate of this neoplasm at an early stage.

The prognosis of MDA was controversial. Silverberg SG and colleagues believed that the survival rates of MDA were similar to invasive adenocarcinoma at the same clinical stages [2]. 26 cases of MDA reviewed by Gilks CB et al. proposed a poor prognosis of MDA [20]. They also considered that early diagnosis and treatment could improve the relatively good prognosis of MDA. Kuragaki et al. [21] confirmed that our patients who had minimal deviation adenocarcinoma with mutations in a serine-threonine kinase gene (STK11) had a poorer prognosis than those without mutations. Mucinous ovarian tumors or ovarian sex cord-stromal tumors often co-exist with MDA, Heinritz W et al. [6] also emphasized that ovarian tumors and Peutz-Jeghers syndrome had a certain impact on the progress of MDA. They also suggested that the

expression level of p53 might be an indicator of the local progression of MDA. Li et al. [5] reported that the mean survival of MDA patients with stage I, stage II, stage III, stage IV were 5 years, 38.1 months, 22.8 months, and 5.4 months, separately.

In conclusion, MDA was a rarity in cervical adenocarcinoma. Early clinical manifestations of MDA were lack of specificity and frequently regarded as cervicitis, the effect of treatment was usually poor. The cytological characteristics of MDA were similar to the normal cervical endometrial glands. It was difficult to distinguish between MDA and benign endometrial lesions. Therefore, early diagnosis difficulties often lead to delayed diagnosis. The prognosis of advanced MDA was usually poor [7, 20]. The most reliable criteria for assessing the malignant nature of minimal deviation adenocarcinoma was the haphazard arrangement of the glandular clumps, beyond the normal range of the endometrial glands (depth > 7 mm), and the occasional mitotic figures of the glandular epithelium [7]. MDA cytological examination and biopsy positive rate were very low, while the gynecological examination was still a very significant means of inspection which could able to detect cervical abnormalities. The use of a disposable biopsy gun (Bard-Magnum Biopsy Instrument, USA) could puncture the deep cervical lesions and increase the depth of biopsy which was contributed to the diagnosis of MDA. Great attention must be paid to combining the clinical basic skills with modern imaging techniques, the use of appropriate diagnostic tools, along with multidisciplinary cooperation and exchange could confirm the diagnosis as early as possible and were the key to improve the prognosis and the survival rate of the patient.

Abbreviations

MDA: Minimal-deviation adenocarcinoma; TCT: Thinprep cytologic test;

HPV: the human papillomavirus; HC2: Hybrid Capture 2; CT: computed tomographic;

GTA: Gastric-type adenocarcinoma; WHO: The World Health Organization;

LEEP: Loop electrosurgical excision procedures; LCT: liquid-based cytology;

MRI: magnetic resonance imaging; CEA: carcinoembryonic antigen; CA125: cancer antigen 125; CA19- 9: cancer antigen 19-9; SCC: squamous cell carcinoma antigen; AFP: alpha-fetoprotein;

CA153: cancer antigen 153; *NSE*: neuron-specific enolase;

HE4: human epididymis secretory protein 4; CA72-4: cancer antigen 72-4;

Free β-HCG: free beta-human chorionic gonadotropin; CYFRA21-1: cytokeratin 19 fragments;

IMRT: Intensity Modulated Radiotherapy; PCTV: Planning Clinical Target Volume;

PGTV: Planning Gross Target Volume; AB / PAS: Alcian blue pH 2.5/ periodic acid-Schiff staining; CEA: carcinoembryonic antigen; SMA: smooth muscle actin; PCNA: proliferating cell nuclei Antigen;

MACs: cervical mucinous adenocarcinomas; LEGHs: lobular endocervical glandular hyperplasias;

STK11: serine-threonine kinase gene.

Declarations

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Not applicable.

Author Contributions

Q. Z. drafted the manuscript. Q. Z. and Z. Y. collected data. B. H. confirmed the pathological analysis G. L., Y. Z., and Z. W. performed treatment. Y. Z. designed and organized the study. J. C. revised the manuscript for important intellectual content. This manuscript has been read and approved by all authors.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

The ethical approval and documentation for a case report were waived by the Ethical Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Consent for publication

The patient agreed to the publication of this case.

Competing interests

The authors declare that they have no competing interests.

References

1. Gusserow ALS. Ueber sarcome des uterus. Arch Gynakol. 1870; 1: 240–251. https://doi.org/10.1007/BF01814006
2. Silverberg SG, Hurt WG. Minimal deviation adenocarcinoma ("adenoma malignum") of the cervix: a reappraisal. Am J Obstet Gynecol. 1975;121: 971-975. https://doi.org/10.1016/0002-9378(75)90920-5

3. Kurman RJ, Carcangiu ML, Herrington CS. World Health Organisation Classification of Tumours of the Female Reproductive Organs. 4th Revised ed. International Agency for Research on Cancer, 2014.
4. Kaminski PF, Norris HJ. Minimal deviation carcinoma (adenoma malignum) of the cervix. Int J Gynecol Pathol. 1983;2: 141-152. https://doi.org/10.1097/00004347-198302000-00005
5. Li G, Jiang W, Gui S, Xu C. Minimal deviation adenocarcinoma of the uterine cervix. Int J Gynaecol Obstet. 2010;110: 89-92. https://doi.org/10.1016/j.ijgo.2010.03.016
6. Heinritz W , Strenge S , Kujat A , et al. Different phenotypes including gynecological cancer in three female patients with Peutz-Jeghers syndrome and mutations in the STK11 gene.[J]. Onkologie, 2008, 31(11):625-628.https://doi.org/10.1159/000162284
7. McKelvey J L, Goodlin R R. Adenoma malignum of the cervix. A cancer of deceptively innocent histological pattern. Cancer, 1963, 16(5): 549-557. https://doi.org/10.1002/1097-0142(196305)16:5<549::AID-CNCR2820160502>3.0.CO;2-M
8. Itoh K, Toki T, Shiohara S, Oguchi O, Konishi I, Fujii S. A comparative analysis of cross sectional imaging techniques in minimal deviation adenocarcinoma of the uterine cervix. Bjog. 2000;107: 1158-1163. https://doi.org/10.1111/j.1471-0528.2000.tb11117.x
9. Doi T, Yamashita Y, Yasunaga T, et al. Adenoma malignum: MR imaging and pathologic study. Radiology. 1997;204: 39-42. https://doi.org/10.1148/radiology.204.1.9205220
10. Gotoh T, Kikuchi Y, Takano M, et al. An extremely rare case of adenoma malignum with large cystic tumor which resulted in urinary obstruction. Gynecol Oncol. 2002;84: 339-343. https://doi.org/10.1006/gyno.2001.6530
11. Yamashita Y, Takahashi M, Katabuchi H, Fukumatsu Y, Miyazaki K, Okamura H. Adenoma malignum: MR appearances mimicking nabothian cysts. AJR Am J Roentgenol. 1994;162: 649-650. https://doi.org/10.2214/ajr.162.3.8109515
12. Oguri H, Maeda N, Izumiya C, Kusume T, Yamamoto Y, Fukaya T. MRI of endocervical glandular disorders: three cases of a deep nabothian cyst and three cases of a minimal-deviation adenocarcinoma. Magn Reson Imaging. 2004;22: 1333-1337. https://doi.org/10.1016/j.mri.2004.08.013
13. McCluggage WG. Immunohistochemistry as a diagnostic aid in cervical pathology. Pathology. 2007;39: 97-111. https://doi.org/10.1080/00313020601123961
14. Ichimura T, Koizumi T, Tateiwa H, et al. Immunohistochemical expression of gastric mucin and p53 in minimal deviation adenocarcinoma of the uterine cervix. Int J Gynecol Pathol. 2001;20: 220-226. https://doi.org/10.1097/00004347-200107000-00003
15. Mikami Y, Kiyokawa T, Moriya T, Sasano H. Immunophenotypic alteration of the stromal component in minimal deviation adenocarcinoma ('adenoma malignum') and endocervical glandular hyperplasia: a study using oestrogen receptor and alpha-smooth muscle actin double immunostaining. Histopathology. 2005;46: 130-136. https://doi.org/10.1111/j.1365-2559.2005.02057.x

16. Hayashi I, Tsuda H, Shimoda T. Reappraisal of orthodox histochemistry for the diagnosis of minimal deviation adenocarcinoma of the cervix. Am J Surg Pathol. 2000;24: 559-562. https://doi.org/10.1097/00000478-200004000-00010
17. Zhu L, Yi X, Lin B, et al. A clinicopathological and immunohistochemical study of minimal d8viation adenocarcinoma of the uterine cervix. Med Hypotheses. 2013;80: 643-648. https://doi.org/10.1016/j.mehy.2012.12.033
18. Kawauchi S, Kusuda T, Liu XP, et al. Is lobular endocervical glandular hyperplasia a cancerous precursor of minimal deviation adenocarcinoma?: a comparative molecular-genetic and immunohistochemical study. Am J Surg Pathol. 2008;32: 1807-1815. https://doi.org/10.1097/PAS.0b013e3181883722
19. Xu JY, Hashi A, Kondo T, et al. Absence of human papillomavirus infection in minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia. Int J Gynecol Pathol. 2005;24: 296-302. https://doi.org/10.1097/01.pgp.0000157918.36354.c1
20. Gilks CB, Young RH, Aguirre P, DeLellis RA, Scully RE. Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol. 1989;13: 717-729. https://doi.org/10.1590/S0103-50531999000300003
21. Kuragaki C, Enomoto T, Ueno Y, et al. Mutations in the STK11 gene characterize minimal deviation adenocarcinoma of the uterine cervix. Lab Invest. 2003;83: 35-45. https://doi.org/10.1097/01.LAB.0000049821.16698.D0

Figures

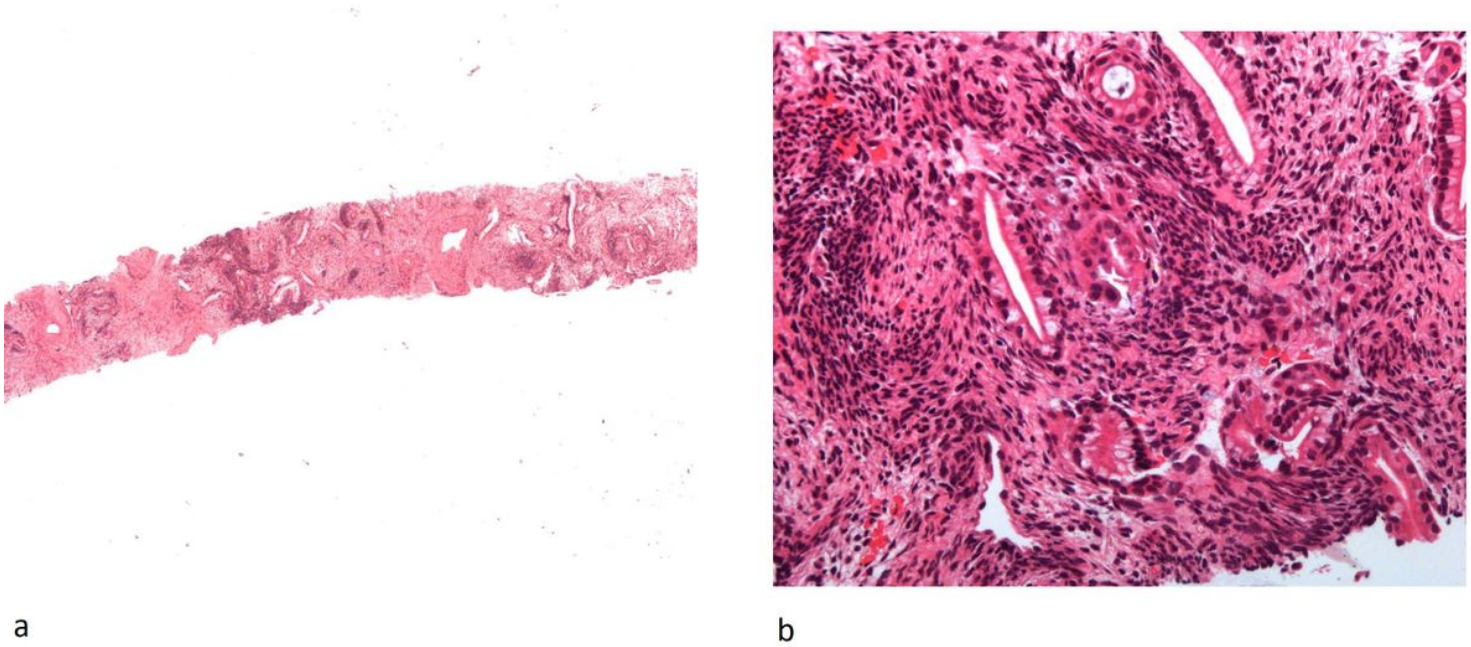

Figure 1

(a) Low power and (b) high power view of minimal deviation adenocarcinoma histopathology. The glands are well-differentiated and show minimal cytological atypia. The density of glands is increased and many glands are back to back. Hematoxylin and eosin (H&E) staining, magnification, (a) x20 and (b) x200.

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