Case Report

Minimal Deviation Adenocarcinoma and Its Mimickers: A Case Report with Review of Literature

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ABSTRACT

Amongst all the glandular lesions of the cervix, minimal deviation adenocarcinoma (MDA) the, so called Adenoma-malignum and its mimickers have been the subject of great interest in the literature. Although a rare entity, MDA commonly requires consultancy to distinguish it from many benign cervical glandular lesions.

MDA is a unique neoplasm of the uterine cervix, characterized by mucinous glands with deceptively benign histological appearance posing difficulty in its diagnosis.

In the present case report MDA was an incidental finding in a 45-year-old female, on the hysterectomy specimen submitted for multiple leiomyomas, and the diagnosis was based on histopathological and immunohistochemical findings.

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Introduction

Amongst all the glandular lesions of the cervix, minimal deviation adenocarcinoma (MDA) the, so called Adenoma-malignum and its mimickers have been the subject of great interest in the literature. Although a rare entity, MDA commonly requires consultancy to distinguish it from many benign cervical glandular lesions. MDA is a unique neoplasm of the uterine cervix, characterized by mucinous glands with deceptively benign histological appearance posing difficulty in its diagnosis.

In the present case report MDA was an incidental finding on the hysterectomy specimen submitted for multiple leiomyomas, and the diagnosis was based on histopathological and immunohistochemical (IHC) findings.

Case Report

A 45 year old female presented with abnormal uterine bleeding, on clinical examination uterus was enlarged and cervix appeared normal. USG revealed multiple leiomyomas. Total abdominal hysterectomy without bilateral salphingo-ophrectomy was performed for leiomyomas and specimen was submitted for histopathological examination.

Gross examination showed multiple leiomyomas and cervix was firm but otherwise unremarkable. Entire cervix was processed for microscopic examination. Low power microscopic examination of the sections from cervix showed proliferation of normal looking endocervical glands deeply infiltrating the underlying stroma. The glands extended into the endocervical stroma beyond the depth of 7mm from the surface, but remained confined to the cervix and no spread to parametrium or myometrium was noted.

Glands were closely spaced and varied markedly in size and shape. Some glands were angulated and showed abnormal out pouching (Fig: 1). Glands were lined by innocuous appearing mucin containing columnar epithelial cells with basal nuclei and inconspicuous nucleoli. Desmoplastic stroma was present around some glands (Fig: 2). However no mitoses, no vascular, perineural invasion and obviously dysplastic or malignant glands were identified. Possibility of endocervical gland hyperplasia, florid deep gland and MDA were considered.

A panel of IHC markers including ER (Estrogen Receptor), PR (Progesterone Receptor), CA-125 and CEA (Carcinoembryonic Antigen) was used and findings were compared with normal endocervical glands and

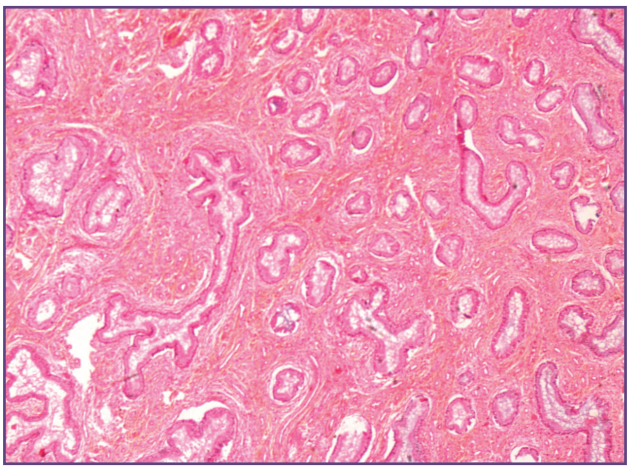

Fig. 1: MDA: Endocervical glands of varying shape & sizes deeply infiltrating cervical stroma (H/E 40X)

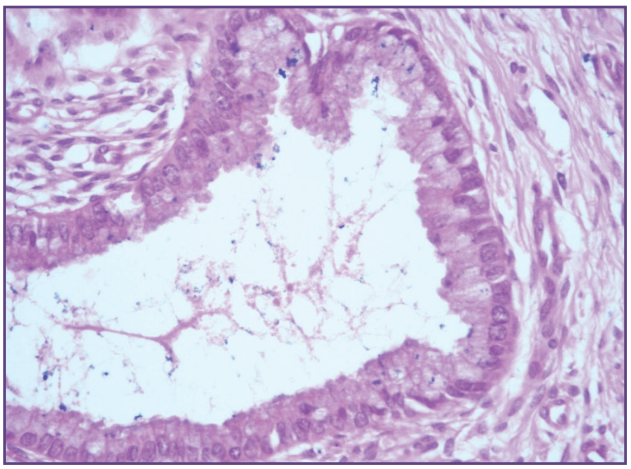

Fig. 2: MDA: Glands lined by bland appearing columnar cells with mild atypia (H/E 400X)

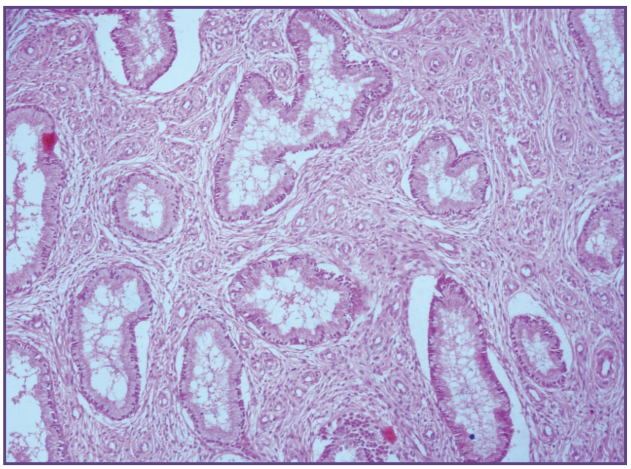

Fig. 3: MDA: Another focus of neoplastic endocervical glands deeply infiltrating cervical stroma (H/E 100X)

tunnel clusters. Our case was ER, PR negative with focal intracytoplasmic positivity for CEA (Table 1). In florid deep gland ER, PR is positive and CEA is negative however we did not have any case of florid deep glands to compare. Based on above findings a diagnosis of MDA was given out.

Discussion

Many pseudoneoplastic glandular lesions of the cervix enter in the differential diagnosis of MDA due to the deceptively benign histologic appearance of the latter such non neoplastic lesions include tunnel clusters, lobular and diffuse laminar endocervical gland hyperplasia, endocervicosis, florid deep gland, microglandular hyperplasia, rarely adenomyomas of endocervical type and deep nabothian cysts. Features of important differentials are discussed in table 2.

Although the glands of MDA have been reported to show slight abnormal histologic findings such as irregular and angular outlines and deep stromal invasion, they often can be misdiagnosed as normal cervical glands or benign lesion in small superficial biopsy specimens.[1] Patients

Table 1: Immunohistochemical findings of present case compared with normal endocervical glands and tunnel clusters.

IHC mArker	Case	Normal endocervical glands	Tunnel cluster
ER	Negative	Positive	Positive
PR	Negative	Positive	Positive
CA-125	Negative	Positive	Positive
CEA	Focal luminal positivity	Negative	Negative

Table 2: Distinguishing features of Minimal Deviation Adenocarcinoma and its differentials.

Features	Minimal Deviation Adenocarcinoma	Florid Deep Glands	Diffuse Endocervical Gland Hyperplasia	Tunnel Clusters (Type A)	Present Case
Depth (>7mm)	>2/3 of cervical wall	Up to 2/3 of cervical wall	Up to inner ½ of cervical wall	–	>2/3 of cervical wall
Architecture	Haphazard arrangement, marked variation in shape & size with abnormal bizarre angular outpouchings	Diffusely scattered uniform glands	Circumferential proliferation & regularly distributed	Lobular architecture of closely packed small glands	Haphazardly arranged glands of varying shape & sizes with abnormal bizarre angulated outpouchings
Cytologic Features	Bland appearing tall columnar cells,+/- focal cytologic atypia or dysplastic glands	Normal endocervical cells	Normal endocervical cells	+/- reactive cytologic atypia	Bland appearing tall columnar cells. No atypia or dysplastic gland
Desmoplastic Stroma	Always present	Absent	Absent	Absent	Present
Mitosis	Present	Absent	Absent	Absent	Present
Vascular & Neural Invasion	+/-	Absent	Absent	Absent	Absent
IHC	ER & PR- Negative CEA-focal I/C & Luminal CA-125- Negative	ER-PR Positive CEA- Negative CA-125 +	ER-PR Positive CEA- Negative CA-125 +	ER-PR Positive CEA- Negative CA-125 +	ER & PR- Negative CEA-focal I/C & Luminal CA-125- Negative

with MDA usually present with watery vaginal discharge, lumbar pain and vaginal bleeding and colposcopic findings vary from firm and indurated cervix to presence of detectable mass lesion in the cervix. [2] In our case the patient presented with abnormal uterine bleeding probably due to multiple leiomyomas and grossly cervix had firm consistency. Available reports show that often the cervix of MDA has gross abnormality however in certain non-neoplastic lesions like tunnel cluster, endocervical lobular hyperplasia [3] and endocervicosis [4], the cervix may be grossly abnormal.

Histopathological findings mentioned in several literature include presence of deeply infiltrating well-differentiated endocervical type glands. Kaminski et al[5] and Gilks et al [6] emphasized that MDA often involves more than two third of the thickness of the cervical stroma and should be regarded as invasive because the normal endocervical crypts and tunnels do not extended beyond 5-7mm. In our case glands extended beyond the thickness of 7mm. Other findings mentioned are desmoplastic stroma at least focally, mitoses, vascular invasion, perineural invasion and presence of occasional glands lined by dysplastic to obviously malignant epithelium. [7]

In the study by Toki et al [1], out of 7 cases of MDA, 5 cases were composed entirely of well-differentiated glands. In our case also tumor comprised entirely of well differentiated glands and lacked any dysplastic or obviously malignant glands.

Tunnel cluster is divided into two forms type A (non – cystic) and type B (cystic) both types show striking lobular architecture. In type A lesions irregularity at the periphery of the cluster and presence of closely packed, small caliber glands may produce a worrisome picture. Neither of the two types have significant cytologic atypia, however reactive cytologic atypia can be seen in type A lesions, other features like desmoplastic stroma, mitotic activity, invasion into deep cervical stroma are consistently absent. [7]

Lobular endocervical hyperplasia [3,7] also has striking lobular arrangement of the hyperplastic glands, which are confined to the inner half of the cervical wall with unremarkable intervening cervical stroma. Cells lining these glands are uniform and lack any cytologic atypia in its pure form however cytologic atypia may be seen in a small subset of cases. Recently an occasional association with adenocarcinoma has been reported.[8] Matsubara et al has drawn attention towards its possible neoplastic nature by showing GNAS mutation [9]. Diffuse laminar endocervical glandular hyperplasia [3,7] has circumferential proliferation of closely packed endocervical glands that form a discrete layer sharply demarcated from the underlying cervical stroma. In MDA glands are irregularly distributed and are often spaced from each others in a desmoplastic stroma.

Endocervicosis is centered in the outer cervical wall and often involves the paracervical connective tissue. [4] There is usually a zone of uninvolved cervical stroma between the glands of this lesion and the overlying ectopic endocervical glands. Glands are of variable size and shape and lining cells are cytologically bland.

Florid deep glands as described by Daya et al [10] show diffusely scattered endocervical glands within the endocervical stroma extending upto outer one third of cervical wall. MDA and florid deep glands may have striking architectural similarity, however the variability in size and shape of the glands in MDA exceeds that seen in florid deep glands and in addition presence of desmoplastic stroma, at least focal cytologic atypia, vascular and or perineural invasion favors the diagnosis of MDA.

Adenomyomas of endocervical type [7,8] are sometimes confused with MDA because the mucinous glands scattered in a myomatous background are misinterpreted as glands of adenoma malignum invading the wall of the cervix. However it is important to recognize the well circumscribed border of the lesion, myomatous nature of its stromal component and lobular pattern of glands lacking any cytologic atypia.

Microglandular hyperplasia is characterized by tightly packed small glands, lined by flattened to cuboidal cells, sometimes arranged in a reticular pattern or as solid cords without a central lumen. Nuclei are often vesicular, nucleoli are indistinct, and mitoses are rare. The cytoplasm is granular, with subnuclear clear vacuoles, resembling endometrial glandular cells in the early secretory phase. [11]

Several reports available on immunohistochemical findings have shown that both ER and PR, which are expressed in nuclei of normal endocervical cells and benign glandular lesions, are consistently absent in glandular cells of MDA.

CEA is negative in normal cervical glands and turns positive in MDA where there is focal cytoplasmic positivity on luminal surfaces and in the luminal secretions.

In the study by Toki T et al [1] all seven cases showed focal positivity for CEA, and their result indicated that an absence of staining for ER and PR is more specific than CEA immunostaining for MDA and more helpful in its differential diagnosis. Similarly Daya et al [10] also emphasized that the diagnosis of MDA should not be

solely based on the immunoreactivity of CEA and its diagnostic utility should be interpreted in the context of other histologic findings.

For CA-125 there is diffuse cytoplasmic staining in normal endocervical glands and in MDA the staining is absent or faintly positive in few glandular cells.

IHC for ER, PR, CA-125 and CEA are helpful in differentiating benign glandular cervical lesions from neoplastic MDA and hence all the cases posing diagnostic difficulty should be subjected to IHC for correct interpretation.

In our case ER and PR were negative where as normal endocervix and tunnel clusters showed positive immunostaining. For CEA there was focal intracytoplasmic positivity and CA-125 was negative in MDA. Zhu L et al performed a detailed immunohistochemical study of MDA involving SMA, Ki67, p53, Vimentin, PCNA, ER, PR, CEA, and CA125 and compared the reactivity with common adenocarcinomas of the uterine cervix. [12]

Unlike squamous cell carcinoma and endocervical adenocarcinoma of cervix, MDA is not associated with HPV infection [13]. Approximately 10% of MDA is accompanied by Peutz Jeghers syndrome [14] and study by McGowan *et al* [15], suggested that the existence of Peutz-Jeghers syndrome or ovarian tumors may contribute to the progression of MDA. Mikami Y demonstrated a close association between MDA and gastric metaplasia [16]. It has been mentioned that pyloric gland metaplasia and endocervical glandular cells present in the cervical

smears of patients with MDA react to mucin giving it a golden yellow staining which is due to acquisition of gastric phenotype and author regarded it as warning sign of MDA requiring immediate histopathologic examination [17]. In a study by Sugihara T et al, lobular endocervical glandular hyperplasia has been suggested as possible precursor lesion of MDA [18]. Various screening modalities like Colposcopy and Acetic Acid Test are not very useful in detection and early diagnosis of MDA however imaging modalities like transvaginal sonography, CT, and MRI are being evaluated for their efficacy to diagnose these cases and MRI has been shown to correlate best with histologic results [19].

Conclusion

To conclude, the glands of MDA loose distinctive features of normal endocervical glands and there is abnormal expression of sex steroid receptors. Thus MDA can present as incidental finding on microscopic examination without any significant gross abnormality and needs to be distinguished from benign glandular proliferations in view of appropriate treatment.

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Competing Interests

None declared

References

1. Toki T, Shiozawa T, Hosaka N, Ishii K, Nikaido T, Fujii S. Minimal deviation adenocarcinoma of the uterine cervix has abnormal expression of sex steroid receptors, CA125, and gastric mucin. Int J Gynecol Pathol. 1997;16:111-6.
2. Kudo R, Sagae S, Kusanagi T, Mizuuchi H, Hayakawa O, Hashimoto M. Minimal-deviation adenocarcinoma (adenoma malignum) of the uterine cervix; four case reports. Eur J Obstet Gynecol Reprod Biol. 1990;34:179-88.
3. Nucci MR, Clement PB, Young RH. Lobular endocervical glandular hyperplasia, not otherwise specified: a clinicopathologic analysis of thirteen cases of a distinctive pseudoneoplastic lesion and comparison with fourteen cases of adenoma malignum. Am J Surg Pathol. 1999;23:886-91.
4. Young RH, Clement PB Endocervicosis involving the uterine cervix: a report of four cases of a benign process that may be confused with deeply invasive endocervical adenocarcinoma. Int J Gynecol Pathol. 2000;19:322-8.
5. Kaminski PF, Norris HJ Minimal deviation carcinoma (adenoma malignum) of the cervix. Int J Gynecol Pathol. 1983;2:141-52.
6. 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;13:717-29.
7. Young RH, Clement PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. Histopathology. 2002;41:185-207.
8. Nucci MR. Pseudoneoplastic glandular lesions of the uterine cervix: a selective review. Int J Gynecol Pathol. 2014;33:330-8.

9. Matsubara A, Sekine S, Ogawa R, Yoshida M, Kasamatsu T, Tsuda H, et al. Lobular endocervical glandular hyperplasia is a neoplastic entity with frequent activating GNAS mutation. Am J Surg Pathol. 2014;38:370-6.
10. Daya D, Young RH. Florid deep glands of the uterine cervix. Another mimic of adenoma malignum. Am J Clin Pathol. 1995;103:614-7.
11. Richard J Zaino. Glandular Lesions of the Uterine Cervix . Mod Pathol 2000;13:261–274.
12. Zhu L, Yi X, Lin B, Gao A, Zhao W, Zhang Y, et al. A clinicopathological and immunohistochemical study of minimal deviation adenocarcinoma of the uterine cervix. Med Hypotheses. 2013;80:643-8.
13. An HJ, Kim KR, Kim IS, Kim DW, Park MH, Park IA, et al. Prevalence of human papillomavirus DNA in various histological subtypes of cervical adenocarcinoma: a population-based study. Mod Pathol. 2005;18:528-34.
14. Kwon SY, Choe MS, Lee HW, Lee HJ, Shin SJ, Cho CH. Minimal deviation adenocarcinoma of the cervix and tumorlets of sex-cord stromal tumor with annular tubules of the ovary in Peutz-Jeghers syndrome. J Gynecol Oncol. 2013;24:92-5.
15. McGowan L, Young RH, Scully RE. Peutz-Jeghers syndrome with 'adenoma malignum' of the cervix. A report of two cases. Gynecol Oncol. 1980;10:125–133
16. Mikami Y, Kiyokawa T, Hata S, Fujiwara K, Moriya T, Sasano H, et al. Gastrointestinal immunophenotype in adenocarcinomas of the uterine cervix and related glandular lesions: a possible link between lobular endocervical glandular hyperplasia/pyloric gland metaplasia and 'adenoma malignum'. Mod Pathol. 2004;17:962-72.
17. Hata S, Mikami Y, Manabe T. Diagnostic significance of endocervical glandular cells with "golden-yellow" mucin on Pap smear. Diagn Cytopathol 2002;27:80–4.
18. Sugihara T, Nakagawa S, Sasajima Y, Matsumoto Y, Takeshita S, Ayabe T. Case of minimal deviation adenocarcinoma: Possible clinical link to lobular endocervical glandular hyperplasia as its origin. J Obstet Gynaecol Res. 2014;26. doi: 10.1111/jog.12538. [Epub ahead of print].
19. 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;107:1158–63.