MESONEPHRIC-LIKE ADENOCARCINOMA OF THE ENDOMETRIUM: A RARE CASE REPORT AND REVIEW OF THE LITERATURE

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Mesonephric-like adenocarcinoma (MLA) of the endometrium is a rare subtype of endometrial carcinoma, accounting for approximately 1% of all endometrial cancers. In the 4th edition of the WHO classification (2014), only "mesonephric carcinoma – MC" of the uterine cervix was recognized, whereas mesonephric-like tumors of the endometrium or ovary were not considered as a separate entity. Following multiple studies describing tumors with morphologic and immunophenotypic features similar to MC but arising from the endometrium or ovary, the 5th edition of the WHO classification (2020) officially designated the term "mesonephric-like adenocarcinoma" to distinguish this entity. MLA exhibits a characteristic immunohistochemical profile, typically showing positivity for GATA-3, CD10, TTF-1 and negativity for ER, PR. A wide spectrum of histologic patterns may be present within the same tumor, which can lead to misdiagnosis as low-grade endometrioid adenocarcinoma, clear cell carcinoma, serous carcinoma, or even carcinosarcoma. Moreover, this type of tumor was reported to be associated with poorer outcome compared to Müllerian-type carcinomas; therefore, an accurate diagnosis is of paramount importance. This article aims to present the first case of MLA in Vietnam in a 62-year-old woman presenting with postmenopausal abnormal bleeding, and to review the literature. We discuss the histopathological, immunoprofile and molecular characteristics, along with differential diagnosis and prognosis, to provide further diagnostic insight for pathologists.

Keywords: Mesonephric-like adenocarcinoma, mesonephric adenocarcinoma, endometrioid carcinoma, case report.

I. INTRODUCTION

Mesonephric-like adenocarcinoma (MLA) of the endometrium is a rare and aggressive malignancy, accounting for approximately 1% of all endometrial carcinomas.[1] It can easily be confused with mesonephric adenocarcinoma (MA), which arises from true Wolffian (mesonephric) remnants and typically occurs in the cervix. These two entities share considerable morphologic, immunohistochemical, and molecular similarities.[2] However, MA has long been officially classified by the WHO as a subtype of cervical epithelial tumor in 4th edition, whereas MLA has only recently been recognized as a distinct histologic entity in the 5th edition. MLA generally arises in the uterine corpus or ovary and exhibits highly heterogeneous histopathologic features, often overlapping with those of Müllerian-type carcinomas. Consequently, distinguishing MLA from more common endometrial carcinomas, including endometrioid, serous, and carcinosarcomatous subtypes, can be particularly challenging.[3] Importantly, MLA is frequently misdiagnosed as another form of endometrial carcinoma, yet it is associated with a more aggressive clinical course and a propensity for early pulmonary

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metastasis.[4-6] Most patients are diagnosed at advanced FIGO stages (II–IV) and tend to experience early recurrence and distant spread.[4] Due to its rarity, diagnostic challenges and distinct prognostic implications, this MLA case report and literature review provides valuable information to the understanding of this entity and to both clinical and pathological practice. This is especially relevant in Vietnam, where no literature review on this case has yet been reported to date.

II. CASE PRESENTATION

Clinical course: A 62-year-old postmenopausal woman, with a history of hypothyroidism under treatment, presented with abnormal vaginal bleeding of moderate volume and mild pelvic discomfort. Initial pelvic ultrasound suggested a possible endometrial polyp and an atypical uterine leiomyoma. Pelvic MRI revealed a space-occupying lesion involving nearly the entire uterine corpus, suspicious for sarcoma. Given these findings, the patient was directly indicated for total hysterectomy without pre-operative endometrial biopsy and allowing for histopathological evaluation and definitive diagnosis.

Pathological findings

Gross findings

+ The uterine corpus measured 10×11×7cm. The serosal surface was smooth, whereas the endometrial surface appeared irregular and granular. Within the myometrial wall, there was a poorly circumscribed yellow-white mass measuring 10×7×7cm, with central areas suggestive of necrosis, occupying nearly the entire myometrial thickness.

+ The cervix and bilateral adnexa showed no gross abnormality.

Microscopic findings: The tumor was located entirely within the uterine corpus, involving nearly the full thickness of the myometrium but without serosal invasion.

+ Architectural feartures: the tumor displayed diverse growth patterns, predominantly consisting of small tubules and glands with eosinophilic luminal secretions, admixed with solid areas and focal papillary or cord-like structures.

+ Cytological feartures: The lining epithelial cells were cuboidal to columnar, with low-grade oval nuclei showing longitudinal grooves and mild nuclear crowding. In some areas, spindle cell differentiation was observed.

Immunohistochemical findings: Tumor cells were positive for CK7, CD10, GATA3, and TTF-1 and negative for ER.

Final diagnosis: Histopathological and immunohistochemical features were consistent with mesonephric-like adenocarcinoma (MLA) of the endometrium;

ICD-O code: 9110/3. FIGO 2023 stage: IB.

III. DISCUSSION

Mesonephric-like adenocarcinoma (MLA) is a rare entity of adenocarcinoma within the female genital tract, recently recognized in the uterus and ovary. It was first described by McFarland et al. in 2016 in a series of twelve cases.[7] Although MLA shares similar morphologic and immunophenotypic features with mesonephric adenocarcinoma (MA) of the uterine cervix, MLA arises in sites lacking true mesonephric remnants - most commonly the uterine corpus and ovary. Therefore, the term “mesonephric-like” is used to reflect the mesonephric-type differentiation occurring in tumors of Müllerian origin. In contrast to classic MA of the cervix, which originates from Wolffian duct remnants, MLA of the uterus typically arises from or is associated with the endometrium, shows no evidence of mesonephric remnants or hyperplasia, and rarely involves the cervix.

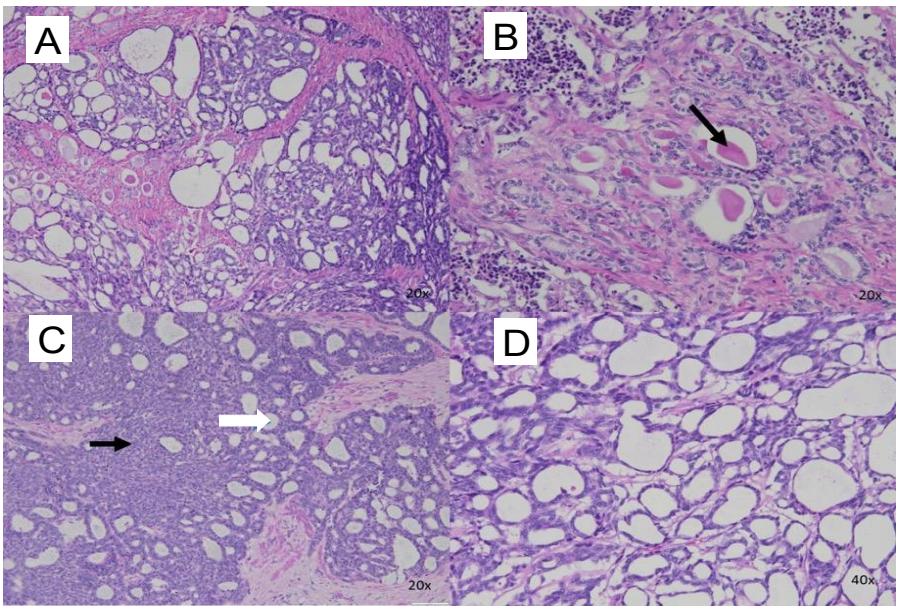

Figure 1. A: Predominantly tubular and ductal architecture resembling low-grade Müllerian-type adenocarcinoma B: Tubular lumina containing eosinophilic, colloid-like secretions mimicking thyroid colloid material (black arrow) C: Foci of spindle cell differentiation (black arrow) adjacent to tubular and glandular areas (white arrow) D: Tumor cells with low-grade, oval to mildly angular nuclei, some showing longitudinal grooves

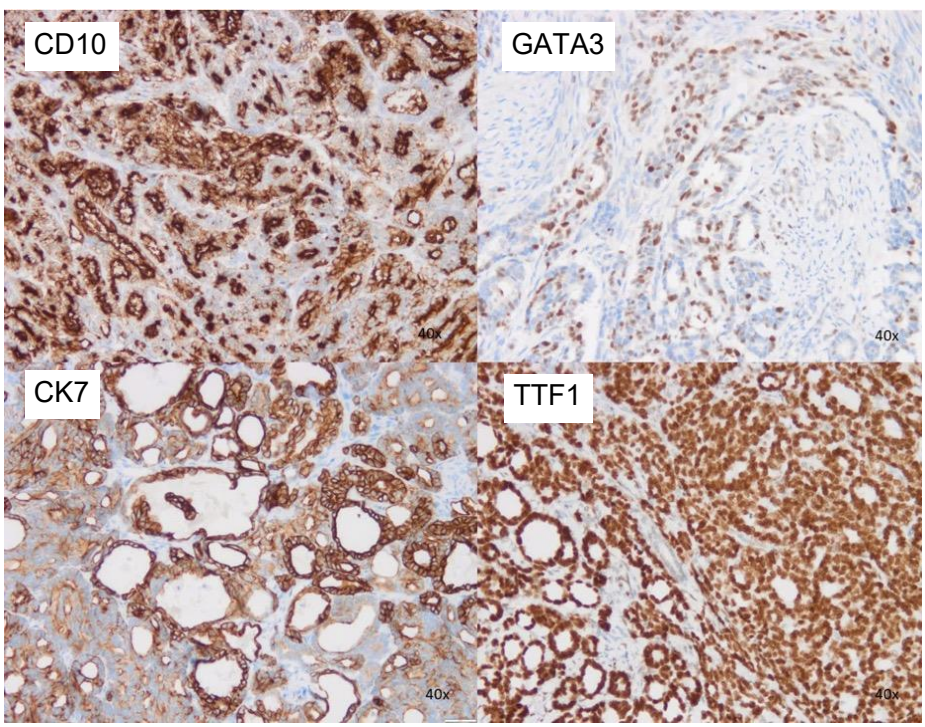

Figure 2. Immunohistochemical staining showing tumor cells positive for CD10, GATA3, CK7, and TTF-1

To contextualize this case within the existing literature, we compiled previously reported cases of endometrial MLA from 2020 to present, including details on authors, year, country, number of cases, stage and outcomes (Table 1). This table aims to provide an updated overview of published uterine MLA cases, emphasizing stage distribution and patient outcomes to better understand the clinical behavior and prognostic patterns of this rare tumor type. Database was conducted using PubMed with the keywords “mesonephric-like adenocarcinoma”, “endometrioid carcinoma”, and “case report”. Only peer-reviewed English-language publications describing histologically confirmed MLA of the endometrium were included.

Table 1. Summary of reported uterine mesonephric-like adenocarcinoma (MLA) cases in the literature (2020 – present)

Author	Year	Country	Number of cases	FIGO Stage	Follow up
Euscher et al.[4]	2020	USA	7	I-III	Poor outcomes in some
Deolet et al.[3]	2021	NA	1	NA	Early local recurrence with metastases
Pors et al.[6]	2021	Canada	12	I-III	Recurrence in 5; deaths reported
Kim et al.[8]	2021	Korea	25	NA	Frequent recurrences and metastases
Ma et al.[9]	2022	China	3	I-II	Favorable short follow up
Current case	2025	Vietnam	1	Ib	Favorable short follow up

NA: Not available

According to previous studies, the age of patients ranges from 42 to 70 years old, with a mean age of approximately 60 years old. The gross features of MLA arising in the uterine corpus have not been fully characterized; however, all reported cases show microscopic evidence of endometrial involvement, and some have been described as having a distinct polypoid appearance on gross examination.[7]

Histologically, MLA consistently demonstrates a heterogeneous architectural pattern, comprising tubular, papillary, sieve-like, ductal, or solid areas lined by cuboidal to columnar epithelial cells. Among these, the ductal and small tubular growth patterns are the most common. The lumina of the small tubules or ducts often contain eosinophilic secretions resembling thyroid colloid. In some cases, foci of spindle-shaped tumor cells may be observed, which can lead to a misdiagnosis of sarcoma. The lining cells are cuboidal or columnar, usually with eosinophilic cytoplasm and oval to angular nuclei that are sometimes overlapping and exhibit longitudinal grooves. The nuclei are generally low-grade, with mild to moderate cytologic atypia. Focal clear cytoplasmic changes may occur but are uncommon. Squamous or mucinous differentiation, as well as any associated mesonephric remnants or hyperplasia, are absent. Consequently, most

reported cases in the literature and all cases from the Leipzig cohort were initially misdiagnosed as low-grade endometrioid adenocarcinoma.[2,5] Even in tumors with a predominantly solid or sarcomatoid appearance, the nuclear features are typically low-grade, with only moderate cytologic atypia.[2,5,7]

The diagnosis of MLA is often challenging, primarily due to its rarity, which means it is frequently not considered or included in the initial differential diagnosis. Differentiating uterine MLA from the more common subtypes of endometrial adenocarcinoma requires a close correlation between histopathologic and immunohistochemical findings. The main differential diagnoses for MLA of the endometrium include tumors that may share tubular, papillary or solid growth patterns and overlapping immunophenotypes, such as endometrioid carcinoma, serous carcinoma, clear cell carcinoma, carcinosarcoma and true cervical mesonephric adenocarcinoma. In particular, when MLA exhibits predominantly tubular or ductal architecture, it is essential to distinguish it from low-grade endometrioid carcinoma, as the two entities have markedly different prognoses. The presence of a precursor lesion, such as atypical endometrial hyperplasia or serous endometrial intraepithelial carcinoma, can aid in the diagnostic process. Therefore, thorough sampling of the specimen is crucial to ensure accurate morphologic evaluation. The distinction between a “true” MA of the cervix and a uterine MLA depends on whether the tumor is located entirely or predominantly within the cervix or the uterine corpus. This distinction can be established through detailed examination of the hysterectomy specimen or by correlating preoperative imaging findings from CT and/or MRI. In the present case, the tumor was confined to the uterine corpus without cervical involvement, confirming its endometrial origin. Histologically, MA of the cervix is typically associated with mesonephric remnants or hyperplasia, which are most often located in the lateral walls of the cervix.

MLA exhibits a characteristic immunohistochemical profile, showing positivity for both “mesonephric-like markers” such as GATA3, TTF1, CD10, and Calretinin, as well as “Müllerian markers” including PAX8 and CK7.[2,10] In contrast, it is typically negative for the hormonal receptors ER and PR, which are diffusely positive in endometrioid carcinoma of the uterus. According to the study by Pors et al., GATA3 and CD10 are highly sensitive and specific markers for tumors showing mesonephric differentiation in the female lower genital tract.[6] GATA3 demonstrates a sensitivity of up to 91% and a specificity of 94%.[1] CD10 is expressed at least focally in most cases, typically showing a luminal or apical staining pattern, with a sensitivity of 73% and specificity of 83%. In some cases, focal and weak ER positivity may be observed; however, PR is consistently negative.[3] Therefore, focal ER expression does not exclude the diagnosis of MLA. The consistent absence of PR expression makes it a more reliable negative marker for this entity. Furthermore, several studies have reported that MLA consistently shows intact mismatch repair (MMR) protein expression and a wild-type p53 staining pattern.[4,6,10]

Emerging molecular data have shown that MLA is characterized by recurrent genetic alterations that support its classification as a distinct tumor entity. The most consistent and defining feature is the presence of KRAS mutations, most commonly at codon 12 or 13, such as KRAS c.38G>A (p.Gly13Asp).[3] These alterations are considered a key molecular hallmark of MLA and assist in

differentiating it from morphologic mimics. In contrast to high-grade endometrial carcinomas, MLA typically demonstrates a wild-type p53 pattern and proficient mismatch repair status, placing it in the “no specific molecular profile (NSMP)” subgroup under current endometrial carcinoma molecular classification systems. Additional mutations that may coexist include PIK3CA and PTEN, which are commonly seen in endometrioid carcinoma.[11] A recent study comprehensively characterized uterine mesonephric-like adenocarcinoma using targeted sequencing, array CGH, and immunohistochemistry on 17, 13, and 17 cases, respectively. Lung metastases occurred in nine patients and disease recurrence in eleven patients. KRAS was the most frequently mutated gene (13/17). In matched primary and metastatic tumors, identical KRAS mutations were identified in three of four pairs and a PTEN mutation in one pair, with no additional mutations detected. This overlap has led to the hypothesis that MLA may arise from Müllerian epithelium undergoing mesonephric-like differentiation rather than from true mesonephric remnants.

MLA of the endometrium is associated with poorer outcome than endometrioid adenocarcinoma, with a higher risk of early metastasis and recurrence. The disease is often associated with features of advanced stage, including larger tumor size, outer half myometrial invasion, lymphovascular invasion, and cervical stromal involvement. Consequently, it is not surprising that MLA is more frequently diagnosed at FIGO stage III or IV compared to low-grade endometrial carcinomas.[4] Notably, MLA demonstrates a markedly higher rate of pulmonary metastasis than other histologic subtypes of endometrial carcinoma.[5,10,12]

IV. CONCLUSION

Mesonephric-like adenocarcinoma (MLA) exhibits several characteristic histopathological features that warrant recognition, including low-grade nuclei with angular contours, overlapping and grooved nuclear membranes and a heterogeneous architectural pattern consisting of tubular, ductal and solid areas. Immunohistochemically, tumor cells show expression of GATA3 and/or TTF-1, together with markedly decreased or absent expression of hormonal receptors ER and PR, supporting the diagnosis of MLA. This tumor type is frequently associated with adverse uterine prognostic factors, compared with more common endometrial carcinoma subtypes. This underscores the importance of recognizing MLA as a distinct pathological entity that should be accurately identified in routine diagnostic practice.

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