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Mesonephric-Like Adenocarcinoma Of The Endometrium: A Potential Diagnostic Pitfall and Institutional Experience

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Abstract

Background: Mesonephric-like adenocarcinoma (MLA) of the female gential tract is a recently described rare adenocarcinoma of the uterine corpus and ovary. This subtype can be very challenging to diagnose as it can mimic other endometrial carcinomas, particularly low grade endometrioid adenocarcinoma and rarely clear cell carcinoma and mucinous carcinoma. MLA of the endometrium often present at an advanced stage with frequent recurrence and distant metastasis, with the most common site being the lung. Misdiagnosis of MLA may prevent patients from benefiting from treatment that is reserved for more aggressive endometrial carcinomas. Post hysterectomy and staging, these patients receive radiation only (stage 1 or 2); and in the metastatic setting (stage 3 or 4) a combination of chemotherapy and radiation. In this case series, a total of eight MLA cases including two metastatic cases are described from a tertiary care Gynecologic Oncology disease site from the regional cancer center.

Conclusion: MLA diagnosis on morphology is challenging as it can mimic a wide range of histologic patterns including endometrioid, mucinous, serous and clear cell carcinoma. Some MLA can have a background of atypical hyperplasia or endometriosis similar to endometrioid adenocarcinoma. Morphology, immunohistochemistry and molecular testing are invaluable in arriving at the diagnosis of MLA given its aggressive clinical course. Clues that may lead to further characterization include but are not limited to glomeruloid, tubular and villous morphology with bland cytology and brisk mitosis, ER/PR negativity, TTF1/GATA3 inverse positivity, PAX-8 positive, p16 negative and KRAS mutations only. All uterine carcinomas resembling low grade ER/PR negative endometrioid adenocarcinoma should have additional immunohistochemical work up and next generation sequencing testing to reach the correct diagnosis and get appropriate treatment.

Keywords: Mesonephric-like adenocarcinoma (MLA); immunohistochemistry; endometrium; morphology; Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations

Introduction

In contrast to mesonephric adenocarcinoma of the cervix arising from mesonephric remnants, which arise from the embryonic remnants of the Wolffian ducts, there is considerable evidence to show that MLA of the endometrium and ovary arises from Müllerian tissue [1, 2]. The process for this potential differentiation to mesonephric function is largely unknown. First reported and identified by [3], MLAs were later included in the 2020 World Health Organization (WHO) Classification of Tumors of the Female Reproductive System [4]. Since then, diagnostic criteria and outcomes have slowly begun to improve with the help of more recent case series and reports. Clinically, MLA shares a similar symptom profile with other gynecologic malignancies. More specifically, early-stage patients present mostly asymptomatic, whereas late-stage patients may experience chronic pelvic pain, abnormal uterine bleeding, abdominal distension, abdominal mass, ascites, and other gastrointestinal symptoms commonly resulting from mesonephric adenocarcinoma [4]. However, unlike other low-grade carcinomas, MLA can become quite aggressive and has the tendency to metastasize to other areas, including the lungs [1, 5]. Currently, prognostication remains challenging due to the limited number of reported cases and sparse long-term clinical follow-up [6]. Additionally, patients with late-stage MLA may still experience disease progression, despite taking various forms of post-operative treatment [6]. Histologically, both mesonephric adenocarcinoma and MLA are virtually identical aside from a lack of mesonephric remnants in the latter [8]. Also, endometriosis or endometrial atypical hyperplasia is also associated with MLAs similar to certain other endometrial carcinomas [7]. As a result, MLA can be easily misdiagnosed as either mesonephric, endometrioid (EC), clear-cell or mucinous carcinomas [1, 2]. This similarity often presents challenges in establishing a definitive diagnosis. Previously, cases of MLA have been shown to notably occur in the uterine corpus and ovaries [3, 4, 6, 7]. Of the eight

cases presented, seven were located in the endometrium, with only one exclusively found in the ovary. Due to its rarity, nonspecific presentation, and overlapping histologic features with other gynecologic carcinomas, MLA can be difficult to diagnose and manage. This case series highlights diagnostic pitfalls and immunohistochemical and molecular profile to aid in correct diagnosis and management.

Materials and Methods

All diagnoses of MLA and EC (initial biopsies and final hysterectomy staging specimens) that were negative for estrogen receptors and progesterone receptors (ER/PR) in the past three years were reviewed by two gynecological pathologists at the Juravinski Hospital and Cancer Centre in Hamilton Ontario. Information was then electronically accessioned to the medical record. Thyroid transcription factor one (TTF1) and GATA binding protein 3 (GATA3) immunohistochemical stains and next generation sequencing were additionally performed on all cases to assist in reclassification. The slides were also reviewed for MMR profile (proficient or deficient) by immunohistochemistry. Next generation sequencing was performed on formalin-fixed paraffin-embedded tissue using the Roche Kit for endometrial biomarkers and using the Thermofisher Scientific system looking for the KRAS mutation.

Results

Table 1: Patient results discussed in Table 1. Summary of cases including patient age at initial diagnosis, tumor location, molecular studies and clinical management.

Age	Location	ER/PR	GATA3/ TTF1	p53	MMR	KRAS mutation by NGS	Initial Diagnosis	Clinical Decision after (initial diagnosis)	Recurrence/ Metastasis	Clinical Decision
74	Endometrium	-/-	-/-	Wild type	intact	c.183A>C, p.(Gln61His)	FIGO grade 1 EC, pT1aN0	Low risk disease, adjuvant radiation would not provide additional survival benefit	-	
52	Ovary	-/-	+/+	Wild type	intact	c.35G>T, p.(Gly12Val)	Ovarian EC type, moderately differentiation, stage lic	6 cycles of Taxol Carboplatinum and Epirubicin (clinical trial w/ addition of epirubicin)	Pelvis, lung, brain, liver, intraperitoneal	27/09/2002: Pelvis; recurrent EC of ovary IND.149 clinical trial, carboplatin plus OSI-774 (Erlotinib;HER1/ EGFR inhibitor) 2022: Brain MLA metastasis Craniotomy and post op radiation with SRS Jan 2023 2023: Lung MLA metastasis Segmental lung dissection 2024 (CT-ABD/P): Progression of disease in abdomen Started single agent carboplatin June 13th, 2024
65	Endometrium	-/-	+/-	Wild type	intact	c.35G>T, p.(Gly12Val)	MLA, pT2 pN0	Pelvic radiotherapy and chemo carboplatin and paclitaxel	-	
61	Endometrium	-/-	+/-	Wild type	intact	c.35G>C, p.(Gly12Ala)	MLA, pT1a pN0	MCC recommendation of sandwich chemoradiation therapy; pelvis radiation + Carbo-Taxol	-	

82	Endometrium, lower uterine segment & cervix	-/-	+/+ (rare focal)	Wild type	intact	c.35G>C, p.(Gly12Ala)	Mesonephric adenocarcinoma, pT3b pN0	MCC recommendation of sandwich chemoradiation therapy; pelvis radiation + Carbo-Taxol; patient declined	-	
48	Endometrium	-/-	+ (very focal)/+	Wild type	intact	c.35G>T, p.(Gly12Val)	FIGO grade 1 EEC, pT1a	No adjuvant treatment required	Pelvis, omentum, liver, urinary bladder	2022/05: Endometrioid adenocarcinoma, FIGO grade 1, ER/PR negative "Given that this is a low-grade and there is no measurable disease, we would not recommend her to go on chemotherapy" 2022/12 (CT-ABD/P): Progression of disease in liver and urinary bladder Palliative chemotherapy with carboplatin and paclitaxel (completed 8 cycles) and now on second-line palliative immunotherapy with pembrolizumab and antiangiogenesis with lenvatinib 2024/03 (2022 diagnosis amendment): MLA
52	Endometrium, lower uterine & cervix	+(40%)/-	+/+ (variably)	Wild type	intact	c.35G>C, p.(Gly12Ala)	MLA and minor component of FIGO grade 1 EEC, pT2 pN1mi(sn)	PORTEC 3 protocol; pelvic radiation w/ 2 cycles of concurrent cisplatin followed by 4 cycles of adjuvant paclitaxel/ carboplatin	-	
80	Endometrium	+(focal)/-	+ (focal)/-	Wild type	intact	c.38G>A, p.(Gly13Asp)	MLA, pT2 pN0	Adjuvant carboplatin & paclitaxel and pelvic radiotherapy	-	Adjuvant carboplatin & paclitaxel and pelvic radiotherapy

A total of eight MLA cases including two metastatic cases were analyzed (Table 1). Age ranged from 42-82 years. Two cases of recurred sites included the pelvis, omentum, brain, lung and liver. A combination of subtle histologic features, immunohistochemistry (ER/PR negative with GATA3/TTF1 mirrored staining pattern) and molecular profile of KRAS mutation with no pathogenic mutation for POLE or TP53 by NGS led to the accurate diagnosis of MLA. The corrected diagnosis was communicated to the clinicians for standard of care treatment. Additionally, all eight cases presented paired box gene 8 (PAX8) positivity, were p53 wild type, and were MMR intact by immunohistochemistry of MLH1, MSH2, MSH6 and PMS2 proteins.

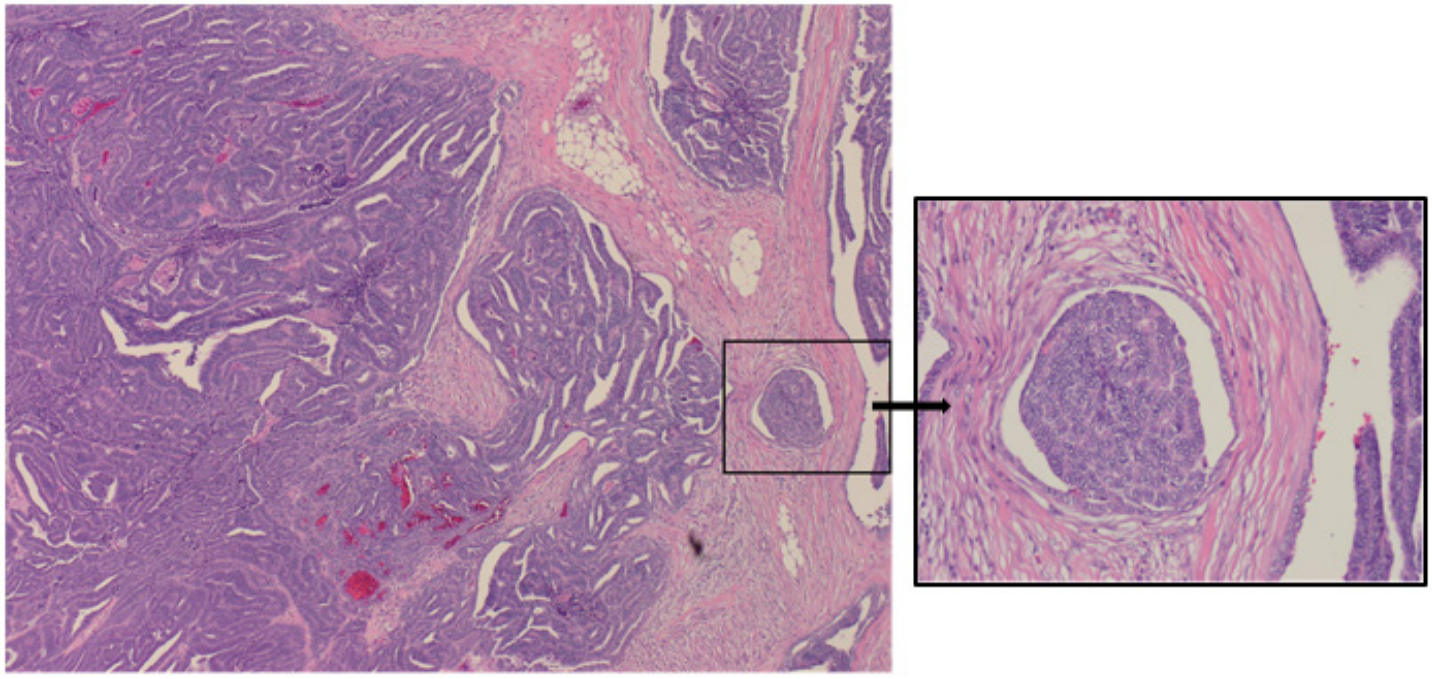

Figure 1. MLA resembling low grade (FIGO 1) endometrioid adenocarcinoma with glandular architecture. H&E staining at 100x magnification. Insert showcasing glomeruloid architecture at 200x magnification.

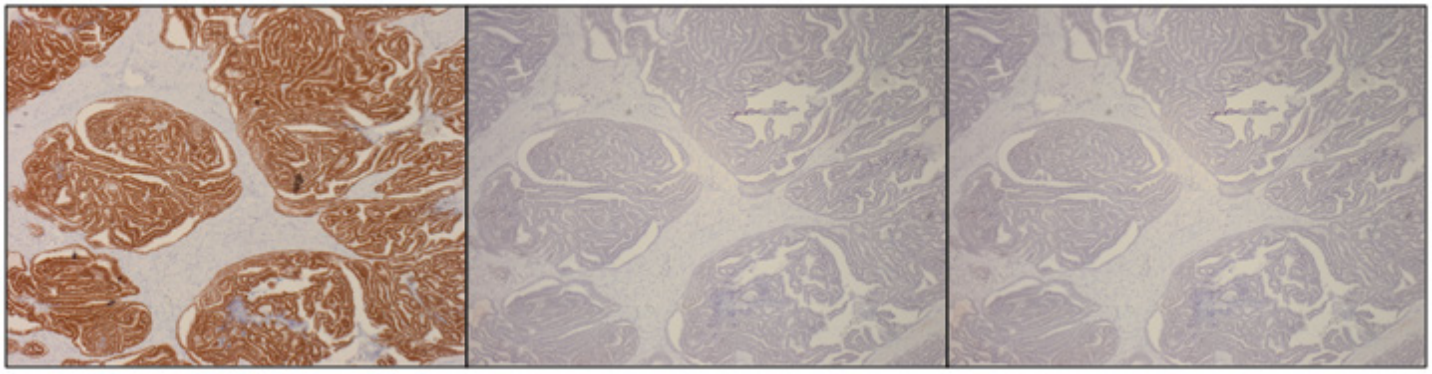

Figure 2. Nuclear staining at 100x magnification showing mirrored GATA-3/TTF1 positivity and negative estrogen and progesterone receptors.

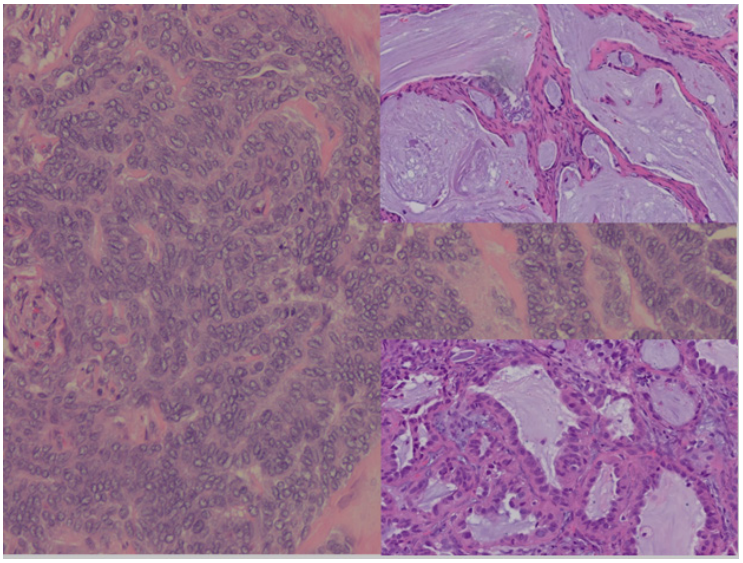

Figure 3. MLA resembling a more solid architectural pattern, with inserts showing MLA with mucinous and clear cell carcinoma features respectively. Eosinophilic cytoplasm and nuclear hobnailing present in the clear-cell carcinoma appearing MLA. H&E staining completed at 100x magnification for all slides.

Discussion

Mesonephric and mesonephric-like carcinomas may showcase a variety of architectural patterns, including tubular, solid, papillary, gonadal, retiform, and ductal, as well as combinations of these factors [8]. All of these patterns can also be associated with increased mitotic activity and cytologic atypia [8]. This wide variety can contribute to the complexity of diagnosis and underscore the need for careful histopathological evaluation (Figures 1-3). Additionally, the nuclei of associated cells can appear to be malformed and can have pseudoinclusions with nuclear overlap, resembling features used more often to describe papillary thyroid carcinoma [2]. These nuclear features can be particularly misleading and may result in diagnostic confusion with other tumor types. Cytologically, the tumor cells can appear flat, columnar or cuboidal, with eosinophilic cytoplasm [4], and may also present with a mixed sarcomatoid or spindle cell component [2]. Due to their rare nature and wide variety of presentation, MLAs cannot fall into a specific category of commonly recognized carcinomas [9]. Similarly, they may initially be recognized as either mesonephric, clear cell or endometrioid carcinoma [5, 10]. In cases where MLA has been overlooked, a lack of observation towards papillary and ductal patterns may have been the cause [10]. Full observation of both morphologic and immunohistologic factors should be considered for proper diagnosis.

There are many different immunohistochemical relations that can support the diagnosis of MLA. Some of these would include positive expressions of PAX-8, GATA3, TTF1, CD10(Variable staining),p53 wild type, MMR IHC intact , and p16 mosaic staining patterns [11]. These markers, while not entirely specific, are frequently used in combination to narrow the differential diagnosis. There has also been evidence to show that negative expression for ER/PR is highly correlated with MLA, and that PR negativity appears to be a more accurate marker when compared to ER [2, 3]. The lack of hormone receptor expression further distinguishes MLA from other gynecologic malignancies, such as low grade endometrioid carcinomas, which often retain ER/PR positivity. Additionally, almost all observed cases of MLA harbored mutations of the KRAS gene [10, 11]. Of the few cases that do not, it is likely that mutations would be present on other segments of the MAPK pathway [2]. In some cases, despite both factors being indicative of MLA, GATA3 and TTF1 may show inverted staining patterns [12]. Though GATA3 on its own has been the most reliable marker for mesonephric differentiation, this inverted pattern with TTF1 can help further confirm a diagnosis if GATA3 is negative on a small biopsy [12]. Similarly, negative SOX17 expression has been shown to support MLA, in contrast to other Mullerian-derived carcinomas [13]. Exactly how this biomarker relates to its probable Mullerian origins remains unknown [13].

Most cancers of the female gynecological tract are typically treated with a combination of surgery, radiation therapy, chemotherapy, and hormone therapy, depending on the type and stage of the cancer. Patients with endometrial MLA often also receive adjuvant radiation [5, 14]. In other reports, about one-fifth of the reported endometrial and ovarian MLAs were treated with both carboplatin and paclitaxel postoperatively [5, 14]. Despite this, the overall efficacy of chemotherapy in improving long-term survival for MLA remains unclear due to limited case numbers and short follow-up periods. Multidisciplinary team discussions are often essential to tailor management strategies for these complex and rare tumors. Though recurrence of MLA isn't uncommon, death as a result of these recurrences has been shown to be significantly lower ([15]. Whether or not the FIGO grading system should be used or if some other method would be more successful remains controversial [1, 15]. As a result, the best treatment plans are not always recommended to patients whose lesions appear low-grade [1]. In our Gynecologic Oncology center, post hysterectomy and staging, these patients receive radiation only (stage 1 or 2); and in the metastatic setting (stage 3 or 4) a combination of chemotherapy and radiation.

MLA of the endometrium or ovary can mimic other gynecologic carcinomas and can often appear very similar to low grade endometrioid carcinoma, despite often showcasing significantly more aggressive behaviour [11]. Therefore, accurate diagnosis has become crucial in ensuring appropriate patient management. Morphological similarities can make diagnosis challenging for even experienced pathologists, increasing the risk of misdiagnosis. Also, these lesions can frequently recur and tend to metastasize to other areas of the body. Areas can include the lungs, brain and spleen. This behaviour even further demonstrates the importance of recognizing MLA accurately and early on. Misdiagnosis of MLA may prevent the patient from benefiting from treatment that is reserved for more aggressive endometrial cancers, potentially affecting the prognosis and survival outcomes. In some cases, an interdisciplinary approach to treatment may be required. Additionally, the true prevalence of MLA may not be accurately known as a result of often misdiagnosis; MLAs are underrecognized when classic morphological features are difficult to identify. Maintaining accurate diagnosis through utilising relevant biomarker tests can significantly affect future patients, as it can enable timely and tailored therapeutic strategies that better reflect the biological behavior of the disease.

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