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Mini Review

Mesonephric Carcinoma and Mesonephric-like Adenocarcinoma of the Female Genital Tract

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Abstract

Background and objectives: Mesonephric carcinoma (MC) is a rare type of cervical carcinoma that arises from mesonephric remnants. It is characterized by a mixture of a wide variety of growth patterns and typically exhibits positive immunoreactivity for GATA binding protein 3, thyroid transcription factor 1, and apical common acute lymphoblastic leukemia antigen. A subset of adenocarcinomas in the uterine corpus and ovary with similar morphology and immunophenotype is classified as mesonephric-like adenocarcinoma (MLA) in the current World Health Organization classification. This review aimed to summarize the clinicopathological features of mesonephric remnants, mesonephric hyperplasia, and MC, provide an update on the current understanding of MLA, and highlight the molecular differences between MC and MLA. ***Methods:*** A literature review was conducted on mesonephric remnants, mesonephric hyperplasia, MC, and MLA. The clinicopathological and molecular features were summarized from previously published studies and compared across these entities. ***Results:*** Both MC and MLA exhibit a mixture of growth patterns and show immunoreactivity for GATA binding protein 3, thyroid transcription factor 1, and common acute lymphoblastic leukemia antigen. They commonly harbor genetic alterations in *KRAS* and *NRAS*. However, key differences exist between these two entities. MC is associated with mesonephric remnants, whereas no such association has been identified for MLA. Additionally, although *KRAS* and *NRAS* mutations are common in both, a subset of MLA cases also harbors *PIK3CA* and/or *PTEN* mutations, genetic alterations commonly seen in endometrioid adenocarcinoma. ***Conclusions:*** Although the exact pathogenesis of MLA remains unclear, it is favored to originate from Müllerian-derived epithelium undergoing differentiation along the mesonephric pathway, rather than from true mesonephric remnants. Both MC and MLA tend to follow a relatively aggressive clinical course, underscoring the importance of accurate diagnosis.

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Introduction

Mesonephric carcinoma (MC) is a rare type of cervical adenocarcinoma that arises from mesonephric remnants.[1–5] MC is characterized by a mixture of growth patterns, including tubular, papillary, ductal, solid, spindled, retiform, sex cord-like, hobnail, glomeruloid, and sieve-like architectures, and it typically shows positive staining for paired-box 8 (PAX8), GATA binding protein 3 (GATA3), and luminal staining of common acute lymphoblastic leukemia antigen (CD10).[6–8] A subset of adenocarcinomas arising in the uterine corpus and ovary with similar morphological features and immunophenotype is currently classified as mesonephric-like adenocarcinoma (MLA) in the World Health Organization classification of female genital tumors.[7] MLA typically exhibits diffuse nuclear staining for thyroid transcription factor 1 (TTF1), but shows less frequent GATA3 expression compared to MC. While both MC and MLA commonly harbor *KRAS* or *NRAS* mutations, MLA may also demonstrate additional genetic alterations in *PIK3CA* and *PTEN*.[9–15] Current evidence suggests that MLA is not associated with mesonephric remnants but rather arises from Müllerian epithelium undergoing mesonephric-like differentiation, although its exact origin remains unclear.[11,16,17]

Given their rarity and significant morphological variability, the diagnosis of MC and MLA can be challenging, with a broad range of entities to consider in the differential diagnosis. The aim of this mini-review was to discuss the clinicopathological features, molecular alterations, current understanding, and differential diagnoses of mesonephric remnants, mesonephric hyperplasia, MC, and MLA. Our goal was to increase awareness of these rare entities and emphasize the importance of ancillary studies in facilitating accurate diagnosis.

Mesonephric remnants and hyperplasia

Mesonephric remnants are vestiges of the mesonephric (Wolffian) ducts. During early embryologic development, human embryos contain paired mesonephric and parame-

sonephric (Müllerian) ducts.[5] In females, the mesonephric ducts regress, leaving only vestigial mesonephric remnants with no known function, while the paramesonephric ducts develop into the fallopian tubes, uterus, and part of the vagina. In males, the paramesonephric ducts regress, and the mesonephric ducts give rise to the efferent ducts of the testis, epididymis, vas deferens, seminal vesicles, ejaculatory ducts, and portions of the prostate and urethra.[18]

Mesonephric remnants are typically identified in asymptomatic women and are most commonly located in the lateral wall of the cervix (at the three or nine o'clock positions), found in up to one-third of cervical specimens.[19] Occasionally, they may be present within the myometrium of the uterine corpus, vagina, ovarian hilum, or mesosalpinx.[5] These remnants are usually non-mass forming and are often identified incidentally in specimens obtained for unrelated reasons.

Histologically, mesonephric remnants are composed of clusters or linear arrays of small to medium-sized tubules lined by cuboidal cells with scant eosinophilic cytoplasm, lacking cilia, mucin, or squamous differentiation. The nuclei are uniform, round to ovoid, with occasional slight irregularities. The tubules often contain dense eosinophilic periodic acid-Schiff-positive intraluminal secretions.[20] Mitoses are generally absent. Mesonephric remnants are typically located deeper within the cervical stroma compared to normal endocervical glands.

Mesonephric hyperplasia is a proliferation of mesonephric tubules with features similar to those of mesonephric remnants. It is usually encountered as an incidental finding but may rarely form a discrete mass, in which complete excision is important to exclude the possibility of potential MC.[20–22] Histologically, it resembles mesonephric remnants, but with a greater abundance of tubules and ducts.[20,21] A size cut-off of 6 mm was arbitrarily proposed by Ferry and Scully to help distinguish remnants from hyperplasia.[20] The most common growth pattern is the lobular variant, in which simple tubules are arranged in lobules with a variable amount of intervening stroma.[19] Diffuse mesonephric hyperplasia lacks a lobular or clustered growth pattern. The least common pattern is ductal hyperplasia, characterized by a proliferation of ductal structures rather than simple round tubules. The ductal variant usually lacks eosinophilic intraluminal secretions.[23]

Immunohistochemically, mesonephric remnants, mesonephric hyperplasia, and MC have similar staining patterns. The mesonephric-derived epithelium is usually positive for PAX8, GATA3, TTF1, and calretinin, and is negative for estrogen receptor (ER), progesterone receptor (PR), and p16.[3,8,24,25] CD10 typically highlights the luminal aspect of the epithelial cells.[26,27]

Entities that commonly enter the differential diagnosis of mesonephric remnants or hyperplasia include endometriosis, deeply sited endocervical glands, endocervical adenocarcinoma (including *in situ*), MC, and endometrial carcinoma with cervical stromal involvement. Endometriosis shows endometrial-type glands with endometrial stroma and/or evidence of old hemorrhage. Deeply sited endocervical glands typically have columnar epithelium containing intracytoplasmic mucin but lack intraluminal secretions. Human papillomavirus (HPV)-associated endocervical adenocarcinoma is characterized by hyperchromatic nuclei, abundant apical mitotic figures, apoptotic bodies, and block-type p16 positivity. Carcinomas show architectural complexity, back-to-back glands without intervening stroma, higher degrees of cytologic atypia, elevated mitotic activity, and haphazard infiltrative growth. Mesonephric hyperplasia does not harbor *KRAS* or *NRAS* mutations, a characteristic feature of MC.[23]

Mesonephric carcinoma

MC affects a wide age range, with a mean age of approximately 53 years.[7] It is frequently associated with mesonephric remnants and mesonephric hyperplasia, and shares similar immunohistochemical characteristics. MC can arise in the uterine cervix, lateral vaginal wall, broad ligament, mesosalpinx, ovarian hilum, and very rarely, in the uterine corpus; however, the vast majority occur in the cervix.[1–5] MC is rare and accounts for less than 1% of cervical adenocarcinomas.[2,4,28]

Patients typically present with vaginal bleeding, abnormal Papanicolaou smears, or a firm mass in the lateral cervical wall; however, MC may also be discovered incidentally.[2,4] Histologically, MC exhibits a wide range of architectural patterns, including tubular, papillary, ductal, solid, spindled, retiform, sex cord-like, hobnail, glomeruloid, and sieve-like formations.[6,7] A mixture of these patterns is frequently present within the same tumor (Fig. 1). The classic tubular pattern is composed of cuboidal cells and may contain densely eosinophilic intraluminal secretions resembling those seen in mesonephric remnants. The ductal (pseudoendometrioid) pattern features angulated glands lined by columnar cells. The nuclei are typically uniform with coarse or vesicular chromatin, irregular membranes, and frequent nuclear grooves. Occasional nuclear pseudoinclusions may also be observed. Overall, the cytologic features can resemble those of papillary thyroid carcinoma (PTC). Mitotic activity is variable. Squamous differentiation and intracytoplasmic mucin are absent.

Immunohistochemically, MC shares a similar staining pattern with mesonephric remnants. PAX8 positivity and apical CD10 staining are typically present. GATA3 is less frequently positive in MC compared to mesonephric remnants and hyperplasia; however, approximately 95% of MC are GATA3 positive (Fig. 1), with wide variability in intensity and extent of staining.[8] TTF1 may be focally positive. The p53 staining pattern is wild-type. Mismatch repair (MMR) proteins (MLH1, PMS2, MSH2, MSH6) show intact nuclear expression. p16 is patchy (non-block-type), and HPV is not detected. Calretinin and inhibin are variably positive. MC is usually negative for ER, PR, Napsin A, and Alpha-methylacyl-CoA racemase (AMACR), although focal positivity for ER and PR may be occasionally observed.[2,3,8,25,27,29–31]

Genetically, the majority of MCs harbor *KRAS*/*NRAS* mutations and a gain in chromosome 1q, with a subset also exhibiting loss of 1p. Two-thirds have mutations in chromatin remodeling genes such as *ARID1A/B* or *SMARCA4*, and one-third harbor *BCOR/BCORL1* mutations. A minority have *CTNNB1* mutations. Other recurrent copy number alterations include gain of 2p and chromosomes 10, 12, and 20, as well as loss of 9p, chromosome 9, and chromosome 19. MCs demonstrate a low tumor mutation burden and lack microsatellite instability. Mutations in *PIK3CA* and *PTEN*, commonly seen in endometrial endometrioid adenocarcinoma, are not identified in MC.[6,32]

Mesonephric-like adenocarcinoma

A subset of endometrial and ovarian adenocarcinomas shares morphological features similar to MC but has a distinct immunophenotype, including negative expression of ER and PR, and often diffuse nuclear staining with TTF1. These adenocarcinomas are found to be associated with endometriosis, cystadenoma, adenofibroma, borderline tumors, and low-grade serous carcinoma in the ovaries.[33,34] In the uterine corpus, they appear to arise from the endometrium, rather than being predominantly myometrial based. Some

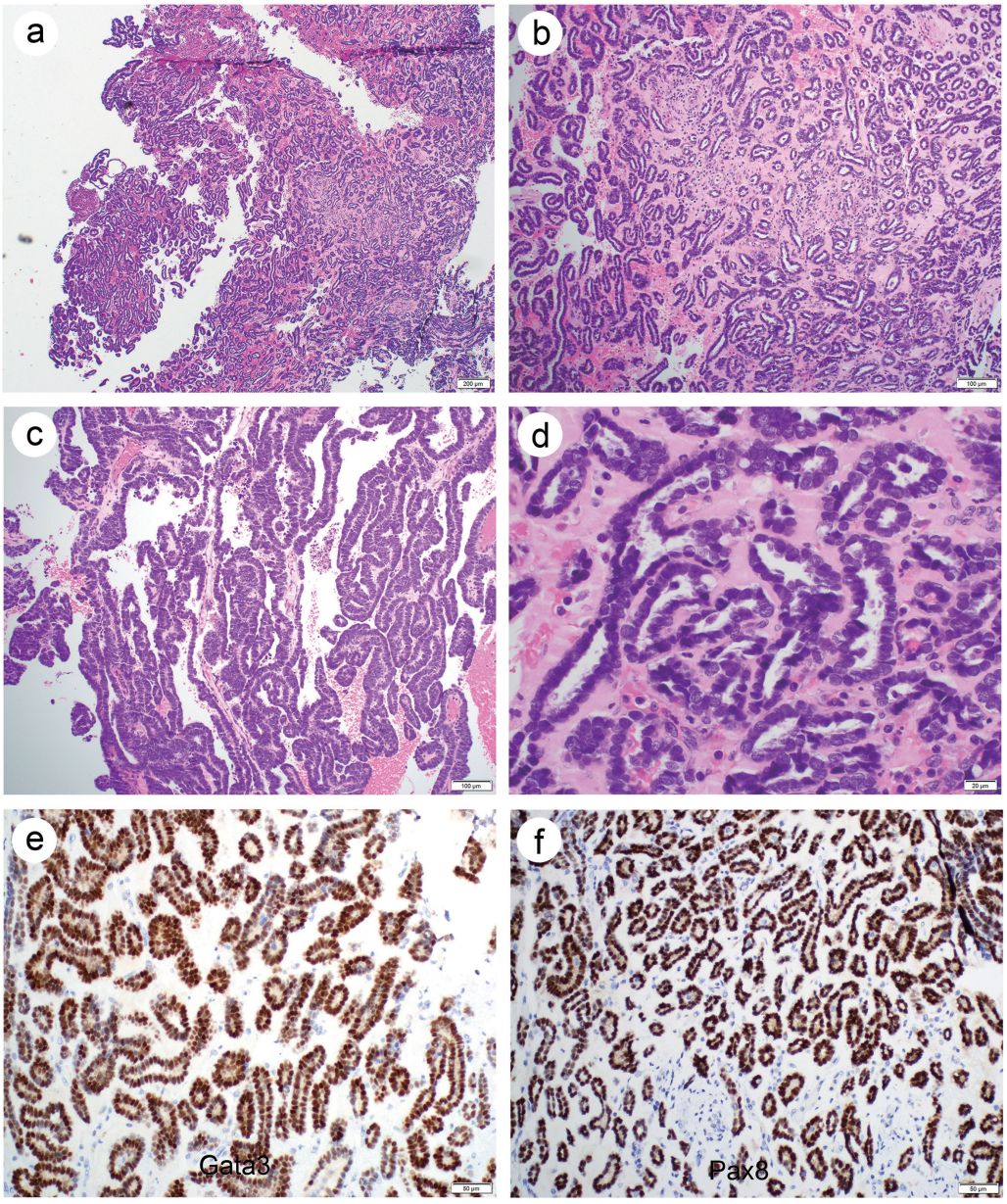

Fig. 1. A mesonephric carcinoma (MC) of the uterine cervix with admixed growth patterns (a, 40×), including classic tubular (b, 100×) and papillary (c, 100×) architecture. Rare intraluminal eosinophilic secretions are present (d, 400×). The neoplastic cells are relatively uniform, with coarse or vesicular chromatin, irregular nuclear membranes, and occasional nuclear grooves (d, 400×). The neoplastic cells are diffusely and strongly positive for GATA3 (e, 200×) and PAX8 (f, 200×). The majority of MC cases are GATA3-positive, though there is considerable variability in both staining intensity and extent of staining. Other types of carcinomas in the female genital tract are usually negative or only focally positive for GATA3. GATA3, GATA binding protein 3; PAX8, paired box gene 8

cases are arising from atypical endometrial hyperplasia. Mesonephric remnants or hyperplasia are not seen in the background.[16,33,35] All available evidence indicates that these neoplasms may not be mesonephric origin but arise from Müllerian epithelium that differentiates along a mesonephric pathway. In 2016, McFarland and McCluggage first proposed the terminology MLA to reflect the uncertainty of tissue origin.[33] This terminology was later incorporated into the 2020 World Health Organization Classification of Female Genital Tumors.[7]

The mean age at diagnosis of MLA is 60 years.[36] The characteristic morphological features of MLA include an admixture of variety of architectural growth patterns in various combination and frequent eosinophilic colloid-like material in tubular lumens, which are identical to those seen in MC.[7] The neoplastic cells typically exhibit moderate nuclear atypia. The nuclei are clear to vesicular and angulated, with a variable number of nuclear grooves. The nuclei are frequently crowded and overlapping, resembling those seen in PTC (Fig. 2). The cytoplasm is generally scant, and mitotic figures are conspicuous. Similar to MC, no squamous or mucinous elements are present. The nuclei can be ovoid or spindled in the solid component.

Immunohistochemically, MLA usually shows, though not

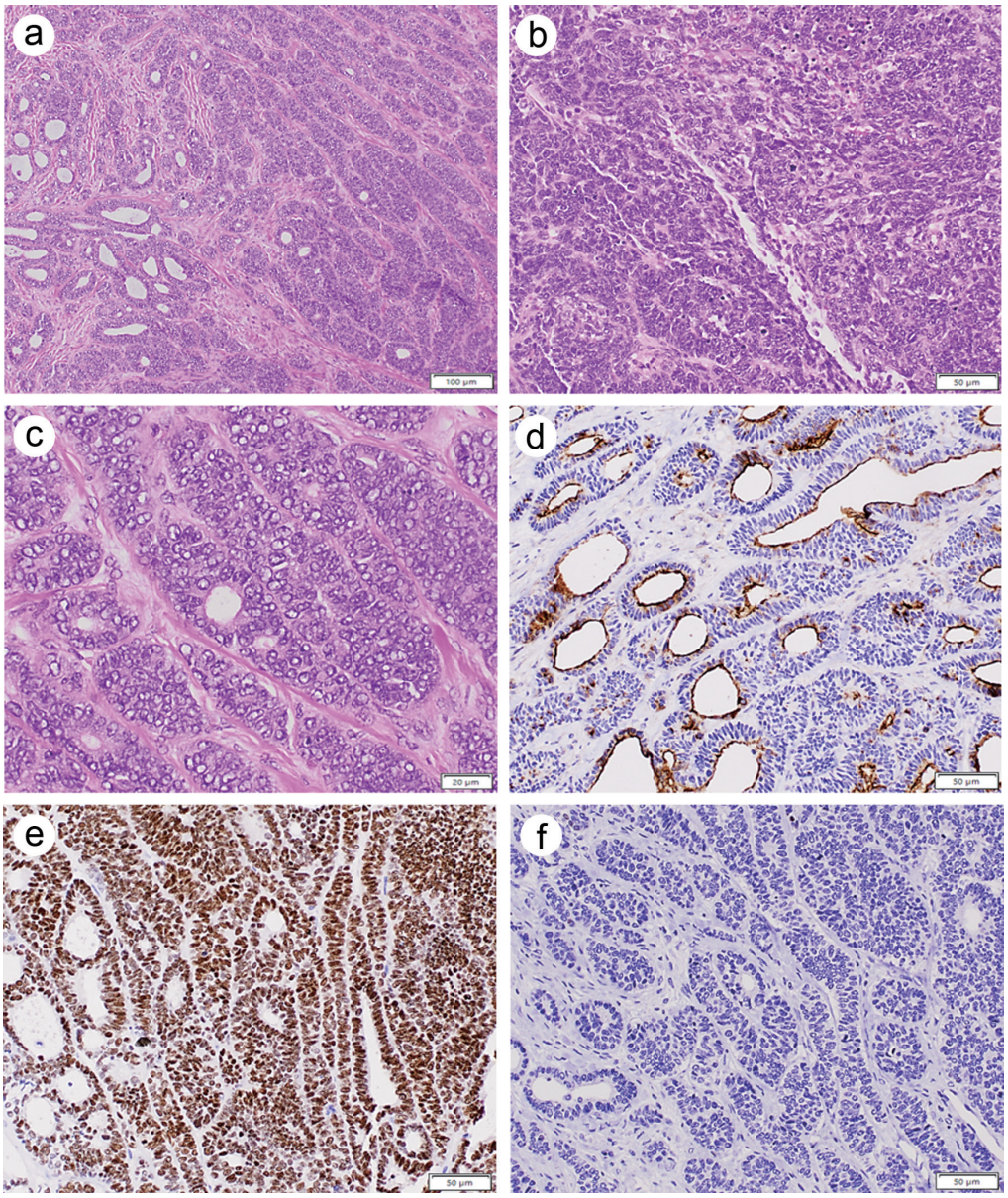

Fig. 2. A mesonephric-like adenocarcinoma (MLA) of the ovary showing tubular and trabecular (a, 100×), solid and spindled (b, 200×) architecture. The nuclei exhibit open chromatin, irregular nuclear contours, and frequent nuclear grooves, reminiscent of papillary thyroid carcinoma (c, 400×). Neoplastic cells are positive for luminal CD10 (d, 200×) and TTF1 (e, 200×), but negative for GATA3 (f, 200×). MLA typically shows diffuse nuclear immunoreactivity for TTF1 and negative or focal staining for GATA3. In some MLA cases, TTF1 and GATA3 expression demonstrate an inverse relationship, as illustrated in this case. CD10, common acute lymphoblastic leukemia antigen; GATA3, GATA binding protein 3; TTF1, thyroid transcription factor 1.

always, diffuse nuclear staining with TTF1. GATA3 may be positive in some cases, but this is less common compared to MC. In some MLA cases, TTF1 and GATA3 show an inverse relationship, meaning that cells positive for GATA3 may be negative for TTF1, and vice versa. CD10 (luminal) and calretinin are positive in a proportion of cases (Fig. 2). ER, PR, HNF1-beta, and Napsin A are characteristically, but not always, negative. Focal positivity for ER (up to 40%) can be seen, but PR is more consistently negative in MLA. MMR is proficient, and the p53 staining pattern is wild-type.[8,33]

Similar to MC, MLA exhibits distinct molecular aberrations, including mutations in *KRAS* or *NRAS*, loss of 1p, gain of 1q, and gains in chromosomes 10 and 12. A subset of MLAs demonstrates additional mutations in *PIK3CA, CTNNB1*, *ARID1A*, and *PTEN*, which are commonly seen in endometrioid adenocarcinoma.[6,9–15] This raises the intriguing possibility that these neoplasms exhibit dual mesonephric and endometrioid differentiation or are alternatively derived from Müllerian epithelium with mesonephric differentiation. Additional studies have shown mixed endometrial endometrioid adenocarcinoma and MLA arising from atypical endometrial hyperplasia, as well as mixed low-grade serous carcinoma and MLA in the ovary, with evidence of shared clonal relationships. These provide evidence supporting divergent differentiation and suggest a Müllerian origin for the entire malignant process.[11,16,17] However, whole-proteomic analysis failed to pro-

vide substantial evidence to separate MLA and MC into two distinct entities.[25] Although both MC and MLA share similarities at the morphological, immunophenotypic, and molecular levels, the precise origin of MLA remains unclear.

MLA does not exhibit alterations in *TP53*,[12] loss of MMR protein expression, or DNA polymerase epsilon exonuclease domain hotspot mutations. Instead, MLA belongs to the molecular group classified as having no specific molecular profile.

Both MC and MLA tend to present at higher stages, with frequent recurrences, most commonly to distant sites, with the lung being the most common metastatic site. The five-year disease-specific survival is poor.[9,10,36–38] Close monitoring, particularly with thoracic imaging, is recommended for patients with MC or MLA to enable early detection of recurrence.

Differential diagnosis of MC and MLA

Due to the wide range of morphological appearances of MC and MLA, often with an admixture of tubular, ductal, papillary, retiform, solid, spindled, and sex-cord-like elements, the differential diagnosis is broad. It includes mesonephric hyperplasia, endocervical adenocarcinoma, endometrioid adenocarcinoma, clear cell carcinoma, high-grade serous carcinoma, and carcinosarcoma, among others. The admixture of growth patterns may serve as a clue to the diagnosis of MC or MLA. Most MC and MLA are positive for GATA3 (less common in MLA), TTF1, and CD10, but none of these markers are sufficiently sensitive or specific. GATA3 is usually positive in mesonephric remnants and hyperplasia, but is less reliable in MC and MLA, especially in solid and spindled patterns.[6] A small percentage of endometrial endometrioid adenocarcinoma (EEC), serous carcinoma, clear cell carcinoma (CCC), and carcinosarcoma may show positivity for GATA3 and/or TTF1.[8,30,36] However, the PTC-like nuclear features of MC and MLA are not characteristic of other types of adenocarcinoma in the female genital tract. Squamous and ciliated differentiation are common features of EEC but are not seen in MC and MLA. Low-grade EEC is usually ER and PR positive. A subset of EEC may harbor *TP53* mutations and exhibit MMR deficiency. High-grade serous carcinoma shows significant cytological atypia with greater than three times variation in cell size and is characterized by *TP53* alterations, which are never seen in MC and MLA. CCC demonstrates papillary, tubulocystic, and/or solid architecture. The papillae often have hyalinized stroma. The neoplastic cells are cuboidal, polygonal, or hobnailing, with clear or eosinophilic cytoplasm. Although ER and PR are negative, CCC is typically positive for Napsin A, HNF1-beta, and AMACR, which are usually negative in MC and MLA. A subset of CCC can harbor *TP53* mutations and be MMR deficient. Hobnail cells and cytoplasmic clearing are rarely seen in MC and MLA. Recent studies have shown that the majority of MLA are negative or exhibit low expression of SRY-box transcription factor 17 (SOX17), in contrast to the diffuse and strong expression commonly seen in other types of Müllerian carcinoma. Therefore, the absence of SOX17 staining is supportive for the diagnosis of MLA when the differential includes other non-mucinous Müllerian carcinomas.[39,40] *KRAS*/*NRAS* mutations are the most common molecular alterations in MC and MLA but are less common in other cervical and endometrial adenocarcinomas.[39,40] MC and MLA may exhibit sarcomatous differentiation, including chondrosarcoma, rhabdomyosarcoma, and osteosarcoma, which supports a diagnosis of mesonephric carcinosarcoma. The carcinomatous components in Müllerian-type carcinosarcoma usually show endometrioid and serous differentiation, though clear cell and undifferentiated carcinomas can also be encountered. The carcinomatous components exhibit the corresponding histopathological features described earlier.

When MLA arises in the ovary, the female adnexal tumor of probable Wolffian origin (FATWO) and serine/threonine kinase 11 (STK11) adnexal tumor may also enter the differential diagnosis. Most FATWOs arise in the broad ligament, with a subset developing in the ovary. FATWO is presumed to be of mesonephric origin and displays an admixture of hollow and solid tubules with solid and sometimes spindled growth. Eosinophilic luminal secretions may be present. The morphology resembles that of MLA, but FATWO is often well-circumscribed with a sieve-like architecture. It is typically negative for PAX8, EMA, GATA3, and TTF1, although focal weak staining may occur.[41] The STK11 adnexal tumor is morphologically diverse, with intermixed architectural patterns and characterized by interanastomosing cords and trabeculae in a myxoid matrix. Its immunohistochemical profile is nonspecific, generally negative for PAX8, EMA, TTF1, and GATA3, and it does not harbor *KRAS*/*NRAS* mutations. As the name implies, STK11 adnexal tumors harbor *STK11* alterations, resulting in the corresponding loss of cytoplasmic staining for STK11. Approximately 50% of patients with STK11 tumors are associated with Peutz-Jeghers syndrome.[41–46]

Distinguishing between MC and MLA can be challenging. While both harbor *KRAS* or *NRAS* mutations, the presence of *PIK3CA* and *PTEN* mutations would support the diagnosis of MLA. The cervical location and the background of mesonephric remnants or hyperplasia can help in recognizing MC. The main characteristic features of morphology, immunohistochemistry, and molecular alterations of MC, MLA, and their common differentials are summarized in Table 1.

Due to word limitations as a mini-review, only selected literature was included in this manuscript. The discussion is limited to characteristic morphological, immunohistochemical features, and key molecular alterations. The manuscript is not comprehensive in covering the entire scope of all entities, particularly the differential diagnoses.

Conclusions

Mesonephric remnants are vestiges of the Wolffian ducts in females and can be identified in multiple anatomical sites, most commonly in the lateral wall of the cervix. MC arising from these remnants exhibits a diverse range of architectural patterns, including tubular, ductal, papillary, solid, spindled, retiform, sex cord-like, glomeruloid, and sieve-like formations. It is typically positive for GATA3, TTF1, CD10, and harbors molecular aberrations in *KRAS* or *NRAS*. MLA, which arises in the endometrium and ovary, shares similar morphology, immunophenotype, and molecular alterations with MC, but lacks an association with mesonephric remnants. MLA shows evidence of shared clonality with background Müllerian neoplasms and frequently harbors additional mutations in *PIK3CA* and *PTEN*. While the exact pathogenesis of MLA remains unclear, it is thought to originate from Müllerian-derived epithelium undergoing secondary mesonephric transdifferentiation. Both MC and MLA exhibit a relatively aggressive clinical course with a propensity for distant metastasis, underscoring the importance of accurate diagnosis.

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Table 1. Characteristic features of morphology, immunohistochemistry, and molecular alterations of MC, MLA, and common differential diagnoses

Entity	Morphology	IHC	Molecular
MC	Uterine cervix; Mixed architectural patterns; Dense eosinophilic luminal secretion; PTC-like nuclear features	Positive: GATA3 > TTF1 (focal), CD10 (luminal), PAX8, calretinin; Negative: ER, PR, Napsin A, AMACR; p53: WT; MMR: intact; HPV: independent	*KRAS*/*NRAS;* gain of 1q; loss of 1p; *ARID1A/B SMARCA4 BCOR/BCORL1 CTNNB1*
MLA	Endometrium or ovary; Similar to MC	Similar to MC; TTF1 (diffuse) > GATA3; Negative: SOX17, inhibin, WT1, ER, PR	*KRAS*/*NRAS;* gain of 1q; loss of 1p; *ARID1A/B*; *CTNNB1*; **PIK3CA; *PTEN*
EEC	Glandular, papillary or solid; Squamous, cilia or intracytoplasmic mucin	Positive: ER, PR, EMA, PAX8; Negative: GATA3, TTF1, inhibin, WT1; MMR: deficient (subset); p53: WT or aberrant; HPV: independent	*PTEN; PIK3CA; ARID1A*; *CTNNB1; KRAS; POLE* EDM hotspot
HGSC	Papillary, glandular, solid; Slit-like spaces; Marked nuclear pleomorphism	Positive: EMA, PAX8; Negative: GATA3, TTF1; p53: aberrant; MMR: intact; ER, PR: variable	*TP53; ERBB2* (HER2); *PIK3CA*
CCC	Papillary, tubulocystic, solid; Hyalinized stroma; Hobnailing; Clear or eosinophilic cytoplasm	Positive: HNF1-beta, Napsin A, AMACR, EMA, PAX8; Negative: ER, PR, GATA3, TTF1; MMR: intact or deficient; p53: WT or aberrant	*ARID1A; PIK3CA; TSPYL2; SPOP; FBXW7; TP53*
FATWO	Broad ligament or ovary; Well circumscribed; Mixed architectural patterns; Sieve-like architecture	Positive: Cytokeratin, inhibin, calretinin, WT1, CD10 (non-luminal), ER, SF1; Negative: PAX8, EMA, GATA3, TTF1	Non-specific; Negative: *KRAS*/*NRAS*
STK11 adnexal tumor	Mixed architectural patterns; Interanastomosing cords and trabeculae in a myxoid matrix; Prominent nucleoli	Positive: Cytokeratin, inhibin, calretinin, WT1, CD10 (non-luminal), ER; Negative: STK11, PAX8, EMA, TTF1, GATA3, SF1	*STK11*

*Alterations identified only in MLA, not in MC. AMACR, alpha-methylacyl-CoA racemase; CCC, clear cell carcinoma; EEC, endometrial endometrioid adenocarcinoma; EMA, epithelial membrane antigen; ER, estrogen receptor; FATWO, female adnexal tumor of probable Wolffian origin; GATA3, GATA binding protein 3; HGSC, high-grade serous carcinoma; HNF1, hepatocyte nuclear factor 1; HPV, human papillomavirus; IHC, immunohistochemistry; MC, mesonephric carcinoma; MLA, mesonephric-like adenocarcinoma; MMR, mismatch repair; PAX8, paired box gene 8; POLE EDM, DNA polymerase epsilon exonuclease domain mutations; PR, progesterone receptor; PTC, papillary thyroid carcinoma; SF1, steroidogenic factor 1; SOX17, SRY-box transcription factor 17; STK11, serine/threonine kinase 11; TTF1, thyroid transcription factor 1; WT, wild type.

Conflict of interest

Dr. Deyin Xing has been an editorial board member of *Journal of Clinical and Translational Pathology* since May 2021. Dr. Zaibo Li has served as an associate editor of *Journal of Clinical and Translational Pathology* since May 2021. The authors declare no other conflicts of interest.

Author contributions

Study concept and design (YH), acquisition of data (YH, DX, ZL), drafting of the manuscript (YH), and critical revision of the manuscript for important intellectual content (YH, DX, ZL). All authors have made significant contributions to this study and have approved the final manuscript.

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