Extraterine Mesonephric-like Neoplasms
Expanding the Morphologic Spectrum

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Abstract: Mesonephric-like adenocarcinomas (MLA) are rare neoplasms arising in the uterine corpus and ovary which have been added to the recent 2020 World Health Organization Classification of Female Genital Tumors. They have similar morphology and immunophenotype and exhibit molecular aberrations similar to cervical mesonephric adenocarcinomas. It is debated as to whether they are of mesonephric or Mullerian origin. We describe the clinical, pathologic, immunohistochemical, and molecular features of 5 cases of extraterine mesonephric-like proliferations (4 ovary, 1 extra-ovarian), all with novel and hitherto unreported features. These include an origin of MLA in extraovarian endometriosis, an association of ovarian MLA with high-grade serous carcinoma, mixed germ cell tumor and mature teratoma, and a borderline ovarian endome trioid tumor exhibiting mesonephric differentiation. Four of the cases exhibited a KRAS variant and 3 also a PIK3CA variant. In reporting these cases, we expand on the published tumor types associated with MLA and report for the first time a borderline tumor exhibiting mesonephric differentiation. We show the value of molecular testing in helping to confirm a mesonephric-like lesion and in determining the relationship between the different neoplastic components. We provide further evidence for a Mullerian origin, rather than a true mesonephric origin, in some of these cases. We also speculate that in the 2 cases associated with germ cell neoplasms, the MLA arose out of the germ cell tumor.

Key Words: Ovary, mesonephric-like adenocarcinoma, extrauterine, immunohistochemistry, molecular

Original Article

Mesonephric adenocarcinomas are rare neoplasms most commonly arising in the uterine cervix from normal or hyperplastic mesonephric remnants.1–4 In 2016, one of us (W.G.M.) coauthored a paper describing a series of uterine corpus and ovarian neoplasms that were termed mesonephric-like adenocarcinoma (MLA).5 The term MLA was suggested since, although these neoplasms closely resembled mesonephric adenocarcinomas morphologically and immunohistochemically, some other features (discussed later) were more in keeping with a Mullerian origin; as such, it was suggested that the term MLA could be used until the histogenesis is firmly established. Cervical mesonephric adenocarcinomas commonly exhibit KRAS or NRAS mutations6 and in a follow-up molecular study to the original publication, it was shown that MLA exhibit similar molecular abnormalities, all of the neoplasms studied exhibiting KRAS mutations.7 MLA was included in the recent 2020 World Health Organization (WHO) classification of both endometrial and ovarian neoplasms.8

While MLA almost always occur as pure neoplasms, recently there have been 3 case reports of ovarian neoplasms with distinct areas of MLA and serous borderline tumor/low-grade serous carcinoma, the 2 separate components exhibiting the expected immunophenotype of the individual neoplasms.9–11 In these reports, identical KRAS or NRAS mutations were demonstrated in the various components suggesting that they are clonally related. In these studies, it was suggested that the serous tumor was the “parent” neoplasm and that the MLA derived from the serous component, providing additional evidence that MLA may be of Mullerian origin.

In this study, we report several novel and hitherto undescribed observations with regard to extraterine MLA. These include an origin in extraovarian endometriosis and associations with high-grade serous carcinoma (HGSC), mixed germ cell tumor, and mature teratoma; we also report for the first time, an ovarian endome trioid borderline tumor exhibiting mesonephric-like differentiation.

MATERIALS AND METHODS

Five cases of extraterine mesonephric-like proliferations with undescribed associations were derived from the institutions to which the authors are affiliated and from

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the referral practice of one of the authors (W.G.M.). The slides were reviewed by the study authors during the preparation of the manuscript.

Clinical information, including follow-up data, was obtained from surgical pathology reports and from the referring pathologists and clinicians.

Immunohistochemistry was performed at the original institutions during the reporting of the cases. Markers included PAX8, TTF1, GATA3, estrogen receptor (ER), progesterone receptor (PR), CD10, WT1, p53, CK7, CK20, hepatocyte nuclear factor 1-beta (HNF1-beta), napsin A, vimentin, pan-cytokeratin AE1/AE3, epithelial membrane antigen (EMA), inhibin, calretinin, steroidogenic factor-1 (SF1), and thyroglobulin. Not all markers were performed in every case.

**Molecular Studies**

In all cases molecular analysis was performed. For cases 1 to 4, a targeted 69-gene solid tumor panel was used which comprised AKT1, ALK, APC, AR, BRAF, BRCAl, BRCa2, CCND1, CDK4, CDK6, CDKN2A, CDKN2B, CTNNB1, Dicer1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESRI, FBXW7, FGFR1, FGFR2, FGFR3, FOXL2, FRK, GNA11, GNAQ, GNAS, H3F3A, H3F3B, Hist1H3B, Hist1H3C, HNF1A, HRAS, ID1, ID2, IL6ST, JAK1, JAK2, KIT, KRAS, MAP2K1, MET, NRAS, NTRK1, PDGFRa, PIK3CA, PIK3R1, POL3, PTEN, RB1, RET, RNF43, ROS1, SMAD4, SMO, SPOP, STAT3, STK11, TERT, TP53, VHL.

DNA was extracted using the Qiagen QIAamp FFPE Tissue Kit (Qiagen), according to the manufacturer’s instructions. DNA shearing to 200 bp fragments was executed by Covaris’ Adaptive Focused Acoustics technology (Covaris, Woburn, MA). Using 200 ng of starting material, library construction was completed by use of the NEXTex Rapid DNA-Seq Kit and NEXTeX DNA Barcodes (Bioo Scientific, Austin, TX). Cluster generation and sequencing were executed by a cBot 2 and HiSeq. 3000 system (Illumina), respectively. The minimal number of reads (single-read; 50-cycle mode) per sample was aimed to be 15 million (mean coverage of 0.25×). Raw reads were mapped by Bowtie 2 (version 2.3.2) onto the human reference genome GRCh38, using the fastlocal flag. Bio-bambam’s bamsormadup2 (version 2.0.87) was used to mark duplicate reads and to sort the resulting.bam files. No additional quality filtering was applied. The latter files were indexed by SAMtools3 (version 1.4.1). The novel WisecondorX (version 1.1.2) was deployed to reliably deduce normalized genome-wide log2 ratios across 100 kb bins, representing the copy number.

In case 5, structural and/or numeric alterations of chromosome 12p were analyzed using a combination of fluorescence in situ hybridization (FISH) probes. A Texas red-labeled probe for chromosome 12 (12p13, Cytocell), FITC-labeled probe for chromosome 21 (21q22, Cytocell), and an aqua-labeled centromeric probe for chromosome 12 (12Z3, Cytocell) were used. The hybridization was performed according to manufacturer’s instructions.

**RESULTS**

The clinicopathologic, immunohistochemical, and molecular features of all 5 cases are summarized in Tables 1-3, respectively. The age of the patients ranged from 33 to 82 years. Four cases were ovarian in origin and the fifth had an extraovarian origin arising in endometriosis of the mesocolon.

**Pathologic Features**

The ovarian tumors ranged from 7 to 15 cm (mean 11 cm) in maximum dimension. In one case (case 4), the ovary was received piecemeal. All the ovarian tumors were solid and cystic in gross appearance with gray-white solid areas, sometimes associated with areas of necrosis. Papillary excrescences were seen in one case (case 3). One case (case 5) had in addition, fleshy and gelatinous areas. The extraovarian tumor (case 1) was a partially ruptured,
TABLE 1. Clinicopathologic Findings of Cases Included in the Study

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Clinical Findings</th>
<th>Site of Tumor</th>
<th>Coexistent Lesion/Tumor</th>
<th>Surgical Treatment</th>
<th>FIGO Stage</th>
<th>Postoperative Clinical Course</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>Subtotal hysterectomy in the past with no histologic details. Presented with a 25 cm retroperitoneal cystic lesion with adherent sigmoid colon</td>
<td>Extraovarian: mesocolon</td>
<td>Endometriosis</td>
<td>Segmental colectomy</td>
<td>Not staged</td>
<td>Adjuvant therapy declined</td>
<td>NED, at 8 mo FU</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>7 cm left ovarian mass diagnosed as malignant struma ovarii associated with teratoma followed by metastasis</td>
<td>Left ovary</td>
<td>Mature teratoma</td>
<td>Left SO</td>
<td>IA</td>
<td>Metastasis 11, 15, and 26 mo after primary surgery. Subsequent TAH and right SO</td>
<td>NED 19 mo FU after last metastasis, 46 mo after primary</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>15 cm solid cystic ovarian mass stuck to sigmoid colon</td>
<td>Left ovary</td>
<td>High-grade serous carcinoma</td>
<td>TAH and BSO</td>
<td>IIIC</td>
<td>CTx (carboplatin and gemcitabine)</td>
<td>NED at 22 mo FU</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>Ovarian mass received piecemeal</td>
<td>Ovary (laterality unknown)</td>
<td>Borderline endometrioid neoplasm</td>
<td>BSO</td>
<td>IC</td>
<td>None</td>
<td>NED at 28 mo</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>11 cm right ovarian mass, acute abdominal pain, hydropneumoshy and bilateral pleural effusions</td>
<td>Right ovary</td>
<td>Mixed germ cell tumor</td>
<td>Right partial oophorectomy</td>
<td>IVB</td>
<td>CTx (bleomycin +etoposide+ cisplatin)</td>
<td>Partial response with extensive residual disease at 8 mo FU</td>
</tr>
</tbody>
</table>

BSO indicates bilateral salpingo-oophorectomy; CTx, chemotherapy; FU, follow-up; NA, not available; NED, no evidence of disease; RTx, radiotherapy; SO, salpingo-oophorectomy; TAH, total abdominal hysterectomy.

TABLE 2. Immunohistochemical Findings of Mesonephric-like Component in Cases Included in Study

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX8</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>GATA3</td>
<td>Focal</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>TFF1</td>
<td>Negative</td>
<td>Focal</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>CD10</td>
<td>Diffuse*</td>
<td>Diffuse*</td>
<td>ND</td>
<td>Diffuse*</td>
</tr>
<tr>
<td>WT1</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>ND</td>
</tr>
<tr>
<td>CK7</td>
<td>ND</td>
<td>Diffuse</td>
<td>ND</td>
<td>Diffuse</td>
</tr>
<tr>
<td>CK20</td>
<td>Negative</td>
<td>Negative</td>
<td>ND</td>
<td>Negative</td>
</tr>
<tr>
<td>HNF1-beta</td>
<td>Negative</td>
<td>ND</td>
<td>Negative</td>
<td>ND</td>
</tr>
<tr>
<td>Napsin A</td>
<td>Negative</td>
<td>ND</td>
<td>Negative</td>
<td>ND</td>
</tr>
<tr>
<td>ER</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>PR</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>p53</td>
<td>Wild-type</td>
<td>Wild-type</td>
<td>Wild-type</td>
<td>Wild-type</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>ND</td>
<td>Negative</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Vimentin</td>
<td>ND</td>
<td>ND</td>
<td>Diffuse</td>
<td>ND</td>
</tr>
<tr>
<td>AE1/AE3</td>
<td>ND</td>
<td>ND</td>
<td>Diffuse</td>
<td>ND</td>
</tr>
<tr>
<td>EMA</td>
<td>ND</td>
<td>ND</td>
<td>Focal</td>
<td>ND</td>
</tr>
<tr>
<td>Inhibin</td>
<td>ND</td>
<td>Negative</td>
<td>Focal</td>
<td>ND</td>
</tr>
<tr>
<td>Calretinin</td>
<td>ND</td>
<td>Negative</td>
<td>Negative</td>
<td>ND</td>
</tr>
<tr>
<td>SF1</td>
<td>ND</td>
<td>ND</td>
<td>Negative</td>
<td>ND</td>
</tr>
</tbody>
</table>

*With luminal staining pattern.
ND indicates not done.

Focal: <50%; Diffuse: ≥50%.

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Immunohistochemically the HGSC showed diffuse positivity for PAX8, WT1, and p16. There was diffuse mutation-type immunoreactivity for p53. ER, GATA3, and TTF1 were negative. The left ovary contained a minor MLA component comprising <10% of the tumor.

The endometrioid borderline tumor (case 4) was composed of a somewhat lobular arrangement of endometrioid-type glands, some of which were cystically dilated, within a fibrous stroma. Some of the glands exhibited mucinous differentiation and a few were ciliated. There are areas with a population of small tubules with eosinophilic luminal colloid-like material. These were interpreted as mesonephric-like tubules and this was supported by the immunophenotype (see below). Stroma still remained between the glands and tubules and there was no glandular confluence or desmoplastic reaction to suggest adenocarcinoma.

Case 5 was a biphasic tumor, comprising a malignant mixed germ cell tumor (~65% of the tumor) and MLA. Both components were spatially separate from each other but closely apposed; there was no intermingling of the 2 components. The mixed germ cell tumor exhibited elements of immature teratoma (with primitive neuroepithelium in rosettes and sheets), yolk sac tumor (YST),

**TABLE 3. Molecular Findings in Cases Included in Study**

<table>
<thead>
<tr>
<th>Case</th>
<th>CNV</th>
<th>KRAS</th>
<th>PIK3CA</th>
<th>ARID1A</th>
<th>PTEN</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ND</td>
<td>c.35G&gt;A p. (Gly12Asp)</td>
<td>−ve</td>
<td>−ve</td>
<td>−ve</td>
<td>−ve</td>
</tr>
<tr>
<td>2</td>
<td>dup(1)(q21.1q44), dup(7)(p22.3p11.2), +10, +12, +16, +17, +18, −19, +21, −X</td>
<td>c.263G&gt;A p. (Arg88Gln) c.311C&gt;T p. (Pro104Leu)</td>
<td>−ve</td>
<td>−ve</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>ND</td>
<td>c.35G&gt;T p. (Gly12Val)</td>
<td>−ve</td>
<td>−ve</td>
<td>−ve</td>
<td>−ve</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>c.35G&gt;C p. (Gly12Ala) c.328_330del p.(Glu110del) c.1258T&gt;C p.(Cys420Ala) c.1258T&gt;C p.(Cys420Ala)</td>
<td>c.563del p. (Pro1878LeufsTer5)</td>
<td>−ve</td>
<td>Amplification</td>
<td>−ve</td>
</tr>
<tr>
<td>5</td>
<td>Isochromosome 12p in both components</td>
<td>c.35G&gt;C p. (Gly12Ala) c.1258T&gt;C p.(Cys420Ala)</td>
<td>−ve</td>
<td>Amplification</td>
<td>−ve</td>
<td></td>
</tr>
</tbody>
</table>

*An identical TP53 mutation to that in the HGSC component was found in the MLA component but the mutation in the latter component was thought to be secondary to contamination (see text).*

**FIGURE 1.** Case 1. Extraovarian endometriosis associated with MLA. Cystically dilated endometrioid glands admixed with adenocarcinoma (A, B). MLA composed of glands (C) and cored pattern (D). Some of the glands have luminal eosinophilic colloid-like material (E). ER is negative in the MLA and positive in the endometrioid glands (F).
and embryonal carcinoma. The embryonal carcinoma component contained glands lined by cells with pleomorphic vesicular nuclei with a moderate amount of cytoplasm and prominent mitotic activity. The YST component was composed of glandular arrangements of cells with a clear cytoplasm, eosinophilic hyaline globules, and Schiller Duvall bodies. Large areas of hemorrhage and necrosis were seen within the germ cell component. In addition, there was a small benign serous cystadenoma with benign ciliated glands within a fibromatous stroma.

Immunohistochemically, the mixed germ cell tumor showed focal positivity for broad spectrum cytokeratin AE1/3, CD30, OCT3/4, and SOX2 were positive in the embryonal carcinoma component. The YST component showed diffuse positivity for SALL4 and glypican-3; alpha fetoprotein was focally positive. CK7 and PAX8 were negative. No human chorionic gonadotrophin expression was seen.

Figures 1–5 illustrate the neoplasms included in the study.

Immunohistochemical Findings in Mesonephric-like Component

The detailed immunohistochemical findings are shown in Table 2.

The mesonephric-like component in all 5 cases was completely negative for ER and PR (PR was not performed

FIGURE 2. Case 2. Mature teratoma associated with MLA. The teratoma contains mature cartilage and respiratory-type epithelium (A) and squamous epithelium (B). MLA composed of glandular structures (C, D). The MLA is positive for GATA3 (E) and exhibits luminal positivity for CD10 (F).

FIGURE 3. Case 3. HGSC associated with MLA. The HGSC is composed of solid and glandular arrangements with severe nuclear atypia (A) and exhibits diffuse mutation-type immunoreactivity with p53 (B). MLA composed of glandular structures and cords of cells with luminal eosinophilic colloid-like material (C, D). The MLA is positive for TTF1 (E) and GATA3 (F).
in 1 case). All 5 cases were positive for GATA3 (3 diffuse, 2 focal) and PAX8 (all diffuse). Four of the 5 cases were positive for TTF1 (1 diffuse, 3 focal). Four cases were stained with CD10 and 3 showed diffuse luminal staining while 1 was negative. Calretinin was negative in the 3 tested cases. All 4 cases exhibited wild-type immunoreactivity for p53.

**Molecular Findings**

Molecular testing showed pathogenic KRAS variants in 4 of 5 cases and pathogenic or likely pathogenic PIK3CA variants in 3 of 5 cases in the mesonephric-like component (Table 3).

Case 1 (the case arising in extraovarian endometriosis) showed a pathogenic variant in the KRAS gene. The MLA and the endometriotic components were not tested separately.

In case 2 (the case associated with a mature teratoma), the MLA component had numerous deletions and duplications. Of note were 1q duplication and tetrasomy of chromosome 12, but isochromosome 12p (i(12)p) was not seen. There were no mutations in the KRAS, NRAS, or PIK3CA genes. The KRAS gene is, however, located on chromosome 12 and gains of KRAS are described in numerous malignancies. Gain of 1q has been described in mesonephric adenocarcinoma and MLA but is not specific.
for these tumors.6,7,9,14,15 The CNV profiles of the teratomata and MLA components showed overlap, suggesting a clonal relationship between both components.

In case 3 (the case associated with HGSC), distinct mutations were seen in each component. The HGSC component showed a pathogenic TP53 variant. This mutation was also seen in the MLA component at a variant allele frequency (VAF) of 6%; however, this was considered as likely secondary to contamination by the HGSC component, given the very low VAF and the fact that the MLA exhibited wild-type immunoreactivity with p53. The MLA component showed a pathogenic KRAS variant and a pathogenic and likely pathogenic PIK3CA variant; these were not present in the HGSC component.

In case 4 (the endometrioid borderline tumor), there was a pathogenic variant in the KRAS gene and a likely pathogenic variant in the PIK3CA and ARID1A genes; in this case, the mesonephric-like component was not analyzed separately from the more typical endometrioid component.

In case 5 (the case associated with a mixed germ cell tumor), both components exhibited identical pathogenic KRAS and PIK3CA variants. i(12)p was identified in both components on FISH analysis.

Staging and Follow-up

Staging and follow-up information was available for all cases (Table 1). Case 1 was not staged since this was a mass arising in the sigmoid mesocolon. One case (case 2) was FIGO stage IA at diagnosis. The other 3 cases were stage IC (the borderline tumor), IIIC, and IVB at the time of diagnosis. One patient received adjuvant radiotherapy and chemotherapy and 3 patients received adjuvant chemotherapy. The follow-up period ranged from 8 to 46 months (median: 15 mo). The patient with associated mature teratoma (case 2) developed metastases to the rectus abdominis muscle 9 months postsurgery, followed by metastases to the paravesical region and omentum 15 months following surgery. Ten months later the patient developed further recurrence in the bladder. One patient (case 5) had a partial response to chemotherapy, but showed significant increase in the size of residual disease leading to ureteric obstruction, 7 months following surgery. The remaining 3 patients showed no evidence of tumor recurrence during the follow-up period.

DISCUSSION

MLA of the uterine corpus and ovary are rare and relatively recently described neoplasms and, as discussed, are characterized by significant morphologic, immunohistochemical, and molecular overlap with cervical mesonephric adenocarcinomas.3,9–11,14,16–23 Histologically, they are characterized by a variety of growth patterns including tubular, glandular, papillary, retiform, glomeruloid, sex-cord-like, and solid. Tubular and glandular patterns often predominate and a frequent finding is the presence of small tubules containing luminal cosinophilic colloid-like material. Squamous and mucinous differentiations are generally absent. Cytologically, the tumor cells have vesicular angulated, often overlapping, nuclei, resembling those seen in papillary thyroid carcinoma. Immunohistochemically, these neoplasms characteristically exhibit diffuse positive staining with PAX8, totally negative staining for ER and PR, negative or focal non–block-type staining for p16 and wild-type immunoreactivity for p53. GATA3 and TTF1 are expressed in most tumors with GATA3 being the best overall marker in terms of sensitivity and specificity.19 TTF1 and GATA3 typically show an inverse staining pattern; in other words, areas that are GATA3 positive are often TTF1 negative and vice versa.19 CD10 and calretinin are expressed in a proportion of cases, while napsin A and HNF1-beta are generally negative.5–7,14,15,20 Euscher et al16 suggested GATA3, TTF1, ER, and PR as first-line markers to help confirm a MLA with CD10 and calretinin serving as supplemental immunostains.

Targeted genomic profiling of 7 cases of MLA by Mirkovic et al7 revealed recurrent KRAS mutations, gain of 1q, lack of PTEN mutations, and gain of chromosomes 10 and 12, these molecular events being similar to those seen in cervical mesonephric adenocarcinomas. PIK3CA mutations were found in 3 of 7 cases in that study.7 All these cases lacked ARID1A mutations that are commonly seen in Mullerian endometrioid and clear cell carcinomas and that have also been described in mesonephric adenocarcinomas; however, subsequently ARID1A mutations have been reported in MLA.15,16

Although there is marked morphologic, immunophenotypic, and molecular overlap with cervical mesonephric adenocarcinoma, there are other parameters suggesting a Mullerian origin for MLA. These include the observation that those tumors arising in the uterine corpus exhibit an “origin” from the endometrium rather than being predominantly located within the myometrium with little or no endometrial involvement as would be expected with a mesonephric origin. There has been a case report of an endometrial MLA associated with an endometrioid component23 and one of us (W.G.M.) has observed several similar cases. In the ovary, these neoplasms are often associated with endometriosis or more uncommonly benign serous neoplasms.10 Moreover, in both the uterine corpus and ovary, these neoplasms have not been associated with mesonephric remnants; in fact, although it is often stated in the literature that mesonephric remnants occur within the outer aspects of the myometrium, none of us has ever observed this. In the original report of these neoplasms and in a subsequent study, it was debated whether these represent true mesonephric adenocarcinomas that arise in the uterine corpus/ovary or Mullerian carcinomas that closely mimic mesonephric adenocarcinoma and it was suggested that the term MLA be used until the histogenesis is firmly established23; this term is now accepted in the literature. Recently, there have been 3 case reports describing the association of ovarian MLA with serous borderline tumor/low-grade serous carcinoma, providing further evidence of a Mullerian origin.9–11

In this study, we report a series of 5 cases of extraterine mesonephric-like lesions (4 MLA and 1 endometrioid
borderline tumor with mesonephric-like glands) with hitherto undescribed associations or features, thus expanding the morphologic spectrum of these neoplasms. The MLA component in all 4 malignant cases exhibited morphologic, immunohistochemical, and molecular features similar to those reported in the literature.

One of the MLAs we report (case 1) arose in the mesocolon (an area devoid of mesonephric remnants) in endometriosis. As far as we are aware, this represents the first report of an MLA arising outside the uterine corpus or ovary and the association with endometriosis is further evidence that these tumors are likely of Mullerian origin. Given the significant association with endometriosis, we suggest that MLA can be added to the list of endometriosis-associated neoplasms, these also comprising endometrioid, clear cell, and seromucinous neoplasms.

It is now well established that true mixed carcinomas of the ovary are extremely rare, representing <1% of ovarian carcinomas. The most common combination is mixed endometrioid and clear cell carcinoma, followed by mixed endometrioid and low-grade serous carcinoma. As discussed, there are 3 case reports describing mixed MLA and low-grade serous carcinoma, these also comprising endometrioid, clear cell, and seromucinous neoplasms.

In case 5, an MLA was associated with a mixed germ cell tumor. Malignant Mullerian epithelial neoplasms coexisting with germ cell tumor or trophoblastic components have been described involving both the endometrium and the adnexa. In these combined tumors, the epithelial neoplasm is usually the “parent” tumor and the most frequent germ cell component is a YST (referred to as so-called derived YST); other elements, such as mature and immature teratoma, have been reported much more uncommonly. The most frequent Mullerian neoplasm is endometrioid carcinoma, with or without endometriosis, but HGSC, mucinous carcinoma, and clear cell carcinoma have also been reported. These neoplasms usually occur in postmenopausal patients and exhibit an aggressive clinical behavior.

Several recent molecular studies have helped confirm a somatic origin of the germ cell component in these neoplasms given the similar mutational profiles in both tumor components, which have generally been those expected in the Mullerian component. Other features in favor of a somatic origin for the germ cell component include lack of i(12)p (see below), their frequent presentation in postmenopausal women (an age group where germ cell tumors, especially YST, are uncommon) and their suboptimal response to germ cell–related chemotherapeutic agents.

In our case of MLA with mixed germ cell tumor (immature teratoma, YST, and embryonal carcinoma), both components harbored identical mutations in KRAS and PIK3CA thus confirming their clonal nature. These mutations were suggestive of the MLA being the “parent” neoplasm. However, FISH analysis showed i(12)p in both components. Gains of chromosome 12p is an early event in the pathogenesis of testicular germ cell tumors, but is not a driver event. Given the molecular findings, in the case we report it is difficult to unequivocally determine whether the germ cell tumor was somatically derived from the MLA and the somatic tumor acquired 12p in its progression or whether the entire tumor is of germ cell origin with the MLA representing a secondary somatic malignancy. Given the abnormalities in both components, this could suggest that the MLA is the “parent” neoplasm with the germ cell component being somatically derived. However, the i(12)p strongly argues in favor of the MLA arising out of the germ cell tumor. It is worth making the point that it is extremely rare for Mullerian neoplasms to arise within a germ cell tumor but the molecular results in cases 2 and 5 in our study raise the possibility that in both cases, the MLA arose out of the germ cell neoplasm.

We also describe a case (case 4) of an ovarian borderline tumor where the glands focally exhibited...
“mesonephric-like” differentiation, a phenomenon which has not been previously reported. The predominant morph-ology was of a borderline endometrioid adenofibroma with crowded endometrioid-type glands, some exhibiting mucinous and ciliated metaplasia, within a fibrous stroma. This was associated with a population of small tubules which were positive with GATA3 and TTF1 and negative with ER, in keeping with mesonephric-like differentiation. Demonstration of pathogenic and likely pathogenic variants in KRAS, PIK3CA, and ARID1A supported meso-nephric-like proliferation.


In summary, we report 5 new cases of extrauterine mesonephric-like tumors including the first report of an ovarian borderline neoplasm exhibiting mesonephric-like differentiation. We report some hitherto unreported associations of MLA, namely an origin in extraovarian endometriosis and association with HGSC, mixed germ cell tumor, and mature teratoma. In reporting these cases, we show the value of molecular testing in helping to con-firm a mesonephric-like lesion and in determining the relationship between the different neoplastic components. We provide further evidence for a Mullerian origin with sub-sequent acquisition of mesonephric-like features (trans-differentiation), rather than a true mesonephric origin, in some of these cases.

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