Research Report

Somatic mutation analysis of Mesonephric-Like adenocarcinoma and associated putative precursor Lesions: Insight into pathogenesis and potential molecular treatment targets

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Abstract

Aims: Mesonephric-like adenocarcinoma (MLA) is a recently described histologic tumor subtype of the Müllerian tract. MLA can arise in association with Müllerian lesions that share common mutations. We report three MLAs and hypothesize that concurrent endometriosis and cystadenofibroma with focal borderline changes might also carry common mutations.

Methods and results: We searched “mesonephric” in our database from 2015 to mid-2021 to retrieve MLA cases. Somatic mutation analysis was performed on tumors and on associated benign proliferative lesions. All MLAs (2 ovarian and 1 uterine) harbored KRAS G12D or G12 V mutations. A PIK3CA alteration (H1047Q) was detected in one MLA and in the associated cystadenofibroma with focal borderline changes. The molecular profile of MLA-associated Müllerian lesions (endometriosis and seromucinous cystadenofibroma with focal borderline changes) was similar to concurrent adenocarcinoma. However, tumor contamination could not be excluded in the endometriotic lesion. Patients presented at various stages, with no evidence of post-operative recurrence after 15 months (FIGO IC) and 33 months (FIGO IIA2). One patient (FIGO IIIA1) died of disease 32 months after surgery.

Conclusions: KRAS mutations commonly characterize MLA. At least some MLA-associated Müllerian lesions show MLA-like genetic profiles, suggesting a precursor role. As far as we are aware, we describe for the first time in MLA the potentially actionable H1047Q variant of PIK3CA.

Keywords: Ovarian Neoplasms, Class I Phosphatidylinositol 3-Kinases, Proto-Oncogene Proteins p21 (ras), Endometriosis, Cystadenofibroma, Adenocarcinoma

1. Introduction

Mesonephric-like adenocarcinoma (MLA) is a recently described malignancy of the gynecologic tract. MLA is a rare adenocarcinoma subtype affecting mostly postmenopausal patients. It has been reported in the ovary, uterine corpus, vagina and para-ovarian soft tissue. MLA can arise from endometriosis (WHO Classification of Tumours Editorial Board, 2020; da Silva et al., 2021; Pors et al., 2021). The association with endometriosis and other Müllerian benign, borderline, and malignant lesions supports a Müllerian origin (WHO Classification of Tumours Editorial Board, 2020; da Silva et al., 2021; Pors et al., 2021; Chapel et al., 2018 Sep; McCluggage et al., 2020 Jan; Dundr et al., 2020). KRAS mutations underpin MLA. Other molecular changes reported in MLA include NRAS, BRAF, PIK3CA, PTEN and CTNNBI mutations and some copy number variations (da Silva et al., 2021; Pors et al., 2021). Recent studies have shown that MLA shares molecular alterations with concurrent benign and proliferative Müllerian lesions, suggesting a putative precursor role. To our knowledge, no association with mesonephric remnants has been described to date. It has, however, been hypothesized that some cases develop from paraovarian remnants (WHO Classification of Tumours Editorial Board, 2020).

MLA presents with vaginal bleeding or as a solid and/or cystic mass (WHO Classification of Tumours Editorial Board, 2020; Pors et al., 2021). It can follow an aggressive course (Pors et al., 2021; Deolet et al., 2022). As the name suggests, MLA’s histologic and immunohistochemical features overlap with those of cervical HPV-independent mesonephric type adenocarcinoma. Solid, papillary, tubular and glandular patterns are seen in MLA. Intraluminal amorphous eosinophilic material is characteristic. MLA is usually positive for GATA3 and/or TTF-1, and negative for hormone receptors. Estrogen receptor (ER) can be focally expressed in some cases. Apical membranous CD10 expression can be seen (WHO Classification of Tumours Editorial Board, 2020; Pors et al., 2021). Some tumors show both GATA3-positive, TTF-1 negative and TTF-1 positive, GATA-3 negative areas. Cervical mesonephric carcinoma...
can also express these markers. TTF-1 seems to be positive in a lower proportion of mesonephric carcinomas than in MLAs. The peculiar inverse pattern of GATA-3 and TTF-1 positivity does not appear to be found in mesonephric carcinoma (Pors et al., 2018). MLA, however, differs from mesonephric carcinoma by its location and absence of associated precursor mesonephric remnants or hyperplasia. Mesonephric remnants may be found in the cervical lateral walls. Some authors have also suggested their presence in the myometrium, vagina, mesosalpinx and ovarian hilum (Howitt and Nucci, 2018 Feb). Others question that they could occur in the uterine corpus wall (Deolet et al., 2022).

Our goal was to further define the molecular signature of MLA and associated findings. We hypothesized that MLA and concurrent lesions might have a similar mutational profile. We performed genetic testing on three MLAs and concomitant lesions.

2. Methods

We retrospectively identified cases by searching the keyword “mesonephric” in pathology reports from January 2015 to July 2021 in our institution’s database. KS and MRQ reviewed haematoxylin & eosin (HE) and immunohistochemistry (IHC) slides. We included in-house tumors fulfilling diagnostic criteria for MLA as per the 2020 World Health Organization (WHO) Classification of Female Genital Tumours (n = 3) (WHO Classification of Tumours Editorial Board, 2020). The morphologic findings of two of these cases were reported in 2021 (Kulkarni et al., 2021). One case was reported as a mesonephric carcinoma. However, upon review, we believe it is more consistent with a diagnosis of MLA. We obtained Institutional Review Board approval.

Clinical information was retrieved from the electronic medical record.

Immunohistochemistry studies were performed as part of the diagnostic workup (Table 1). We used the following antibody panel in all samples: GATA3, TTF-1, estrogen receptor (ER), CD10 and p16 INK4a antigen. Other markers were evaluated in only one or two of the cases.

We chose one to three block(s) of interest for every case, each either from the same formalin-fixed paraffin embedded (FFPE) tissue block. Each sample consisted of fifteen unstained sections and one HE slides -thick sections were prepared on uncharged slides µm. Solid tumour m -thick sections were prepared on uncharged slides µm. Solid tumour m -thick sections were prepared on uncharged slides µm.

Next generation sequencing using Centogene US LLC’s solid tumour panel was performed. This panel covers 149 genes (full sequencing of 106 genes and hotspot analysis of 43 genes), with a > 97% > 200x coverage. Targeted genes are the following: ABL1, AKT1, AKT2, AKT3, ALK, APC, AR, ARAF, ARID1A, ASXL1, ATM, ATR, ATRX, AXL, BAP1, BRAF, BRCA1, BRCA2, BTX, CBL, CCND1, CDH1, CDK12, CDK4, CDK6, CDKN1B, CDKN2A, CDKN2B, CHEK1, CHEK2, CREBBP, CSF1R, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ERCC2, ESR1, EZH2, FANCA, FANCD2, FANCI, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FAN1, DDR1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ERCC2, ESRI, EZH2, FANCA, FANCD2, FANCI, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FOXL2, GATA2, GNA11, GNAQ, GNAS, H3-3A, H3C2, HNF1A, HRAS, ID1H, ID2H, JAK1, JAK2, JAK3, KDR, KEAP1, KIT, KMT2A, KMT2C, KMT2D, KNYNTR, KRAS, MAOGH, MAP2K1, MAP2K2, MAP2K4, MAPK1, MAX, MDM4, MED12, MEN1, MET, MLH1, MLI, MRE11, MSH2, MSH6, MTO1, MYC, MYCN, MYD88, NBN, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NRS, NTRK1, NTRK2, NTRK3, PALB2, PDGFRA, PDGFRB, PIK3CA, PIK3CB, PIK3R1, PMS2, POLE, PPP2R1A, PTCH1, PTEN, PTPN11, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAF1, RB1, RBM10, RET, RHEB, RHOA, RIT1, RNF43, ROS1, SETD2, SF3B1, SLC4, SMAD4, SMARCA4, SMARCB1, SMO, SPOP, SRC, STAT3, STK11, TERT, TOP1, TP53, TSC1, TSC2, TSHR, U2AF1, VHL, XPO1.

| Table 1 | Immunostaining results. |
|---------|------------------------|
| IHC stain | Clone and vendor | Case 1 | Case 2 | Case 3 |
|----------|---------------------|--------|--------|--------|
| GATA3    | L50-823, Cell Marque| Positive| Positive| Rare positive foci |
| TTF-1    | 8G7G3/1, Dako       | Negative| Negative| Positive |
| ER       | EP1, Dako           | Negative| Negative| Focally positive N/A |
| PR       | PgR 1294, Dako      | Negative| N/A    | N/A    |
| CD 10    | 5G65, Dako          | Focal apical membrane staining | Focal patchy positive staining | Focal patchy positive staining |
| p16      | BC42, BioCare Medical| N/A    | N/A    | Patchy positive |
| PAX8     | BC12, Biocare Medical| N/A    | N/A    | Strong and diffuse |
| Calretinin| DAK-Calret 1, Dako | N/A    | N/A    | Negative |
| p53      | DO-7, Dako          | Wild-type pattern | Wild-type pattern N/A > 60 % |
| Ki-67    | MIB-1, Dako         | Focally increased | Focally increased N/A |
| Synaptophysin| DAK-SYNAP, Dako  | Negative| N/A    | N/A    |
| Chromogranin A| DAK-A3, Dako  | Negative| N/A    | N/A    |
| CD56     | 1293C, Roche        | Negative| N/A    | Focally positive |
| Cytokeratin (pan) | AE1 & AE3, Dako | N/A    | N/A    | Patchy positive |
| Cytokeratin CAM 5.2| CAM5.2, BD Biosciences | Positive | Positive N/A |
| Cytokeratin 7| OV-TL12/30, Dako | N/A    | N/A    | Patchy positive |
| Cytokeratin 20 | Ks20.8, Dako        | Negative| N/A    | N/A    |
| Cytokeratin 5/6| D5/16 B4, Dako      | N/A    | N/A    | Negative |
| EMA      | E29, Dako           | N/A    | Patchy positive | Patchy positive |
| CA 125   | M11, Dako           | N/A    | Positive | Intact |
| hMLH1    | ES05, Dako          | Intact | Intact | Intact |
| hMSH2    | FE11, Dako          | Intact | Intact | Intact |
| hMSH6    | EF49, Dako          | Intact | Intact | Intact |
| PMS2     | EP51, Dako          | Intact | Intact | Intact |
| CDX2     | DAK-CDX-2, Dako     | N/A    | N/A    | Negative |
| Inhibin alpha | R1, Dako           | N/A    | Negative | Negative |
| WT1      | 6F-H2, Dako         | N/A    | Negative | Negative |
| Alpha fetoprotein AR| Polyclonal, Ge Marque | N/A    | Positive | Negative |
| Desmin   | D33, Dako           | N/A    | N/A    | Negative |
| Vimentin | BC42, Dako          | N/A    | N/A    | Positive |

N/A: not performed.

3. Results

Three cases of MLA were included, arising in the ovary (n = 2) and in the uterine corpus (n = 1). Clinical findings are summarized in Table 2. Patient age at diagnosis ranged from 65 to 67 years, with a median of 66 years. Median follow-up was 32 months. Patient 3 underwent cancer genetic testing which was negative for pathogenic mutations; a variant of uncertain significance in the ATM gene was found.
4. Pathologic and molecular features

4.1. Case 1

Gross evaluation revealed an 8-cm solid and cystic unilateral right ovarian mass, adhering to the uterine serosa and invading the subserosal myometrium. Histologic examination of the right ovary confirmed the presence of tubular and solid MLA with focal necrosis. Nuclei were crowded, with open chromatin. Immunostains supported the diagnosis (Fig. 1, Table 1). There was also an endometriotic cyst involved by carcinoma in the right ovary. Endometrial atypical hyperplasia was identified. The cervix, left ovary, bilateral fallopian tubes and omentum appeared benign. A right paraaortic lymph node biopsy was positive for metastatic MLA. No other nodes were sampled.

The G12V (c.35G>T p.(Gly12Val)) pathogenic KRAS variant was identified in MLA (Table 3). Endometriosis was analyzed separately. It exhibited the KRAS G12V variant. However, a piece of tumor noted in the sample could account for the mutation.

4.2. Case 2

Macroscopic findings included the presence of a necrotic and hemorrhagic 8.5-cm myometrial mass. Microscopic examination confirmed the diagnosis of MLA (Fig. 2, Table 1) based in the uterine corpus and extending into the lower uterine segment and cervix. The lesion grew in a glandular pattern, with necrosis and intraluminal colloid-like secretions. Tumor nuclei were crowded, with dense chromatin. The entire cervix was submitted, and mesonephric remnants were not identified. Focal mucosal endometriosis was noted in both fallopian tubes. Right and left ovaries were unremarkable. Bilateral pelvic lymph node regional resection was negative for metastatic carcinoma.

MLA exhibited the KRAS G12D variant (c.35G>A p.(Gly12Asp)).

Table 2
Clinical findings.

| Case | Presentation | Site | Concurrent lesions | FIGO Stage | Treatment | Follow-up |
|------|--------------|-----|--------------------|------------|-----------|----------|
| 1    | 66 y.o., 8-cm pelvic mass | Right ovary | Endometriotic cyst, right ovary. Endometrial atypical hyperplasia. | IIIA1 | TAH-BSO, infracolic omentectomy and right paraaortic lymph node biopsy, adjuvant CTx (Taxol/Carboplatin/Avastin, maintenance Avastin followed by Carbo/Doxil) | Deceased 32 months post-surgery |
| 2    | 65 y.o., 8.5-cm pelvic mass | Uterine corpus | Endometriosis, bilateral fallopian tubes. | IIA2 | Radical hysterectomy-BSO, bilateral pelvic lymphadenectomy, adjuvant radiation therapy and CTx (Cisplatin) | No recurrence 33 months post-surgery |
| 3    | 67 y.o., 18-cm pelvic mass and postmenopausal bleeding | Left ovary | Endometriosis and seromucinous cystadenofibroma with focal borderline changes, left ovary. | IC | TAH-BSO, bilateral pelvic node dissection and omentectomy, adjuvant CTx | No recurrence 15 months post-surgery |

TAH indicates total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; CTx: chemotherapy; Y.o.: years old.

**Table 3**
Molecular findings.

| Case | Lesion | KRAS variant | PIK3CA mutation |
|------|--------|--------------|-----------------|
| 1    | Mesonephric-like carcinoma | G12V | N.D. |
| 1    | Endometriotic cyst | G12V | N.D. |
| 2    | Mesonephric-like carcinoma | G12D | N.D. |
| 3    | Mesonephric-like carcinoma | G12V | H1047 hotspot |
| 3    | Seromucinous cystadenofibroma with focal borderline changes | G12V | H1047 hotspot |

N.D.: not detected.

* Contamination by mesonephric-like carcinoma favoured/not excluded.

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Fig. 1. Case 1. A. Mesonephric-like adenocarcinoma (MLA) in tubular and solid patterns with focal necrosis. B. CD10, focal apical membranous staining. C. GATA3, positive. D. ER, negative.
4.3. Case 3

The specimen consisted of an 18-cm disrupted solid and cystic unilateral left ovarian mass. Cystic cavities contained clear yellow mucinous fluid and brown serous fluid. No necrosis nor haemorrhage was identified. The tumor exhibited solid and tubular histological patterns, with intraluminal eosinophilic colloid-like material. Nuclei were crowded, with dense chromatin. Morphologic and

4.3. Case 3

The specimen consisted of an 18-cm disrupted solid and cystic unilateral left ovarian mass. Cystic cavities contained clear yellow mucinous fluid and brown serous fluid. No necrosis nor haemorrhage was identified. The tumor exhibited solid and tubular histological patterns, with intraluminal eosinophilic colloid-like material. Nuclei were crowded, with dense chromatin. Morphologic and
immunohistochemical findings supported the diagnosis of MLA (Fig. 3, Table 1). Endometriosis and a seromucinous cystadenofibroma with focal borderline changes were also present in the ipsilateral ovary.

Molecular testing revealed a pathogenic KRAS G12V variant (c.35G > T p.(Gly12Val)), with a relatively high allele frequency (86.3 % out of 1260 NGS reads). Besides the KRAS alteration, a PIK3CA mutation in the H1047 hotspot (c.3141 T > A p.(His1047Gln) variant) was detected, both in the MLA and in the cystadenofibroma with focal borderline changes. Both lesions were analyzed separately.

5. Discussion

We report the molecular alterations of three MLAs and associated lesions. We believe our most interesting finding is the identification of a potentially actionable target, the PIK3CA H1047Q variant. Mutations in the PIK3CA gene have been formerly described in KRAS-mutated MLA. To the best of our knowledge, this variant has not been previously reported. Other variants in the same hotspot predict response to a treatment combination of the ER antagonist fulvestrant and the "-specific PIK3 inhibitor alpelisib in ER-positive advanced breast carcinoma. This medication combination was shown to extend progression-free and overall survival in PIK3CA-mutated cases (Juric et al., 2019; André et al., 2021). This raises the possibility that variants in H1047 might be predictive biomarkers in carcinomas of other sites; like MLA. This ought to be further investigated, as one might wonder if these drugs could increase life expectancy after an MLA diagnosis. Additionally, the PIK3CA H1047Q variant found in case 3 was also present in the associated cystadenofibroma with focal borderline changes. This supports a relationship between the two lesions.

We report KRAS G12D and G12V in MLA. Associated seromucinous cystadenofibroma with focal borderline changes shared the G12V variant. This variant was also detected in the endometriosis sample; however, we could not exclude tumor contamination. According to the 2020 WHO blue book, pathogenesis of seromucinous cystadenofibroma is unknown. KRAS mutations have been described in seromucinous borderline tumors (WHO Classification of Tumours Editorial Board, 2020). Although literature is still limited, KRAS mutations in MLA are well recognized. In a study of 28 MLAs, 89 % of tumors were KRAS-mutated. KRAS mutations are also known to occur in other gynecologic cancers, including cervical mesonephric carcinoma (da Silva et al., 2021). KRAS-mutated endometrial carcinoma histological subtypes include endometrioid, serous, mixed, dedifferentiated and poorly differentiated carcinoma and carcinosarcoma (Kolin et al., 2019). Ovarian tumors harboring KRAS mutations include serous borderline tumor, low-grade serous carcinoma, mucinous cystadenoma/adenofibroma, mucinous borderline tumor, mucinous carcinoma, endometrioid carcinoma, clear cell carcinoma, seromucinous borderline tumor, borderline Brenner tumor and struma ovarii. KRAS mutations are common in MLA, but not specific to this neoplastic process in the gynecologic tract. Their presence in at least some associated Müllerian disease might also support a common pathogenesis.

As far as we are aware, there are no guidelines requiring molecular testing for MLA diagnosis (WHO Classification of Tumours Editorial Board, 2020). This entity was introduced a few years following the integrated genomic characterization of endometrial carcinoma by The Cancer Genome Atlas (TCGA) Research Network. This study focused on endometrioid and serous histological subtypes (Levine, 2013). Hence, the ProMisE classifier does not apply to MLA. This algorithm includes evaluation of POLE mutational status, microsatellite stability and p53 status. As discussed by Pors et al., MLA is usually microsatellite stable with a wild type p53 status (Pors et al., 2021; Levine, 2013). As far as we are aware, POLE mutations have not been reported in MLA either. This tumor would fall within the “copy-number low” molecular category.

Our findings also support the currently limited evidence of MLA’s Müllerian differentiation (WHO Classification of Tumours Editorial Board, 2020; da Silva et al., 2021; Pors et al., 2021; Chapel et al., 2018 Sep; McCluggage et al., 2020 Jan; Dundr et al., 2020). This distinguishes MLA from mesonephric carcinoma. The latter is thought to arise from mesonephric remnants (WHO Classification of Tumours Editorial Board, 2020). Proof of Müllerian origin in our cases includes concurrent Müllerian neoplasia and endometriosis. This association is already known.

Stage and follow-up information was presented in result Table 2. Case 1 (stage FIGO IIIA1; deceased 32 months postoperatively) provides further evidence of MLA’s possible dismal prognosis. Further follow-up is required in cases 2 and 3 to determine their long-term disease-related outcome.

Overall, we provide further evidence of KRAS mutations in MLA, sometimes concurrent with PIK3CA mutations. One of our MLA cases shares a PIK3CA variant in the potentially actionable H1047 hotspot with a seromucinous cystadenofibroma with focal borderline change. To the best of our knowledge, this is the first description of an alteration in this hotspot in MLA. As previously reported in the literature, coexisting Müllerian neoplasia, sometimes with proof of shared molecular origin, support a Müllerian rather than a mesonephric differentiation.

Patient consent statement

This is an academic institution and all patients receiving medical care here sign a consent form agreeing that their material can be used for educational purposes without using any unique identifiers.

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CRediT authorship contribution statement

Elizabeth Arslanian: Investigation, Writing – original draft. Kamaljeet Singh: Writing – review & editing. C. James Sung: Writing – review & editing. M. Ruhl Quddus: Conceptualization, Methodology, Writing – review & editing. Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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