Gynecologic Oncology Reports 42 (2022) 101049

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Research Report

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

Elizabeth Arslanian [a], Kamaljeet Singh [a], C. James Sung [a], M. Ruhul Quddus [a,*]

[a] Brown University/Women & Infants Hospital Department of Pathology, Providence, Rhode Island, 101 Dudley Street, Providence, RI 02905, USA

ARTICLE INFO

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

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*.

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*-adnexal 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 *CTNNB1* 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 Mullerian 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

* Corresponding author at: Department of Pathology, Women & Infants Hospital, 101 Dudley Street, Providence, RI 02905, USA.
E-mail address: mquddus@wihri.org (M.R. Quddus).

https://doi.org/10.1016/j.gore.2022.101049
Received 3 June 2022; Accepted 16 July 2022
Available online 19 July 2022

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 displaying MLA or an associated finding, namely endometriosis and adenofibroma. When a tissue block with a pure concomitant lesion (without MLA being present on the same block) was not available, we selected a block representing both the associated lesion and the MLA. Each sample consisted of fifteen unstained sections and one HE slides from the same formalin-fixed paraffin embedded (FFPE) tissue block. The unstained 10 μm-thick sections were prepared on uncharged slides without additives under DNA extraction precautions. Microdissection for tumour enrichment was not conducted.

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, BTK, 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, FOXL2, GATA2, GNA11, GNAQ, GNAS, H3-3A, H3C2, HNF1A, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KDR, KEAP1, KIT, KMT2A, KMT2C, KMT2D, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAPK1, MAX, MDM4, MED12, MEN1, MET, MLH1, MPL, MRE11, MSH2, MSH6, MTOR, MYC, MYCN, MYD88, NBN, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NRAS, 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, SLX4, 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
PR	PgR 1294, Dako	Negative	N/A	N/A
CD 10	56C6, Dako	Focal apical membrane staining	Focal patchy positive	Negative
p16	BC42, BioCare Medical	Focal staining	Focal patchy positive	Patchy positive
PAX-8	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	N/A	Wild-type pattern
Ki-67	MIB-1, Dako	Focally increased	N/A	> 60 %
Synaptophysin	DAK-SYNAP, Dako	Negative	N/A	Negative
Chromogranin A	DAK-A3, Dako	Negative	N/A	N/A
CD56	123C3, Roche	N/A	N/A	Focally positive
Cytokeratin (pan)	AE1& AE3, Dako	N/A	N/A	Patchy positive
Cytokeratin CAM 5.2	CAM5.2, BD Biosciences	Positive	N/A	Patchy positive
Cytokeratin 7	OV-TL12/30, Dako	N/A	N/A	Strong and diffuse
Cytokeratin 20	Ks20.8, Dako	N/A	N/A	Rare positive foci
Cytokeratin 5/6	D5/16 B4, Dako	N/A	N/A	Negative
EMA	E29, Dako	N/A	N/A	Patchy positive
CA 125	M11, Dako	N/A	N/A	Positive
hMLH1	ES05, Dako	Intact	N/A	Intact
hMSH2	FE11, Dako	Intact	N/A	Intact
hMSH6	EP49, Dako	Intact	N/A	Intact
PMS2	EP51, Dako	Intact	N/A	Intact
CDX2	DAK-CDX-2, Dako	N/A	N/A	Negative
Inhibin alpha	R1, Dako	N/A	N/A	Negative
WT1	6F-H2, Dako	N/A	N/A	Negative
Alpha fetoprotein	Polyclonal, Cell Marque	N/A	N/A	Negative
AR	SP107, Cell Marque	N/A	N/A	Negative
Desmin	D33, Dako	N/A	N/A	Negative
Vimentin	V9, 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.

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 *para*-aortic 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.

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 haemorrhagic 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 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.

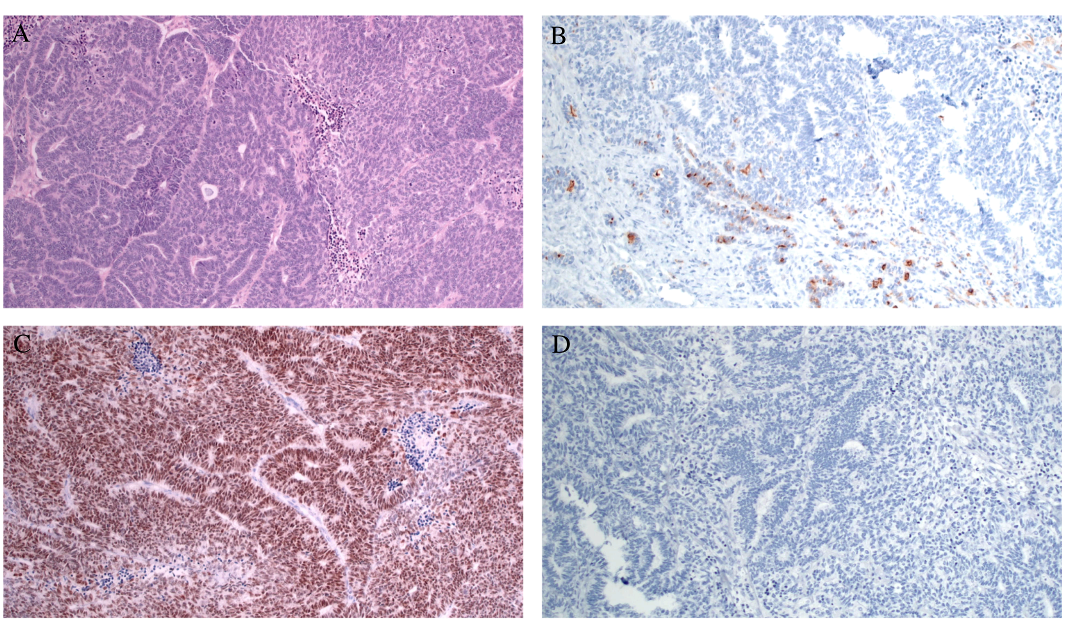

Fig. 1. Case 1. A. Mesonephric-like adenocarcinoma (MLA) in tubular and solid patterns with focal necrosis. B. CD10, focal apical membranous staining. C. GATA3, positive. D. ER, negative.

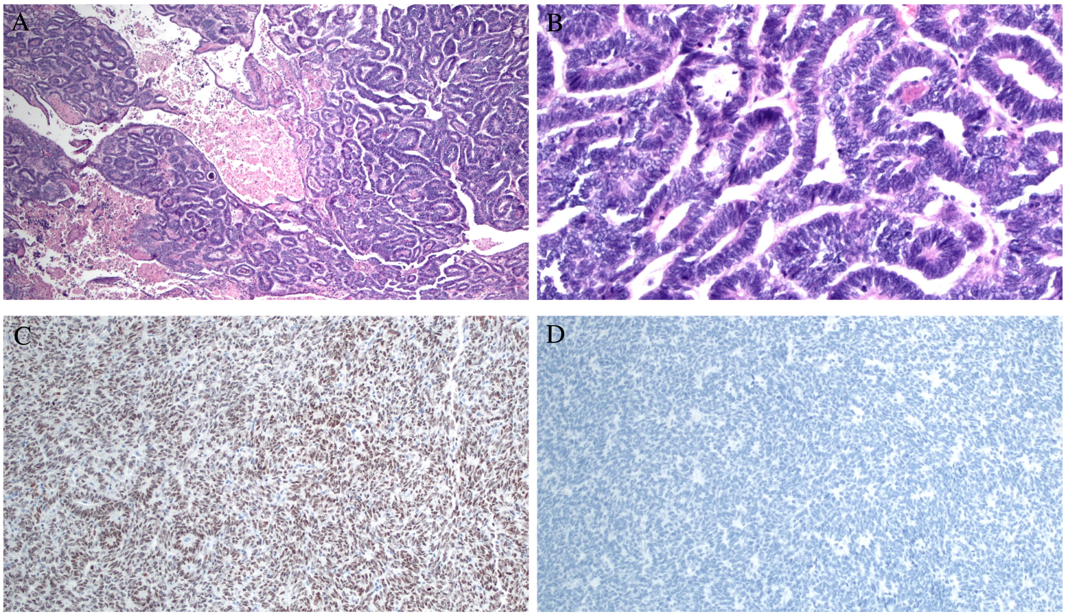

Fig. 2. Case 2. A and B. MLA in glandular pattern with necrosis. C. GATA3, positive. D. ER, negative.

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

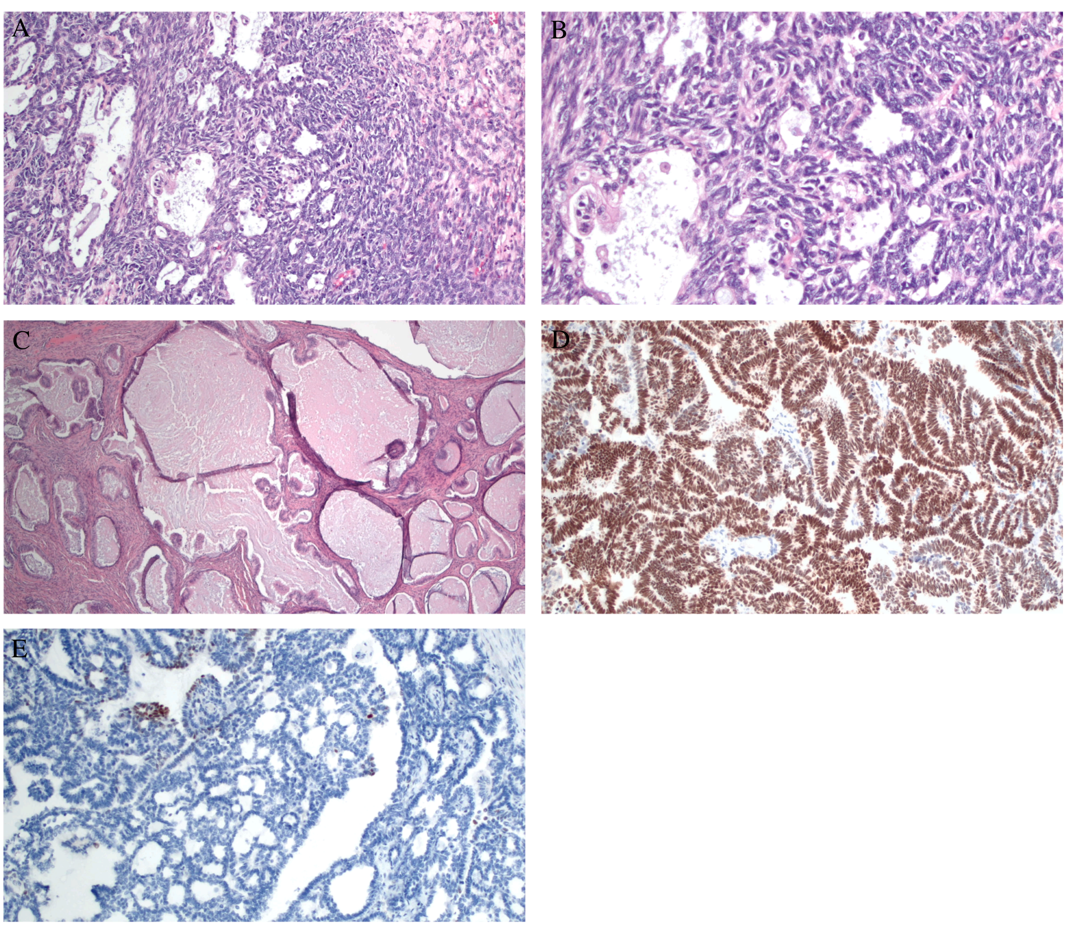

Fig. 3. Case 3. A and B. MLA in solid and tubular patterns C. Seromucinous cystadenofibroma with focal borderline changes. D. TTF-1, positive. E. GATA3, rare positive foci.

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 α-specific PI3K 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 *PICK3CA* 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.

Funding statement

The expenses were covered by the departmental education fund; no outside funding was obtained.

CRediT authorship contribution statement

Elizabeth Arslanian: Investigation, Writing – original draft. **Kamaljeet Singh:** Writing – review & editing. **C. James Sung:** Writing – review & editing. **M. Ruhul 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.

References

André, F., Ciruelos, E.M., Juric, D., Loibl, S., Campone, M., Mayer, I.A., Rubovszky, G., Yamashita, T., Kaufman, B., Lu, Y.-S., Inoue, K., Pápai, Z., Takahashi, M., Ghaznawi, F., Mills, D., Kaper, M., Miller, M., Conte, P.F., Iwata, H., Rugo, H.S., 2021. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann. Oncol. 32 (2), 208–217.

Chapel, D.B., Joseph, N.M., Krausz, T., Lastra, R.R., 2018. An ovarian adenocarcinoma with combined low-grade serous and mesonephric morphologies suggests a müllerian origin for some mesonephric carcinomas. Int. J. Gynecol. Pathol. 37 (5), 448–459.

da Silva, E.M., Fix, D.J., Sebastiao, A.P.M., Selenica, P., Ferrando, L., Kim, S.H., Stylianou, A., Da Cruz Paula, A., Pareja, F., Smith, E.S., Zehir, A., Konner, J.A., Cadoo, K., Reis-Filho, J.S., Abu-Rustum, N.R., Mueller, J.J., Weigelt, B., Park, K.J., 2021. Mesonephric and mesonephric-like carcinomas of the female genital tract: molecular characterization including cases with mixed histology and matched metastases. Mod. Pathol. 34 (8), 1570–1587.

Deolet, E., Arora, I., Van Dorpe, J., Van der Meulen, J., Desai, S., Van Roy, N., Kaur, B., Van de Vijver, K., McCluggage, W.G., 2022. Extrauterine mesonephric-like neoplasms: expanding the morphologic spectrum. Am. J. Surg. Pathol. 46 (1), 124–133.

Dundr, P., Gregová, M., Němejcová, K., Bártů, M., Hájková, N., Hojný, J., Stružinská, I., Fischerová, D., 2020. Ovarian mesonephric-like adenocarcinoma arising in serous borderline tumor: a case report with complex morphological and molecular analysis. Diagn. Pathol. 15 (1).

Howitt, B.E., Nucci, M.R., 2018. Mesonephric proliferations of the female genital tract. Pathology 50 (2), 141–150.

Juric, D., Janku, F., Rodón, J., Burris, H.A., Mayer, I.A., Schuler, M., Seggewiss-Bernhardt, R., Gil-Martin, M., Middleton, M.R., Baselga, J., Bootle, D., Demanse, D., Blumenstein, L., Schumacher, K., Huang, A., Quadt, C., Rugo, H.S., 2019. Alpelisib plus fulvestrant in PIK3CA-altered and PIK3CA-wild-type estrogen receptor-positive advanced breast cancer: a phase 1b clinical trial. JAMA Oncol. 5 (2), e184475.

Kolin, D.L., Costigan, D.C., Dong, F., Nucci, M.R., Howitt, B.E., 2019. A Combined Morphologic and Molecular Approach to Retrospectively Identify KRAS-Mutated Mesonephric-like Adenocarcinomas of the Endometrium. Am. J. Surg. Pathol. 43 (3), 389–398.

Kulkarni, A., Chiem, A., Singh, K., Mathews, C., DiSilvestro, P.A., Beffa, L., 2021. The similarities and differences between mesonephric carcinoma and mesonephric-like carcinoma: two cases. Gynecol Oncol Rep. 37, 100856.

Levine, D.A., 2013. Integrated genomic characterization of endometrial carcinoma. Nature 497 (7447), 67–73.

McCluggage, W.G., Vosmikova, H., Laco, J., 2020. Ovarian combined low-grade serous and mesonephric-like adenocarcinoma: further evidence for a mullerian origin of mesonephric-like adenocarcinoma. Int. J. Gynecol. Pathol. 39 (1), 84–92.

Pors, J., Cheng, A., Leo, J.M., Kinloch, M.A., Gilks, B., Hoang, L., 2018. A Comparison of GATA3, TTF1, CD10, and calretinin in identifying mesonephric and mesonephric-like carcinomas of the gynecologic tract. Am. J. Surg. Pathol. 42 (12), 1596–1606.

Pors, J., Segura, S., Chiu, D.S., Almadani, N., Ren, H., Fix, D.J., Howitt, B.E., Kolin, D., McCluggage, W.G., Mirkovic, J., Gilks, B., Park, K.J., Hoang, L., 2021. Clinicopathologic characteristics of mesonephric adenocarcinomas and mesonephric-like adenocarcinomas in the gynecologic tract: a multi-institutional study. Am. J. Surg. Pathol. 45 (4), 498–506.

WHO Classification of Tumours Editorial Board. WHO Classification of Tumours: Female Genital Tumours. 5th ed. Vol. 4. Lyon: International Agency for Research on Cancer, 2020.