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Papillary and ductal patterns of mesonephric-like adenocarcinomas are often overlooked: a retrospective revaluation of over 1000 endometrial carcinomas

Ardalan Akbari,[1] Jennifer Pors,[2] Amy Lum,[3] Samuel Leung,[3] Dawn Cochrane,[3] Amy Jamieson,[4] Jessica McAlpine,[4] Stefan Kommoss,[5] Jutta Huvila,[6] David Huntsman,[1,3,7] Aline Talhouk,[4] Naveena Singh,[1] C Blake Gilks[1,8] & Lynn Hoang[1,8]

[1]*Pathology and Laboratory Medicine, University of British Columbia and Vancouver General Hospital,* [2]*Pathology and Laboratory Medicine, University of British Columbia and British Columbia Cancer Agency,* [3]*Molecular Oncology, British Columbia Cancer Research Centre, Vancouver, BC,* [4]*Gynecologic Oncology, University of British Columbia, Vancouver, BC, Canada,* [5]*Department of Women's Health, Tübingen University Hospital, Tübingen, Germany,* [6]*Department of Pathology, University of Turku, Turku University Hospital, Turku, Finland,* [7]*Imagia Canexia Health, Inc. and* [8]*Genetic Pathology Evaluation Center (GPEC) and Molecular and Advanced Pathology Core, (MAPCore), University of British Columbia, Vancouver, BC, Canada*

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Papillary and ductal patterns of mesonephric-like adenocarcinomas are often overlooked: a retrospective revaluation of over 1000 endometrial carcinomas

Aims: Mesonephric-like adenocarcinoma (MLA) of the endometrium is often a diagnostic challenge, due to its morphological resemblance to other more common Müllerian neoplasms. This study aimed to retrospectively identify overlooked MLA in a large endometrial carcinoma cohort, using a combination of immunohistochemistry (IHC), morphology and *KRAS* sequencing.

Methods and results: IHC was conducted on 1094 endometrial carcinomas, identifying 16 potential MLA cases based on GATA3+ and/or TTF1+ and ER− staining patterns, which subsequently underwent detailed histological review, *KRAS* sequencing and ProMisE molecular classification. Of the IHC screen-positive cases, one was positive for both GATA3 and TTF1, nine were positive for GATA3 only and six were positive for TTF1 only. All IHC screen-positive cases were *POLE* wild-type. All five tumours in the NSMP category showed morphological features of MLA, while the three MMRd and eight p53abn tumours did not show MLA morphology. The five cases diagnosed as MLA on review were all originally diagnosed as low-grade endometrioid adenocarcinoma probably because of rare morphological patterns, being predominantly papillary or ductal. Four of the five cases harboured a *KRAS* mutation.

Conclusion: This study highlights the importance of a comprehensive diagnostic approach for accurately

Address for correspondence: L Hoang, Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver General Hospital, 1215–910 West 10th Avenue, Vancouver, BC V5Z 1M9, Canada. e-mail: lien.hoang@vch.ca

Abbreviations: CCC, clear cell carcinoma; CS, carcinosarcoma; DSS, disease-specific survival; EA, endometrioid adenocarcinoma; FFPE, formalin-fixed paraffin-embedded; H&E, haematoxylin and eosin; IHC, immunohistochemistry; MLA, mesonephric-like adenocarcinomas; MMRd, mismatch repair deficient; MMRp, mismatch repair proficient; MNC, mesonephric adenocarcinomas; NSMP, no specific molecular profile; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; ProMisE, Proactive Molecular Risk Classifier for Endometrial Cancer; TCGA, The Cancer Genome Atlas; TMAs, tissue microarrays.

identifying endometrial MLA and for pathologists to be aware of papillary and ductal patterns in endometrial carcinoma assessment. Further exploration into the molecular landscape of MLA is essential for refining diagnostic criteria and developing targeted therapies.

Keywords: endometrial carcinoma, ER, GATA3, mesonephric-like adenocarcinoma, MMR, NSMP, ProMisE, TP53, TTF1

Introduction

Mesonephric-like adenocarcinomas (MLA) of the endometrium represent approximately 0.7–3% of primary endometrial carcinomas.[1–3] Mounting evidence in the literature suggests that MLA arise from a Müllerian substrate, due to their association with endometriosis and co-occurrence with other Mullerian type neoplasms.[4–13] Mesonephric adenocarcinomas (MNC) of the cervix, unlike MLA, are thought to be derived from true mesonephric remnants, which reside more frequently in the lateral walls of the cervix.[14] Although MLA are uncommon, pathologists often find them difficult to recognise—they often have mixed morphological patterns in one tumour and there is a diverse range of patterns including ductal (sharply-angulated glands), tubular (often with intraluminal eosinophilic secretions), solid, spindled, papillary, retiform, sex cord-like/trabecular, corded and hyalinised, hobnail, glomeruloid, sieve-like, clear cell (cytoplasmic clearing) and, more recently, dedifferentiated.[14–19] Furthermore, they bear a close resemblance to low-grade endometrioid adenocarcinoma (EA) and other Müllerian neoplasms, such as clear cell carcinoma (CCC).[20–22] For example, both CCC and MLA are typically ER-negative, p53-wild-type (although both MLA and CCC can harbour *TP53* mutations) and can show similar morphology (cytoplasmic clearing and hobnail formation). Although MLA can sometimes be overlooked, they are also at risk of being overdiagnosed with loose morphological and/or immunohistochemical requirements— in some instances it is important to comprehensively assess morphology, immunohistochemistry (IHC) and molecular data to establish an accurate diagnosis.

In terms of IHC expression, GATA3 and TTF1 are recognised as the most reliable and sensitive markers for identifying MLA, particularly when utilised in tandem.[23–27] There is often an inverse relationship between these markers; regions of tumour can be positive for GATA3 and negative for TTF1, and vice versa.[24] Among the two IHC markers, GATA3 has a higher sensitivity and specificity in detecting a mesonephric phenotype but can be negative in more solid/spindled areas of tumour.[24] Absence or focal ER expression is also essential, especially when used in combination with GATA3 and TTF1.[23–27] Additionally, pathogenic *KRAS* missense mutations are the most common molecular drivers in both MNC and MLA, found in > 90% of cases.[1,7,13,28] Both MNC and MLA show losses of chromosome 1p and gains of chromosome 1q and 2.[9,13,29]

It is crucial to differentiate between endometrial MLA and EA because the former is regarded as high-grade, and presumably surgical and adjuvant therapy may differ between them. Furthermore, MLA is associated with an aggressive clinical course compared to low-grade EA, for which it is often mistaken. MLA demonstrate clinical behaviour paralleling that of high-grade endometrial carcinomas.[3,15,17,23] Secondly, MLA can be a challenge in cases of metastasis and recurrence. For instance, MLA may show a similar immunoprofile to that of papillary thyroid carcinoma, characterised by negative ER expression and positive TTF1 and PAX8 expression. Finally, as targeted treatments continue to evolve, MLA may potentially benefit from different therapeutic approaches in the future. The discovery of *KRAS* G12C mutations in a subset of MLA cases opens possibilities for targeted therapy with Sotorasib,[30] and clinical trials specifically for MLA are ongoing.

A deeper understanding of the clinicopathological characteristics, molecular alterations and precise diagnostic criteria of MLA is crucial for its accurate identification and effective management as a distinct entity. With a large cohort of endometrial carcinomas at hand, we wanted to more closely evaluate the histological features of overlooked MLA and which diagnostic criteria could be used. We used GATA3, TTF1 and ER IHC as an initial screen. We cast a broad net, and chose not to exclude mismatch repair-deficient or *TP53* mutant tumours in the screening process. Screen-positive cases then underwent histological review and *KRAS* sequencing to determine if any cases represented overlooked MLA.

Materials and methods

Endometrial carcinoma cases were collected as previously described.[31–37]

TISSUE MICROARRAYS AND IMMUNOHISTOCHEMISTRY

Tissue microarrays (TMAs) were constructed using formalin-fixed paraffin-embedded (FFPE) tissue blocks. Duplicate 0.6-mm cores were obtained for each tumour. IHC for GATA3, TTF1, ER, p53, PMS2, MSH6, MSH2 and MLH1 were performed using Dako Omnis, Cell Marque or Leica systems following the manufacturer's protocols with proprietary reagents (Supporting information, Table S1). Only cases demonstrating complete ER negativity were included. GATA3 and TTF1 staining were evaluated on a scale from 0 to 2, where 0 indicated no staining, 1 represented staining of intensity or proportion below the threshold for a score of 2 and 2 corresponded to moderate or strong staining observed in more than 50% of the cells. Cases with GATA3 or TTF1 staining > 0 were included for further review. p53 IHC was categorised as wild-type or abnormal (null, overexpressed or cytoplasmic). Mismatch repair proteins (MLH1, PMS2, MSH2, MSH6) were considered deficient (MMRd) if there was loss of nuclear staining in the presence of a positive internal control and proficient (MMRp) if there was retained nuclear staining.

KRAS SEQUENCING AND PROMISE CATEGORISATION

KRAS sequencing data were retrieved for the flagged cases (ER-negative and GATA3 and/or TTF1 positivity). The ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) molecular classifier for each case was also obtained. As described previously, FFPE tumour tissue samples were extracted using the Qiagen Generead DNA FFPE kit. DNA was amplified using the Contextual Genomics FIND IT version 4.0 assay, a targeted NGS gene panel for somatic hot-spot mutations, followed by sequencing on the Illumina Miseq platform. Results were then analysed through the Contextual Genomics proprietary Quality Nexus analysis pipeline.[31–37]

HISTOLOGY REVIEW

Flagged cases were reviewed by three gynaecological pathology subspecialists (L.H., N.S., C.B.G.) who were blinded to molecular analysis and additional IHC data (PMS2, MSH6, MSH2, MLH1 and p53). Each pathologist was tasked with achieving a histological description and diagnosis (MLA, equivocal or definitely not MLA). The histological features of each case, pertinent positives (e.g. mixed architectural patterns) and negatives (i.e. squamous or mucinous differentiation) were noted.

FINAL CLASSIFICATION OF CASES

Given that all flagged cases satisfied the IHC criteria for MLA (positive GATA3 and/or TTF1, negative ER), the final classification was determined using an integrated approach of assessing morphology and molecular information (*KRAS* sequencing). For the purposes of this study, the term 'typical MLA' was proposed to encompass cases meeting all four defining features of classic MLA. The four defining features included the following: (i) characteristic morphology compatible with MLA, (ii) GATA3 and/or TTF1 positivity, (iii) ER negativity and (iv) *KRAS* mutant. The term 'atypical MLA' was proposed in this study to identify cases meeting all criteria of MLA, but lacking a *KRAS* alteration. The case was deemed to have compatible morphology when at least two of the three pathologists made the diagnosis of MLA. Cases that did not meet the above criteria were not revised to MLA.

Results

A total of 1094 endometrial carcinoma cases of varying histotypes [endometrioid carcinoma, serous carcinoma, carcinosarcoma (CS), mixed carcinoma, undifferentiated carcinoma] initially diagnosed from 2016 onwards were screened for GATA3 and TTF1 IHC on TMAs. Thirty-five cases were positive for GATA3 and/or TTF1, 17 cases of which were negative for ER; 16 cases had haematoxylin and eosin (H&E)-stained slides available for review. The histological features, IHC data (ER, GATA3, TTF1, MMR, p53), ProMisE molecular classification, *KRAS* sequencing data, original histotype, pathologists' H&E interpretation and the final classification (whether or not the case represented overlooked MLA) are summarised in Table 1. All IHC screen-positive cases were previously tested for *POLE*, which were all wild-type.

Figure 1 shows the breakdown of the 16 flagged cases and whether or not they were considered to represent overlooked mesonephric carcinomas. Cases 1–4 fulfilled the criteria for 'typical MLA' (positive GATA3 and/or TTF1, ER negativity, compatible MLA morphology, *KRAS* mutant). Cases 1 and 2 exhibited

Table 1. Classification of cases integrating immunohistochemistry and *KRAS* sequencing

Case	ER	GATA3	TTF1	MMR	p53	ProMisE classification	KRAS	Original histotype	H&E description	Histology review opinion*	Revised histotype
1	–	1	2	Proficient	WT	NSMP	G12D	Endometrioid	• Predominant pattern: large gaping glands with intraluminal papillae • Secondary patterns: ductal (pseudoendometrioid) • Overlapping mildly atypical columnar cells with vesicular chromatin • No squamous or mucinous differentiation • No necrosis	Accepted	Typical MLA
2	–	2	0	Proficient	WT	NSMP	G12A	Endometrioid	• Predominant pattern: large gaping glands with intraluminal papillae • Secondary patterns: ductal, tubules containing soft eosinophilic intraluminal secretions • Overlapping mildly atypical cuboidal and columnar cells with vesicular chromatin • No squamous or mucinous differentiation • Foci of comedo-type necrosis	Accepted	Typical MLA
3	–	2	0	Proficient	WT	NSMP	G12V	Endometrioid	• Predominant pattern: ductal pattern with distinct sharply-angulated contours • Secondary patterns: NA • Conspicuous mitotic activity • Overlapping cuboidal and columnar cells with mild-to-moderate nuclear atypia • No squamous or mucinous differentiation • No necrosis	Accepted	Typical MLA
4	–	0	1	Proficient	WT	NSMP	G12V	Endometrioid	• Predominant pattern: ductal • Secondary patterns: retiform, compact tubular, papillary and focal solid growth • Overlapping mildly atypical columnar and cuboidal cells • Areas of subnuclear vacuolisation • No squamous or mucinous differentiation • No necrosis	Accepted	Typical MLA

Continued

Table 1. (*Continued*)

Case	ER	GATA3	TTF1	MMR	p53	ProMisE classification	KRAS	Original histotype	H&E description	Histology review opinion*	Revised histotype
5	–	2	0	Proficient	WT	NSMP	WT	Endometrioid	• Predominant pattern: papillary • Secondary patterns: widely-spaced glands, cribriforming, labyrinthine growth • Overlapping columnar and cuboidal cells with moderate- atypia and prominent nucleoli; severe atypia is focal and majority of tumour is low-to-moderate atypia • No squamous or mucinous differentiation • No necrosis	Accepted	Atypical MLA
6	–	2	0	Deficient (MLH1 and PMS2 loss)	Null	MMRd	WT	Serous	• Glandular, solid and focal papillary architecture with extensive high-grade nuclear atypia • Brisk mitotic activity, pleomorphic nuclei with prominent nucleoli • No squamous or mucinous differentiation • Multiple foci of necrosis	Rejected	Not revised
7	–	0	2	Deficient (MLH1 and PMS2 loss)	WT	MMRd	G13D; G12D	Endometrioid	• Predominantly solid growth with poorly formed glands • Brisk mitotic activity, pleomorphic nuclei with prominent nucleoli • No squamous or mucinous differentiation • Moderate amount of necrosis	Rejected	Not revised
8	–	0	2	Deficient (MLH1 loss)	WT	MMRd	G12D	Endometrioid	• Solid growth composed of monomorphic round epithelioid cells with entrapped endometrial glands (raises differential diagnosis of dedifferentiated carcinoma) • Brisk mitotic activity • No squamous or mucinous differentiation • No necrosis	Rejected	Not revised
9	–	2	0	Proficient	Overexpressed	p53abn	Q61H	Endometrioid	• Mixed glandular, tubular, solid/spindled architecture • Intraluminal eosinophilic secretions • Conspicuous mitoses, foci of moderate–high-grade nuclear atypia • No squamous or mucinous differentiation • Comedo-type necrosis	Equivocal	Not revised
10	–	0	1	Proficient	Overexpressed	p53abn	G12A	Endometrioid	• Mixed solid and glandular with cribriforming • Brisk mitotic activity, moderate nuclear pleomorphism • No squamous or mucinous differentiation • Intraluminal necrosis	Equivocal	Not revised

Continued

Table 1. (*Continued*)

Case	ER	GATA3	TTF1	MMR	p53	ProMisE classification	KRAS	Original histotype	H&E description	Histology review opinion*	Revised histotype
11	–	1	0	Proficient	Overexpressed	p53abn	G13C	Serous	• Complex glandular proliferation including ductal pattern • Brisk mitotic activity; severe nuclear atypia • No squamous or mucinous differentiation • Foci of intraluminal necrosis	Equivocal	Not revised
12	–	1	0	Proficient	Overexpressed	p53abn	WT	Serous	• Mixed ductal proliferation composed of sharply angulated glands, papillary and solid architecture • Brisk mitotic activity; moderate–severe nuclear atypia • No squamous or mucinous differentiation, or necrosis	Equivocal	Not revised
13	–	0	1	Proficient	Overexpressed	p53abn	WT	Carcinosarcoma	• Mixed poorly differentiated solid, glandular, papillary architecture • Severe nuclear atypia • Focal cytoplasmic clearing • Brisk mitotic activity with atypical mitotic figures • No squamous or mucinous differentiation • Foci of tumour necrosis	Equivocal	Not revised
14	–	2	0	Proficient	Overexpressed	p53abn	WT	Carcinosarcoma	• Mixed high-grade solid, tubulo-glandular and trabecular/sex cord-like architecture • Brisk mitotic activity; moderate–severe nuclear atypia • No squamous or mucinous differentiation • Intraluminal necrosis	Equivocal	Not revised
15	–	0	2	Proficient	Null	p53abn	WT	Carcinosarcoma	• Poorly differentiated solid, glandular architecture with sarcomatous differentiation (cartilaginous differentiation) • Brisk mitotic activity with atypical mitoses; severe nuclear atypia and pleomorphism • No squamous or mucinous differentiation • Foci of intraluminal necrosis	Equivocal	Not revised
16	–	2	0	Proficient	Overexpressed	p53abn	G12V	Carcinosarcoma	• Mixed solid, glandular architecture with areas of prominent cytoplasmic clearing • Brisk mitotic activity; moderate–severe nuclear atypia • No squamous or mucinous differentiation • Foci of necrosis	Equivocal	Not revised

–, Denotes cases with negative immunohistochemical staining; 2 is moderate or strong intensity in more than 50% of cells and 1 includes cases with stain intensity/proportion not meeting criteria for a 2; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; NA, not applicable or available; p53abn, p53 abnormal; WT, wild-type; haematoxylin and eosin; MLA, mesonephric-like adenocarcinoma.

*Accepted, at least two of three pathologists made the diagnosis of MLA; equivocal, 1–2 pathologists thought MLA was a possibility; rejected, consensus agreement by three pathologists that the tumour was not MLA.

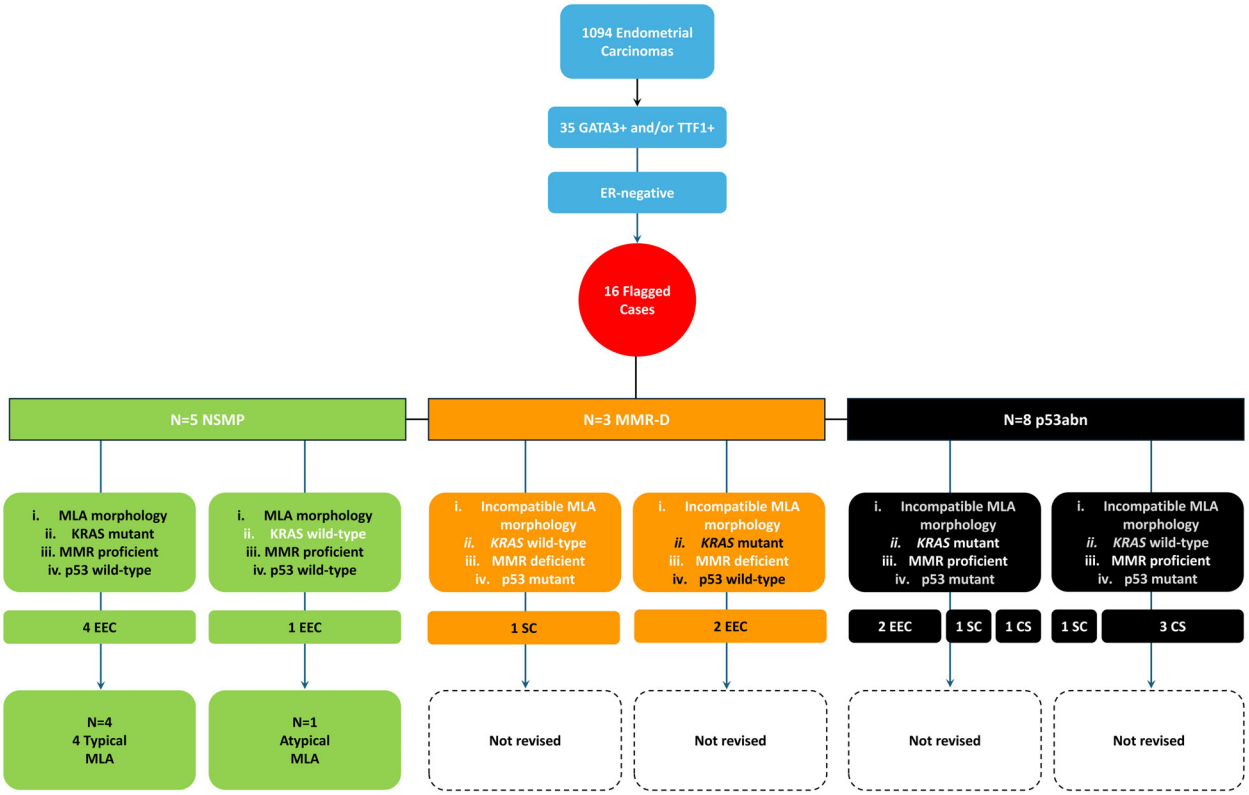

Figure 1. Flowchart for identifying endometrial mesonephric-like adenocarcinomas.

remarkable architectural patterns, consisting of large gaping glands with intraluminal papillae bearing fibrovascular cores. The papillae were lined by a single layer of cuboidal to columnar epithelium and were similar in appearance to non-villous papillae. In case 2, the cells of the intraluminal papillae displayed greater eosinophilic tincture. The appearance in both cases were reminiscent of a serous borderline tumour of the ovary (Figure 2). Cases 3–4 displayed ductal growth patterns, characterised by sharply angulated glands lined with cuboidal or tall columnar cells (Figure 3). Of note, case 4 contained areas of subnuclear vacuolisation, reminiscent of secretory-phase endometrium (Figure 3). Case 4 was the only case where all three pathologists agreed on the diagnosis of MLA. Case 5 exhibited predominantly papillary architecture, with areas of cribriform and labyrinthine growth (Figure 4). Although it did not harbour a *KRAS* mutation, it was deemed overall consistent with MLA (compatible morphology, ER-negative, GATA3/TTF1-positive). In cases 1–3 and 5, two of three pathologists made the diagnosis of MLA. All cases considered to represent MLA (cases 1–5) did not exhibit the classic tubular pattern with dense eosinophilic secretions or, alternatively, had this as only a very minor component of the overall tumour. All cases (1–5) were originally diagnosed as low-grade (FIGO grades 1 or 2) endometrioid carcinoma. None of the cases exhibited squamous metaplasia or mucinous differentiation. They were all p53 wild-type and mismatch repair proficient.

The remaining 11 cases were MMRd (two cases), p53 abnormal (p53abn) (eight cases) or both (one case). Half harboured *KRAS* mutations (six of 11, 55%).

Cases 6–8 were MMRd by the ProMisE molecular classifier (Figure 5). Case 6 exhibited extensive high-grade cytological atypia and wild-type *KRAS* status. The high-grade morphology of case 6 was consistent with its molecular classification: p53 IHC was null and MLH1 IHC was lost (ProMisE classification MMRd); given the MMRd profile, the p53 mutation was favoured to be a secondary mutation and it was reclassified as a high-grade endometrioid carcinoma. Case 7, which was MMRd, also had severe nuclear pleomorphism and atypia. The tumour was predominantly solid, with only poorly formed glands. Case 8 exhibited undifferentiated morphology—two of three

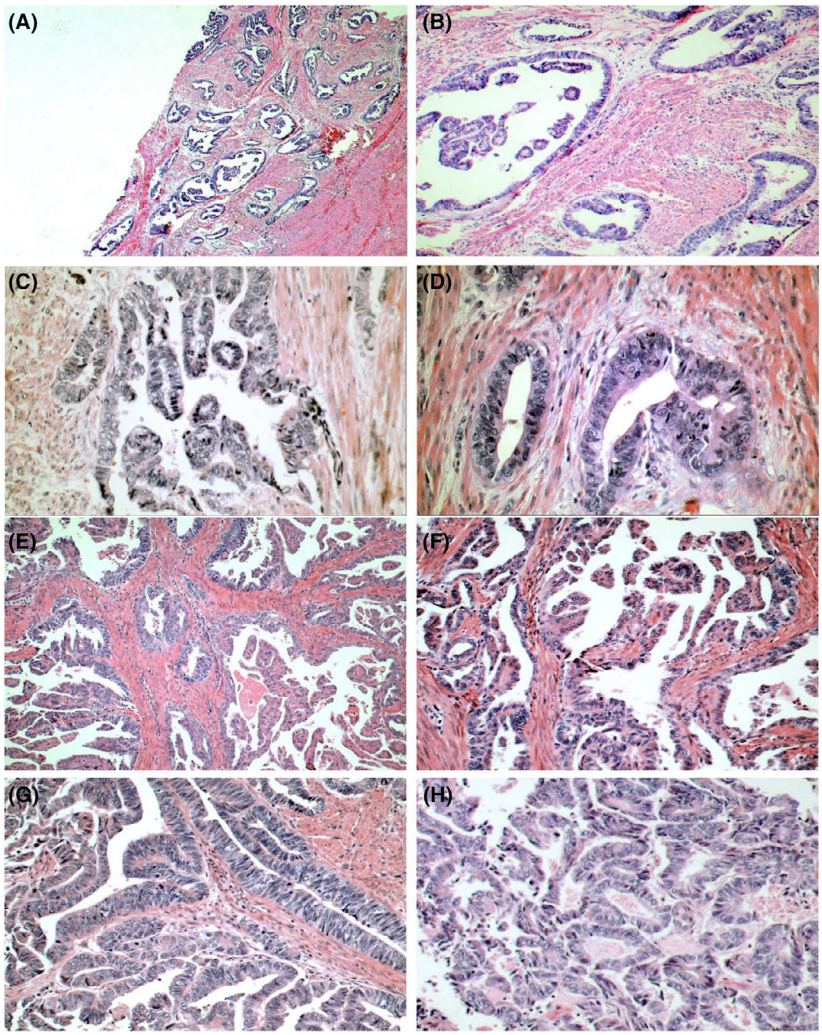

Figure 2. Typical mesonephric-like adenocarcinomas. Case 1 shows intraluminal papillae (**A**, **B**), papillae (**C**) and low-grade glandular architecture (**D**). Case 2 shows large-gaping glands with intraluminal papillae (**E**, **F**), ductular growth (**G**) and characteristic tubules with eosinophilic secretions (**H**).

pathologists considered the undifferentiated histological appearance to be more compatible with a diagnosis of undifferentiated/de-differentiated carcinoma rather than MLA, despite the presence of a *KRAS* mutation. In cases 6–8, all three pathologists unanimously rejected the diagnosis of MLA.

Cases 9–16 were under the p53abn group as per the ProMisE classifier (Figure 6). Cases 9 and 10 were originally named 'endometrioid carcinoma' and both harboured a *KRAS* mutation. Case 9 consisted of mixed architectural patterns, including glandular, tubular and solid/spindled growth. The tubules contained eosinophilic secretions very focally. Case 10 showed a mixed solid/glandular proliferation with cribriforming. Cases 11–12 were originally named 'serous carcinoma' and one case had a *KRAS* mutation (case 11). Case 11 showed glandular architecture. Interestingly, case 12 was composed of sharply angulated glands and destructive myometrial growth. In cases 9–12 there was widespread severe cytological atypia (in keeping with being p53abn) and no convincing MLA histology. Therefore, none of the diagnoses were revised to MLA, despite being flagged as GATA3/TTF1-positive. The remaining cases 13–16 were initially classified as carcinosarcoma. Similarly, there was diffuse high-grade cytological atypia and no convincing MLA morphology; the diagnoses of carcinosarcoma remain unchanged. Case 16 harboured a *KRAS* mutation, containing a component resembling CCC; however, napsin A IHC was negative, making the diagnosis of a clear cell carcinoma component less likely.

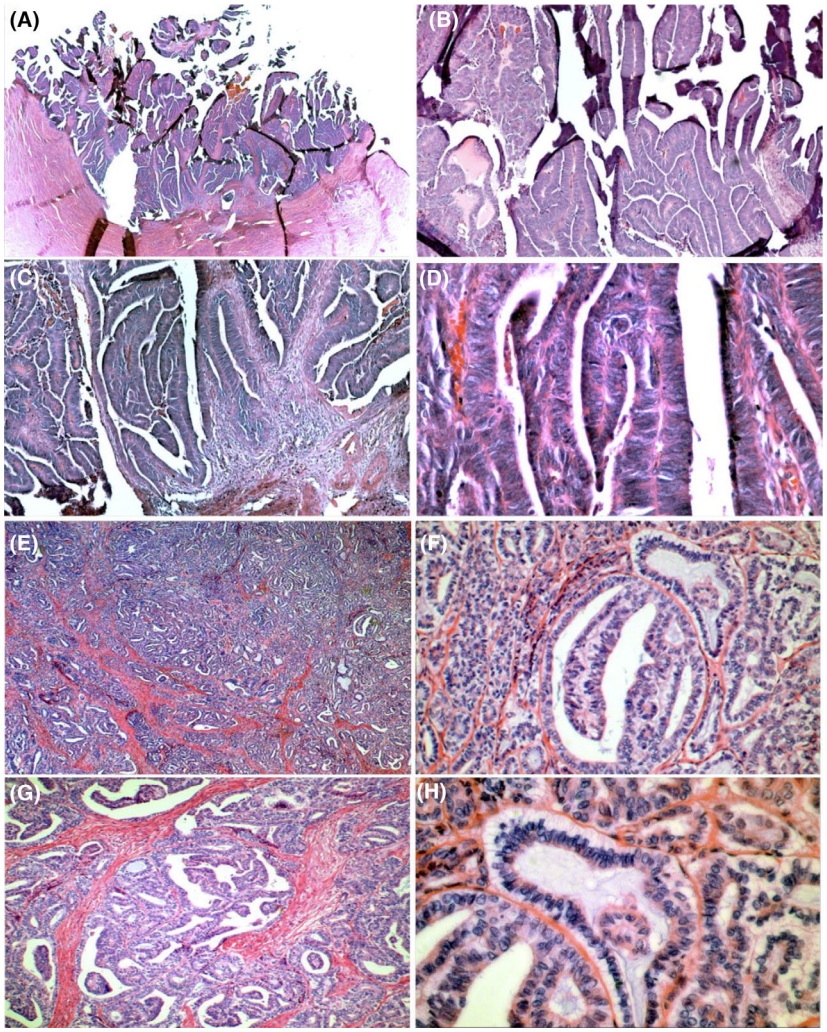

Figure 3. Additional examples of classic mesonephric-like adenocarcinomas. Case 3 shows a ductal pattern with distinct sharply angulated contours (**A**–**D**). Case 4 shows ductal pattern (**E**–**G**) and closely packed glands with subnuclear vacuoles mimicking secretory-phase endometrial glands (**H**).

In terms of clinical outcomes (Table 2), each case was evaluated for FIGO stage, time to recurrence (progression-free survival, PFS), disease-specific survival (DSS), overall survival (OS) and site(s) of recurrence. Of the five MLA, four cases (80%) recurred during follow-up, and the average time to recurrence was 2.5 years. Three cases recurred in the lung (recurrence site not available for one MLA case). Table 3 summarises the IHC, molecular and ProMisE molecular classifier for each case.

Discussion

In our analysis of 1094 endometrial carcinoma cases, screened via GATA3/TTF1/ER IHC and subsequently reassessed through histological and *KRAS* mutation analysis, we found that 0.5% (five of 1094) represented overlooked MLA. Our study approach aligns with methodologies used by Kolin *et al.*,[1] Mills *et al.*[2] and Kim *et al.*,[3] who extensively reviewed endometrial carcinoma cases, identifying misclassified MLA. Kolin *et al.*[1] reported a prevalence of 0.7% using *KRAS* and microsatellite stable (MSS) status as the initial screen, Mills *et al.*[2] reported 0.7% using GATA3/TTF1/CD10 +/− ER IHC as the initial screen and Kim *et al.*[3] reported 1.2% using histological reassessment as the screen. In these three studies and our own, accurate MLA diagnosis hinged upon comprehensive evaluation incorporating morphology, IHC and molecular data.

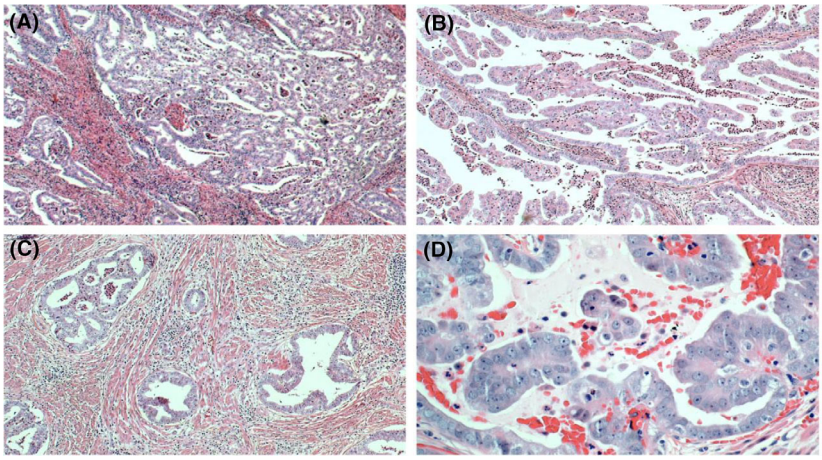

Figure 4. Atypical mesonephric-like adenocarcinoma (case 5; *KRAS*-wild-type) exhibiting multiple architectural patterns including cribriforming and labyrinthine pattern (**A**), papillary (**B**) and glandular with subtle angulated edges (**C**) with focal areas of higher-grade nuclear atypia (**D**). The mixed architectural patterns, GATA3 positivity, ER negativity and absence of squamous or mucinous differentiation were more in keeping with mesonephric-like adenocarcinoma as opposed to an endometrioid adenocarcinoma, despite the wild-type *KRAS* status.

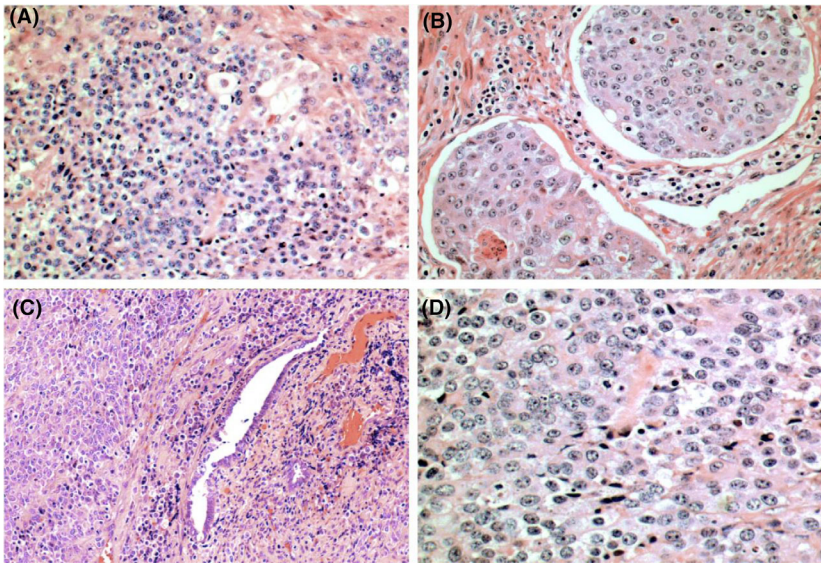

Figure 5. Cases of mismatch repair-deficient (MMRd) carcinoma deemed incompatible with mesonephric-like adenocarcinoma (MLA). Case 6 shows solid sheets of pleomorphic cells with severe atypia (**A**). Case 7 shows poorly differentiated solid tumour in intravascular spaces (**B**). Case 8 shows a focal glandular component (**C**) admixed with monomorphic undifferentiated epithelioid cells on higher power (**D**).

Our study also adds to the growing body of literature that MLA show mixed architectural patterns, display low-to-moderate cytologic atypia and are most commonly misclassified as low-grade endometrioid carcinoma.[1,2,15,28,38] In our study, all five of the MLA were originally misclassified as endometrioid carcinoma. We infer that our five MLA cases were overlooked because they did not have the classic MLA tubular growth pattern with dense eosinophilic secretions. In three of the five cases, papillary architecture was the predominant pattern. This often consisted of large gaping glands with intraluminal papillae often resembling the appearance of serous borderline tumour. Na *et al.*[39] has also commented on the close resemblance of the mesonephric adenocarcinoma papillary pattern to serous borderline tumour of the ovary. Kolin *et al.* similarly found papillary architecture in three of four overlooked MLA and Mills *et al.* in one of two overlooked MLA.[1,2] Quddus *et al.* recently reported an MLA with papillary

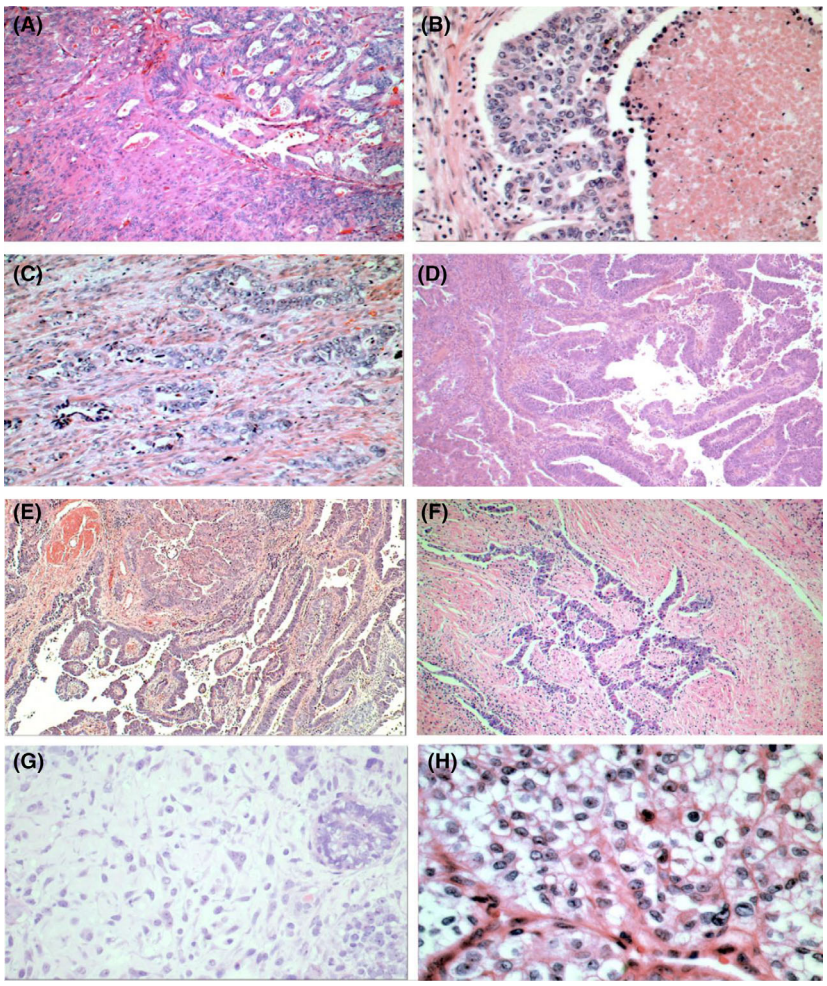

Figure 6. Cases of p53abn carcinomas deemed incompatible with mesonephric-like adenocarcinoma (MLA). Case 9 (**A**) shows mixed solid and glandular components. Case 10 (**B**) shows extensive intraglandular necrosis. Case 11 (**C**) shows atypical infiltrative glands. Cases 12 (**D**) and 13 (**E**) show mixed glandular and papillary patterns. Case 14 (**F**) shows trabecular/sex cord-like growth pattern. Case 15 (**G**) displaying sarcomatous cartilaginous component admixed with high-grade glandular growth. Case 16 (**H**) shows component of solid tumour with clear cell features (napsin A was negative in the tumour).

architecture thought to be on endometrial biopsy papillary proliferation of the endometrium. In addition, they described intestinal mucinous differentiation with goblet cells and another case with squamous morular metaplasia.[40] We did not notice any squamous or mucinous metaplasia in the MLA of our case series. Many authors consider the presence of squamous or mucinous metaplasia exclusionary in the diagnosis of MLA, but with greater awareness of MLA it is not surprising that the morphologic spectrum may be widening.[1,27] In the remaining two of our five MLA cases the morphological pattern was predominantly ductal, which is also suitably known as 'pseudoendometrioid'. Clement *et al.* described the ductal pattern as composed of angulated glands lined with columnar cells, which can have intraglandular villous papillae and resemble villoglandular endometrioid carcinoma.[41] Without ancillary IHC staining, it may be impossible to distinguish between the ductal pattern of MLA and villoglandular pattern of endometrioid carcinoma. Our study emphasises the need for pathologists to be wary of the papillary and ductal pattern when assessing uterine carcinomas, and have a low threshold to perform ER in these cases to exclude the possibility of MLA. Given the known challenges in MLA diagnosis and emerging use of ER as a therapeutic and prognostic biomarker, some institutions may choose to perform reflex ER testing on all endometrial carcinomas (together with reflex testing for MMR and p53).[31,42]

Table 2. Clinical summary of GATA3/TTF1 screen-positive cases

Case	Original histotype	Revised histotype	FIGO stage at diagnosis	Time to recurrence (years)	Disease specific survival (years)	Overall survival (years)	Follow-up duration (years)	Site of recurrence
1	Endometrioid	Typical MLA	IB	1.2	NDD	ND	3.1	Lung
2	Endometrioid	Typical MLA	IIIA	NR	NDD	ND	2.4	NA
3	Endometrioid	Typical MLA	IA	4.0	NDD	ND	4.3	NA
4	Endometrioid	Typical MLA	IIIA	0.9	NDD	ND	1.4	Lung
5	Endometrioid	Atypical MLA	IIIC1	4.0	NDD	ND	4.6	Lung
6	Serous	Endometrioid	II	3.4	NDD	ND	3.6	Vaginal, pelvic and para-aortic lymph nodes
7	Endometrioid	Not revised	IVA	NR	NDD	ND	0.3	NA
8	Endometrioid	Not revised	IIIC	NR	NDD	ND	4.3	NA
9	Endometrioid	Not revised	IIIC	1.6	NDD	ND	1.7	Lung
10	Endometrioid	Not revised	IB	NR	NDD	ND	2.4	NA
11	Serous	Not revised	IIIC1	NR	NDD	ND	2.8	NA
12	Serous	Not revised	IIIB	2.4	3.8	3.8	3.8	Pelvic
13	Carcinosarcoma	Not revised	IB	NR	NDD	ND	3.8	NA
14	Carcinosarcoma	Not revised	IVB	0.8	Unknown	3	4.0	Vaginal
15	Carcinosarcoma	Not revised	IA	NR	NDD	ND	4.3	NA
16	Carcinosarcoma	Not revised	IB	1.2	2.4	2.4	2.4	Para-aortic lymph nodes and lung

NA, not applicable or available; ND, no death during follow-up; NDD, no death from disease during follow-up; NR, no recurrence during follow-up.

Case 1 was the only case exhibiting dual staining with GATA3 and TTF1. Conversely, none of the remaining cases exhibited dual staining. Dual GATA3/TTF1 positivity has been quite specific for MLA, being found in 45% of MNC/MLC and in only 3% of CCC, 0.9% of CS 0.4% of endometrioid carcinoma and no cases of serous carcinoma thus far.[2,22] It is intriguing that the GATA3/TTF1/ER IHC screen identified a set of tumours enriched in *KRAS* mutations. After the IHC screen, *KRAS* mutations were found in four of four (100%) endometrioid carcinomas [versus 17% (51 of 307) reported in The Cancer Genome Atlas (TCGA)], one of three (33%) serous carcinomas [versus 2% (one of 53) reported in the TCGA] and one of four (25%) of the CS [12% (five of 57) reported in the TCGA].[43–47] It is difficult to draw any conclusions from the serous and CS categories due to the small numbers, but the finding of *KRAS* mutations in all IHC flagged endometrioid carcinomas is peculiar. The significance of this finding is unclear without additional molecular testing (such as copy number changes) to more confidently rule out MLA. Despite the small sample size, the clinical behaviour of MLA aligned with that reported in the literature.[17] Four of the five (80%) MLA experienced disease recurrences, with a mean interval of 2.5 years, and three of the five MLA presented at advanced stage (stage III). These findings are congruent with the prior multi-institutional study by Pors *et al.* reporting that 58% of patients with MLA of the endometrium presented at advanced stage (FIGO stages II–IV) and the 5-year PFS was 27.5%.[17] The current line of thinking is that MLA fall within the 'no specific molecular profile' (NSMP) in the ProMisE classifier or 'copy number low' group by the TCGA.[48] Indeed, all five of our MLA were originally classified as

Table 3. Classification of cases integrating immunohistochemistry and *KRAS* sequencing

Case	MMR	ER	GATA3	TTF1	p53	ProMisE classification	KRAS	Original histotype	Revised histotype
1	Proficient	–	1	2	WT	NSMP/p53wt	G12D	Endometrioid	Typical MLA
2	Proficient	–	2	–	WT	NSMP/p53wt	G12A	Endometrioid	Typical MLA
3	Proficient	–	2	–	WT	NSMP/p53wt	G12V	Endometrioid	Typical MLA
4	Proficient	–	–	1	WT	NSMP/p53wt	G12V	Endometrioid	Typical MLA
5	Proficient	–	2	–	WT	NSMP/p53wt	WT	Endometrioid	Atypical MLA
6	Deficient (MLH1 and PMS2 loss)	–	2	–	Null	MMRd	WT	Serous	Endometrioid
7	Deficient (MLH1 and PMS2 loss)	–	–	2	WT	MMRd	G13D; G12D	Endometrioid	Not revised
8	Deficient (MLH1 loss)	–	–	2	WT	MMRd	G12D	Endometrioid	Not revised
9	Proficient	–	2	–	Overexpressed	p53 abnormal	Q61H	Endometrioid	Not revised
10	Proficient	–	–	1	Overexpressed	p53 abnormal	G12A	Endometrioid	Not revised
11	Proficient	–	1	–	Overexpressed	p53 abnormal	G13C	Serous	Not revised
12	Proficient	–	1	–	Overexpressed	p53 abnormal	WT	Serous	Not revised
13	Proficient	–	–	2	Null	p53 abnormal	WT	Carcinosarcoma	Not revised
14	Proficient	–	2	–	Overexpressed	p53 abnormal	G12V	Carcinosarcoma	Not revised
15	Proficient	–	–	1	Overexpressed	p53 abnormal	WT	Carcinosarcoma	Not revised
16	Proficient	–	2	–	Overexpressed	p53 abnormal	WT	Carcinosarcoma	Not revised

–, Denotes cases with negative immunohistochemical staining; 2 is moderate or strong intensity in more than 50% of cells, and 1 includes cases with stain intensity/proportion not meeting criteria for a 2. MMRd, mismatch repair deficient; WT, wild-type.

ER-negative NSMP tumours. It is difficult, however, to deem *TP53* mutations as exclusionary for the diagnosis of MLA. Within the literature, there are cases of *TP53*-mutated MLAs reported in the gynaecological tract.[9,11,13,49,50] Lin *et al.*[49] reported a novel *TP53* mutation detected by peripheral blood liquid biopsy 6 years after solid tumour testing in a patient with metastatic cervical mesonephric adenocarcinoma. Perhaps the greatest challenge in diagnosing *TP53* mutant MLA lies in their tendency to display higher-grade morphology. In our study's 16 flagged cases, nine were p53abn. All demonstrated significant areas of severe nuclear atypia, making pathologists reticent in considering a MLA diagnosis, and none of the nine cases exhibited areas of classic MLA morphology. The absence of classic MLA morphology is not surprising, as we would expect those cases to be detected on the original pathological examination and excluded from the TMAs—our study focuses upon overlooked MLA. It is extremely plausible that MLA with *TP53* mutations exist biologically, but pathologists tend to be dissuaded from the diagnosis in this context. Whether MLA with *TP53* mutations is acceptable for the diagnosis remains a matter of academic debate, as an endometrial carcinoma with *TP53* mutation of any histotype would be considered for more aggressive treatment as per the ESGO/ESTRO/ESP guidelines.[51] The major rationale for recognising MLA is to separate it from other NSMP tumours, given that MLA tend to exhibit more aggressive clinical behaviour.

The majority of existing evidence in the literature suggests that both MNC and MLA are MMRp/MSS.[1,2,9,52] Kolin *et al.*[1] used MMRd as an exclusionary criterion in their diagnostic algorithm of endometrial MLA. Mills *et al.*[2] found intact MMR IHC in their two endometrial MLA cases. In a study examining 25 endometrial MLA, MMR IHC and MSI testing were performed, and nine of 25 cases were initially presumed to be MMRd based on IHC.[52] However, on

closer re-examination of slides and repeat IHC they found at least focal expression on IHC, which was considered compatible with an MMRp profile. Furthermore, all cases were tested for MSI via polymerase chain reaction (PCR) and they were MSS. Koh *et al.*[53] also re-examined some uterine MLA cases initially interpreted as MMRd on IHC, and they noted that these cases should have been interpreted as MMRp tumours. Therefore, it is important to carefully examine MMR IHC for at least focal IHC expression, and consider repeating IHC and resort to MSI testing, especially for MLA. Recently however, Angelico *et al.* reported a case of MLA with three components: endometrioid carcinoma, undifferentiated/de-differentiated carcinoma and MLA. The MLA component was GATA3+/TTF1+/ER− and the *KRAS* mutation (Q16L) was restricted to the MLA component. The MLA component also showed IHC loss of MLH1 and PMS2.[54] However, it is important to note that *KRAS* Q16L is not a canonical pathogenic mutation which is not characteristic for MLA, raising the possibility that the reported case may not represent a true MLA. We did not use MMR status as exclusionary for MLA. As the prevailing theory is that MLA is Mullerian-derived, given its association with other Mullerian type neoplasms and endometriosis, we believe it is plausible for MLA to also show MMR deficiencies. In our study three MMRd cases were excluded from being MLA, not for their MMR IHC expression loss, but instead due to incompatible morphology with MLA. Curiously, there was consensus agreement among all three pathologists for rejecting MLA in only three cases (the pathologists were blinded to the MMR and p53 data). Those three cases were all MMRd and there were only three MMRd screen-positive cases in the series. Cases 6–7 were excluded due to the poorly differentiated morphology, which is thought not to be compatible with MLA. Case 8 was thought to be more compatible with an undifferentiated/de-differentiated carcinoma based on morphology and being MMRd, despite also exhibiting a *KRAS* mutation. Undifferentiated morphology has also been raised recently as a histological pattern seen in MLA. Mirkovic *et al.*, Na *et al.* and Choi *et al.* reported undifferentiated carcinoma components in MLA, and in two cases the undifferentiated carcinoma was MMR-proficient.[2,4,15] More in-depth molecular testing is needed to ascertain whether or not MLAs can harbour MMR abnormalities. Again, this remains a matter of academic debate, as no cases of MLA have been reported in Lynch Syndrome and it not likely to not impact treatment. Shen *et al.*[55] reported two cases of *KRAS*-mutated endometrial MLA that showed excellent and durable responses to lenvatinib and pembrolizumab. Interestingly, one of these cases was MSS, while the other case lacked MSI information. As more clinical and molecular data about MLA emerge, it is worth exploring the question of whether MLA strictly belong in the NSMP group or whether they can be placed in other molecular groups. A similar histotype to consider are endometrial clear cell carcinomas—they can be grouped in both the MMRd and p53-abnormal molecular groups. MMRd and p53-abnormal CCC will be treated according to the respective molecular group, respectively, so the histotype is clinically impactful only in NSMP. According to our data, MLAs are similar to CCC in the sense that the histotype of MLA is very impactful in NSMP, as they portend a poorer prognosis and may have different treatment implications compared to low-grade NSMP endometrioid carcinomas.

Our study faced certain limitations, primarily the lack of comprehensive molecular data. Molecular data such as copy number gain of 1q, loss of 1p, *CTNNB1*, *ARID1A*, *PTEN*, *PIK3CA*, *NRAS* and other molecular alterations were not available, which hindered our ability to classify all cases conclusively. Additionally, we were unable to include one screen-positive case due to the unavailability of H&E slides and tissue blocks. Further cases of endometrial MLA could have been missed in our cohort because we only analysed cases exhibiting negative ER IHC screening and did not include cases with weak or focal ER expression. We also did not review the histology for all the endometrial carcinoma cases, potentially missing rare cases of MLA that could be GATA3- and TTF1-negative. Furthermore, given that IHC was performed on TMAs, cases with focal GATA3/TTF1 expression may have been missed on screening.

In summary, we add to the growing body of literature addressing the morphological patterns and clinical significance of overlooked MLA. We found that papillary and ductal patterns were the most often overlooked, and recommend a low threshold to perform GATA3, TTF1 and ER in this scenario. All five MLA were originally diagnosed as ER-negative low-grade endometrioid carcinoma of NSMP. This diagnosis should similarly trigger consideration of MLA and performance of additional testing. We also advocate for further research into the molecular landscape of MLA, particularly to address the ongoing question of whether *TP53* abnormalities or MMR deficiency should be exclusionary or acceptable in diagnosing MLA.

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Conflicts of interest

None to declare.

Data availability statement

Data are available upon reasonable request to the corresponding author.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Immunohistochemistry antibody details.