which plays a role in the regulation of cellular proliferation. The most common genetic alteration found in ganglioglioma is *BRAF* V600E mutation, occurring in 20–60% of cases;¹ this mutation is also frequently observed in other low-grade neoplasms, including pleomorphic xanthoastrocytoma and pilocytic astrocytoma. Gain of chromosome 7 is also commonly seen.¹ Other mutations found in a cohort of 40 gangliogliomas using next-generation sequencing included alternative *BRAF* mutations, *BRAF* fusion, *KRAS* mutations, and *FGFR1/2* alterations.² The various alterations did not show significant association with disease progression, but analysis was limited by small case numbers.

High-grade transformation of ganglioglioma in the absence of radiation therapy is extremely rare. A review of the literature found 17 cases of malignant transformation of grade I ganglioglioma, with 14 of these describing transformation to anaplastic ganglioglioma (WHO grade III).³ Two of the remaining cases described transformation to glioblastoma without additional detail, with the final case showing transformation to anaplastic ganglioglioma, designated as WHO grade IV, with glioblastomatous change of the astrocytic component. Molecular testing in two cases showed *BRAF* V600E mutation in both the initial and transformed lesions by immunohistochemistry and sequencing.^{3,4} Epithelioid morphology in the transformed lesion was not described in either case. Two cases showed *H3F3A* (*p.K27M*) mutations in both lesions, with one case having both *BRAF* V600E and *H3F3A* mutations.^{4,5} Prognosis amongst the transformed tumours was universally poor with survival ranging from 4 to 42 months. A case series of 54 midline paediatric grade I gangliogliomas found *H3 K27M* and *BRAF* V600E mutations in five cases, with one showing progressive disease after 8 years.⁶ Although *H3K27M* alterations are required for the diagnosis of diffuse midline glioma WHO grade IV, this case series shows that they are not pathognomonic for, or invariably associated with, poor outcomes in glioneuronal tumours. Mutations in *H3F3A* have also been reported in high-grade neuroepithelial neoplasms with glial and dysplastic ganglion cell components.⁷ However, histone H3 alteration was not demonstrated in our case.

High-grade transformation of *BRAF*-mutant pleomorphic xanthoastrocytoma to *BRAF*-mutant epithelioid glioblastoma has been previously reported, but this has not been documented for *BRAF*-mutant ganglioglioma.⁸ One case report has described an anaplastic ganglioglioma with focal epithelioid cells at diagnosis, with *BRAF* V600E mutation demonstrated by immunohistochemistry in both components. The authors suggest that the lesion may have eventually evolved into epithelioid glioblastoma, but a temporal relationship was not clearly demonstrated.⁹

The pathogenesis of high-grade transformation of ganglioglioma remains poorly understood due to the paucity of cases in the literature, and relatively few cases detailing molecular associations. Identification of molecular alterations that may be associated with potential high-grade transformation could allow for closer clinical supervision or targeted therapy. This case highlights the potential for malignant transformation of ganglioglioma, in particular to epithelioid glioblastoma, and the need for clinical follow up.

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Ovarian mesonephric-like adenocarcinoma: morphological diversity and histogenetic considerations of an unusual tumour

To the Editor,

Pathologists are familiar with various vestiges of the female apparatus. One of these vestiges, the mesonephric remnants, are frequently encountered in the cervix or the vagina and lesions developing from these remnants, such as mesonephric hyperplasia or adenocarcinoma, are rare but well-recognised. In 2016, McFarland *et al.*¹ described a similar type of adenocarcinoma arising in the ovary, and called it mesonephric-like adenocarcinoma (MLA). Since their description, only a few similar cases have been reported, but given the addition of a new chapter in the latest World Health Organization (WHO) classification, more studies are expected to arise, and more information is needed for this rare histological subtype.

A 74-year-old patient was incidentally found to harbour a left ovarian mass. The patient had a family history (daughter) of an ovarian low grade serous carcinoma. Total non-conservative hysterectomy with omentectomy, and peritoneal lesions and lymph node excision was decided. Macroscopic examination revealed a partly solid partly cystic (large cystic space) ovarian left mass measuring 19×14.5×11 cm,

Fig. 1 (A) Macroscopic aspect showing that the tumour is partly cystic, partly solid. (B) The morphology corresponding to the solid area is that of an adenocarcinoma composed of glandular and tubular structures (H&E; inset: diffuse strong TTF1 expression). (C) Higher magnification of the adenocarcinoma area. (D) Inset: macroscopic aspect of the periphery of the tumour, where smaller cystic spaces often with endocystic excrescences were found. The corresponding slide of this area shows that the intracystic excrescences corresponded to papillary structures, though with less hierarchical branching than the typical serous borderline tumours. Presence of an endometriotic focus (lower right). (E) The intracystic borderline-like component with the mesonephric-like glands at the bottom. (F) The papillae are lined by less atypical cells without significant mitotic count.

weighing 1505 g. Some smaller cystic spaces often containing vegetations were also present (Fig. 1A). Microscopic examination of the solid component showed an adenocarcinoma of glandular, tubular, retiform and papillary architecture composed of moderately atypical cells with numerous mitoses and scant cytoplasm (Fig. 1B,C). The large cystic part of the lesion often showed loss of the lining, with only few residual foci of the same tumour cells recognised. Interestingly, the

smaller cystic component had a more variable appearance (Fig. 1D–F): cysts were lined by less atypical cells arranged in papillae resembling a borderline tumour, or by mucinous cells with no atypia and no proliferation, resembling mucinous metaplasia. In these areas (Fig. 2), tubular elements surrounding the cysts frequently showed a luminal eosinophilic material, while glandular and microcystic elements showed larger cells with more abundant eosinophilic cytoplasm,

Fig. 2 (A) Also intermixed with the mesonephric-like component, there were mucinous lined cystic spaces. (B) The transition from a more cuboidal (left) to a mucinous lining (right) consistent with mucinous metaplasia. (C) These mucous-secreting cells showed no atypia. (D) Eosinophilic cells and eosinophilic material. (E) ER expression by the focus shown at F. (F) Hobnail cells with eosinophilic cytoplasm and nuclear inclusions.

compatible with eosinophilic metaplasia. Rare endometriotic foci were found. The immunohistochemical profile was as follows: GATA3+ (mild to moderate patchy expression), TTF1+ (strong and diffuse), CD10+, calretinin-, CK7+ patchy, CK20-, WT1-, PAX8+, ER-, PR-, p53 non-mutated profile, thyroglobulin-. This profile was found in the solid component of the tumour.

In the smaller cystic areas, the following differences were observed: the more eosinophilic glands showed ER expression, while the mucinous component was TTF1-, GATA3 focally+ and CK20 focally+ but CK7 diffusely+. Also, the borderline-like component was more diffusely GATA3+ and less TTF1+. The tumour was diagnosed as a mesonephric-like adenocarcinoma, TNM stage pT3bN1b and FIGO IIIB. Immunohistochemistry for the four MMR proteins showed retained expression. Next generation sequencing (NGS) was performed in the solid (adenocarcinoma) component and the intracystic papillary borderline-like component revealing *KRAS* [exon 2, c.35G>T, p.(Gly12Val)] mutation in both, as well as a *CTNNB1* mutation [exon 3, c.122 C>T, p.(Thr41Ile)] only in the latter. NGS was further performed for the homologous recombination deficiency genes and the *PIK3CA* showing no mutations in *BRCA1*, *BRCA2*, *RAD51C*, *TP53*, *PIK3CA*, nor large genomic rearrangements for *BRCA1*, *BRCA2*, *RAD51C*. The patient was treated with carboplatin/taxol and is alive and free of disease at 6 months after the initial diagnosis.

Mesonephric lesions of the cervix/vagina are well-documented; however, their counterpart in the upper female genital tract is rare, essentially represented by the female adnexal tumour of Wolffian origin. It is possible that before the original description of McFarland *et al.*,¹ similar cases had also been reported, such as the case of Moerman *et al.* reporting a mesonephric adenocarcinoma of the broad ligament arising in association with a benign lesion, maybe a papillary cystadenoma,² and the case of Ordi *et al.* 20 years earlier describing a mesonephric carcinoma of the uterine corpus showing no association with the endometrium.³ However, the more recent concept of mesonephric-like adenocarcinoma of the ovary or the endometrium probably starts with the report by McFarland *et al.*¹ They described five ovarian MLAs showing absence of ER/PR and WT1 for all cases, diffuse positivity for CK7 in all cases, diffuse ($n=4$) or focal ($n=1$) positivity for TTF1, diffuse ($n=3$) or focal ($n=2$) positivity for PAX8, focal positivity for CD10 (in 2/3 cases studied), focal ($n=1$) or diffuse ($n=1$) positivity for GATA3, and wild type p53 expression ($n=3$). This immunohistochemical profile was further supported by a subsequent study of mesonephric and mesonephric-like adenocarcinomas of the female genital tract, including one ovarian case; however, it is worth noting that almost 40% of other uterine and cervical carcinomas, especially carcinosarcomas, also showed GATA3 expression, but only rarely TTF1 expression.⁴

In the original report of McFarland *et al.*, the authors suggest a probable mesonephric origin for these neoplasms given their morphology, the absence of squamous and mucinous elements, and the characteristic immunophenotype.¹ However, the authors do discuss the possibility that these tumours represent Müllerian tumours, especially endometrioid adenocarcinomas differentiating along a mesonephric phenotype, and given the uncertainty, they propose the term MLA for these ovarian and endometrial cases. In a subsequent molecular study of four of the same

ovarian cases, a *KRAS* mutation [p.(Gly12Asp)] was found in all four with additional *PIK3CA* mutations in two.⁵ In another four ovarian cases, *KIT* harboured no mutations, despite immunohistochemical cKIT expression; however, the same cases revealed *KRAS* mutation in all four, and additional *CTNNB1* (similarly in exon 3) in one and *PIK3CA* mutations in another.⁶ The presence of *KRAS* mutations, already known to occur in cervical mesonephric adenocarcinomas,⁷ further reinforced their mesonephric differentiation. However, given their endometrial localisation when uterine tumours, the presence of endometriosis for ovarian cases, the lack of an obvious mesonephric precursor, and the presence of *PIK3CA* mutations, and despite the lack of squamous/mucinous metaplasia or adjacent atypical endometrial hyperplasia, the authors finally suggest that these ovarian/endometrial neoplasms are likely of Müllerian origin, but display morphological, immunophenotypic and molecular differentiation of mesonephric type.⁶

Shortly after the original report of McFarland *et al.*¹ and before the molecular analysis of these tumours, Chapel *et al.* presented an ovarian mesonephric-like carcinoma combined with low-grade serous carcinoma, each showing distinct morphology and immunophenotype but both harbouring the same *NRAS* p.(Gln61Arg) mutation, suggesting a clonal relationship and not a collision tumour.⁸ Soon after this observation, McCluggage *et al.* reported another case of ovarian MLA associated with serous borderline tumour/low grade serous carcinoma, both showing the same *KRAS* p.(Gly12Asp) mutation despite their individual phenotypes, and describe that in another three of four unpublished cases, a Müllerian lesion (one with borderline endometrioid adenofibroma, one with endometriosis and mixed serous and mucinous cystadenoma, and one with serous cystadenoma) was also present in the same ovary. These findings along with the presence of endometriosis in three of the five ovarian cases originally reported suggested a Müllerian origin for ovarian MLA according to the authors.⁹

A recent study including 15 ovarian MLAs similarly suggested that 'MLAs are derived from a Müllerian substrate with differentiation along Wolffian/mesonephric lines' and found another component, serous borderline or low-grade, and mucinous borderline, in five cases.¹⁰ We believe that the case described here further supports the Müllerian and mostly the endometrioid origin of at least a subset of these tumours. The features described in our case such as the presence of mucinous metaplasia, the presence of a glandular component with more eosinophilic cells often ER+ resembling endometrioid adenocarcinomas, and the presence of a *CTNNB1* mutation, further support that at least a subset of ovarian adenocarcinomas showing mesonephric morphology and immunoprofile derive from Müllerian epithelium. Indeed, *CTNNB1* and *PTEN* mutations seem to be present only in MLA in comparison to mesonephric carcinomas.¹⁰

Along with the current case, there seems to exist three ovarian MLAs with a *CTNNB1* mutation.^{6,10} Also, we found the *CTNNB1* mutation in a component with a more borderline-like architecture without significant atypia and with the same immunophenotype (although more GATA3+, and less TTF1+ cells) that could correspond to the borderline component of this subtype. The phenotypical diversity found in the current case is reminiscent of seromucinous tumours, harbouring mucinous cells, cells with eosinophilic

cytoplasm, serous-like cells, squamous cells, and similarly considered to derive from an endometrioid lineage, leading to deletion of the seromucinous carcinoma¹¹ (but not borderline) chapter from the latest WHO classification. Of note, the possible association of ovarian MLAs with microsatellites or HRD gene status is largely unknown; we found no relevant abnormality in the current case.

Finally, given the rarity of these tumours, reports have been limited to only a few cases without considerable follow up, so their clinical course was virtually unknown until recently. However, a recent multicentre, retrospective study gathering 25 ovarian cases (four of which were previously published),^{4,6} among cases from other localisations, revealed a mean age at diagnosis of 61 years (range 36–81), FIGO stage II–IV in almost 40% of cases and recurrences in 42% of them, usually distant, often pulmonary, with a 5-year progression-free and overall survival of 68% and 71%, respectively, implying that these are aggressive tumours.¹²

To conclude, ovarian MLAs should be suspected when an endometrioid morphology is encountered, but with more variable architectures and absence of hormone receptors. GATA3 and TTF1 positivity will then help in the diagnosis. To the best of our knowledge, the features of the current neoplasm have not been reported before: mucinous metaplasia, ER+ eosinophilic cells, and a *CTNNB1* mutation in a borderline-like component. The morphological, immunohistochemical and molecular features presented here further support the Müllerian, and mostly the endometrioid, origin of a subset of ovarian mesonephric-like adenocarcinomas.

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Recurrent plexiform angiomyxoid myofibroblastic tumour (PAMT) of the stomach with aggressive behaviour

To the Editor,
Plexiform angiomyxoid myofibroblastic tumour (PAMT), also known as plexiform fibromyxoma (PF), is a myofibroblastic tumour, first described by Takahashi *et al.* in 2007.¹ As per the World Health Organization (WHO) 2018 classification of digestive system tumours, the term plexiform fibromyxoma has been accepted as a distinct entity among the benign mesenchymal tumours of the stomach.² Despite this nomenclature set by WHO, many authors still prefer PAMT as a better terminology as it literally describes the morphology well. As it is a rare and recently described entity, many clinicians and pathologists are unaware of this tumour. Hence, it poses diagnostic difficulties as compared with other mesenchymal tumours of the stomach and most often gets misinterpreted as gastrointestinal stromal tumour (GIST). There has been only one such case report from India.³ Our case is the second with many undescribed features which necessitate a fresh insight into its natural history and nomenclature.

A 50-year-old female underwent upper gastrointestinal (GI) endoscopy (July 2017) 1.8 years previously for the complaint of one episode of upper GI bleeding, which demonstrated a 2×2 cm ulcerated nodular lesion located along the lesser curvature of the body of the stomach (Fig. 1A). Endo-ultrasonography confirmed a hypoechoic lesion arising from the muscularis propria of the gastric wall, suggestive of either GIST or leiomyoma (Fig. 1B). She