



Sustained response to lenvatinib and pembrolizumab in two patients with *KRAS*-mutated endometrial mesonephric-like adenocarcinoma

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ARTICLE INFO

Keywords

Endometrial
Mesonephric
Mesonephric-like
Lenvatinib
Pembrolizumab
KRAS

1. Introduction

Endometrial mesonephric-like adenocarcinoma (MLA) has recently been categorized as a rare and aggressive subtype of epithelial endometrial cancer (EMC) (McFarland et al., 2016). These tumors are characterized by *KRAS* and *NRAS* mutations, GATA3 and TTF1 positivity, and estrogen receptor (ER) and progesterone receptor (PR) negativity (Pors et al., 2021, 2018). In comparison with more common endometrial carcinomas, endometrial MLA presents at a more advanced stage. Several case series have shown that patients with endometrial MLA have worse progression-free survival (PFS) and overall survival (OS) compared with matched cohorts of patients with serous EMC (Pors et al., 2021, 2018). Given the rarity of these tumors, limited data exist regarding the treatment of endometrial MLA.

Carboplatin and paclitaxel is the standard first-line systemic regimen for metastatic EMCs; targeted therapies and other cytotoxic agents have shown limited efficacy and/or are associated with substantial toxicities. In the second-line setting, pembrolizumab, a programmed cell death receptor-1 (PD-1) inhibitor, is approved for a subset of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancers; however, only 13–30% of recurrent EMC cases are MSI-H/dMMR (O'Malley et al., 2019; Prendergast et al., 2019). For microsatellite stable (MSS) advanced/recurrent EMCs, the combination of pembrolizumab and lenvatinib, an oral multikinase inhibitor, has dramatically changed the treatment paradigm with an objective response rate of 36% and a median OS of 16.4 months (Makker et al.,

2020). In a randomized phase III trial, lenvatinib and pembrolizumab significantly prolonged PFS (7.2 vs. 3.8 months) and OS (18.3 vs. 11.4 months) compared with physician's choice chemotherapy in patients with advanced EMC, regardless of MMR status (Makker et al., 2021). However, whether these agents have activity in endometrial MLA is unknown. Here, we report two cases of endometrial MLA with excellent and durable responses to lenvatinib and pembrolizumab.

2. Patient 1

Patient 1 presented at age 60 with postmenopausal bleeding. She underwent total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection. Pathology was initially reported as grade 1 endometrioid type adenocarcinoma with <50% myometrial invasion, stage IA (Fig. 1A); 10 lymph nodes were removed, all of which were benign. One year later, she had a recurrence in her pelvic lymph nodes and was treated with external beam radiation with 3960 cGy for 22 fractions with boost to the right pelvic lymph nodes of 1440 cGy for 8 fractions. Eight months later, imaging revealed peritoneal carcinomatosis and omental biopsy showed metastatic endometrial carcinoma with features consistent with MLA (Fig. 1B). Immunohistochemistry staining showed GATA3 positivity while ER and PR were negative, supporting this diagnosis. Next generation sequencing (NGS) using the MSK-IMPACT platform revealed a *KRAS* exon2 p.G12V (c.35G > T) mutation as well as *ERBB4*, *FANCA*, *MLL2*, *PTEN*, and *TRAF7*, further supporting mesonephric differentiation. Notably, MLA as a

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<https://doi.org/10.1016/j.gore.2021.100844>

Received 31 May 2021; Received in revised form 29 July 2021; Accepted 2 August 2021

Available online 8 August 2021

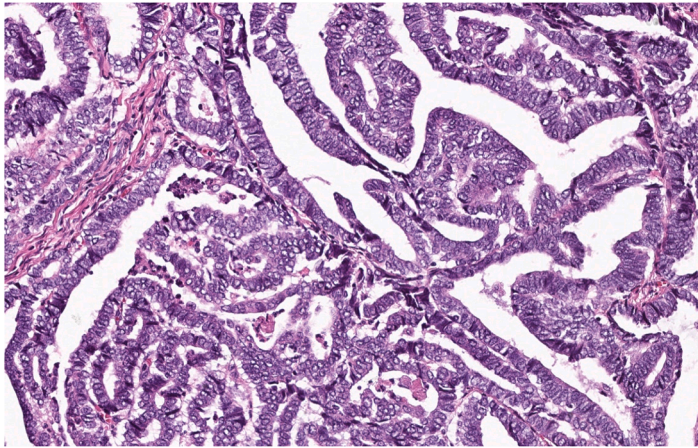
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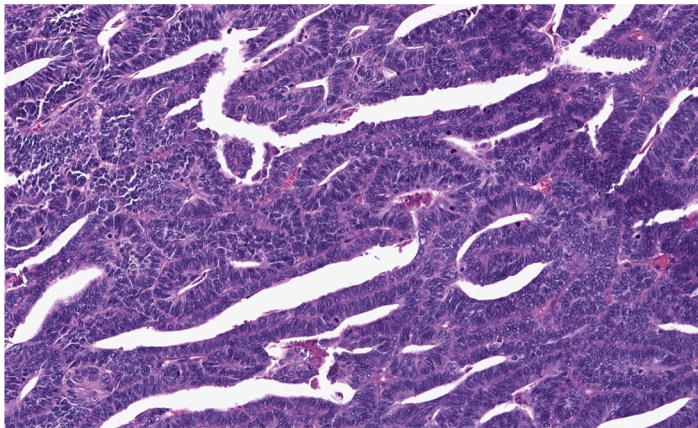
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A) Tumor from the endometrium with complex glandular proliferation lined by cuboidal to columnar cells with ovoid, optically clear nuclei resembling papillary thyroid carcinoma, typical of mesonephric-like carcinoma.



B) Omental metastasis showing similar morphology in addition to some nuclear grooves.



C) Contrast-enhanced abdomen and pelvis computed tomography (CT) scans showing decreased size of the largest peritoneal implant while on treatment with lenvatinib and pembrolizumab.

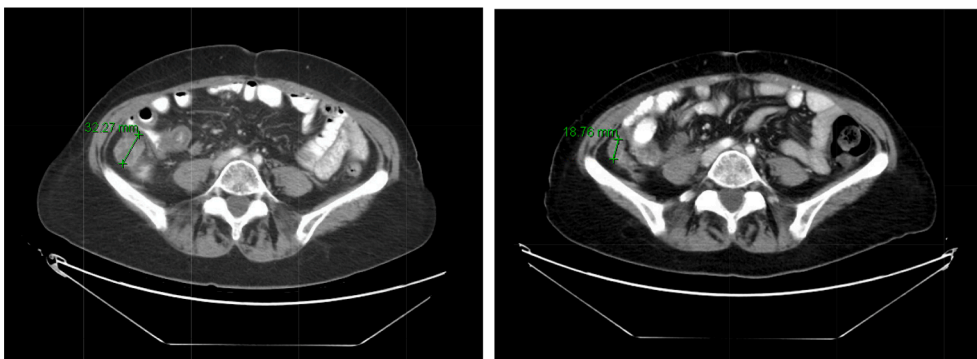
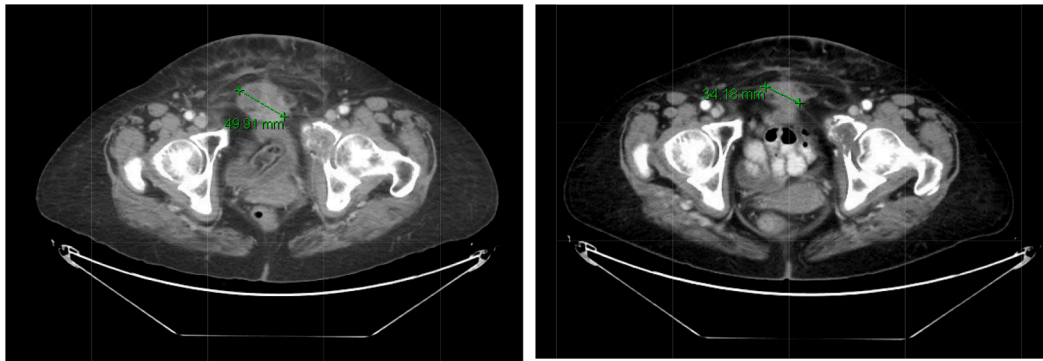


Fig. 1. (A) Tumor from the endometrium with complex glandular proliferation lined by cuboidal to columnar cells with ovoid, optically clear nuclei resembling papillary thyroid carcinoma, typical of mesonephric-like carcinoma. (B) Omental metastasis showing similar morphology in addition to some nuclear grooves. (C) Contrast-enhanced abdomen and pelvis computed tomography (CT) scans showing decreased size of the largest peritoneal implant while on treatment with lenvatinib and pembrolizumab.

defined entity was not described at the time of initial diagnosis and the first description was published between the time of the hysterectomy and the omental metastasis (McFarland et al., 2016). Tumor mutational burden (TMB) and microsatellite instability testing results were not available. She was treated with carboplatin and paclitaxel for 3 cycles; treatment was discontinued for thrombocytopenia and near-complete response. Seven months later, imaging demonstrated progression of disease and weekly paclitaxel was initiated. Over the ensuing 4-year period, she received several monotherapy agents sequentially upon progression of disease: 9 cycles of weekly paclitaxel followed by a 1-year

treatment-free interval, 4 cycles of bevacizumab, 5 cycles of carboplatin followed by a 4-month treatment-free interval, 5 cycles of weekly paclitaxel followed by a 5-month treatment-free interval, 15 cycles of bevacizumab, and 6 cycles of cisplatin. Five years after initial diagnosis, her CA-125 rose to 501 and peritoneal carcinomatosis worsened. Standard treatment options were limited by cytopenias, renal insufficiency, and peripheral neuropathy. She then initiated 8th line systemic therapy with lenvatinib 20 mg daily and pembrolizumab 200 mg every 3 weeks. Treatment was complicated by grade 1 diarrhea requiring lenvatinib dose reduction to 10 mg and grade 2 fatigue requiring dose reduction to

A) Contrast-enhanced abdomen and pelvis CT scans showing decreased size of the inferior rectus mass while on treatment with lenvatinib and pembrolizumab.



B) Contrast-enhanced chest CT scans showing decreased size of the largest lung lesion while on treatment with lenvatinib and pembrolizumab.

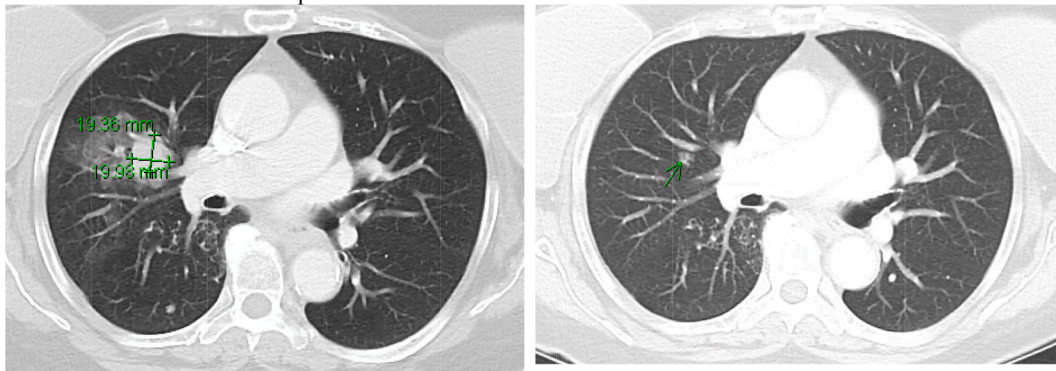


Fig. 2. (A) Contrast-enhanced abdomen and pelvis CT scans showing decreased size of the inferior rectus mass while on treatment with lenvatinib and pembrolizumab. (B) Contrast-enhanced chest CT scans showing decreased size of the largest lung lesion while on treatment with lenvatinib and pembrolizumab.

4 mg. While on treatment, her CA-125 normalized and the largest implant decreased from 3.2 to 1.8 cm (Fig. 1C). She remained on lenvatinib and pembrolizumab for 15 months until disease progression, at which time she was switched to paclitaxel.

3. Patient 2

Patient 2 was initially diagnosed at age 48 with endometrioid adenocarcinoma and underwent supracervical hysterectomy and left salpingo-oophorectomy. She had myometrial and serosal involvement, stage IIIA. She received 6 cycles of carboplatin and paclitaxel, external beam radiation to the pelvis, and high-dose rate brachytherapy; the doses are not available. Ten years later, she developed abdominal bloating; imaging showed bilateral pulmonary nodules, a bulky mass near the inferior rectus abdominis muscles, and soft tissue nodules in the pelvis. Pathology from an abdominal wall mass biopsy was positive for PAX8 and TTF1, and negative for GATA3, ER, and PR, consistent with endometrial MLA. NGS showed a TMB of 2.6 mutations/Mb, MSS tumor with a *KRAS* exon2 p.G12D (c.35G > A), *CTNNB1*, and *KMT2C* mutations. She received 6 cycles of carboplatin and paclitaxel with partial response by RECIST. Four months after completion of chemotherapy, imaging showed progression of disease at all sites; the inferior rectus mass increased from 5.0 × 2.5 cm to 5.0 × 3.8 cm. CA-125 was 20. She initiated therapy with lenvatinib 20 mg daily and pembrolizumab 200 mg every 3 weeks. Repeat imaging showed improvement; for example, the inferior rectus mass decreased to 3.4 × 2.4 × 4.2 cm, (Fig. 2A) and the largest lung lesion decreased from 2.0 × 1.9 cm to 0.7 × 0.5 cm (Fig. 2B). After 3 months, lenvatinib was decreased to 10 mg due to grade 2 myalgia and thrombocytopenia to platelet nadir of 67,000, then further decreased to 4 mg for grade 2 diarrhea. Given concern for

possible immunotherapy-related colitis she was started on prednisone empirically; biopsy showed immune-related microscopic colitis so she was transitioned to budesonide with improvement and pembrolizumab was subsequently resumed. Repeat imaging five months after initiation of lenvatinib and pembrolizumab showed sustained response, and she continues with this regimen presently with lenvatinib at a dose of 8 mg.

4. Discussion

It has been estimated that endometrial MLA represents approximately 1% of all endometrial carcinomas (Kolin et al., 2019). These rare cancers tend to be aggressive in nature, with the majority presenting at an advanced stage (Mao et al., 2020). In a case series of 40 patients with endometrial MLA, 51.4% developed a recurrence or died within the mean follow-up period of 24.7 months (Horn et al., 2020). In another series of 21 patients with endometrial MLA, 17 patients never achieved remission or developed recurrences from 4 to 84 months following diagnosis (Euscher et al., 2020).

Treatment of endometrial MLA varies widely. Almost all patients undergo upfront surgery, but adjuvant treatments differ and include radiation therapy, hormone therapy, or chemotherapy; the optimal adjuvant treatment regimen remains unknown (Deolet et al., 2021). The use of platinum-based chemotherapy regimens in the recurrent setting has shown mixed results (Montagut et al., 2003).

Our 2 patients with endometrial MLA developed recurrence following initial surgery. Patient 1 developed metastatic disease approximately 1 year following surgery, consistent with the literature showing that the majority of patients developing recurrence within 2 years (Horn et al., 2020). Notably, her initial surgical pathology was read as endometrioid adenocarcinoma whereas her omental mass

pathology showed mesonephric differentiation. Patient 2 had no evidence of disease for a decade before recurrence in the pelvis and lungs which progressed after briefly responding to chemotherapy. Her original slides were read as endometrioid adenocarcinoma by the original institution but upon review at Memorial Sloan Kettering at the time of recurrence, was revealed to be endometrial MLA. These discrepancies likely reflect the fact that endometrial MLA was not well described at the time of either patient's initial surgery.

NGS of tumor samples from both of our patients showed *KRAS* mutations, which are characteristic in patients with endometrial MLA. Genomic profiling in 7 endometrial or ovarian MLAs showed that all harbored canonical activating *KRAS* mutations (G12D or G12V) (Mir-kovic et al., 2018). In another series of 20 patients with mesonephric or MLA of the female genital tract, 5 had endometrial MLA and among them only 1 was *KRAS* wild-type; the other 4 had activating *KRAS* mutations (Lin et al., 2020). Unlike mesonephric carcinomas of the cervix which are derived from embryologic mesonephric (Wolffian) remnants, endometrial and ovarian MLA are thought to be derived from Müllerian substrates through a process of transdifferentiation, as they often harbor co-mutations in genes more typically affected in Müllerian tumors (da Silva et al., 2021) Accordingly, our cases harbored *KRAS* mutations, in addition to *PTEN* and *CTNNB1*, respectively, two commonly affected genes in endometrioid endometrial adenocarcinoma.

Tumors with *KRAS* mutations may be particularly sensitive to lenvatinib. In a phase II trial of 58 patients with papillary or follicular thyroid carcinoma treated with lenvatinib, 35% of the patients had a *RAS* (*NRAS* or *KRAS*) mutation; among this group, there was a 100% response rate to lenvatinib and significantly improved median PFS (80% compared to 20% in the *RAS* wild-type group) (Sherman et al., 2011). Patients with *KRAS* mutations have lower baseline levels of vascular endothelial growth factor (VEGF), which is predictive of improved treatment responses to lenvatinib (Ball et al., 2012). Both preclinical and clinical studies have shown that treatment of solid tumors with the combination of lenvatinib and pembrolizumab results in greater responses than treatment with either agent alone (Kato et al., 2016; Taylor et al., 2020). Prospective evaluation of association of *KRAS* mutation with responses to this combination is warranted.

Since the FDA accelerated approval in 2019, the combination of lenvatinib and pembrolizumab is increasingly being used in patients with advanced EMC. To the best of our knowledge, the use of lenvatinib and pembrolizumab for endometrial MLA has not been previously reported in the literature. Our case report demonstrates efficacy of this regimen in 2 heavily pretreated patients with substantial disease burden of metastatic endometrial MLA. This suggests that lenvatinib and pembrolizumab can be considered in the treatment of patients with this rare and aggressive cancer subtype.

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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