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Esophagitis as a complication of the combination of lenvatinib and pembrolizumab for advanced endometrial cancer: A case report

Massine Fellouah [a], Marie-Hélène Auclair [b], Suzanne Fortin [b], Jérémie Berdugo [c], Lara de Guerké [b,*]

[a] Faculty of Medicine, Université de Montréal, Montréal, QC, Canada
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, CIUSSS de l'Est-de-l'Île-de-Montréal, Université de Montréal, Montréal, QC, Canada
[c] Department of Pathology, CIUSSS de l'Est-de-l'Île-de-Montréal, Université de Montréal, Montréal, QC, Canada

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ABSTRACT

Background: Pembrolizumab is a monoclonal antibody targeting the programmed cell death protein 1 (PD-1). It is used in the management and treatment of various oncologic conditions. To name a few: refractory and advanced melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma and gastric cancer. It is also approved for metastatic mismatch repair deficient (dMMR) endometrial carcinoma after failure of front-line chemotherapy. Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor-a, RET, and KIT. The combination of lenvatinib and pembrolizumab has proven to be more effective together than as monotherapy. Here, we present the case of a patient who probably developed lenvatinib-related esophagitis, a complication not previously described in the literature to our knowledge.

Case presentation.

We describe a 65 years old female with metastatic endometrial cancer who presented dysphagia after a few months of lenvatinib plus pembrolizumab treatment. Upper endoscopy results revealed a very fragile upper esophageal mucosa with mucosal lacerations, consistent with grade 2 esophagitis. The biopsy showed esophagitis with mixed lymphocytic and eosinophilic inflammation and apoptotic component. Pembrolizumab was then stopped pending the results of the biopsy, following the recommendations of the gastroenterologist. Dysphagia, however, remained unchanged. In the meantime, the lenvatinib had to be stopped due to a dental procedure, and the patient noted a marked improvement in her symptoms. After discussion with the gastroenterologist, pembrolizumab was resumed and lenvatinib was suspended. The patient was also started on a PPI twice daily since the first digestive exploration. 1 month later, upper endoscopy showed complete recovery, the patient's symptoms improved, and lenvatinib was resumed. However, symptoms of dysphagia resumed a few days later. Lenvatinib was finally resumed at a reduced dose without reappearance in her symptoms.

Conclusions: We present a case of oesophagitis as a likely complication of lenvatinib for advanced endometrial cancer. The initiation of PPI and dose reduction of the lenvatinib allowed the patient to successfully go back on treatment.

1. Introduction

Endometrial cancer remains the most common gynecological cancer, with nearly 66,000 new cases listed each year in the United States (American Cancer Society Key statistics for endometrial cancer, N.D.). Several risk factors have been identified, such as obesity, exposure to hormones and advanced age (American Cancer Society Endometrial Cancer Risk Factors. N.D.). Although early-stage cancer is associated with favorable 5-year survival (96%), survival for advanced (i.e. metastatic) cancer is quite different (20%) (American Cancer Society Endometrial cancer survival rates, by stage. N.D.).

Platinum-based chemotherapy is the first-line treatment for advanced endometrial cancer in first line or in recurrence. According to NCCN, cyclin-dependent kinase 4/6 inhibitors (CKIs) can be offered in

* Corresponding author at: Hôpital Maisonneuve-Rosemont, 5415 Bd de l'Assomption, Montréal, QC H1T 2M4, Canada.
E-mail address: lara.deguerke@gmail.com (L. de Guerké).

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combination with carboplatin/paclitaxel type chemotherapy as adjuvant or recurrent treatment for endometrial cancer. The combination of Lenvatinib and pembrolizumab is recommended in endometrial cancers after a first exposure to platinum salts with the presence of MMRp biomarkers (Eskander et al., 2023; Mirza et al., 2023; Makker et al., 2022). Pembrolizumab is a monoclonal antibody targeting the PD-1 protein and it is approved for solid tumors with high microsatellite instability. It has a lot of indications, to name a few: refractory and advanced melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma and gastric cancer. Many more are currently in clinical development (Mirza et al., 2023; Makker et al., 2022). It can also be used for metastatic endometrial carcinoma after failure of first-line chemotherapy. Lenvatinib is a multikinase inhibitor that targets vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor-a, RET and KIT (Makker et al., 2020). Lenvatiniband pembrolizumab have proved significantly longer progression-free survival and overall survival than chemotherapy among patients with advanced endometrial cancer. Indeed, data from phase III study showed significantly longer progression-free survival with lenvatinib plus pembrolizumab (median, 6.6 months; 95% CI, 5.6 to 7.4) rather than with chemotherapy (median, 3.8 months; 95% CI, 3.6 to 5.0). The data for the overall survival point in the same direction: it was significantly longer with lenvatinib plus pembrolizumab (median, 17.4 months; 95% CI, 14.2 to 19.9) than with chemotherapy (median, 12.0 months; 95% CI, 10.8 to 13.3) (Makker et al., 2022).

The most frequent side effects of pembrolizumab are fatigue, diarrhea, rash, nausea and hypothyroidism (Kwok et al., 2016). The most common side effects of lenvatinib are hypertension (68%), asthenia (59%), diarrhea (59.4%), anorexia (50%), nausea (41%) and proteinuria (31%) (Suyama and Iwase, 2018; Hao and Wang, 2020). When the 2 therapies are combined, the side effects are relatively similar. Indeed, most frequent side effects described for the combined therapie are: hypertension (64%), fatigue (12–59,1%), hypothyroidism (57,4%), diarrhea (54,2%) and nausea (49,5%) (Makker et al., 2022; Mo et al., 2021).

We present the case of a patient with advanced endometrial carcinoma who developed probably lenvatinib-induced esophagitis. To our knowledge, this complication has not been previously described in the literature.

2. Case report

A 65-year-old woman consulted a gynecologist in a community hospital center for postmenopausal bleeding. She also complained of fatigue, loss of appetite and weight loss (8 lbs in 2 months). She had a history of scleroderma, hypothyroidism and diverticulosis. She was G2P2, postmenopausal at 52 years old and took hormone replacement therapy for one year (2016–2017). Her maternal grandmother and one of her cousins both had breast cancer. She was a non-smoker.

Initial laboratory work-up showed hemoglobin 111 g/L, ferritin 520 μg/L, platelets 522 × 10*9/L, CRP 120 mg/L, and CA-125 176 U/mL. Endometrial biopsy showed a poorly differentiated carcinoma FIGO grade III/ III, with an immunophenotype that favored a serous carcinoma of the endometrium. Immunohistochemical analysis showed the following results: p16-positive, p53-mutated, WT1-negative, Pax8-positive, RH-negative and Her2-negative MMRp. She was subsequently referred to our hospital center in the gyneco-oncology department.

CT Scan of the abdomen and pelvis (11/2020) showed a thickened endometrium at 25 mm, a complex right adnexal mass of 5.5 × 4.5 × 7.3 cm and external iliac and right common iliac adenopathies. There was no significant carcinomatosis or ascites. Thepatient underwent a laparoscopic total hysterectomy with bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, and an infracolic omentectomy. The himmuhistochemistry analysis were positive for MLH1, MSH2, MSH6 and PMS2 with no instability (MMRp). The final pathology was consistent with a stage IV serous carcinoma of the endometrium, with up to 80% myometrial invasion, right adnexal involvement. There was also paraaortic lymph node and pelvic peritoneum involvement.

The patient received IV carboplatin and paclitaxel every 3 weeks in the adjuvant chemotherapy setting. After 4 cycles, she complained of post-coital vaginal bleeding (02/2021). A pelvic MRI (04/2021) confirmed a recurrence in the form of peritoneal carcinomatosis at the vaginal vault. In the context of disease progression while on first-line chemotherapy, lenvatinib plus pembrolizumab was started (Mirza et al., 2023). Given her autoimmune history (scleroderma), this decision was discussed with her rheumatologist. The conclusions were to remain vigilant if the side effects of immunotherapy would require the introduction of corticoids.

After 9 cycles of lenvatinib plus pembrolizumab, dysphagia to solids appeared gradually. An upper endoscopy showed a fragile mucosa with laceration of the upper esophagus, consistent with grade 2 esophagitis (Fig. 1). On histology, esophageal biopsies showed esophagitis with mixed lymphocytic and eosinophilic infiltrate and scattered apoptotic bodies in the surface epithelium (Fig. 2). No fungal microorganisms, herpesvirus or cytomegalovirus were found in the biopsies. Pembrolizumab was then stopped pending the results of the biopsy, following the recommendations of the gastroenterologist. Dysphagia, however, remained unchanged. In the meantime, the lenvatinib had to be stopped due to a dental procedure, and the patient noted a marked improvement in her symptoms, which reappeared after the treatment was resumed. After discussion with the gastroenterologist, pembrolizumab was resumed and lenvatinib was suspended. The patient was also started on a PPI twice daily since the first digestive exploration.

1 month later, endoscopy showed complete recovery (Fig. 3), symptoms improved and lenvatinib was resumed at 14 mg daily. A few days after resuming lenvatinib, the symptoms of dysphagia recured and the treatment dose was further reduced to 10 mg daily without reappearance of her symptoms. So far, the patient is tolerating Lenvatinib 10 mg well and her disease is remaining stable 1 year after starting pembrolizumab plus lenvatinib.

3. Discussion and conclusion

In this case report, we present the case of a 65-year-old patient with advanced endometrial cancer who developed esophagitis probably secondary to lenvatinib. Several side effects are associated with immunotherapy, such as diarrhea, hypertension, hypothyroidism, anorexia, fatigue and nausea (Motzer et al., 2021). For Pembrolizumab, the side effects are due to an immune phenomenon, which is a consequence of impaired self-tolerance due to loss of T-cell inhibition. These effects can affect any organ, but they most commonly involve the gastrointestinal

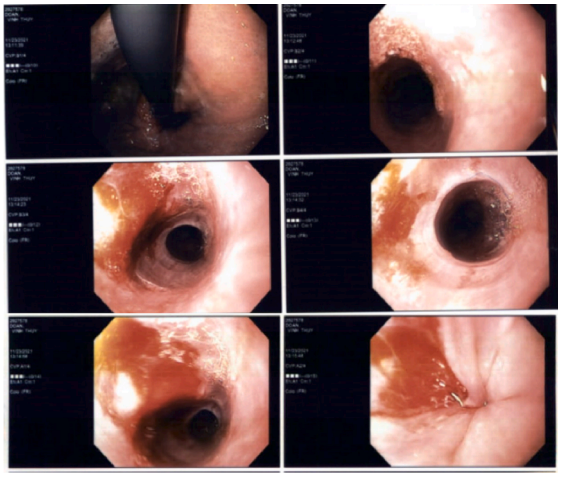

Fig. 1. OGD showing fragile mucosa with laceration of the upper esophagus, consistent with grade 2 esophagitis.

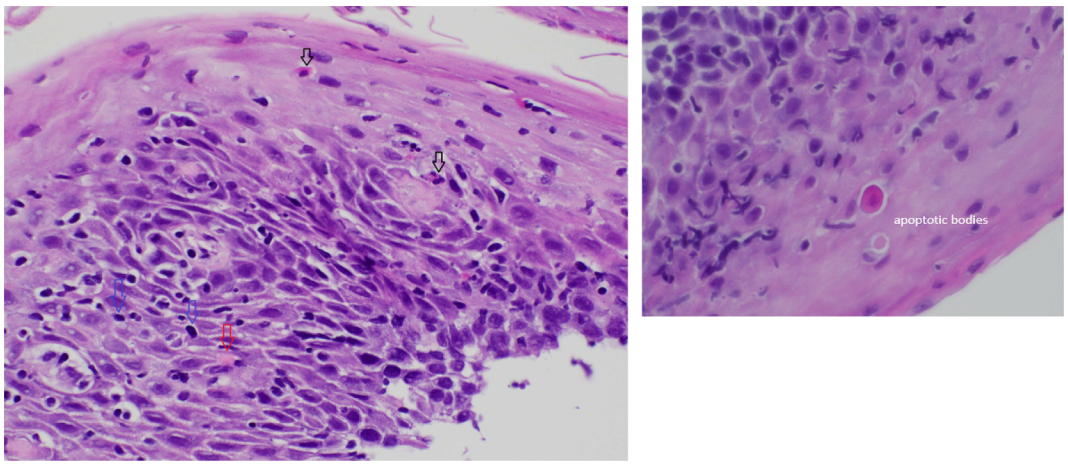

Fig. 2. Histologic analysis demonstrates esophagitis with mixed lymphocytic and eosinophilic inflammation. Black arrow: eosinophils (rare). Blue arrow: lymphocytes (predominant). Red arrow: apoptotic body. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

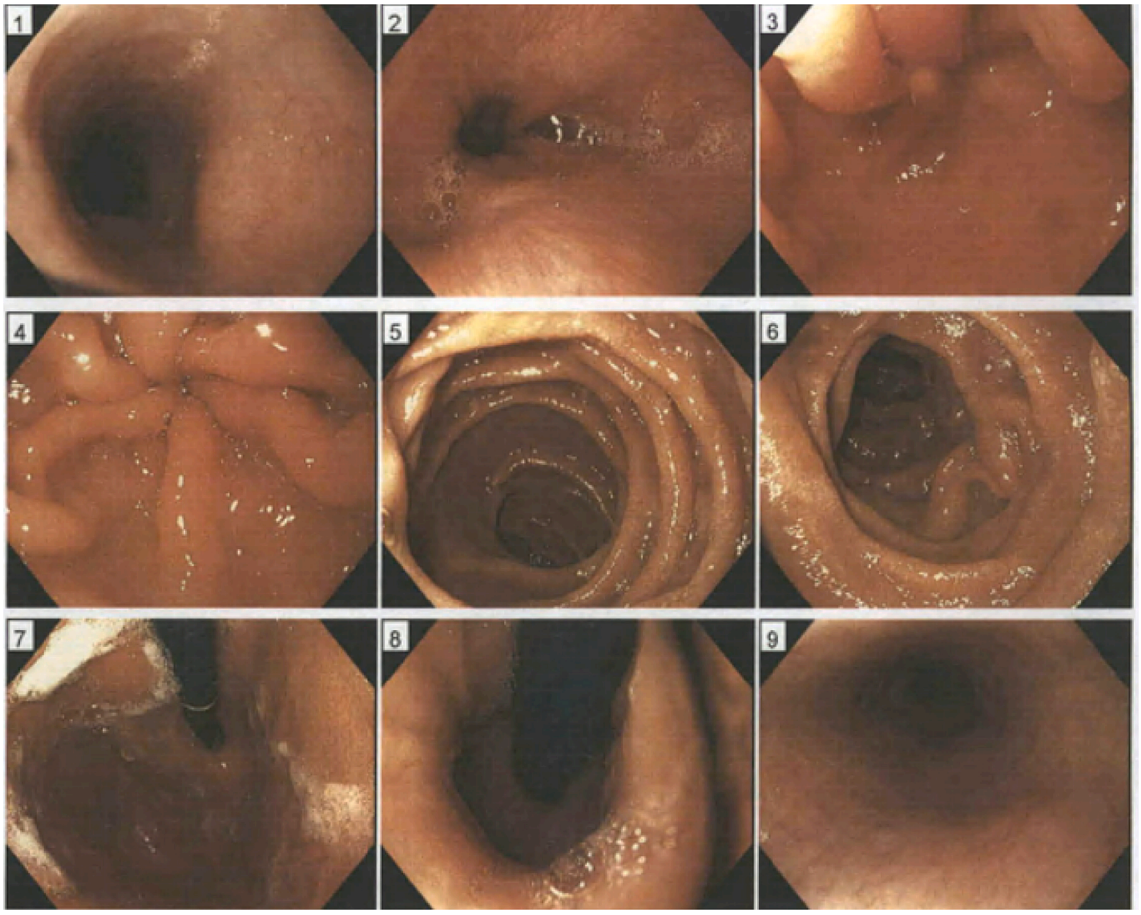

Fig. 3. Normal OGD showing complete recovery.

system (Spain et al., 2016). Regarding lenvatinib, the reported side effects are related to their tyrosine kinase inhibitory activity (Cabanillas and Takahashi, 2019). In the case of our patient, our diagnosis (esophagitis associated to lenvatinib) was a diagnosis of exclusion. Indeed, when we stopped the pembrolizumab, the patient still had symptoms. However, in the mean time, the patient had to stop the lenvatinib for a dental procedure, and her symptoms gradually disappeared. Symptoms were therefore presumed to be due to the latter.

To the best of our knowledge, there is little mention of pembrolizumab nor lenvatinib induced esophagitis in the English literature. The most frequent digestive complications are diarrhea and stomatitis (Motzer et al., 2021). One study describes esophagitis as a complication associated with an anti-PD-1 treatment, and the patient was treated conservatively with pantoprazole (Hofmann et al., 2016). Thus, gastrointestinal side effects are common with this type of treatment, but most of these adverse effects are reversible and are managed by stopping

or reducing the dose of treatment and by controlling symptoms (Motzer et al., 2021; Hofmann et al., 2016).

In the case of our patient, the complete cessation of treatment allowed healing, both endoscopically and clinically. The symptoms unfortunately recurred after the treatment was resumed. Dose reduction was attempted in combination with PPI, and there was no recurrence of symptoms. It therefore seems that the.

symptomatology is dose dependent. Oesophagitis has been described in one study as a complication of pembrolizumab, and it was treated conservatively with pantoprazole (Hofmann et al., 2016). As we strongly associate in the case of our patient the complication due to lenvatinib, it is difficult to establish strong recommendations on how to manage esophagitis in the future for patient on combination therapy. However, a solution that seems possible to us is to treat immediately with a PPI twice daily, and to reduce the dose of lenvatinib.

In conclusion,we present a case of oesophagitis as a likely complication of lenvatinib for advanced endometrial cancer.. One case is reported in the literature (Hofmann et al., 2016). In the case of our patient, an improvement in symptoms was noted with the reduction of lenvatinib and initiation of PPI. This allowed us to resume treatment at a reduced dose.

Consent section.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Massine Fellouah: Conceptualization, Methodology, Investigation, Writing – original draft, Project administration. **Marie-Hélène Auclair:** Conceptualization, Validation, Writing – review & editing, Supervision. **Suzanne Fortin:** Validation, Writing – review & editing, Supervision. **Jérémie Berdugo:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Lara de Guerké:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision, Project administration.

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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