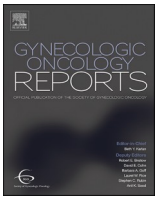
Gynecologic Oncology Reports 48 (2023) 101239

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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



Radiation recall dermatitis during treatment of endometrial cancer with pembrolizumab plus lenvatinib: A case report

Elise Heisler [a,*], Irina Tunnage [b], Whitfield Growdon [b]

[a] Department of Obstetrics and Gynecology, NYU Langone Health, 550 First Avenue, New York, NY 10016, USA
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, NYU Langone Health, 550 First Avenue, New York, NY 10016, USA

A B S T R A C T

Radiation Recall encompasses an array of inflammatory reactions, most commonly dermatitis, that occurs in response to a systemic medication with distribution in a previously irradiated field. While historically cytotoxic chemotherapy was a major culprit, this case report describes radiation recall dermatitis in response to pembrolizumab and lenvatinib in a 62-year old female with ongoing advanced endometrial cancer and history of breast cancer. Discontinuation of lenvatinib alone lead to complete resolution of the dermatitis, and she ultimately resumed her previous lenvatinib dose without recurrent symptoms. This case represents an important possible adverse effect of a commonly used targeted therapy, particularly in a population likely to have a history of prior radiation exposure.

1. Introduction

Radiation Recall Dermatitis (RRD) is an inflammatory skin reaction that occurs following exposure to systemic medication with distribution in a previously irradiated field (McKay & Foster, 2021; Yigit et al., 2021). The most frequent presenting symptom is erythema, which can progress to desquamation and necrosis in severe cases (McKay & Foster, 2021). Traditionally, RRD has been caused by certain classes of cytotoxic chemotherapy, notably taxanes like docetaxel and antimetabolites like gemcitabine (Bhangoo et al., 2022). However, as immunotherapy and targeted biologic therapies have become a mainstay of many cancer regimens, multiple case studies have emerged reporting different forms of radiation recall caused by monoclonal antibodies, immune checkpoint inhibitors, tyrosine kinase inhibitors and other targeted therapies in patients with previous radiation exposure (Billena et al., 2020; Chung et al., 2010; Moon et al., 2013; Sandhu et al., 2023). This case study reports the first documented episode of RRD in the setting of dual therapy with Lenvatinib, a multi-targeted tyrosine kinase inhibitor, plus Pembrolizumab, an anti-programmed-death 1 antibody, in a patient with advanced endometrial cancer and history of breast radiation therapy.

2. Case report

A 62-year-old female was diagnosed with mismatch repair-proficient, microsatellite stable stage IVB endometroid endometrial adenocarcinoma and concurrent stage IA, ER + PR + HER2- infiltrating ductal carcinoma of the right breast in 09/2020. The initial sites of disease included the uterus, bilateral ovaries, and abdominal wall, with peritoneal carcinomatosis and tumor nodules involving the posterior cul de sac, bladder peritoneum, pelvic sidewall, omentum, spleen, liver surface, right diaphragm, small and large bowel. She first underwent a radical abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, small bowel resection with side-to-side anastomosis, right diaphragm stripping, and splenectomy in 10/2020. At the end of the case, all visible disease greater than one centimeter was removed, though multiple sub-centimeter areas of residual disease remained on the sigmoid colon, ileum and cecum. This major cytoreductive surgery was followed by right breast lumpectomy with sentinel lymph node dissection in 11/2020. Once both surgeries were complete, chemotherapy was initiated with six cycles of adjuvant carboplatin/paclitaxel 12/2020–04/2021. Her lumpectomy was followed by adjuvant whole breast radiation therapy with 2,600 cGy in 5 fractions (520 cGy per fraction) to the right breast in 04/2021, complicated by mild localized erythema but was otherwise tolerated well.

In 01/2022, the patient was found to have a mass at the vaginal cuff as well as peritoneal implants, together consistent with endometrial cancer recurrence. Given the diffuse nature of her recurrence, local treatments with radiation therapy or surgery were not considered; instead, she was started on immunotherapy with pembrolizumab 200 mg infusion every three weeks and lenvatinib 20 mg orally daily. A few months into this therapy, the lenvatinib dose was reduced to 14 mg in

* Corresponding author.
E-mail addresses: Elise.heisler@nyulangone.org, Eyheis44@gmail.com (E. Heisler), Irina.tunnage@nyulangone.org (I. Tunnage), Whitfield.growdon@nyulangone.org (W. Growdon).

https://doi.org/10.1016/j.gore.2023.101239
Received 5 June 2023; Received in revised form 7 July 2023; Accepted 8 July 2023
Available online 18 July 2023

the setting of fatigue, hypertension, and nausea. The patient subsequently tolerated the new dose well despite a new diagnosis of hypothyroidism, appropriately treated with levothyroxine. The patient remained on dual therapy until her eighth cycle in 07/2022, when she experienced a nonpruritic, erythematous rash and subjective warmth without lymphadenopathy on the right breast in the previously irradiated field, consistent with radiation recall dermatitis. She was evaluated by both Gynecologic Oncology and General Surgery, with no evidence of breast cancer recurrence or other explanation for localized erythema. Given that the patient had previously experienced adverse side effects of lenvatinib requiring a dose adjustment, with seemingly excellent tolerance of pembrolizumab, the decision was made to discontinue lenvatinib therapy alone. Additionally, there is emerging data to suggest that some patients with advanced mismatch repair-proficient endometrial cancer may have a clinically meaningful response to the addition of pembrolizumab alone, which was considered when deciding to solely discontinue lenvatinib (Eskander et al., 2023). Notably, the patient reported complete resolution of all symptoms after three weeks of lenvatinib discontinuation. The mild intensity of her symptoms did not warrant additional therapy with corticosteroids, antihistamines, or antibiotics. Five weeks after the initial presentation, lenvatinib was restarted at the prior dose of 14 mg, and the patient ultimately continued pembrolizumab and lenvatinib without RRD recurrence.

Between 12/2022 and 02/2023, the patient was found to have liver metastasis and bilateral ureteral obstruction requiring bilateral percutaneous nephrostomy tubes, all consistent with progression of disease. Pembrolizumab and lenvatinib were both discontinued at that time. The patient was briefly enrolled in a clinical trial but ultimately developed further progression of disease, and a decision was made to withdraw all cancer-directed therapies given the patient's strong desire to repatriate to her home country and pursue comfort care.

3. Discussion

Radiation recall is a poorly understood phenomenon, historically induced by systemic agents such as chemotherapy, antibiotics, vaccines, and only more recently, immunotherapy. These agents trigger, or "recall", an acute inflammatory response in an area previously treated with radiotherapy. RRD falls into a larger category of Radiation Recall Reactions which can include pneumonitis, gastritis, myositis and more, though dermatitis is the most common (McKay & Foster, 2021; Wang et al., 2020). Biopsies of such skin reactions have shown histopathological evidence of acute and chronic inflammation, likely due to damage by reactive oxygen species and cytokine release (McKay & Foster, 2021). The overall incidence is thought to be between 7 and 8.8 %, though this is hard to ascertain due to an array of potential offending agents and different system presentations (McKay & Foster, 2021; Wang et al., 2020).

As immunotherapy has become more widely used, multiple case reports have emerged suggesting a link between certain monoclonal antibodies or small molecules and radiation recall. For example, the anti-programmed-death 1 antibodies pembrolizumab and nivolumab, both used as second-line therapy in certain metastatic cancers, have been individually reported to trigger RRD (Billena et al., 2020; Sibaud et al., 2015; Wang et al., 2020; Yigit et al., 2021). Pembrolizumab has also been associated with radiation recall pneumonitis and myelitis (Wang et al., 2020). Additionally, there are a few reports of RRD following treatment with sunitinib and sorafenib, two tyrosine kinase inhibitors that, similar to lenvatinib, target vascular endothelial growth factor and platelet-derived growth factor receptors (Chung et al., 2010; Robbins et al., 2011). Some case reports have also commented the potential relationship between erlotinib, a tyrosine kinase inhibitor of epidermal growth factor receptors, and radiation recall pneumonitis and gastritis (Awad & Nott, 2016; Chiang et al., 2016). Despite this emerging literature, there are no reported cases of radiation recall of any kind with lenvatinib, a multi-targeted tyrosine kinase inhibitor, as suggested in our presented case.

Lenvatinib is often used in conjunction with Pembrolizumab immunotherapy and has become prominent in the management of advanced endometrial cancer. In fact, treatment of platinum-resistant endometrial cancer with Lenvatinib plus Pembrolizumab lead to longer progression-free and overall survival than chemotherapy; the two together are found to have exceptional anti-tumor activity compared to Pembrolizumab monotherapy in microsatellite-stable or mismatch repair-proficient disease (pMMR) (Makker et al., 2020, 2022). While the phase 3 trial of this dual therapy displayed a low side effect profile, severe skin reactions were reported in 26.9 % of participants, though the type of reactions were not described (Makker et al., 2020). Furthermore, these skin reactions were not stratified by prior radiation exposure, and therefore there is no method to determine if skin reactions are more likely to occur in those with radiation history. Similarly, there is no method to distinguish if the described skin reactions were consistent with RRD or something entirely distinct. Further analysis would be necessary to evaluate this question.

Given the usual treatment course of endometrial cancer, individuals taking Pembrolizumab and Lenvatinib for recurrence likely have a personal history of radiation and thus it is vital to consider RRD as a potential cause of adverse skin reactions. In addition to surgery, vaginal brachytherapy and pelvic radiotherapy, with or without chemotherapy, are common first line treatments for endometrial cancer. In this setting, progression to immunotherapy not uncommonly follows a previous radiation course. Unlike breast radiation where skin can have exposure, common radiation for endometrial is internal or has targets well below the skin suggesting this effect may have limited consequences. Additionally, endometrial cancer can co-occur with other cancers that require radiation therapy. For example, estrogen exposure is a shared risk factor between endometrial and breast cancer, the latter of which is often treated with external beam radiation. Additionally, hereditary cancer disorders like Lynch syndrome may increase the risk for colorectal, ovarian and/or stomach cancer, any of which may require radiotherapy. Because of this high likelihood of prior radiation exposure, radiation recall should be considered in these patients with inflammatory skin reactions in order to diagnose RRD early and treat it appropriately.

Treatment of RRD is dependent on the severity of the presentation. In all cases, the first step is to eliminate the offending agent. Typically, first line treatment is targeted at supportive care and symptomatic relief via topical or oral antihistamines and steroids, though these medications may not affect the clinical course (McKay & Foster, 2021). In cases of severe reactions, treatment can escalate to administration of IV corticosteroids, and antibiotics may be considered if there is a superimposed infection (Bhangoo et al., 2022). It is important to highlight that reintroduction of the trigger drug often does not lead to RRD recurrence, and many patients tolerate the inciting drug at the prior dose without complications, as evidenced by this case (McKay & Foster, 2021).

4. Conclusion

Checkpoint immune therapy with pembrolizumab in concert with oral lenvatinib has become a mainstay of therapy for pMMR endometrial cancer in the recurrent setting. In this case report, the patient presented with RRD that resolved with cessation of the lenvatinib therapy. It is unclear which agent drove the development of RRD, as it is possible the complementary action of both agents are required. This report highlights that in a population with a likely history of prior radiotherapy, RRD is a crucial consideration on the differential of skin reactions to ensure early detection and to prevent significant morbidity.

5. Consent

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.

Author contributions

Elise Heisler: Wrote, reviewed and edited original draft and incorporated all author edits to form working manuscript.

Irina Tunnage: Edited and revised all drafts of manuscript, provided intellectual direction and supervision.

Whitfield Growdon: Conceptualized initial idea for case report, revised manuscript drafts and provided 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.

Works cited

Awad, R., Nott, L., 2016. Radiation recall pneumonitis induced by erlotinib after palliative thoracic radiotherapy for lung cancer: Case report and literature review. Asia Pac. J. Clin. Oncol. 12 (1), 91–95. https://doi.org/10.1111/ajco.12447.

Bhangoo, R.S., Cheng, T.W., Petersen, M.M., Thorpe, C.S., DeWees, T.A., Anderson, J.D., Vargas, C.E., Patel, S.H., Halyard, M.Y., Schild, S.E., Wong, W.W., 2022. Radiation recall dermatitis: A review of the literature. Semin. Oncol. 49 (2), 152–159. https://doi.org/10.1053/j.seminoncol.2022.04.001.

Billena, C., Padia, S., O'Brien, B., Knoble, J., Gokhale, A., Rajagopalan, M., 2020. Radiation recall dermatitis after treatment of stage IV breast cancer with nivolumab: a case report. Immunotherapy 12 (2), 123–130. https://doi.org/10.2217/imt-2019-0020.

Chiang, C.-L., Chen, Y.-W., Wu, M.-H., Huang, H.-C., Tsai, C.-M., Chiu, C.-H., 2016. Radiation recall pneumonitis induced by epidermal growth factor receptor-tyrosine kinase inhibitor in patients with advanced nonsmall-cell lung cancer. J. Chinese Med. Assoc. JCMA 79 (5), 248–255. https://doi.org/10.1016/j.jcma.2016.01.008.

Chung, C., Dawson, L.A., Joshua, A.M., Brade, A.M., 2010. Radiation recall dermatitis triggered by multi-targeted tyrosine kinase inhibitors: sunitinib and sorafenib. Anticancer Drugs 21 (2), 206–209. https://doi.org/10.1097/CAD.0b013e328333d679.

Eskander, R.N., Sill, M.W., Beffa, L., Moore, R.G., Hope, J.M., Musa, F.B., Mannel, R., Shahin, M.S., Cantuaria, G.H., Girda, E., Mathews, C., Kavecansky, J., Leath, C.A., Gien, L.T., Hinchcliff, E.M., Lele, S.B., Landrum, L.M., Backes, F., O'Cearbhaill, R.E., Al Baghdadi, T., Hill, E.K., Thaker, P.H., John, V.S., Welch, S., Fader, A.N., Powell, M.A., Aghajanian, C., 2023. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N. Engl. J. Med. 388 (23), 2159–2170. https://doi.org/10.1056/nejmoa2302312.

Makker, V., Taylor, M.H., Aghajanian, C., Oaknin, A., Mier, J., Cohn, A.L., Romeo, M., Bratos, R., Brose, M.S., DiSimone, C., Messing, M., Stepan, D.E., Dutcus, C.E., Wu, J., Schmidt, E.V., Orlowski, R., Sachdev, P., Shumaker, R., Casado Herraez, A., 2020. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J. Clin. Oncol. 38 (26), 2981–2992. https://doi.org/10.1200/JCO.19.02627.

Makker, V., Colombo, N., Casado Herráez, A., Santin, A.D., Colomba, E., Miller, D.S., Fujiwara, K., Pignata, S., Baron-Hay, S., Ray-Coquard, I., Shapira-Frommer, R., Ushijima, K., Sakata, J., Yonemori, K., Kim, Y.M., Guerra, E.M., Sanli, U.A., McCormack, M.M., Smith, A.D., Keefe, S., Bird, S., Dutta, L., Orlowski, R.J., Lorusso, D., 2022. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N. Engl. J. Med. 386 (5), 437–448. https://doi.org/10.1056/NEJMoa2108330.

McKay, M.J., Foster, R., 2021. Radiation recall reactions: An oncologic enigma. Crit. Rev. Oncol. Hematol. 168, 103527 https://doi.org/10.1016/j.critrevonc.2021.103527.

Moon, D., Koo, J.S., Suh, C.O., Yoon, C.Y., Bae, J., Lee, S., 2013. Radiation recall dermatitis induced by trastuzumab. Breast Cancer 23 (1), 159–163. https://doi.org/10.1007/s12282-013-0462-6. Epub 2013 Mar 31 PMID: 23543400.

Robbins, J., Wollner, I., Ryu, S., 2011. Sorafenib induced radiation recall dermatitis after spine radiosurgery. J. Radiosurg. SBRT 1 (1), 71–74. http://www.ncbi.nlm.nih.gov/pubmed/29296300.

Sandhu, M., Ashok Kumar, P., Deck, J., Zerdan, M.B., Lacombe, M., Sivapiragasam, A., 2023. Radiation recall dermatitis following treatment with pembrolizumab: A case report and review of the literature. J. Investig. Med. High Impact. Case Rep. 11 https://doi.org/10.1177/23247096231168114. PMID: 37096743; PMCID: PMC10134185. 23247096231168114.

Sibaud, V., David, I., Lamant, L., Resseguier, S., Radut, R., Attal, J., Meyer, N., Delord, J.-P., 2015. Acute skin reaction suggestive of pembrolizumab-induced radiosensitization. Melan. Res. 25 (6), 555–558. https://doi.org/10.1097/CMR.0000000000000191.

Wang, Y.-Y., Tian, X.-C., Zhu, L., Bai, X.-H., Zhao, R., 2020. Concomitant radiation recall dermatitis and radiation recall pneumonitis induced by pembrolizumab. J. Thor. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer 15 (10), e160–e162. https://doi.org/10.1016/j.jtho.2020.05.014.

Yigit, E., Guven, D.C., Aksoy, S., Yazici, G., 2021. Radiation recall dermatitis in patients treated with immune checkpoint inhibitors: A case report and literature review. Cureus 13 (6), e15548.