



## Case report

## Vaginal mucositis related to immunotherapy in endometrial cancer

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## ABSTRACT

Immunotherapy, specifically immune checkpoint inhibitors (ICPi), has revolutionized our approach to treating all solid tumors, including gynecologic malignancies. Compared to standard chemotherapy, the adverse events associated with immunotherapies, are often mild and localized, although more severe systemic responses can also occur. While dermatitis is a most commonly reported side effect of ICPi therapy, cutaneous toxicities have a range of clinical manifestations and can provide a challenge in an otherwise favorable treatment protocol. There have been few documented cases of mucositis caused by ICPi therapy and to our knowledge, no documented case of an ICPi therapy causing vaginal mucositis. As such, we present a case of a patient with metastatic uterine serous carcinoma (USC) treated with immunotherapy, who developed grade 3 vaginal mucositis.

This is a case presentation of a 67-year-old woman with a history of stage I metastatic uterine serous carcinoma who was initially treated with a hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. Eight months after surgery, patient was found to have a vaginal recurrence treated with external beam radiation therapy and vaginal brachytherapy, as well as port site recurrence treated with resection and 6 cycles of systemic chemotherapy with Carboplatin and Paclitaxel. The patient was found to have progression of her disease and was treated with a combinatorial therapy using PD-L1 inhibitor and TK inhibitor. Patient tolerated first two cycles of treatment without severe side effects. Nine days after administration of the second cycle, the patient reported new onset of severe non-radiating vaginal and perineal pain, that worsened with sitting down, and was refractory to pain medications. Pelvic examination revealed multiple, deep, erythematous ulcerations on the vaginal mucosa involving the left and anterior vaginal introitus, distal vagina and necrosis around the periurethral area, consistent with grade 3 mucositis. The treatment was immediately discontinued, and the patient was started on prednisone 100 mg by mouth daily for 7 days, which was tapered over the course of 10 days and Gabapentin and Oxycodone were given for pain control. The patient started to report improvement in symptoms after 3 weeks and re-examination in 1 month showed decreased amount of fibrinous material involving 50% of the lesions, indicating that the initial grade 3 mucositis had improved to grade 1.

As immunotherapy is becoming more widely used in gynecologic and other malignancies, providers need to be aware of rare but significant complications associated with these therapies. Such toxicities should be correctly identified and treated appropriately and expeditiously. Most patients will continue to benefit from administered immunotherapy and often times can be restarted once the toxicities are alleviated. To our knowledge, this is a first reported case of vaginal mucositis associated with immunotherapy treatment with ICPi in a patient with gynecologic malignancy.

## 1. Introduction

Immunotherapy has revolutionized our approach to treating cancers. Use of immune checkpoint inhibitors (ICIs) lead to improved survival outcomes in many solid tumors including gynecologic malignancies. Compared to standard chemotherapy, the adverse events associated

with immunotherapies, are often mild and localized, although more severe systemic response can also occur. A majority of adverse side effects include cutaneous manifestations and are reported to occur in 30–50% of patients treated with ICI therapy (Brahmer et al., 2018). These often manifest within 4–8 weeks of initiating therapy and can be long lasting (Lacouture and Sibaud, 2018). While a rash is most

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commonly reported side effect of ICPI therapy, cutaneous toxicities have a range of clinical manifestations and can provide a challenge in an otherwise favorable treatment protocol (Brahmer et al., 2018).

Programed cell death-1 (PD-1) checkpoint receptors are expressed on lymphocytes. Tumors are able to evade an immunologic response by expressing ligands, which interact with PD-1 receptors and inhibit the function of kill lymphocytes (Brahmer et al., 2018; Zulay et al., 2018; Topalian et al., 2014). Most common side effects of ICIs include fatigue (32%), rash (23%), diarrhea (18%), nausea, and decreased appetite (Topalian et al., 2014). More importantly, ICIs may cause inflammatory reactions resulting in mucositis of other epithelial-lined organ systems, such as colitis, pneumonitis, hepatitis, and thyroid dysfunction (Topalian et al., 2014). Tyrosine kinase (TK) inhibitors primarily target vascular endothelial growth factor (VEGF) receptor 2 and tyrosine kinase mesenchymal epithelial transition (MET) receptors, both of which are implicated in cancer growth, metastasis, and angiogenesis (Vigarios et al., 2017). The side effect profile includes thrombocytopenia, neutropenia, anemia, GI manifestations, and rash (Matulonis et al., 2019). The incidence rates of the side effects of TK inhibitors are not well documented in literature (Matulonis et al., 2019).

To our knowledge there have been no documented cases in literature of immunotherapy agent causing vaginal mucositis. As such, we present a case of a woman undergoing treatment with a combinatorial therapy using PD-L1 inhibitor and TK inhibitor for recurrent, metastatic endometrial serous carcinoma who developed grade 3 vaginal mucositis.

## 2. Case presentation

Our patient is a 67-year-old woman with a history of metastatic uterine serous carcinoma (USC) who was initially treated with a hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy for stage I USC. Eight months after surgery, patient was found to have a vaginal recurrence treated with external beam radiation therapy and vaginal brachytherapy, as well as port site recurrence treated with resection and 6 cycles of systemic chemotherapy with carboplatin and paclitaxel.

After completion of adjuvant chemotherapy, patient was found to have an 18 mm unresectable lesion at vaginal apex with biopsy confirming recurrent disease. The patient was started on combinatorial therapy using PD-L1 immune checkpoint inhibitor and TK inhibitor. Patient tolerated first two cycles of treatment without major toxicities.

Nine days after administration of second cycle of a PD-L1 inhibitor, the patient reported new onset of severe non-radiating vaginal and perineal pain that worsened with sitting down and was refractory to pain medications. The patient did not report any inciting events or prodromal symptoms prior to the onset of the vaginal pain. Pelvic examination revealed multiple, deep, erythematous ulcerations on the vaginal mucosa involving the left and anterior vaginal introitus, distal vagina and necrosis around the periurethral area, consistent with grade 3 vaginal mucositis. No lesions or rashes were noted on the external genitalia and perineal areas and there was no discharge or other signs of infectious process. No other cutaneous lesions were noted on physical examination.

The treatment was immediately discontinued, and the patient was started on prednisone 100 mg by mouth daily for 7 days, which was tapered over the course of 10 days. Gabapentin and Oxycodone were given for pain control. The patient was also advised to use topical lidocaine 1% and barrier creams. Frequent vulvar cleansing was recommended with Sits baths to remove topical irritants, such as urine. Patient was evaluated on weekly bases and monitored for signs of infections. She started to note improvement in symptoms after 3 weeks and re-examination in 1 month showed decreased amount of fibrinous material involving 50% of the lesions, indicating that the initial grade 3 mucositis had improved to grade 1. The patient desired to discontinue the treatment and was started on a clinical trial with a targeted agent.

## 3. Discussion

Immunotherapy, specifically ICIs, has resulted in improved clinical outcomes among patients with multiple tumor types. Recently, pembrolizumab has been FDA-approved for use in all tumor mutation burden-high solid tumors, most frequently found in endometrial and colon cancers (US Food and Administration, 2020). It has also been FDA-approved in combination with tyrosine kinase inhibitor, lenvatinib, for all uterine cancers after failing standard of care therapy (Makker, 2019). Multiple other ICIs are undergoing clinical testing for safety and efficacy. Current ongoing investigations of ICI therapies in endometrial cancer include: ipilimumab, nivolumab, pembrolizumab, atezolizumab, and avelumab (Ferris et al., 2016; Konstantinopoulos et al., 2018).

Toxicities of ICI therapies most commonly manifest in the integumentary system but they can also have an effect on the gastrointestinal, pulmonary, endocrine, and cardiovascular system (Brahmer et al., 2018). Oral mucositis is typically the most common side effect of mammalian target of rapamycin (mTOR) inhibitors, which are known to cause aphthous like ulcers, but there is only one documented case of oral mucositis associated with PD-1 inhibitor (pembrolizumab) therapy (Zulay et al., 2018; Lacouture and Sibaud, 2018). There has been documentation of multikinase angiogenesis inhibitors causing stomatitis and the use of both nivolumab and pembrolizumab has been found to be associated with stomatitis or oral mucosal inflammation in sporadic cases, but there are no documented cases of vaginal mucositis. In the management guidelines of adverse events secondary to immunotherapies there was no mention of neither oral nor vaginal mucositis as a side effect, and its prevalence remains unknown in new emerging ICI therapies (Brahmer et al., 2018).

Our patient with recurrent USC underwent 2 cycles of immunotherapy before developing grade 3 vaginal mucositis. Due to this severe toxicity, treatment was immediately discontinued, and patient recovered appropriately with supportive care. If her symptoms were refractory to systemic steroids, further management with use of TNF inhibitors and other immunosuppressive agents could be pursued (Zulay et al., 2018).

Patient did not display any signs for infectious vaginitis, but if infection was suspected cultures would have been obtained to further delineate the cause of infection (fungal versus bacterial in nature) and pursue appropriate antibiotic therapy. Differential diagnosis should include herpes simplex viral infections, bullous impetigo, erythema multiforme, contact dermatitis, Lipschutz ulcers, and lichen sclerosis.

Our patient did undergo salvage radiation therapy to the pelvis two years prior, for a vaginal recurrence of her tumor. While acute injury to epithelium after radiation can persist for weeks, given the timeline of her treatment, it is unlikely that patient's current symptoms are attributed to prior radiation therapy.

Due to the rarity of vaginal mucositis, other etiology should be excluded prior to proceeding with cessation of immunotherapy and conservative management with prednisone. With the addition of appropriate perineal care, our patient was able to have complete resolution of symptoms without recurrence.

## 4. Conclusion

As novel immunotherapies are entering clinical practice, new toxicities related to ICI agents are being reported. Many studies have suggested that the increasing manifestation of cutaneous toxicities may indicate a favorable therapeutic outcome as patients who develop these toxicities have shown to have a longer overall survival (Brahmer et al., 2018). Vaginal mucositis, reported here, is a rare cutaneous immune-related adverse event, previously undocumented in literature. Clinicians should familiarize themselves with variable clinical manifestations of immune-related toxicities, which should be promptly recognized and appropriately managed to allow continuation of effective therapy.

**Author contributions**

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**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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