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Case report

Recurrent pembrolizumab-induced mechanical small bowel obstruction in a patient with metastatic cervical cancer

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1. Introduction

Pembrolizumab, a programmed cell death protein-1 (PD-1) receptor blocker, has become integrated into the treatment landscape of many malignancies, including of the lung, head and neck, gastrointestinal, bladder, and gynecologic (Patil and Zhang, 2020). In 2018, the Food and Drug Administration (FDA) approved single agent pembrolizumab for patients with recurrent or metastatic cervical cancer on or after chemotherapy, if their tumors express program cell death ligand 1 (PD-L1) as determined by a combined positive score (CPS) ≥ 1. The indication was expanded in combination with chemotherapy, with or without bevacizumab in 2021 (Schepisi et al., 2021).

Immune-mediated gastrointestinal side effects of pembrolizumab have been well described in the literature, including ulcerative esophagitis, pancreatitis, enterocolitis, colitis, and even in rare cases, perforation due to colitis. Each of these findings has been associated with unique histopathologic features (Patil and Zhang, 2020; Thota et al., 2021). However, pembrolizumab as a direct cause of recurrent mechanical small bowel obstruction (SBO) in gynecological cancer has not yet been well documented or described. Here, we present a patient who developed recurrent small bowel obstruction while receiving pembrolizumab treatment for recurrent metastatic cervical cancer. Based on histopathological analysis of specimens obtained at the time of the bowel resections, we postulate that the SBO was caused by pembrolizumab therapy.

2. Case study

The patient is a 73-year-old gravida 2, para 2 female with a past medical history of breast cancer (treated with mastectomy, chemotherapy, and tamoxifen), excision of skin basal cell carcinoma, former smoking status who presented in 2017 as a referral for adenocarcinoma of Mullerian origin. Family history was noncontributory. Recent pap smear demonstrated atypical squamous cells, cannot rule out high grade squamous intraepithelial lesion (ASC-H), atypical glandular cells (AGC), and negative human papillomavirus (HPV) testing. She had routine cervical cancer screening and no prior history of cervical dysplasia. Physical exam was significant for an enlarged, discoid-shaped cervix suggestive of cancer. Repeat physical exam, endometrial sampling, imaging, and a second outside pathology opinion confirmed diagnosis of Stage IIB cervical adenocarcinoma. She received primary treatment of chemoradiation (whole pelvic and brachytherapy) with weekly cisplatin, completed in August 2017. There were no interruptions in treatment or significant toxicity.

During surveillance, a routine computed tomography (CT) scan was concerning for metastatic disease to the lungs. A CT-guided biopsy of the lung lesion confirmed metastatic adenocarcinoma. Testing with PD-L1 assay (22C3 pharmDX) demonstrated a CPS score of 30. In March 2020, she began palliative pembrolizumab, receiving first two cycles of 200 mg on a 3-week schedule followed by 400 mg beginning Cycle 3 on a 6-week cycle for a total of 6 cycles through September 2020, which

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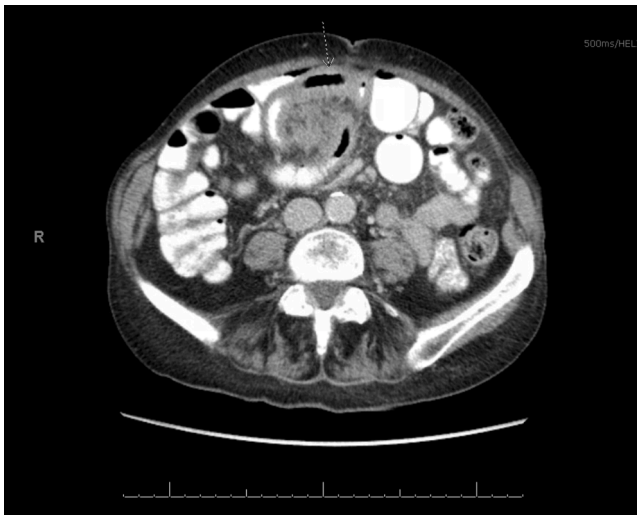
Panel 1A:



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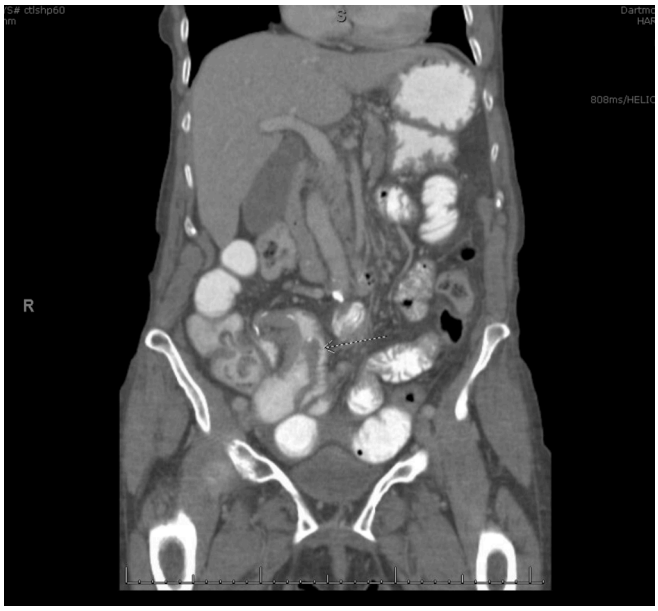

Fig. 1. CT findings showing suspected small bowel obstruction, obtained prior to first laparotomy (A) and second laparotomy (B). The arrow in Fig. 1A points to a representative loop of abnormally thickened small bowel in the axial view which is a new finding compared to prior imaging scans, with multiple loops of dilated small bowel proximally, associated with diffuse mesenteric and soft tissue thickening. Fig. 1B shows a coronal view of gradual dilation of the small bowel, becoming abnormally dilated in the lower abdomen with the transition at the level of prior anastomosis in the distal ileum, concerning for a second partial bowel obstruction.

resulted in a partial response. One month later, she presented to our emergency department with a partial small bowel obstruction (SBO) presumed to arise from omental and mesenteric metastases (Fig. 1A). Failing conservative therapy, she underwent an exploratory laparotomy, and enterectomy with primary anastomosis of the small intestine. Operative findings were notable for a 4 cm mass within the small bowel mesentery resulting in contraction, obstruction, and some ischemia. She was discharged home on day 4 post-operatively. On gross examination, the bowel appeared to contain a transmural mass with associated enlarged lymph nodes amidst extensive serosal adhesions. Final pathology demonstrated no evidence of malignancy within the resected specimens, but rather transmural inflammation and lymphoid hyperplasia. Histologically, there were features of active enterocolitis with expansion of the lamina propria by a mixed inflammatory infiltrate (Fig. 2A). On higher power, the infiltrate was composed of neutrophils, eosinophils, lymphocytes, and plasma cells with neutrophilic crypt abscesses (Fig. 2B).

Given prior response to therapy and no known reports of pembrolizumab-induced SBO, with shared decision making, she resumed pembrolizumab on December 2020. She then re-presented with liquid stools and CT imaging confirmed a partial SBO at the level of the entero-enteric anastomosis (Fig. 1B). During surgery, the area of stricture, fibrosis, and obstruction was resected and an anastomosis was completed. She was discharged on day 4 after surgery without complications. Grossly, the bowel was stenotic with adhesions, again demonstrating full-thickness inflammation without evidence of malignancy. On microscopic examination, the findings were similar to features seen in inflammatory bowel disease (IBD)-type colitis with mucosal erosion, transmural inflammation of the bowel wall (Fig. 2C), lymphoid aggregates and diffuse expansion of the lamina propria by a predominantly lymphoplasmacytic infiltrate. Crypt distortion, neutrophilic crypt abscesses, and granulomas were present (Fig. 2D).

She was subsequently referred to gastroenterologists for management of problematic, frequent stools. A colonoscopy was performed in February 2021, and biopsies of the anastomosis demonstrated histologically unremarkable pathology without inflammation or ulceration. An extensive workup was performed, including calprotectin which was non-elevated and stool cultures, *Clostridiodes difficile* screen, which were negative. She began a short course of vedolizumab for presumed immune-mediated enteritis, and was able to resume pembrolizumab in May 2020 (200 mg every 3 weeks). She completed a tenth and final cycle of pembrolizumab in June 2020 with a complete response. She continues to be followed by our department, with last CT completed October 2023 stable without evidence of disease progression or recurrence.

3. Discussion

Targeted therapies have gained significant traction in oncology. Cervical cancer is the fourth most commonly diagnosed cancer in women and fourth leading cause of death. In 2020, there were over 600,000 estimated new cases and 342,000 globally attributed to cervical cancer (Birrer et al., 2022). Overall, cervical cancers are not as responsive to chemotherapy compared to other malignancies, leading to great interest in the evolution and development of targeted immunotherapies in this field. This is especially important for recurrent or metastatic cervical cancer as less than 20 % of women are projected to survive after 5 years (Schepisi et al., 2021; Birrer et al., 2022). The rationale behind checkpoint immunotherapy in cervical cancer derives from high levels of PD1/PD-L1 and cytotoxic T-lymphocyte-associated protein (CTLA-4) levels detected in tumor specimens and elevation of PD1/PD-L1 levels in cervical intraepithelial neoplasia (CIN) samples (Schepisi et al., 2021). Data from the Phase 3 KEYNOTE-826 trial in patients with recurrent or metastatic cervical cancer whose tumors express PD-L1 with CPS $\geq$ 1 demonstrated a median progression free survival (PFS) with pembrolizumab vs. placebo of 10.4 vs. 8.2 months (hazard ratio of 0.62, $p < 0.001$) and a median duration of response (DOR) vs. placebo was 18.0 vs. 10.4 months (Birrer et al., 2022).

Our patient was initially treated with definitive chemoradiation for Stage IIB cervical cancer. She met criteria for pembrolizumab for recurrent disease after diagnosis of biopsy-proven metastatic disease to the lung. While on pembrolizumab treatment, she experienced two separate episodes of small bowel obstruction requiring surgical intervention, initially thought to be metastatic progression of disease. After the first surgical decompression, which occurred after receiving six cycles, the patient made a full recovery. Pathological analysis was negative for tumor in the resected specimen. It was unclear at that point whether pembrolizumab was definitively the cause of the SBO, as no such occurrences had been reported in the literature.

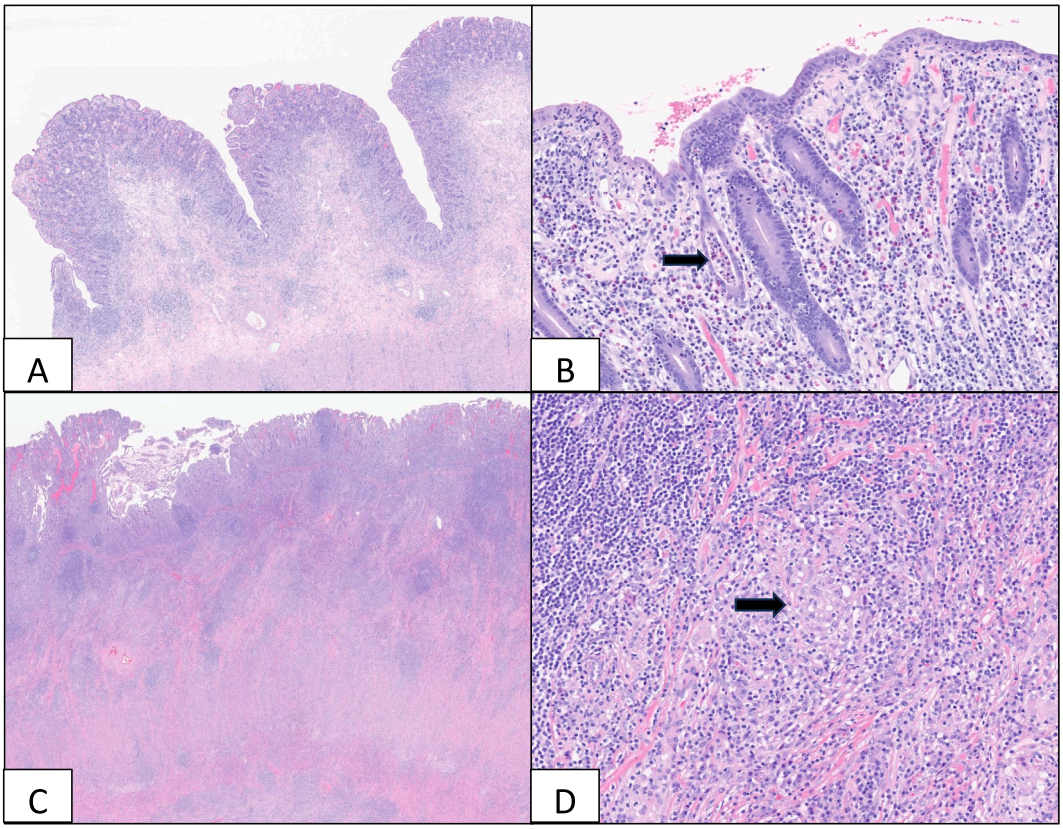

Fig. 2. Panels A, B: Microscopic findings from the initial small bowel obstruction resection specimen. Panels C, D: from the recurrent small bowel obstruction resection specimen. (A) There is expansion of the small bowel lamina propria and submucosa by a mixed inflammatory infiltrate consisting of (B) neutrophils, lymphocytes, plasma cells, and eosinophils. The arrow denotes a neutrophilic crypt abscess. (C) There is marked transmural inflammation of the small bowel wall with diffuse expansion of the lamina propria. (D) The arrow denotes a non-caseating granuloma, as can be seen in IBD-type colitis.

Given the limited number of treatments available for metastatic cervical cancer and her initial response to therapy, we felt a rechallenge with additional pembrolizumab was reasonable. After the second enterectomy specimen demonstrated no malignancy with similar inflammatory changes on pathology, we can now more confidently postulate that pembrolizumab was the causative agent of the inflammatory changes resulting in a mechanical bowel obstruction for the additional reasons outlined below.

Firstly, both pathology and intraoperative findings are inconsistent with those typically seen with radiation enteritis-induced SBO. Radiation enteritis is microscopically associated with the presence of atypical or bizarre-appearing fibroblasts, neither of which were present in either resected specimen. While acute inflammation with eosinophils is a hallmark finding in acute radiation enteritis, more chronic findings would be anticipated since the radiation and resection specimens were greater than three years apart. These chronic changes include fibrosis, Paneth cell metaplasia, mild inflammation, and endothelial damage with obliterative endarteritis – features were not present in the examined sections. Therefore, the overall histologic findings are more consistent with PD-1-associated colitis or active colitis. Although radiation effect cannot be completely excluded, on gross appearance intraoperatively during both laparotomies, the remainder of the bowel did not have a fibrotic appearance and the blockage appeared to be more focal. Secondly, our colleagues in the gastroenterology department performed extensive testing to rule out other infectious and autoimmune causes of inflammation. A colonoscopy with direct visualization of the resection and anastomosis site was completed and all biopsies were negative for a primary gastrointestinal cause of inflammation, e.g. Crohn's disease or ulcerative colitis. Importantly, patient also had no previous history of IBD.

From a clinical management perspective, we do not feel that a trial of steroid therapy would have been appropriate in this scenario. The goal of both surgeries was to provide relief from the partial SBO which was progressively worsening symptomatically. In retrospect, a trial of steroid medication was unlikely to resolve the fibrosis and complete obstruction noted intraoperatively and on final pathology. However, if the diagnosis of pembrolizumab-induced SBO is made earlier, it would be reasonable to consider a trial of steroids to potentially avoid unnecessary procedures. This further underscores the need to raise awareness regarding SBO as a potential side effect of pembrolizumab treatment.

We would also like to highlight the novelty of our case report, which to our knowledge is the first documented recurrent small bowel obstruction caused by pembrolizumab treatment in any gynecological cancer. A literature review, last refreshed at the end of 2023, was performed using the PubMed Search engine using the words "pembrolizumab" in conjunction with "small bowel obstruction", "bowel obstruction", "enteritis", "colitis", with relevant articles highlighted here. Mourad et al published a case report in 2021 describing a 62-year-old male patient with metastatic non-small cell lung cancer (NSCLC), who presented with vomiting on pembrolizumab. A CT demonstrated thickened distal small bowel without a mass lesion, which the authors believed to be consistent with mechanical SBO. As the patient successfully recovered with conservative measures, there was no specimen available for pathology confirmation, and the authors conceded that the absence of histological analysis makes it difficult to associate this acute obstruction with chemoimmunotherapy side effects (Mourad and De Robles, 2021). Beck et al (2019) described a 62-year-old female with Stage IV lung cancer who received pembrolizumab and developed severe enteritis and bowel perforation necessitating laparotomy. Microscopic examination showed non-caseating granulomatous inflammation

Reference	Age and Gender	Cancer Type	Symptoms	CT Imaging Findings	Pathology Findings	Diagnosis and Treatment
Mourad et al 2021 [5]	62M	Metastatic NSCLC	Vomiting, constipation	Thickened distal small bowel without any mass lesion, with upstream dilatation	None available	Mechanical SBO due to enteritis, managed conservatively
Beck et al 2019 [6]	62F	Metastatic NSCLC	Constipation, abdominal pain	Possible small bowel obstruction on first CT, ischemia and volvulus on second CT	focal, nonspecific, mesenteric non-caseating granulomatous inflammation of the resected specimen without any signs of tumor	Exploratory laparotomy performed after second CT with signs of small bowel perforation, resection and anastomosis
Besaw et al 2019 [7]	71F	Metastatic GEJ adenocarcinoma	Abdominal pain, nausea, vomiting	No evidence small obstruction	None available	CIPO, managed conservatively
Tso et al 2020 [8]	58F	Metastatic NSCLC	Abdominal pain	Dilated distal ileum proximal to bowel with mural thickening and perforation near transition point	Mural thickening at the site of stricture without evidence of malignancy, focal necrosis and perforation at the transition point	Exploratory laparotomy with signs of small bowel perforation, resection and anastomosis

Fig. 3. Selected relevant case studies in patients presenting with similar symptoms while on PD-1/PD-L1 immunotherapy. Abbreviations: male (M), female (F), non-small cell lung cancer (NSCLC), small bowel obstruction (SBO), gastro-esophageal junction (GEJ), chronic intestinal pseudo-obstruction (CIPO).

without evidence of tumor. Given adequate response to treatment and the patient's preference to avoid chemotherapy, pembrolizumab was restarted and was tolerated well (Beck et al., 2019). Chronic intestinal pseudo-obstruction was seen in a 71-year-old woman with gastro-esophageal cancer who presented with persistent and recurrent abdominal pain, distension, and nausea, in the setting of CT imaging without signs of mechanical bowel obstruction, that eventually resolved with supportive care, glucocorticoids, and motility agents (Besaw et al., 2019). In another case report published in 2020 by Tso et al, a 58-year-old female patient was treated with nivolumab, an anti-PD-1 inhibitor, who developed abdominal pain concerning for bowel obstruction. She underwent surgical management, and pathology results were significant for mural thickening at the site of stricture without evidence of malignancy, which led the authors to conclude that this event was nivolumab-induced (Tso et al., 2019). Perhaps the occurrence of small bowel obstruction as an unintended adverse event is not unique to pembrolizumab, but rather the entire class of PD-1/PD-L1 inhibitors. Fig. 3 summarizes key findings from the above selected relevant reported cases of gastrointestinal obstruction in patients receiving pembrolizumab therapy.

4. Conclusion

Recurrent pembrolizumab-induced small bowel obstruction is a rare but potentially life-threatening complication that necessitates prompt diagnosis and management. This novel case report describes a patient with metastatic cervical cancer who experienced recurrent small bowel obstruction after initiation of pembrolizumab treatment that required surgical management, while realizing a complete response of the lung metastasis to this therapy. Both bowel resection specimens were negative for malignancy. They were however notable for inflammatory changes consistent with enteritis, and given an overall negative gastrointestinal workup and inconsistency with radiation-induced changes, points to pembrolizumab as the likely cause of obstruction. This case further highlights the importance of careful monitoring and patient counseling for adverse events during immunotherapy treatment.

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Consent statement

Written and informed consent was obtained from the patient, which is currently on file at our institution and can be viewed upon request. Non-human subjects research designation was provided by our institution's IRB prior to any research efforts involved in the writing of the manuscript. The manuscript was written with great care taken to avoid any reference to patient identifying details or information.

CRediT authorship contribution statement

Sha Sha: Writing – original draft, Project administration, Data curation. **Evan R. J. Goyette:** Writing – original draft, Data curation. **Loyd A. West:** Supervision, Visualization, Conceptualization, Supervision, Writing – review & editing. **Jessica L. Bentz:** Writing – review & editing, Supervision, Conceptualization.

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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