

CASE REPORT

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Case report: reinitiating pembrolizumab treatment after small bowel perforation



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Abstract

Background: Immune checkpoint inhibitors (ICIs) have emerged as paradigm shifting treatment options for a number of cancers. Six antibodies targeting the immune checkpoint proteins programmed cell death 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1) or cytotoxic T-lymphocyte associated protein 4 (CTLA4) have been approved. In some cases, response rates have been impressive, but not uniformly so and not consistently; similarly, toxicity to this class of therapeutic is often unpredictable and can be life threatening. Predicting treatment response and toxicity are two main obstacles to truly individualize treatment with ICIs. One of the most severe and life-threatening adverse events is colitis induced colonic perforation, estimated to occur in 1.0 to 1.5% of patients treated with ICIs. An important question to address is, under what circumstances is it appropriate to reinitiate ICI treatment post-bowel perforation?

Case presentation: The patient is a 62-year-old woman, who presented with stage IV lung cancer. Immunohistochemical staining indicated that 80% of the patient's tumor cells expressed PD-L1. The patient was started on a three-week cycle of pembrolizumab. Subsequent reducing in tumor burden was observed within ten weeks. Initially, pembrolizumab was tolerated fairly well, with the exception of immunotherapy related hypothyroidism. However, the patient experienced a second, more serious immune-related adverse event (irAE), in the form of enteritis, which led to small bowel perforation and necessitated exploratory laparotomy. The concerning part of the small bowel was resected, and a primary anastomosis was created. Based on the pathological and surgical findings, the patient was diagnosed with pembrolizumab-associated small bowel perforation. The patient recovered well from surgery and, considering the patient's remarkable response to treatment, a collective decision was made to reinitiate pembrolizumab on post-operative day twenty-eight. The patient is continuing her immunotherapy with ongoing partial response and is able to continue her full-time job.

Conclusions: This case report highlights the challenges of identifying patients likely to respond to ICIs and those that are likely to experience irAEs and it discusses the impressive work that has been done to start to address these challenges. Lastly, the topic of reinitiating pembrolizumab treatment even after colonic perforation is discussed.

Keywords: Pembrolizumab, Bowel perforation, Immunotherapy, Immune-related adverse events, Toxicity, Cancer, PD-1, CTLA4, PD-L1, Immune checkpoint inhibitors

Background

Immunotherapy has emerged as a promising treatment approach for several different types of cancer, including malignant melanoma [1], mismatch repair deficient colorectal cancer [2], non-small cell lung cancer (NSCLC) [3–

5] and others. Programmed cell death-1 (PD-1), cytotoxic T-lymphocyte associated protein 4 (CTLA4) and programmed cell death ligand-1 (PD-L1) are three molecular targets of particular focus. Blocking PD-1/PD-L1 or CTLA4 activity prevents initiation of immune-inhibitory signals within activated T-cells and thereby sustaining the immune response [6]. Two major challenges surrounding this class of inhibitors are being actively investigated to further personalize treatment: 1) identify molecular markers predictive of treatment response rates and 2)

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identify molecular markers predictive of immune-related adverse events (irAEs).

Breakthrough studies have contributed to the approval of six major immune checkpoint inhibitors (ICIs): ipilimumab (anti-CTLA4), pembrolizumab (anti-PD-1), nivolumab (anti-PD-1), atezolizumab (anti-PD-L1), avelumab (anti-PD-L1) and durvalumab (anti-PD-L1) [7, 8]. Outcomes for these inhibitors vary widely and are dependent upon a number of factors. In NSCLC for cases where $\geq 50\%$ of tumor cells express PD-L1, response rates as high as 44.8% have been reported [9]. Response rates can be significantly less robust if PD-L1 expression is not considered or is expressed at low levels (Fig. 1; Additional file 1: Table S1).

irAEs are generally mild and can be managed medically; however, severe adverse events, such as colonic perforation, a rare but life-threatening event that has been reported to occur in 1.0 to 1.5% of patients treated with ICIs, are predicted to continue to increase in incidence as immune inhibitors are used with increasing frequency and as patients are treated with multiple ICIs simultaneously [1, 10]. This case report highlights the importance of using molecular markers (Fig. 1; Additional file 1: Table S1) to determine the likelihood of treatment success and to limit irAEs. Furthermore, this monograph highlights that reinitiation of pembrolizumab treatment, even after immune-related bowel perforation, may be appropriate and that the current recommendation to permanently discontinue ICI treatment in the case of perforation should be considered on an individual basis.

Case presentation

The patient in this case report (Additional file 1: Figure S1), is a 62-year-old woman with a 35-pack year smoking history, who presented with an enlarging, non-tender right neck mass, hoarseness and a twenty-pound weight loss. The initial differential included primary head and neck cancer versus metastatic disease. A subsequent neck biopsy revealed adenocarcinoma consistent with primary lung disease (Fig. 2a): found to be positive for thyroid transcription factor 1 (TTF-1) and negative for p40 and thyroglobulin (Fig. 2b).

Molecular studies of the patient's biopsy were ordered. Wild type EGFR and no ALK or ROS1 rearrangements were detected, precluding the patient from targeted tyrosine kinase inhibitors. However, immunohistochemical (IHC) staining indicated that 80% of the patient's tumor cells expressed PD-L1 (Fig. 2c), predicting a favorable response to immune checkpoint inhibition (Fig. 1; Additional file 1: Table S1) [3, 4, 11]. The patient was started on a three-week cycle of 200 mg pembrolizumab.

The primary mass on baseline staging was a 17×13 mm left upper lobe lesion consistent with primary lung cancer as well as multiple positron emission tomography

(PET) avid lesions. PET/computed tomography (PET/CT) imaging for staging revealed multi-station mediastinal adenopathy, the right paratracheal region, the pre-carinal region, the right neck and the aortopulmonary window; left hilar adenopathy was also seen, and a single splenic lesion was also identified (Fig. 2d). The patient was therefore diagnosed with stage IV lung cancer (cT1aN3M1b).

The patient responded well to pembrolizumab and significant reduction in tumor burden was observed within ten weeks. Imaging showed reduction in size of the left upper lobe mass, the mediastinal lymphadenopathy and a reduction in the size of the splenic mass: collectively consistent with treatment effect for metastatic disease (Fig. 3a). Of note, after nine weeks of treatment, the patient's thyroid function dropped precipitously, and the patient was diagnosed with hypothyroidism secondary to immunotherapy, necessitating levothyroxine treatment.

Regrettably, the patient experienced a second, more serious irAE, in the form enteritis, presenting in a clinically atypical form, without diarrhea. Constipation and abdominal discomfort developed around week eight of treatment. At that time, the patient presented to the direct referral unit at our center and imaging showed possible partial small bowel obstruction. The patient was hydrated and treated with metoclopramide; she declined an NG tube. Furthermore, she declined hospital admission. She progressively started to feel better for another four to five days after this discharge. An outpatient gastroenterology referral was placed, which the patient did not follow-up on.

The symptoms worsened significantly after the week ten-treatment cycle of pembrolizumab, forcing the patient to seek emergent medical care. The patient presented to the emergency department with anorexia, worsening continuous abdominal pain, nausea, vomiting and tachycardia, lasting for about ten days. On physical examination, the patient had involuntary guarding and rebound tenderness in the lower abdominal quadrants. Laboratory results indicated an elevated total white blood cell (WBC) count of 15.1. CT imaging with contrast of the abdomen and pelvis showed signs concerning for mural thickening of the proximal to mid jejunum, in the area of the mid pelvic cavity, with mucosal and submucosal edema and enhancement, concerning for a target sign and suggestive of ischemic etiology. Additionally, the patient had a cluster of mesenteric vessels concerning for mesenteric volvulus or internal hernia in the midline region of the pelvic cavity (Fig. 3b). Several small foci of non-dependent extraluminal air adjacent to the bowel and a trace amount of free fluid were detected (Fig. 3c).

Exploratory laparotomy revealed one liter of purulent ascites. Part of the ileum was extremely erythematous

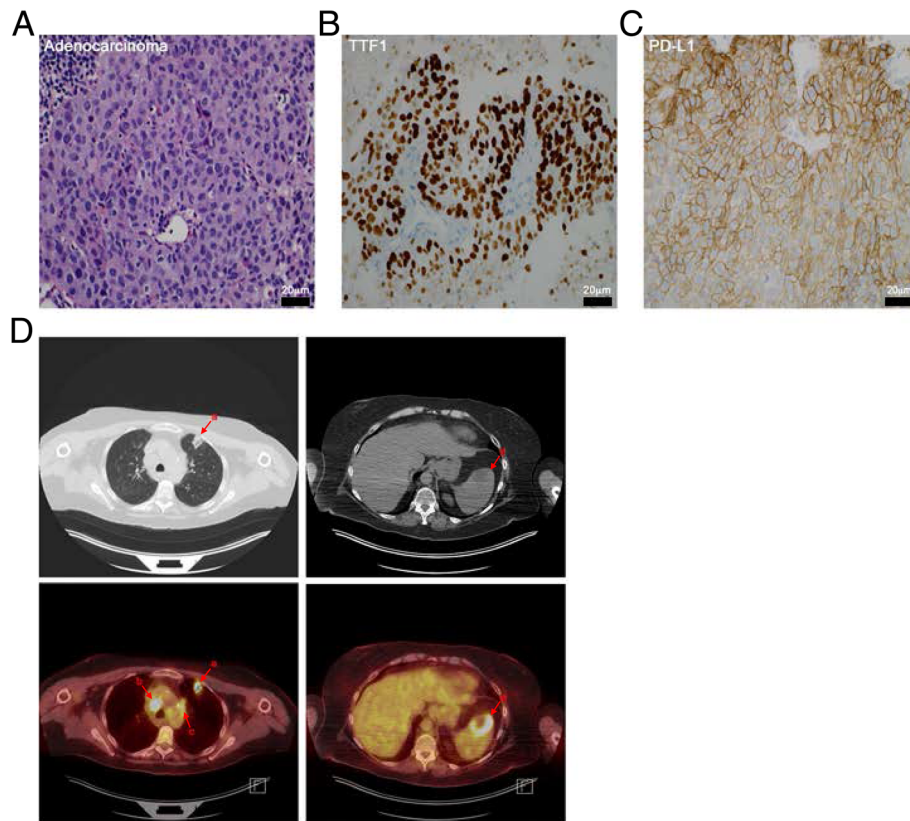


Fig. 2 Diagnosis of PD-L1 positive, metastatic NSCLC and pre-treatment PET/CT imaging. **a.** Hematoxylin and eosin (H&E) stained neck mass biopsy showing adenocarcinoma cells consistent with primary lung disease. Scale bar = 20 mm. **b.** Thyroid transcription factor 1 (TTF-1) positive (dark brown staining) tumor cells. Bar = 20 mm. **c.** Immunohistochemical staining of the patient's biopsy sample for PD-L1 (Dako 22C3). In the representative image, greater than 80% of tumor cells were PD-L1 positive (brown staining). Scale bar = 20 mm. **d.** Transverse computed tomography (CT) images with matching positron emission tomography (PET) images below. Detected lesions: *a* = anterior left upper lung lobe, *b* = right paratracheal region, *c* = left lung hilum, *d* = single splenic lesion

and signs of perforation with significant inflammatory changes were evident. The concerning part of the small bowel was resected, and a primary anastomosis was created. The cecum, ascending colon, transverse, descending colon, sigmoid and rectum were without signs of injury. Surgical pathology of the resected portion of the small bowel showed focal, nonspecific, mesentery, non-caseating granulomatous inflammation, negative for tumor (Fig. 4a). Other commonly cited features were partially appreciated: there was indeed a lack of prominent intra-epithelial lymphocytes and crypt rupture; however, lamina propria expansion and villous blunting was not prominent [12].

Mesenteric vessels were negative for vasculitis and thromboembolism (Fig. 4b). Trichrome stain demonstrated loss of outer muscular wall due to ischemia and inflammation (Fig. 4c). Based on the pathological and surgical findings, the patient was diagnosed with pembrolizumab-associated small bowel perforation. Anti-TNF- α medications were not an appropriate treatment option due to fact that perforation of the bowel

had occurred [13]. The patient recovered well from surgery. After extensive discussions, and with consideration of the patient's remarkable response to treatment and the fact that she was resuming working full time and preferred to avoid chemotherapeutic side effects, the decision was made to resume pembrolizumab. Immunotherapy was restarted on post-operative day twenty-eight. Currently, twelve months since the start of treatment, the patient is continuing her immunotherapy with ongoing partial response and is able to continue her full-time job.

Discussion and conclusions

Response predictive markers

ICIs are revolutionizing the treatment of cancer, with an increasing number of patients benefiting from this class of therapeutic. To maximize treatment efficacy and to minimize severity of adverse events, establishing prognostic and response predictive markers is essential. Several response predictive markers have been identified (Fig. 1; Additional file 1: Table S1), two of which

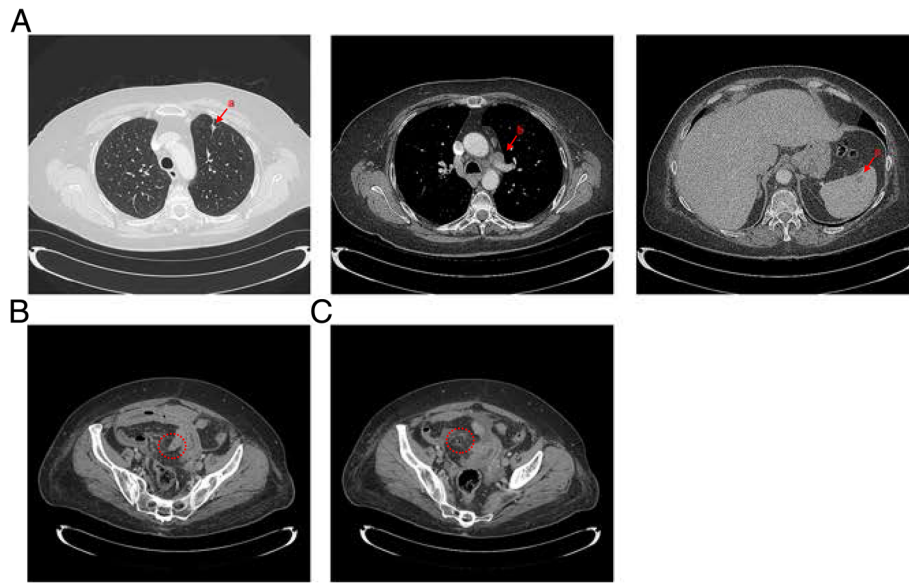


Fig. 3 Post-treatment CT images of the lungs and spleen and abdominal images indicating small bowel perforation. **a.** Transverse CT images of the chest and abdomen showing significant reduction of the (a) anterior left upper lung lobe lesion, (b) left lung hilar lesion and (c) single splenic lesion. **b.** Transverse CT image showing submucosal edema (“target sign”) of the small bowel (red circle). **c.** Transverse CT image showing foci of non-dependent extraluminal air adjacent to the bowel (red circle)

standout and one of which has been approved as standard pre-treatment assessment.

PD-L1 expression is now routinely assessed for cancer patients, with the recommended cutoff for anti-PD1 therapy being PD-L1 expression in $\geq 50\%$ of tumor cells for frontline pembrolizumab treatment instead of chemotherapy [9], or PD-L1 expression in at least 1% of cells for second line treatment with pembrolizumab [14]. In NSCLC, the response rate to pembrolizumab has been reported to be 24.8% in previously untreated patients, with median progression free survival (PFS) and overall survival (OS) of 6.0 months and 16.2 months, respectively, when PD-L1 expression levels were not considered (Fig. 1; Additional file 1: Table S1). Among untreated patients with PD-L1 expression in $\geq 50\%$ of tumor cells, the response rate, PFS and OS were significantly higher, with 50%, 12.5 months and not reached, respectively [4]. Garon et al. report that roughly 23.2% of patients with NSCLC have a PD-L1 score of at least 50% [4]. Importantly, PD-L1 expression has also been reported to frequently, 62% of the time, be concordant between primary tumor and metastases [15].

There remain several concerns regarding the detection and consideration of IHC detected PD-L1 expression: inconsistencies among PD-L1 specific antibodies; tumor heterogeneity in terms of PD-L1 expression; and dynamic changes in PD-L1 expression [11]. Additional studies are needed to help ensure clear and reliable standards when it comes to the assessment of PD-L1, particularly considering that the negative predictive value of PD-L1 IHC is not perfect.

A second particularly intriguing response predictive marker in lung cancer is based on overall mutational tumor load [16]. In advanced NSCLC, high nonsynonymous mutation burden (> 200) correlated with an increased rate of partial or stable responses to treatment with pembrolizumab, lasting at least 6 months. The response rate was 91% (10 of 11 patients) in cases with high mutational burden, compared to just 10% (1 of 10) in patients with low mutation burden (Fig. 1; Additional file 1: Table S1). Higher mutational burden also correlated with a significantly higher median progression free survival of 14.5 months compared to 3.7 months for cases with low mutational burden [17]. In the case of nivolumab treatment, patients with both, a high mutation burden and PD-L1 expression of $\geq 50\%$ had a remarkably high response rate (75%), compared to 32 and 34% in patients with a high tumor-mutation burden or PD-L1 expression of $< 50\%$, respectively [18, 19].

Several additional potential markers have been proposed as predictive for response to ICIs. For example, epithelial-mesenchymal transition (EMT) is known to play an important role in terms of therapy resistance in lung cancer [20] and there seems to be a correlation between EMT and resistance to immune checkpoint blockade as well [16]. T cell-inflammation gene expression profiles based on RNA levels – heavily focused on IFN-gamma-responsive genes, chemokine expression, cytotoxic activity and antigen presentation – showed promise in predicting PD-1 checkpoint blockade response across a wide variety of tumor types and is being

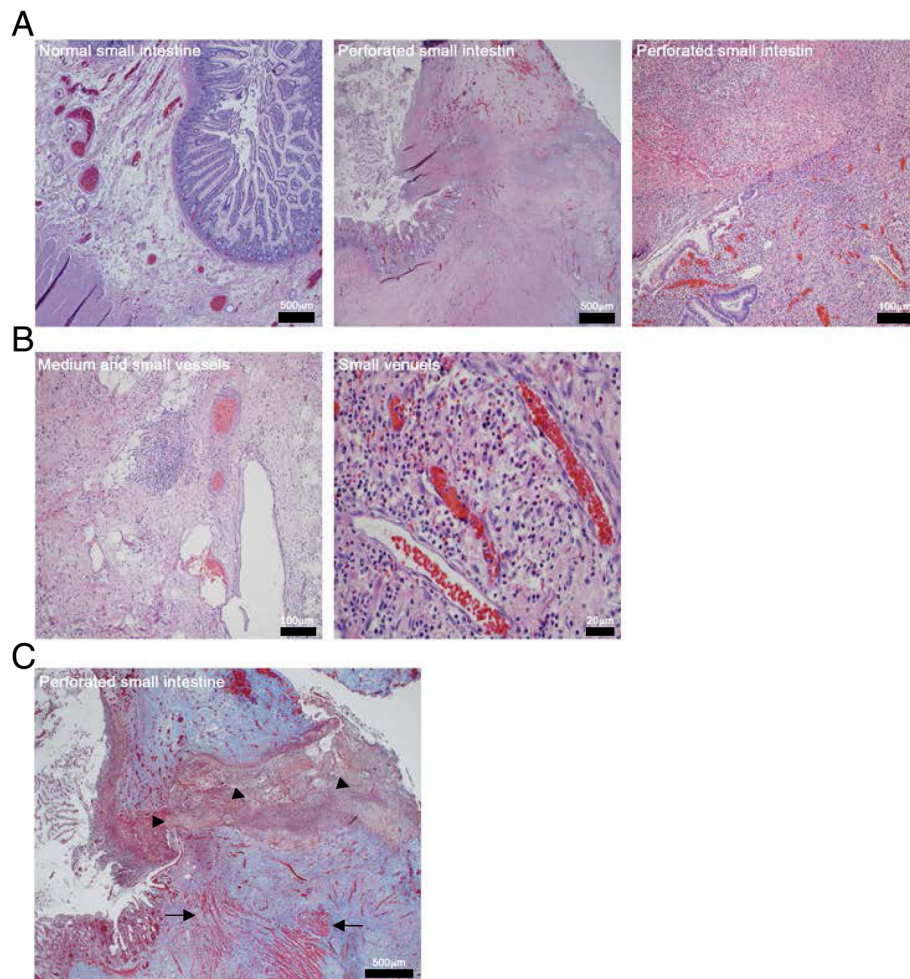


Fig. 4 Microscopy evaluation of small bowel perforation. **a.** Hematoxylin and eosin (H&E) stained slides of normal small intestine (*left panel*), low magnification of perforated small intestine showing ulceration and perforation (*center panel*) and high magnification of perforated small intestine showing acute inflammation and mucosal ulceration (*right panel*). **b.** H&E slides of medium (*left panel*) and small (*left and right panel*) vessels associated with the small intestine. No evidence of vasculitis is seen. **c.** Section of small intestine H&E and trichrome stained showing ulceration with perforation through the serosa (arrow heads) with loss of muscularis propria (arrows) and acute and chronic inflammation and fibrosis

developed as a clinical assay [21]. Lactate dehydrogenase (LDH) levels and absolute lymphocyte count have also been reported as promising [22]. In the case of nivolumab, a small prospective study has shown that patients with irAEs have improved progression free survival compared to patients who did not have irAEs: 6.4 months versus 1.5 months ($P = 0.01$), respectively [23].

ICI enterocolitis

Generally, enterocolitis presents with diarrhea, abdominal pain, nausea and vomiting. Several specific risk factors for ICI-associated enterocolitis have been identified and should be considered when ICI therapy is initiated. The type of treatment is relevant, with anti-CTLA-4 therapy carrying a higher risk of enterocolitis compared to anti-PD-1 therapy, and with combination therapy having the greatest probability of inducing colitis [24]. Not

surprisingly, therapy dose is also important, with higher doses correlating with a higher risk of inducing therapy-associated colitis. Pre-treatment diagnosis of inflammatory bowel disease (IBD) is an additional risk factor for the development of enterocolitis. Microbiota enriched in *firmicutes* and poor in *Bacteroidetes* may also predispose patients to treatment-associated enterocolitis, specifically when treated with anti-CTLA-4 therapy [25]. Lastly, primary tumor histology appears to be significant, with melanoma being associated with a higher risk of treatment-associated enterocolitis compared to NSCLC and renal cell carcinoma (RCC) [24, 26, 27].

ICI-associated enterocolitis presents with distinguishing characteristics, depending on the specific molecular therapeutic target: CTLA-4 versus PD-1 [28]. Enteric biopsies after anti-CTLA-4 therapy have shown that CTLA-4-induced colitis presents with increased CD4+

T-cells within the lamina propria; whereas, PD-1-induced colitis generally presents with high mucosal and intraepithelial CD8+ T-cell populations. Furthermore, high mucosal TNF- α concentrations were only observed in cases of CTLA-4-induced colitis. Lower mucosal TNF- α levels correlated with steroid sensitivity [28].

Endoscopically, ICI-associated enterocolitis frequently presents with erythema, erosion, ulceration and luminal bleeding, which, as seen in this case report, can eventually lead to perforation [24]. Ulcerations have been reported in up to 79% of patients with enterocolitis and the majority of cases involve the distal colon. Endoscopic findings prior to the onset of symptoms do not however correlate with the occurrence of enterocolitis [29].

Anti-CTLA-4 induced enterocolitis frequently appears to be more severe compared to anti-PD-1 associated colitis, and shares some of the naturally occurring features associated with IBD: including both, Crohn's disease and ulcerative colitis [30, 31]. The pathophysiology seems to involve development of antibodies to antigens of the enteric flora and thereby causing mucosal immunity dysregulation [29]. Nevertheless, histologically and in terms of fecal calprotectin levels and specific antibodies to enteric flora, ICI-induced colitis can be distinguished from IBD [29]. Additionally, both, elevated calprotectin prior to initiation of ICI treatment and rapid rise upon start of therapy were associated with severity of autoimmune-related colitis [13].

In terms of managing ICI-induced colitis, the main stay therapy is corticosteroids, which are effective against both, anti-CTLA-4 induced colitis and anti-PD-1 induced colitis. The majority of patients with colitis, 60–80%, respond to corticosteroids [24, 26]. Cases of steroid refractory colitis may require infliximab. Less well studied options include mesalazine, vedolizumab, toclizumab and adalimumab-methotrexate [24]. Overall, TNF- α inhibitors are recommended for ICI-associated diarrhea, but should be avoided if the clinical picture is concerning for colonic perforation [25].

Predictive irAE markers

The incidence rate of irAEs for ICIs has been reported to be 65% and higher [32]. This rate is likely to increase as dual ICI treatments are implemented with increasing regularity [1]. Large clinical trials have reported minor adverse events such as rash, pruritus, fatigue, nausea and diarrhea to be most common; with more severe events, grade 3 and 4, including colitis, pneumonitis, neutropenia and colonic perforation occurring much less frequently [1, 32]. ICI associated colitis has been reported in 0.3 to 7% of patients treated with immune checkpoint inhibitors [33], with an estimated rate of 1.0 to 1.5% for colonic perforation [10]. The incidence of colitis can be substantially higher for combination treatment, having

been reported to affect 56% of patients treated with nivolumab and ipilimumab [34–36].

Colitis caused by immune checkpoint inhibitors most commonly occurs within the rectum and sigmoid colon, but it can also affect the small intestine, as seen in this case report, and other regions of the upper gastrointestinal tract [10, 37]. In the case of ICI-associated colitis or enteritis, it is recommended to first rule out alternative causes, particularly infection with cytomegalovirus, hepatitis B virus and *Clostridium difficile*, celiac disease and inflammatory bowel disease [33]. Histologically, colitis associated with immune checkpoint inhibitors generally presents with acute focal or patchy areas of inflammation with infiltrating eosinophils and neutrophils and abscesses within the crypts [10]. Endoscopy with biopsies should be utilized to assess the regional extent of inflammation. Medical treatment includes corticosteroid treatment dosed at 1–2 mg/kg/day with a 1–2-month taper once symptoms have improved. In steroid refractory cases, treatment with infliximab (anti-TNF- α) is recommended [33].

Molecular markers for irAEs have not been investigated in as much detail as for therapeutic response rates; however, several potential candidates have emerged. These include immune related factors, such as elevated pre-treatment eosinophil levels; increased IL-17 (correlated with colitis); increased expression of CD177 and CEACAM1 (markers of neutrophil activation; associated with increased toxicity); increased neutrophil invasion and signs of inflammation on pre-treatment colonic biopsies (indicated higher incidence of digestive toxicity) [22]; and WBC count analysis [38]. Additional factors, including a family history of autoimmune disease, previous hepatitis or HIV infection and exposure to medication known to cause autoimmune toxicities, have been proposed as potential additional predictors of ICI-associated toxicity [39]. It has also been reported, based on a retrospective study of eighty-four patients treated with ipilimumab, that sarcopenia (OR = 5.34, 95% CI: 1.15–24.88, $P = 0.033$) and low muscle attenuation (defined as increased intramuscular adipose tissue; OR = 5.23, 95% CI: 1.41–19.30, $P = 0.013$) were significantly associated with high-grade adverse events [40].

Conclusion

Our case highlights one of the most severe irAEs associated with immunotherapy and it lays out the management thereof as well as current and potential response and toxicity predictive markers. The enormous success of immune checkpoint inhibitors for the treatment of several different types of cancers continues to change the landscape of cancer treatment. To maximize the impact of these inhibitors, it is critical to systematically study treated patients and optimize treatment whilst

minimizing undesirable outcomes. Further studies are needed to help better define predictive markers in terms of treatment response and probability of irAEs. This case also highlights that reinitiating pembrolizumab treatment after bowel perforation should be considered, albeit with caution, for specific patients.

Additional file

Additional file 1: Supplemental Materials. **Table S1** Consideration of PD-L1 and/or tumor-mutation burden in clinical trials of immune checkpoint inhibitors in non-small cell lung cancer. **Figure S1.** Case timeline. (ZIP 74 kb)

Abbreviations

ALK: Anaplastic lymphoma kinase; CD177: CD177 molecule; CEACAM1: Carcinoembryonic antigen related cell adhesion molecule 1; CI: Confidence interval; CT: Computed tomography; CTLA4: Cytotoxic T-lymphocyte associated protein 4; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; HIV: Human immunodeficiency virus; ICI: Immune checkpoint inhibitor; IFN: Interferon; IHC: Immunohistochemical; IL-17: Interleukin 17; irAE: Immune-related adverse event; LDH: Lactate dehydrogenase; OS: Overall survival; PD-1: Proteins programmed cell death 1; PD-L1: Programmed cell death 1 ligand 1; PET: Positron emission tomography; PFS: Progression free survival; RNA: Ribonucleic acid; ROS1: ROS proto-oncogene 1; TNF- α : Tumor necrosis factor alpha; TTF-1: Thyroid transcription factor 1; WBC: White blood cell

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Availability of data and materials

Not applicable.

Authors' contributions

YB interacted with the patient. TNB and YB interpreted data. TNB, YB and AEK wrote the manuscript. TNB designed and generated all of the submitted Figs. ED prepared pathology slides and analyzed the pathology. All authors have read and approve the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient provided written informed consent to publish this report and associated images.

Competing interests

Y.B. has served on advisory boards of Astra Zeneca, Abbvie, and Caris Life Sciences. The authors have no other conflicts to disclose.

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References

- Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, et al. Overall survival with combined Nivolumab and Ipilimumab in advanced melanoma. *N Engl J Med.* 2017;377(14):1345–56.
- Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, Horwood FC, Piccolo F, Lam DCL, Garske LA, et al. Effect of an indwelling pleural catheter vs talc Pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. *JAMA.* 2017;318(19):1903–12.
- Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung Cancer. *N Engl J Med.* 2015;373(17):1627–39.
- Garon EB, Rizvi NA, Hui R, Leigh N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med.* 2015;372(21):2018–28.
- Bansal P, Osman D, Gan GN, Simon GR, Boucher Y. Recent advances in immunotherapy in metastatic NSCLC. *Front Oncol.* 2016;6:239.
- Shields BD, Mahmoud F, Taylor EM, Byrum SD, Sengupta D, Koss B, Baldini G, Ransom S, Cline K, Mackintosh SG, et al. Indicators of responsiveness to immune checkpoint inhibitors. *Sci Rep.* 2017;7(1):807.
- Blumenthal GM, Theoret MR, Pazdur R. Treatment beyond progression with immune checkpoint inhibitors-known unknowns. *JAMA Oncol.* 2017.
- Kim ES. Avelumab: First Global Approval. *Drugs.* 2017;77(8):929–37.
- Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Coszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung Cancer. *N Engl J Med.* 2016;375(19):1823–33.
- Haanen J, Carbone F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K, Committee EG. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28(suppl_4):iv119–42.
- Mino-Kenudson M. Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: could it be predictive and/or prognostic in non-small cell lung cancer? *Cancer Biol Med.* 2016;13(2):157–70.
- Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM, Shi C. PD-1 inhibitor gastroenterocolitis: case series and appraisal of 'immunomodulatory gastroenterocolitis. *Histopathology.* 2017;70(4):558–67.
- Hofmann L, Forschner A, Loqui C, Goldinger SM, Zimmer L, Ugurel S, Schmidgen MI, Gutzmer R, Utikal JS, Goppner D, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer.* 2016;60:190–209.
- Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387(10027):1540–50.
- Uruga H, Bozkurtlar E, Huynh TG, Muzikansky A, Goto Y, Gomez-Caraballo M, Hata AN, Gainor JF, Mark EJ, Engelman JA, et al. Programmed cell death ligand (PD-L1) expression in stage II and III lung adenocarcinomas and nodal metastases. *J Thorac Oncol.* 2017;12(3):458–66.
- Hugo W, Zaretsky JM, Sun L, Song C, Moreno BH, Hu-Lieskovan S, Berent-Maoz B, Pang J, Chmielowski B, Cherry G, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. *Cell.* 2017;168(3):542.
- Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, et al. Cancer immunology/Mutational landscape

- determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124–8.
18. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu TE, Badin F, et al. First-line Nivolumab in stage IV or recurrent non-small-cell lung Cancer. *N Engl J Med*. 2017;376(25):2415–26.
 19. Hellmann MD, Nathanson T, Rizvi H, Creelan BC, Sanchez-Vega F, Ahuja A, Ni A, Novik JB, Mangarin LMB, Abu-Akeel M, et al. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung Cancer. *Cancer Cell*. 2018;33(5):843–852 e844.
 20. Beck TN, Korobeynikov VA, Kudinov AE, Georgopoulos R, Solanki NR, Andrews-Hoke M, Kistner TM, Pepin D, Donahoe PK, Nicolas E, et al. Anti-Mullerian hormone signaling regulates epithelial plasticity and Chemoresistance in lung Cancer. *Cell Rep*. 2016;16(3):657–71.
 21. Ayers M, Luceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, Albright A, Cheng JD, Kang SP, Shankaran V, et al. IFN-gamma-related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest*. 2017;127(8):2930–40.
 22. Manson G, Norwood J, Marabelle A, Kohrt H, Houot R. Biomarkers associated with checkpoint inhibitors. *Ann Oncol*. 2016;27(7):1199–206.
 23. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, Nagata K, Nakagawa A, Otsuka K, Uehara K, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung Cancer patients treated with Nivolumab: a prospective cohort study. *J Thorac Oncol*. 2017;12(12):1798–805.
 24. Soularue E, Lepage P, Colombel JF, Coutzac C, Faleck D, Marthey L, Collins M, Chaput N, Robert C, Carbonnel F. Enterocolitis due to immune checkpoint inhibitors: a systematic review. *Gut*. 2018;67(11):2056–67.
 25. Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, Boselli L, Routier E, Cassard L, Collins M, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol*. 2017;28(6):1368–79.
 26. Collins M, Michot JM, Danlos FX, Mussini C, Soularue E, Mateus C, Loirat D, Buisson A, Rosa I, Lambotte O, et al. Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies. *Ann Oncol*. 2017;28(11):2860–5.
 27. Yasuda K, Tanaka T, Ishihara S, Otani K, Nishikawa T, Kiyomatsu T, Kawai K, Hata K, Nozawa H, Masui Y, et al. Intestinal perforation after nivolumab immunotherapy for a malignant melanoma: a case report. *Surg Case Rep*. 2017;3(1):94.
 28. Coutzac C, Adam J, Soularue E, Collins M, Racine A, Mussini C, Boselli L, Kamsukom N, Mateus C, Charrier M, et al. Colon immune-related adverse events: anti-CTLA-4 and anti-PD-1 blockade induce distinct Immunopathological entities. *J Crohns Colitis*. 2017;11(10):1238–46.
 29. Berman D, Parker SM, Siegel J, Chasalow SD, Weber J, Galbraith S, Targan SR, Wang HL. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. *Cancer Immunol*. 2010;10:11.
 30. Marthey L, Mateus C, Mussini C, Nachury M, Nancey S, Grange F, Zallot C, Peyrin-Biroulet L, Rahier JF, Bourdier de Beauregard M, et al. Cancer immunotherapy with anti-CTLA-4 monoclonal antibodies induces an inflammatory bowel disease. *J Crohns Colitis*. 2016;10(4):395–401.
 31. Celli R, Kluger HM, Zhang X. Anti-PD-1 therapy-associated perforating colitis. *Case Rep Gastrointest Med*. 2018;2018:3406437.
 32. De Velasco G, Je Y, Bosse D, Awad MM, Ott PA, Moreira RB, Schutz F, Bellmunt J, Sonpavde GP, Hodi FS, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in Cancer patients. *Cancer Immunol Res*. 2017;5(4):312–8.
 33. Prioux-Klotz C, Dior M, Damotte D, Dreanic J, Brieau B, Brezault C, Abitbol V, Chaussade S, Coriat R. Immune checkpoint inhibitor-induced colitis: diagnosis and management. *Target Oncol*. 2017;12(3):301–8.
 34. Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(13):1270–1.
 35. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K, Committee EG. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Supplement_4):iv264–6.
 36. Reddy HG, Schneider BJ, Tai AW. Correction: immune checkpoint inhibitor-associated colitis and hepatitis. *Clin Transl Gastroenterol*. 2018;9(11):206.
 37. Gupta A, De Felice KM, Loftus EV Jr, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. *Aliment Pharmacol Ther*. 2015;42(4):406–17.
 38. Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Fujimura T, Yamamoto Y, Hata H, Gosho M, Tanaka R, Yamaguchi K, et al. Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab. *J Dermatol Sci*. 2017;88(2):225–31.
 39. Hopkins AM, Rowland A, Kichenadasse G, Wiese MD, Gurney H, McKinnon RA, Karapetis CS, Soric MJ. Predicting response and toxicity to immune checkpoint inhibitors using routinely available blood and clinical markers. *Br J Cancer*. 2017;117:913.
 40. Daly LE, Power DG, O'Reilly Á, Donnellan P, Cushen SJ, O'Sullivan K, Twomey M, Woodlock DP, Redmond HP, Ryan AM. The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. *Br J Cancer*. 2017;116:310.

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