

## CASE REPORT

# Acute colonic pseudo-obstruction following nivolumab and ipilimumab combination therapy for metastatic melanoma

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## ABSTRACT

Immune-related adverse events (irAEs) are commonly observed in patients treated with immune checkpoint inhibitors (ICI), and prompt diagnosis and treatment of irAEs is of utmost importance. Gastrointestinal (GI) events are among the most frequent irAEs and the hallmark symptom is diarrhea. Intestinal hypomotility as irAEs is exceedingly rare, and needs wider recognition given that the presentation is insidious.

Here, we report a case of 79-year-old woman with metastatic melanoma under nivolumab and ipilimumab combination therapy. She developed ileus symptom, and was diagnosed with acute colonic pseudo-obstruction. The symptom relieved soon after administering high-dose prednisolone five days after the onset. ICI therapy was discontinued.

Intestinal hypomotility as GI irAEs is exceedingly rare and there have been five reported cases to our knowledge. In reviewing past cases, we speculate that the prompt initiation of corticosteroids resulted in a favorable outcome. Our case illustrates that early recognition of these rare irAEs is essential in order to ensure prompt treatment.

**Keywords:** Immune-related Adverse Events; Immune Checkpoint Inhibitor; Melanoma; Acute Colonic Pseudo-obstruction; Ileus

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## 1. Introduction

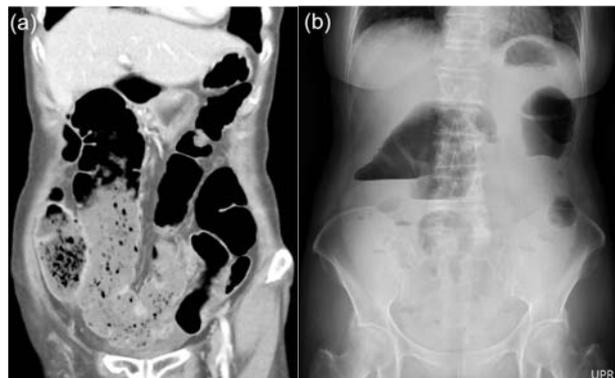
Immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed death-1/ligand (PD-1/PD-L1) have become a new standard of treatment in several cancers including melanoma<sup>[1]</sup>. Immune-related adverse events (irAEs) of CTLA-4 and/or PD-1/PD-L1 inhibition are commonly observed in the skin, gastrointestinal tract, liver and endocrine systems and include pruritus, rash, nausea, diarrhea and thyroid disorders<sup>[2-4]</sup>. In contrast to the direct cytotoxic action of traditional antineoplastic agents, ICI enhance antitumour T-cell activity. This leads to a systemic loss of tolerance, with resulting irAEs, of which gastrointestinal (GI) irAEs are among the most frequent and severe, and the hallmark symptom is diarrhea<sup>[5]</sup>. Here, we report an atypical and insidious presentation of GI irAEs during ICI therapy, and speculate early recognition and prompt treatment of this rare adverse effect lead to favorable outcome, reviewing past cases.

## 2. Case report

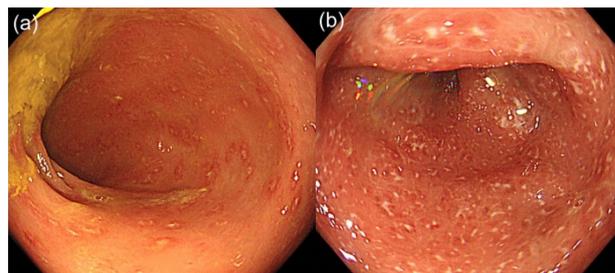
A 79-year-old female with metastatic amelanotic vulvar melanoma after three doses of nivolumab and ipilimumab as second-line treatment was admitted to our hospital. She was diagnosed with right vulvar melanoma with sentinel lymph metastasis, and underwent palliative resection of the primary tumor seven months ago. After the surgery, she began nivolumab infusion every two weeks. Liver metastasis was detected at the ninth nivolumab infusion and her treatment was switched to combination therapy with nivolumab and ipilimumab every three weeks. At the time of admission, she complained anorexia and fatigue, which had begun one day after the last administration of nivolumab and ipilimumab. She did not present diarrhea, nausea or abdominal pain, and had no history of abdominal surgery. She underwent palliative resection of the primary tumor seven months before and began nivolumab treatment. Liver metastasis was detected at the ninth nivolumab infusion and her treatment was switched to combination therapy with nivolumab and ipilimumab. After the first infusion of the combination treatment, she was diagnosed with adrenal insufficiency due to immunotherapy-related hypophysitis and started on corticosteroid replacement treatment.

After admission, stress-dose corticosteroid therapy was started. Since day 4 of admission, she developed intermittent fever. Laboratory data showed white blood cell count 5,840/ $\mu$ L with 75.9% neutrophils; AST 68U/L; ALT 37U/L; LDH 428U/L; ALP; 281U/L; CRP 5.8 mg/dL; and normal serum amylase, and creatinine levels. Two sets of blood culture and cytomegalovirus antigen were negative. On day 5 of admission, she presented abdominal distention, vomiting and constipation. Clinical examination revealed moderate abdominal distension painless to palpation with decreased bowel sounds, unaccompanied by signs of peritoneal irritation or low back pain. Abdominal CT scan revealed distended large intestine without discernible transition point or tumor lesions (**Figure 1a**). Patient received laxatives without success. On day 6 of admission, abdominal X-ray showed niveau formation in the entire large intestine (**Figure 1b**). Colonoscopy re-

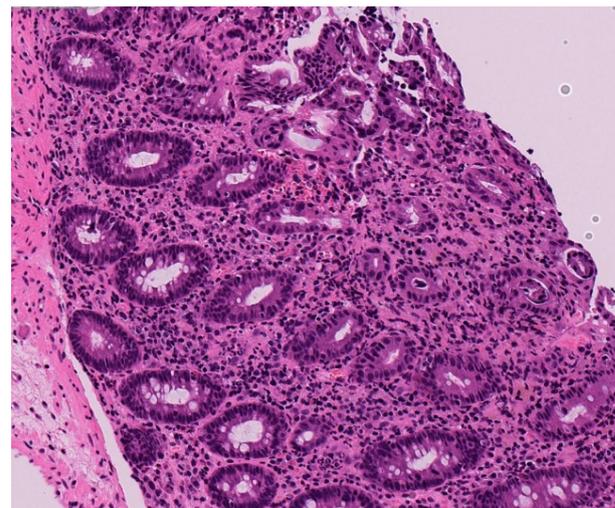
vealed mild colitis affecting continuously from the rectum to the descending colon (**Figure 2**). Sigmoid colon biopsies showed cryptitis infiltrated with neutrophils, lymphocytes and plasma cells without granuloma or intranuclear inclusion bodies (**Figure 3**).



**Figure 1.** Radiological findings. **(a)** On day 5 of admission, the coronal plane of abdominal CT scan revealed a highly distended large bowel loop. **(b)** Abdominal X-ray on day 6 of admission revealed niveau formation in the entire large intestine.



**Figure 2.** Colonoscopy findings. Colonoscopy revealed edematous mucosa, erythema, loss of vascular markings and mucosal friability continuously in the rectum **(a)** and sigmoid colon **(b)**.



**Figure 3.** Sigmoid colon biopsy findings. Sigmoid colon biopsies showed cryptitis and crypt abscess infiltrated with neutrophils, lymphocytes and plasma cells without granuloma or intranuclear inclusion bodies.

No pathogenic bacteria were detected in the biopsy culture. Metastatic tumors to the spinal

cord and brain were not detected and paralytic ileus due to metastasis to the brain or spinal cord was deniable. She was not administered antimuscarinics or opioids which can cause drug-induced paralytic ileus. After excluding the possibility of infection, malignancy and drug-induced paralytic ileus, we diagnosed the patient with acute colonic pseudo-obstruction related to ICI. ICI treatment was ceased, and intravenous prednisolone (1 mg/kg/day) started on day 10 of admission. On day 20, she defecated normally. After switching to oral administration, prednisolone was tapered and discontinued after 8 weeks. Abdominal symptoms did not recur, and no abnormal findings were detected in colonoscopy after three months in spite of the progressive disease.

### 3. Discussion

Our report describes a rare presentation of acute colonic pseudo-obstruction during ICI therapy. The abdominal CT scan revealed no discernible obstructive point, and paralytic ileus due to metastasis to the brain or spinal cord was deniable. Infectious or drug-induced paralytic ileus was also deniable. We concluded that acute colonic pseudo-obstruction was induced by ICI therapy, and administered high-dose prednisolone five days after the onset. ICI therapy was discontinued. The symptom relieved within ten days, and did not recur regardless of progressive disease of melanoma. According to the Naranjo Algorithm, the symptom described in the patient case yielded an adverse drug reaction probability score of 7, which indicates a probable adverse event<sup>[6]</sup>.

Intestinal hypomotility as GI irAEs is exceedingly rare and there have been five reported cases to our knowledge<sup>[7-11]</sup>. These cases paint a highly variable picture; in three cases, intestinal hypomotility developed late after initiating ICI treatment (11-cycle pembrolizumab, 14-cycle nivolumab and 8-cycle pembrolizumab, respectively)<sup>[7-9]</sup>. The other two cases, reported from the same institution, developed GI symptoms acutely (2 cycles of ipilimumab and 1 cycle of combination therapy with nivolumab plus ipilimumab, respectively) and were examined by autopsy<sup>[10,11]</sup>. The former died of unrelated cause, and the latter was refractory to high

dose steroids and fatal<sup>[10,11]</sup>. In both cases, they identified myenteric ganglionitis at autopsy<sup>[10,11]</sup>. In the former case, autopsy slides revealed lymphocytes infiltrating myenteric ganglia throughout the gastrointestinal tract<sup>[10]</sup>. The latter case showed near complete loss of ganglion cells within the myenteric and submucosal plexuses, and no conspicuous inflammatory infiltrate was seen around the ganglia at the time of autopsy, suggesting a ‘burned out’ phase of illness<sup>[11]</sup>.

Overlooking the past four cases of irAE-related intestinal hypomotility excluding the one case which resulted in unrelated death, corticosteroids seem to be the treatment of choice, resulting in complete resolution in one case, limited efficacy in another case, no response and/or death in two cases<sup>[7-9,11]</sup>. Among the five cases, two reports mentioned the timing of initiation of corticosteroid administration. In one case, high-dose prednisone administration started seven days after the onset, and resulted in gradual improvement of symptoms and immunotherapy was restarted<sup>[8]</sup>. The other case was started on high-dose prednisone treatment on the sixteenth day of onset, but refractory and fatal<sup>[11]</sup>. Prompt initiation of therapy appears to be necessary to attain favorable response<sup>[8,11]</sup>.

Our case presented with acute colonic pseudo-obstruction, which relieved soon after administering high-dose prednisolone five days after the onset. Although we could not obtain deep biopsy, we consider myenteric ganglionitis related with immunotherapy contributed to pseudo-obstruction since the severity of colitis examined by colonoscopy was relatively mild. We speculate that the prompt initiation of corticosteroids resulted in a favorable outcome. Our case illustrates that early recognition of these rare irAEs is essential in order to ensure prompt treatment.

### Consent

Written informed consent was obtained for publication of this case report and any accompanying images.

### Declaration of conflicting interests

The authors declare that there is no conflict of

interest with respect to the research, authorship, and/or publication of this article.

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