Severe inflammatory ileitis resulting in ileal perforation in association with combination immune checkpoint blockade for metastatic malignant melanoma

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SUMMARY
Immune checkpoint inhibitors have become standard of care in metastatic malignant melanoma management. Despite superior effectiveness to chemotherapy, significant immune-related adverse events (irAE) may occur, particularly if used in combination. Gastrointestinal irAEs were reported with different patterns of involvement. Here, we report the case of a patient who had ileal perforation as a complication of terminal ileitis, without colitis, induced by combination immune checkpoint blockade.

DESCRIPTION
Immune checkpoint inhibitors have become standard of care in metastatic malignant melanoma management. Despite superior effectiveness to chemotherapy, significant immune-related adverse events (irAE) may occur, particularly if used in combination.1 Gastrointestinal irAEs induced by anti-CTLA-4 and anti-PD-1 agents and their patterns were reported by Marthey et al and Collins et al, respectively.2 3 Although a few patients had evidence of ileitis, none of these cases reported resulted in ileal perforation. There were five cases of colonic perforation in the study by Marthey et al.2 Here, we report the case of a patient who had ileal perforation as a complication of terminal ileitis, without colitis, induced by combination immune checkpoint blockade.

A 52-year-old woman with a diagnosis of metastatic vulval malignant melanoma presented prior to cycle three of combination ipilimumab–nivolumab treatment, with severe abdominal pain, mouth ulcers, nausea and appetite loss. Examination revealed generalised abdominal tenderness with guarding but no rigidity and bowel sounds present. Vital signs were within normal range.

Figure 1 Contrast-enhanced coronal-view CT scan of the lower chest, abdomen and pelvis showing bowel wall thickening of the distal ileum (arrow) with numerous small volume ileocolic lymph nodes suggestive of enteritis.

Figure 2 A shows acute transmural ischaemic necrosis of the small bowel with perforation and peritonitis (H&E magnification ×40). B shows acute ischaemic changes to the small bowel with ulceration (H&E magnification ×40). C is a higher power image of acute ischaemic changes to the small bowel mucosa with ulceration (H&E magnification ×250).
Laboratory tests were satisfactory except an elevated C reactive protein (89 mg/L). A prompt CT scan of the chest to pelvis revealed evidence of terminal ileitis but no colitis, perforation or bowel obstruction (figure 1). An excellent tumour response was also reported. She commenced intravenous methylprednisolone (1.5 mg/kg/day) and fluids. She initially responded to steroid treatment both clinically and biochemically. However, on night 6 after admission, while an inpatient she had a sudden and significant increase in her abdominal pain. A repeat CT scan of the abdomen confirmed our clinical suspicion of bowel perforation. She underwent an urgent laparotomy where her terminal ileum was resected and an ileostomy fashioned. At surgery, throughout the ileum, there were multiple circular areas measuring 10–20 mm in diameter with significant inflammation. Only the most distal lesions were resected, as removal of all lesions would have risked short bowel syndrome. Histologically, each lesion was associated with complete loss of the mucosa—only attenuated muscularis propria and serosa remained—with florid neovascularisation at the periphery of each lesion (figure 2). A single small ileal perforation was present in the centre of one lesion. There was no vasculitis. Two days postoperatively, a single dose of intravenous infliximab (5 mg/kg) was administered, aiming to prevent further perforation of known residual inflamed sites. She made a rapid, unremarkable recovery, being discharged home 10 days postoperatively.

To our knowledge, only one case of ipilimumab-induced ileitis without colitis that resulted in ileal perforation has been reported in the literature. The authors hypothesise that there could be two different pathways activated against colic and ileal epitopes resulting in two distinguished pattern of gastrointestinal involvement.

In conclusion, our case study highlights the importance of early recognition of gastrointestinal irAEs of checkpoint inhibitors particularly in patients receiving combination immunotherapy. Spain et al have outlined the general approach to the management of irAEs, and this needs to be expanded. We call for expert consensus on clear guidelines for the management of gastrointestinal irAEs to try preventing complications and the need for surgical intervention.

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