Two Cases of Immunotherapy-Induced Colitis in Metastatic Melanoma Resulting in Colectomy

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Background

- Ipilimumab, nivolumab and pembrolizumab are checkpoint-inhibitors used to treat various cancers including melanoma.
- They are associated with serious immune-mediated gastrointestinal adverse events.
- Most cases of colitis respond to a short course of pulse steroids.
- We report two cases of severe immune-mediated colitis refractory to steroids necessitating colectomy.

Clinical Features

Case 1:

- 38-year-old Caucasian male admitted with abdominal pain and ongoing diarrhoea for past week.
- Background of stage 3-metastatic melanoma and liver haemangioma (treated with pembrolizumab for the past year).
- Recent admission for obstructive jaundice and pancreatitis → Endoscopic retrograde cholangiopancreatography (ERCP) and stent
- Discharged nine days prior on 100mg prednisone to be weaned gradually.

Case 2:

- 58-year-old Caucasian male presented with diarrhoea for past nine days refractory to 100mg prednisone.
- On ipilimumab and nivolumab for stage 4-metastatic melanoma for past 3 months.
- Other past medical history included intravenous drug use, anxiety and depression.

Diagnosis

Colonoscopy and CT of the abdomen and pelvis showed inflammation indicative of immune-mediated colitis in both patients. A gastroenterologist was consulted for expert opinion and management.

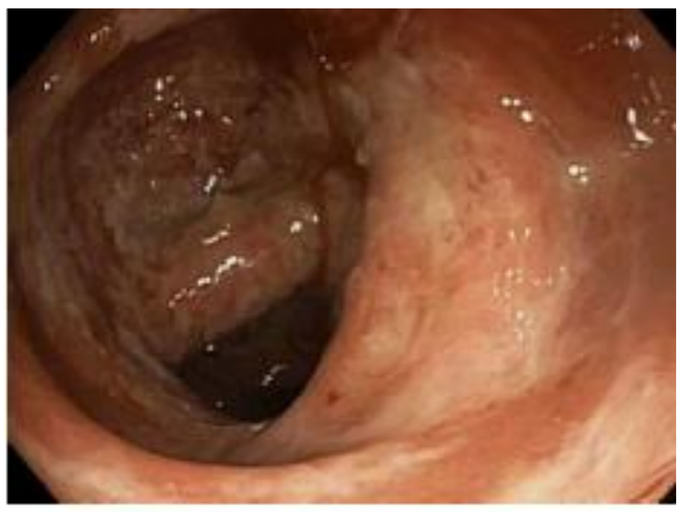

Figure 1: Image from colonoscopy of Case 1 showing colitis, characterised by inflammation and adherent blood throughout the colon

Case Progress and Outcomes

Case 1:

- With minimal symptom improvement after 15 days of 100mg IV hydrocortisone QID and oral mycophenolate 500mg BD, treatment was escalated to 5mg/kg IV infliximab with step down to oral prednisone on discharge.
- Patient re-presented three weeks later with flare of similar initial symptoms of diarrhoea and up to 12 loose bowel motions a day.
- Symptoms did not respond to a second infliximab dose. Repeat colonoscopy showed severe pancolitis and worsening inflammation on tissue biopsy.
- Due to refractory nature of colitis, patient underwent subtotal colectomy with good recovery of symptoms post-surgery.

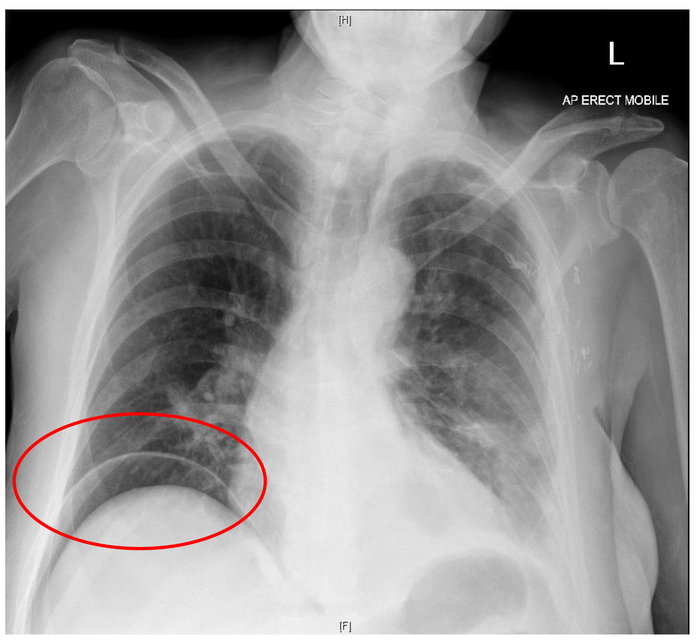

Figure 2: Chest X-ray of Case 2 showing gas beneath the right hemidiaphragm consistent with bowel perforation

Case 2:

- Patient received 3 days treatment of 1g IV methylprednisolone. Symptoms improved and patient was weaned down starting with 100mg IV hydrocortisone TDS. However patient experienced ongoing melaena.
- Chest X-ray and CT abdomen showed intra-abdominal gas beneath the diaphragm consistent with multiple bowel perforations.
- Underwent emergency subtotal colectomy and ileostomy.
- Diarrhoea symptoms fully resolved on weaning steroids, however recovery was complicated by post-operative pain, laparotomy site infection and disease progression.
- Since discharging, patient has changed treatment to dabrafenib and trametinib.

Discussion

- Increasing use of checkpoint-inhibitors has led to emergence of severe immune-related adverse effects including diabetes, hepatitis, pneumonitis and colitis.
- In 2017, 4 cases of colitis were reported to the Therapeutic Goods Administration (TGA) for pembrolizumab, 17 cases for nivolumab and 34 cases for ipilimumab. Colitis was the most reported adverse drug reaction for ipilimumab.
- Onset of GI symptoms start at 6-week mark with a higher incidence of severe colitis and bowel perforation observed with ipilimumab (10-40%) than pembrolizumab or nivolumab (<5%)[1,2]. This explains the more severe melaena experienced by Case 2 who received both nivolumab and ipilimumab.
- Existing literature recommends complex cases refractory to 3 days of high dose IV steroids warrant early consultation with a gastroenterologist and consideration for treatment with 5mg/kg IV infliximab if no signs of perforation or sepsis. A repeat dose of infliximab can be given after two weeks if no symptom resolution.[1,2,3] Hospital pharmacy Drug Committee approval was obtained for non-formulary use of infliximab in Case 1.
- Colectomy is rarely required and reserved as a final resort for patients with refractory enterocolitis or bowel perforation.

Conclusion

- Although regarded as safer and better tolerated than traditional chemotherapy, checkpoint-inhibitors are not benign as they can cause severe immune-mediated toxicities as highlighted in these cases.
- Pharmacists play a key role informing and educating clinicians and patients of the potential side effects on initiation of treatment. Close monitoring, early identification and intervention, and a multidisciplinary approach are critical to recovery.

Acknowledgements

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References

1. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol. 2015;33(18):2092-9.
2. Kroschinsky F, Stolzel F, von Bonin S, Beutel G, Kochanek M, Kiehl M, et al. New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management. Crit Care. 2017;21(1):89.
3. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016;54:139-48.

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