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Two cases of severe gastritis associated with immune check point inhibitor therapy

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Abstract

In recent years Immune Check Point Inhibitors (ICIs) have played an integral role in the treatment of a wide variety of malignancies. Despite improvements in survival outcomes with immunotherapy, immune related Adverse Events (irAEs) are increasing in incidence. Gastrointestinal toxicity in the form of immunotherapy-induced colitis appears to be a relatively common irAE, affecting up to 25% of patients [1]. There is limited discussion however regarding immune-related gastritis, which is a relatively rare adverse event. A recent retrospective review over a 10-year-period reported that only 0.84% of a cohort of 6450 patients treated with ICIs developed immune-gastritis [2]. Despite increasing reports of ICI-gastritis, no definitive guidelines for assessment, management and re-introduction of ICI therapy exists for this patient cohort.

This report reviewed two cases of immune-related gastritis associated with the use of ICIs, specifically ipilimumab and nivolumab. The first case involved a 50-year-old male with a background of renal cell carcinoma treated with four cycles of ipilimumab and nivolumab. He presented acutely with two episodes of haematemesis and subsequent endoscopy revealed diffuse ulceration and mucosal oedema throughout the stomach. Case 2 involved a 48-year-old female with a background of oral squamous cell carcinoma who presented with gradual onset central abdominal pain following long term administration of nivolumab (64 cycles). Outpatient endoscopy revealed severe non-erosive antral gastritis. Both cases displayed evidence of lymphocytic infiltration with no evidence of *H. pylori*-like organisms. These cases differed significantly in their degree of severity at presentation and the intensity of treatment undertaken. Case 2 was managed by withholding ICI therapy and oral steroids. Case 1 required inpatient management with three days of intravenous methylprednisolone, a short course of mycophenolate mofetil and subsequent step down to long term oral steroid therapy.

Immune-related gastritis is a rare complication of immune check point inhibitor therapy. Symptoms are often vague and vary significantly in time to onset and severity at presentation as highlighted in this report. Given the increasing reported incidence of ICI-related gastritis, established guidelines are needed to allow for prompt diagnosis and individualized treatment of this potentially severe irAE.

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Introduction

Immune Checkpoint Inhibitors (ICIs) that target PD-1 (nivolumab) and CTLA-4 (ipilimumab) receptors act through upregulation of T-cell activity and have improved prognosis in a wide variety of advanced malignancies [3]. Due to their potential to dysregulate the immune response, ICI therapy is often complicated by immune related Adverse Events (irAEs). ICI-induced colitis is the most frequently reported gastrointestinal irAE with a reported overall incidence of up to 25% [1]. Presentation may vary based on specific agent, dose and combination of ICI used [1]. ICI-induced gastritis however, is relatively rare with only 54 cases identified in a cohort of 6450 patients treated with ICIs at a single institution over a 10-year-period [2]. As such, no established treatment guidelines are currently available for this adverse event. We herein present two cases of ICI-induced gastritis that vary in acuity of presentation, severity of symptoms and treatment regimen undertaken.

Case presentations

Case 1

A 50-year-old male with a background of stage IV renal cell carcinoma metastatic to lung and axillary nodes presented acutely with two episodes of haematemesis and severe epigastric pain on cycle 4 day 6 of ipilimumab and nivolumab combination therapy. There was no other significant past medical history. He was a non-smoker with no identified psycho-social stressors. On admission he was febrile at 38.5°C with otherwise normal clinical observations. Physical examination revealed a diaphoretic patient with a tender epigastrium and left upper quadrant. Initial bloods showed haemoglobin 137 mmol/L and platelet count 270 x 10^9. Serum creatinine, lipase, Aspartate Aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), bilirubin and Alkaline Phosphatase (ALP) were normal. Alanine Aminotransferase (ALT) levels were mildly elevated at 53 U/L.

Gastric parietal cell, intrinsic factor and *H. pylori* antibodies were negative.

Urgent gastroscopy revealed diffusely ulcerated and oedematous mucosa throughout the stomach, most severe proximally, with widespread areas of superficial clean-based ulceration (Figure 1). Subsequent histopathology revealed multiple biopsy fragments of gastric mucosa with prominent surface erosion and acute inflammatory exudate consistent with ulceration. Extensive extravasation of red blood cells and glandular damage was seen in the lamina propria with some glands containing necroinflammatory material. CD4 and CD8 immunostains highlighted a mixed population of lymphocytes. No viral cytopathic effects or *H.pylori*-like organisms were identified. A diagnosis of immune-related gastritis was made.

Treatment with intravenous methylprednisolone was initially commenced with 500 mg daily for three days, followed by 250 mg for three days. A continuous pantoprazole infusion was commenced at 200 mg over 24 hours for 72 hours along with sucralfate 1 g four times daily. A short course of mycophenolate mofetil 500 mg three times daily was subsequently commenced for a total of six doses due to persisting severe abdominal pain. Treatment was de-escalated to oral prednisolone on discharge following resolution of symptoms with no adverse effect to treatment reported on outpatient follow up.

Gastroscopy two weeks post discharge showed a markedly improved appearance of the stomach with some superficial sloughing and mild residual gastritis. No significant mucosal oedema was observed. Persisting moderately active gastric body and antral gastritis was noted on histopathology, however no further abdominal symptoms were reported. Ipilimumab treatment was permanently discontinued. Single agent nivolumab was recommenced 4 months later following disease progression with no recurrence of gastritis.

Case 2

A 48-year-old female with recurrent stage IVA oral Squamous Cell Cancer (SCC) treated with 64 cycles of nivolumab was reviewed in an outpatient setting with gradual-onset central abdominal pain, gastric reflux and diarrhoea. Clinical observations were within normal limits. Physical exam revealed a soft abdomen with tenderness on deep palpation of the epigastrium. Initial blood tests were unremarkable with haemoglobin, platelet count, liver function and renal function found to be within normal range. Past medical history was significant for type 1 diabetes mellitus and arthritis, both of which were diagnosed following commencement of ICI therapy. No psychosocial stressors were identified.

Non-urgent endoscopy revealed severe non-erosive antral gastritis with easy contact bleeding and surface slough. No mucosal breaks were noted. Mild gastritis was seen in the gastric body and fundus (Figure 2). Colonoscopy showed mild mucosal oedema in distal colon and rectum (Figure 3). Gastric biopsies had features suggestive of reactive gastropathy along with increased inflammation and evidence of lymphocytic gastritis suggestive of immune-related gastritis. No viral cytopathic effects or *H. pylori*-like organisms were identified. Biopsies of colonic mucosa revealed mildly increased chronic inflammation in the lamina propria with lymphocytes seen within the surface epithelium in keeping with immunotherapy-related colitis.

Prednisolone 75 mg daily was started and tapered weekly until completion of course, with no adverse effects reported. Symptomatic improvement was described shortly after initiating therapy and no inpatient admission was necessary. No follow up gastroscopy was performed. Nivolumab was discontinued permanently at the time of initial symptom onset and not recommenced.

Discussion

Immune-related gastritis is a rarely reported complication of ICI therapy. A recent retrospective review of 359 patients treated with ICIs reported only four cases of immune-related gastritis over a three-year-period [4]. The two cases outlined in this report vary significantly in their manner of presentation, degree of exposure to ICIs, and the extent of treatment required.

Case 1 presented emergently with severe abdominal pain and haematemesis following only four cycles of ipilimumab and nivolumab and required immediate inpatient admission with urgent gastroscopy. Case 2 however presented far less acutely with mild central abdominal pain, reflux and diarrhoea after 64 cycles of nivolumab alone. In previously reported cases of ICI-gastritis haematemesis was an extremely rare presenting complaint [5]. As discussed previously, immune-related gastritis often presents with a vague symptomatology and as such may

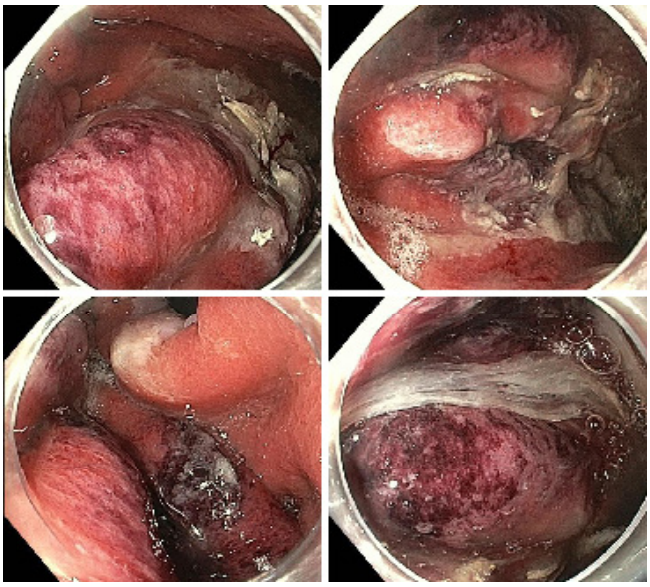

Figure 1: Diffusely ulcerated and oedematous mucosa throughout stomach.

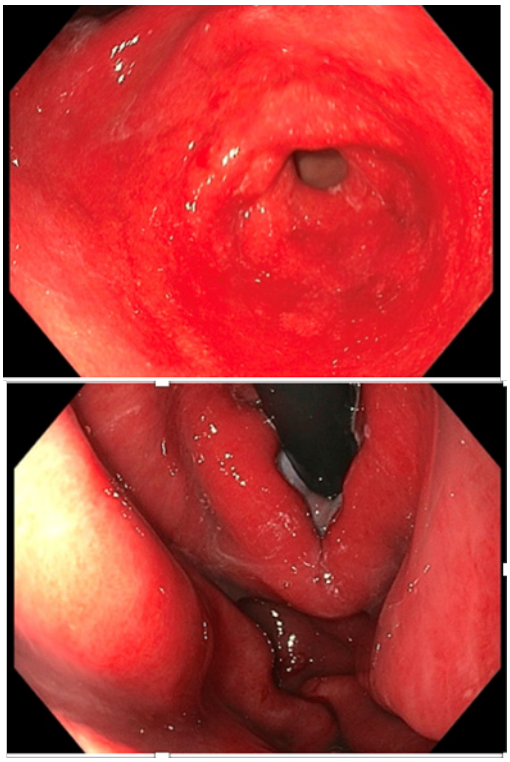

Figure 2: Severe non erosive antral gastritis (left) and mild fundal gastritis (right).

be difficult to distinguish clinically from other cancer-related sequelae such as disease progression, chemotherapy-induced nausea and vomiting and mechanical bowel obstruction.

The majority of cases reported in the literature developed gastritis shortly after initiation of ICI-therapy with a median time to onset of 6 weeks [6]. This is in contrast to our second case which developed after 64 cycles of treatment. This variation in time to onset and severity of symptoms highlights the need for enhanced clinical awareness to allow for prompt endoscopic and histopathological investigation in this cohort of patients. Of note, case 2 also presented with co-existing mild ICI-induced colitis, which was not seen in case 1. Concurrent colitis has been reported in up to 70% of cases of ICI-gastritis [2]. As such, colonoscopic examination should be considered

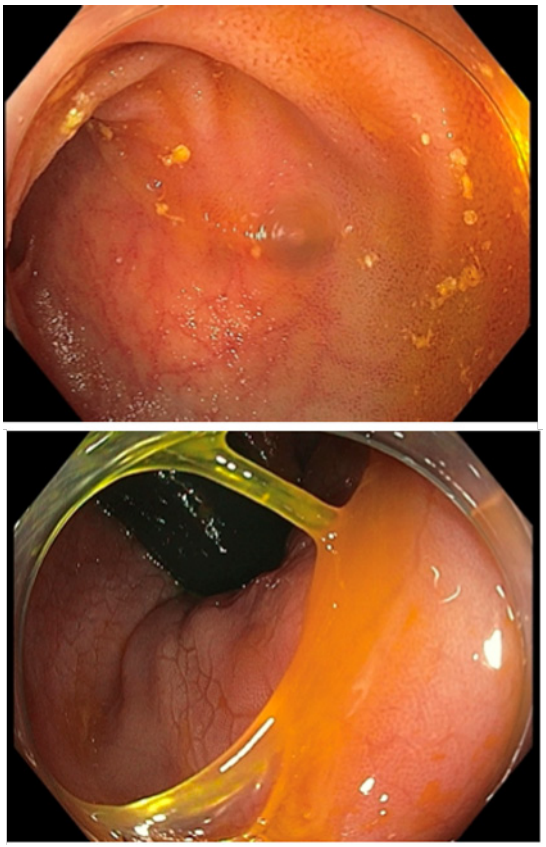

Figure 3: Mild mucosal oedema in rectum and distal colon.

in patients with confirmed ICI-gastritis if there are co-existing symptoms suggestive of colitis.

The spectrum of severity of ICI-induced gastritis displayed in figure 1 and figure 2 highlights the need for an individualised approach to management of this condition. In case 1 inpatient treatment was unavoidable due to the widespread mucosal ulceration and oedema noted throughout the stomach. In case 2 however hospitalisation was not required as gastritis was mild and limited to the antrum of the stomach. Case 1 required IV methylprednisolone and a short course mycophenolate mofetil to achieve symptomatic resolution, in contrast to case 2 which settled with a tapering course of oral prednisolone alone. As is the case with other systemic manifestations of irAEs, the mainstay of treatment for ICI-related gastritis is steroid therapy with either oral prednisolone or pulsed IV methylprednisolone [4]. There has however, been a small number of steroid refractory cases reported in the literature which required further immunosuppression in the form of steroid sparing agents [5]. Only one of these cases utilised mycophenolate mofetil for ICI-gastritis [5].

Current guidelines from the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) for immunotherapy-related gastrointestinal toxicity include detailed guidelines for the management of colitis and enterocolitis only [6,7]. Treatment is based upon stratification of severity using CTCAE (Common Terminology Criteria for Adverse Events) for diarrhoea and involves withholding ICI therapy (grade 2 or above), endoscopic evaluation (grade 2 or above) and steroid therapy with oral prednisolone 1 mg/kg/day or IV methylprednisolone 1-2 mg/kg/day (depending on severity). Steroid sparing agents such as infliximab (anti-TNF) and vedolizumab (anti-integrin) are recommended if no symptomatic improvement is seen after 72 hours of steroid therapy or high risk features are identified on initial endoscopy [5].

Although recently updated ASCO guidelines for ICI-induced irAEs state that the treatment strategy for immune-related gastritis is similar to that of immune-related colitis, these recommendations are based on case studies alone. No standardised approach for risk stratification or severity assessment of ICI-related gastritis is currently incorporated in the ESMO or ASCO guidelines for management of ICI-related adverse events. Current guidelines also lack specific recommendations for the re-introduction of ICIs following an episode of ICI-related gastritis. Australian guidelines (EVIQ) include general advice for management of ICI-induced gastrointestinal toxicity however specific guidance on assessment and management only exists for ICI-related colitis [8]. Given the increasing reported incidence of this potentially severe adverse event, clinical practice guidelines should be broadened to include gastritis to ensure timely referral for endoscopy and initiation of appropriate therapy.

The external validity of this report is limited by selection bias owing to the fact that both cases were observed in a single metropolitan centre with a significant focus on the care and treatment of those with advanced malignancy. It should also be noted that practice altering conclusions should not be extrapolated from case reports alone. Further analysis of the literature in the form of systematic review or meta-analyses should be performed to guide alterations to clinical practice guidelines and subsequently enhance clinician awareness of this rare side effect of ICI therapy.

Conclusion

This case report provides further information on immunotherapy-related gastritis, which remains a rarely reported irAE. It highlights the need for a clear consensus on the assessment, treatment and follow up of this potentially severe complication of immune checkpoint inhibitor therapy.

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