Immunotherapy-related gastritis: Two case reports and literature review

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ABSTRACT: Immunotherapy is increasingly defining a role in a wide variety of tumours such that as use becomes more ubiquitous, so too will the complications. A relatively rare complication of immunotherapy use is immune-related gastritis. In this case series, we present two cases of immunotherapy-related gastritis from our institution and undertake a comprehensive review and analysis of the literature around this less common adverse event.

KEYWORDS: Immunotherapy, combination immunotherapy, toxicity management, adverse event management, gastritis, immune related adverse events

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Introduction

Immunotherapy-related gastritis is less common than other gastrointestinal immune-related adverse events of colitis or hepatitis, with reports in the literature largely limited to individual cases. However, with the increase in use and indications for immune checkpoint inhibitors, it is to be expected that a corresponding increase in incidence will be observed. In this case series and literature review of immunotherapy-related gastritis, we attempted to better characterise this under-recognized condition to assist with early clinician detection and initiation of appropriate management.

Cases

Case 1

A 71-year old Caucasian lady, with a background of atrial fibrillation on dabigatran, presented with localised, epigastric abdominal pain after undergoing three doses of pembrolizumab for metastatic sarcomatoid variant lung cancer. She had been experiencing the same pain for 6–8 weeks, initially attributed to reflux. The pain was unchanged with movement or respiration but markedly worsened with food and fluids, to the extent that her oral intake had become impaired.

Anti-intrinsic factor antibodies, immunoglobulin G subsets and parietal cell antibodies were negative. Serum lipase was normal. Serology for *Helicobacter pylori* and coeliac disease was negative and her liver function tests were unremarkable.

Computed tomography (CT) abdomen with triple phase-contrast noted only biliary distension of unknown aetiology, a very faintly calcified 2 cm calculus in the gallbladder but no evidence of inflammation in the stomach.

Gastroscopy with biopsies of the pylorus showed chronic active gastritis with neutrophilic and eosinophilic infiltration, foveolar epithelial hyperplastic changes and marked lymphocytic exocytosis. Immunostaining was negative for cytomegalovirus (CMV) and *H pylori* and cytokeratin immunostains were additionally negative for metastatic infiltration (Supplemental Figures S1 and S2).

She received 3 days of pulsed methylprednisone at 1 mg/kg/day and then was commenced on a weaning dose of prednisone, reducing at a rate of 10–20 mg/week, with improvement in her pain. On the last review at a dose of 10 mg prednisone, she remained symptom-free.

Case 2

A 50-year old male with a background of melanoma metastatic to brain, lung and lymph nodes presented with epigastric pain. This radiated to his left upper quadrant, was worse with sitting forward, and associated with vomiting and decreased oral intake.

He had been treated with combination of nivolumab and ipilimumab as part of the CHECKMATE-401 clinical trial and was four cycles into treatment at the time of presentation. He had tolerated immunotherapy well until presentation, although had intermittent anorexia and nausea. Previous management had included a surgical resection of cerebral metastasis and volume modulated arc therapy to brain. Only other history was of depression managed with paroxetine.

On admission, a CT scan showed significant thickening of the stomach wall. He was commenced on a pantoprazole infusion, intravenous fluids and a gastroscopy was performed, noting grossly erythematous, friable gastric mucosa. Biopsies were taken and he was commenced on 80 mg methylprednisone for 2 days, followed by a weaning schedule of prednisone, aiming for reduction and cessation over 6 weeks.

Throughout his admission, his CRP (C-reactive protein) was only mildly elevated at a level of 24 mg/L. The white cell count was not elevated. Lipase was normal on admission.

Histopathology showed severe active chronic inflammation, a mixed active chronic inflammatory infiltrate and marked distortion of the glandular architecture, making further interpretation impossible.

He required a dose increase and re-weaning 2 weeks after commencement due to an increase in this same abdominal pain. He was able to decrease prednisone to 10 mg daily, and was well until 1 year later, when a further flare of gastritis was demonstrated on gastroscopy. Steroids were reinstituted and a repeat gastroscopy 12 months later showed resolution of gastritis.

Literature review

Three databases (PubMed, EMBASE, and Medline) were searched for publications of cases of gastritis related to immunotherapy administration in the treatment of malignancy between January 2000 and August 2020. Search terms used included 'gastritis OR autoimmune gastritis' AND 'immunotherapy OR pembrolizumab OR nivolumab OR atezolizumab OR durvalumab OR avelumab', with selection for English language. 25 case reports from conference proceedings and journal publications were identified, and 23 were able to be obtained for analysis (Supplemental Table S1). Cases were included if gastritis was identified on gastroscopy following treatment with either programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors or anti-CTLA4 drugs, and if biopsy results were available. Demographics, symptoms and results of relevant investigations were extracted for analysis. Cases were excluded if no biopsy was available or if another cause was thought more likely from the presentation than immunotherapy-related gastritis.

Twenty-five cases of immunotherapy-related gastritis were analysed, together with the two presented above (Table 1). The mean age of patients was 59, ranging from 16–93 years. 14 (56%) of patients developing gastritis were female. Melanoma was the most predominant cancer subtype, comprising 11 (44%) patients. The most common causative agent was anti-PD-1 therapy (nivolumab/pembrolizumab) in 16 patients (64%), however in two patients, this had been sequenced with prior anti-CTLA4. Only 6 (24%) of patients developed gastritis following combination immunotherapy (anti-PD-1 + anti-CTLA4). Time-to-onset of symptoms was calculated as 29.3 weeks, with a wide range of 2 weeks to 156 weeks.

The most common symptom was epigastralgia in 15 (60%) of patients, with frequently associated anorexia (9 (36%)), nausea (8 (32%)) and vomiting (8 (32%)). Only one patient (4%) was asymptomatic at time of diagnosis.

All patients underwent gastroscopy and biopsy, noting a chronic active inflammatory infiltrate with mixed inflammatory cells and corresponding architectural change. Most cases did not report on serology, but did test for the presence of CMV, tumour infiltration or *H pylori* presence through immunohistochemistry. One case reported on subsequent development of CMV infection following 3 weeks of steroid therapy and one identified concurrent CMV infection, with the authors of the opinion that dual pathologies were involved in the presentation. Not all cases specified

Table 1. Analysis of cases of immunotherapy-related gastritis.

	N (%)
Age (mean [median])	59 [66]
Sex	
Male	11 (44)
Female	14 (56)
Cancer subtype	
Melanoma	11 (44)
Lung	7 (28)
Other†	7 (28)
Time to event (weeks*)	29.3
Agent	
CTLA4 + PD-1	6 (24)
PD-1◊	16 (64)
PD-L1	1 (4)
CTLA4	1 (4)
Symptoms	
Anorexia	9 (36)
Epigastric pain	15 (60)
Weight loss	3 (12)
Vomiting	8 (32)
Diarrhoea	1 (4)
Nausea	8 (32)
Asymptomatic	1 (4)
Other°	6 (24)
Additional IRAEs	
All	7 (28)
UGI sites	2 (8)
LGI sites	2 (8)
Time frame of additional IRAEs	
Concurrent	3 (12)
Prior	3 (12)
Post	1 (4)

*Months calculated as 4 weeks or 30 days. Timing not given for three cases.
°Abdominal distension, dysphagia, haematemesis, dyspepsia.
†Endometrial, colorectal cancer, Hodgkin lymphoma, head and neck squamous cell carcinoma.
◊Two of those treated with a PD-1 at the time of occurrence of symptoms had previously been treated with CTLA4 monotherapy, one treated with CTLA4 had prior nivolumab.

follow-up gastroscopy to confirm resolution, and of the seven that did, this was performed at 1–3 weeks following initiation of steroid treatment.

All patients were treated with high-dose corticosteroid therapy, with most common regimens being 1–2 mg/kg/day of intravenous methylprednisone or oral prednisone, with prolonged tapering. Treatment was not specifically mentioned for one patient. Two patients required infliximab rescue, and one of these also was treated with mycophenolate mofetil. Two patients received anti-viral therapy and one patient underwent concurrent *H pylori* eradication, based on identification on biopsy specimens. Only three cases mentioned a recurrence of symptoms following resolution on steroids, suggesting a recurrence rate around 13%. Five (22%) patients experienced a prior, concurrent or subsequent immune-related adverse event (seven distinct pathologies), of which two were upper gastrointestinal located (8%), and two lower gastrointestinal (8%).

Discussion

Immunotherapy has revolutionised treatment of many cancers. Through release of tumor-mediated down-regulation of cytotoxic T-cell action, the agents within this class have a marked anti-neoplastic effect.[1] These drugs can be divided into PD-1 inhibitors (nivolumab, pembrolizumab), PD-L1 inhibitors (atezolizumab, durvalumab, avelumab), and the cytotoxic T-lymphocyte antigen ipilimumab,[2] taking their names from the cell-surface proteins on which they act. It is this very action that leads to their most unique side effect: the generation of autoimmunity against other organs in the body, so-called immune-related side effects (IRAEs), due to reactivation of cellular immunity.[3-6]

Unlike the well-recognised side effect of colitis,[5,7] gastritis is a relatively rare immune-related side effect, however in the last 2 years has been increasingly reported in the literature. Gaffuri et al[8] presented a clinical case series of four patients with adverse upper gastrointestinal events related exclusively to use of pembrolizumab, and DeMalet et al[9] presented a clinical series of 80 patients with gastrointestinal IRAEs, four of whom had upper tract involvement. Several have presented histopathological case series, with the largest by Tang et al.[10] However, most presentations are limited to case reports, with variable reporting of outcomes and investigations (Supplemental Table S1).

Combination therapy has been noted to produce a higher rate of IRAEs, as opposed to single-agent PD-1 inhibitors,[3,7] although surprisingly gastritis did not appear to be particularly strongly associated with use of combination immunotherapy as presented here. This likely represents current practice in prescribing, with many more patients qualifying for, as well as tolerating, immunotherapy monotherapy. The same situation would explain melanoma as the predominant tumour histology in this analysis.

Time-to-onset of gastritis is highly variable, from 2 weeks to >3 years, reflecting the unpredictable nature of immune-related adverse events. This is posited as due to changes in T-cell population and clonal diversification[7] and is the reason why a slow weaning steroid protocol is required, as demonstrated in the cases presented here. Unfortunately, due to small numbers definite conclusions regarding association of gastritis with other immune-related adverse events or rates of recurrence cannot be made. The calculated rate of recurrence in the reported cases suggests at least a recurrence rate of 13%, which compares favourably to colitis with reported recurrence rates in excess of 30%.[11] Rechallenge of causative agents appears reasonable, and was inferred from the included case reports, although decisions to restart or continue agents must be shared with the patient and is dependent on severity of presentation.

Oedema of the gastric wall can be a finding on imaging and there have been instances of gastric uptake on functional fluorodeoxyglucose-positron emission tomography imaging suggesting the diagnosis. However, confirmation of a diagnosis of IRAE gastritis must be made on gastroscopy with histopathological examination to exclude additional causes, as well as to assess for concurrent upper tract immune-related adverse events, which can be present and considered by some as a continuum of inflammation.[9] Careful history and assessment of patients are essential to rule out alternative causes and serological assessment should be considered for conventional causes of gastritis. In the first case presented, medications such as dabigatran were considered as possible contributants, and subsequently changed.

Subsequent gastroscopies, although not performed in one of the two cases presented here, are essential to confirm resolution and to titrate therapy accordingly. It is suggested, and is the trend from the reviewed literature, to rescope at 2–3 weeks. As with colitis, patients respond well to steroid therapy, with very few requiring steroid-sparing immunosuppressive agents or infliximab.[3-6]

Conclusion

In summary, gastritis is an increasingly reported complication of immunotherapy. As with other IRAEs, recognition and appropriate treatment of gastritis cannot be underestimated, with the potential for death through complications such as hematemesis, the frequent need for treatment delay, withdrawal and the not-insignificant effects of high-dose steroids and immunosuppressive therapy.[5] Symptoms are typically vague and display significant overlap with constitutional symptoms of cancer, and clinicians should be sensitive to the development of epigastric pain as the most commonly associated feature for IRAE gastritis.

Author Contributions

Rachel Woodford: Data analysis, manuscript preparation, review.
Ankit Jain: Conception of study, data analysis, review.
Karen Briscoe: Data analysis, review.
Richard Tustin: Data analysis, review.

All authors have read and approved the final version of this manuscript.

Consent for publication

Written consent was obtained from patients for publication of details included in this manuscript.

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Supplemental material

Supplemental material for this article is available online.

REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252-264.
2. Galluzi L, Zitvogel L, Kroemer G. Immunological mechanisms underneath the efficacy of cancer therapy. *Cancer Immunol Res*. 2016;4:895-902.
3. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol*. 2016;2:1346-1353.
4. Powstow MA, Sidlow RA, Hellman MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158-168.
5. Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5:1008-1019.
6. Weinmann SC, Pisetsky DS. Mechanisms of immune-related adverse events during the treatment of cancer with immune checkpoint inhibitors. *Rheumatology*. 2019;58:vii59-vii67.
7. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol*. 2017;4:173-182.
8. Gaffuri P, Espeli V, Fulciniti F, Paone G, Bergmann M. Immune-related acute and lymphocytic gastritis in a patient with metastatic melanoma treated with pembrolizumab immunotherapy. *Pathologica*. 2019;111:92-97.
9. De Malet A, Antoni G, Collins M, et al. Evolution and recurrence of gastrointestinal immune-related adverse events induced by immune checkpoint inhibitors. *Eur J Cancer*. 2018;106:106-114.
10. Tang T, Abu-Sbeih H, Luo W, et al. Upper gastrointestinal symptoms and associated endoscopic and histological features in patients receiving immune checkpoint inhibitors. *Scand J Gastroenterol*. 2019;54:538-545.
11. Abu-Sbeih H, Ali FS, Naqash AR, et al. Resumption of immune checkpoint inhibitor therapy after immune-mediated colitis. *J Clin* Oncol. 2019;37:2738-2745.