Case report

Nivolumab-induced exocrine pancreatic insufficiency

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ABSTRACT

Immune checkpoint inhibition is the standard-of-care for many advanced cancers. Side effects of therapy may prevent optimal treatment of the cancer. Management of side effects is dominated by recommendations derived from oncological, not gastroenterological practice. We report a patient who developed pancreatic insufficiency during checkpoint inhibitor therapy with a programmed cell death receptor 1 inhibitor, nivolumab, which if not diagnosed would have prevented ongoing treatment. This is a problem which affects approximately 1 in 100 patients treated with this agent but is rarely recognised. Gastroenterologists need to be aware of the spectrum of gastrointestinal disorders which occur after immunotherapy to treat cancer.

INTRODUCTION

Immune checkpoint inhibition is the standard-of-care for an expanding number of advanced malignancies. Many patients need to remain on long-term treatment to maintain remission. Inadequately treated side effects of therapy in patients with cancer may lead to premature discontinuation of treatment. Gastroenterologists are increasingly asked to see patients with gastrointestinal (GI) complications of immunotherapy.

It is widely assumed that diarrhoea, the most frequent GI side effect of immune checkpoint inhibitors is inflammatory, however, little effort has been made to characterise the potential causes of diarrhoea in these patients accurately. The term 'colitis' is widely used to characterise 'diarrhoea' in the oncology literature. Yet, studies show that is not possible to use clinical criteria to differentiate accurately diarrhoea with an inflammatory aetiology from that with a non-inflammatory aetiology.[1 2] In the context of immunotherapy diarrhoea, this is important because multiple observational studies suggest that in approximately one in five patients with diarrhoea, the macroscopic appearance at endoscopy is normal and the histological appearance may also be normal or demonstrate only mild changes of uncertain significance.[3] It is noteworthy that specific histopathological criteria diagnostic of checkpoint inhibitor toxicity in the gut are yet to be defined.

Guidelines for the management of diarrhoea are based on the severity of symptoms assessed using Common Toxicity Criteria for Adverse Events (CTCAE) (table 1) although the reliability of the CTCAE is questionable.[4] Guidelines have been developed from expert opinion, observational cohorts and case series and generally discourage early investigation and recommend empirical treatment (table 2).[5] Despite these guidelines, diarrhoea leads to permanent discontinuation of treatment in >50% of patients[6] and symptoms are often prolonged.

Nivolumab is a fully human IgG_4 monoclonal antibody which by blocking binding of the programmed cell death receptor one (PD-1) receptor to the PD-1 and PD-2 ligands, activates tumour-specific cytotoxic T-lymphocytes in the tumour microenvironment and restimulates antitumour immunity. When used as a single agent, nivolumab causes diarrhoea (table 1) of all grades of severity in 17%–43%. Grade 3–4 diarrhoea occurring in 0.9%–5% of patients, mandates discontinuation of treatment. Nivolumab causes less frequent diarrhoea than other immunotherapies, for example, ipilumimab, an anti-cytotoxic T-cell lymphocyte-associated antigen 4 immunotherapy.

We have previously diagnosed new-onset pancreatic exocrine insufficiency in several patients who received combination therapies which have included nivolumab but the aetiology was unclear. Here, we present a case of pancreatic exocrine

Table 1 Common Toxicity Criteria Adverse Events grading of GI toxicity following immunotherapy

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea	Increase of <4 stools/day over baseline or Mild increase in stomal output	Increase of 4–6 stools/day or Moderate increase in stomal output	Increase of 7 or more stool/day and incontinence and limited ability to cope or Severe increase in stoma output		
Colitis	Asymptomatic	Abdominal pain and mucus or Blood in the stool	Severe abdominal pain, change in bowel habit, peritonism	Life threatening	Death
Enterocolitis	Asymptomatic	Abdominal pain and mucus or Blood in the stool	Severe or persistent abdominal pain, change in bowel habit, ileus, peritonism.	Life threatening	Death

GI, gastrointestinal.

insufficiency for which there is no other likely cause other than nivolumab.

CASE STUDY

A 58-year-old man (table 3) was diagnosed with poor prognosis stage 4 renal cancer with liver and lung metastases. He had previous lifelong normal bowel function.

He was treated with cytoreductive nephrectomy, four cycles of ipilimumab and nivolumab and then maintenance Nivolumab monotherapy. A CT scan at 6 and 12 months showed complete radiological tumour remission.

At 20 months, he reported sudden-onset change in his bowel habit (table 1) exacerbated by fried and fatty food and minimal weight loss. Nivolumab was stopped, however, no improvement was seen following 2 weeks of treatment with 40 mg prednisolone orally and a gastroenterology opinion was sought.

Blood tests were normal apart from a chronically reduced glomerular filtration rate (GFR) (44 mL/min). His C reactive protein(CRP), tissue transglutaminase and thyroid function were normal. His faecal calprotectin was <26 μg/g. CT imaging showed no measurable cancer, no GI abnormality and in particular, the pancreas and small bowel were normal. Upper GI endoscopy showed a small hiatus hernia and two small gastric ulcers, histology from which showed reactive changes. Duodenal biopsies were normal. Flexible sigmoidoscopy apart from the presence of grade 1 haemorrhoids and scattered diverticuli was normal. Random colonic biopsies were normal. A 75-selenium homocholic acid taurine (SeHCAT) scan was normal (47%, 7-day retention).

A trial of rifaximin 550 mg two times per day for 1 week to treat potential small bowel bacterial overgrowth, led to no improvement. However, a trial of 8–10, 25 000iu Creon capsules per day led to immediate normalisation of his bowel function. A subsequent stool sample for pancreatic faecal elastase was 3 μg/g (normal >800 μg/g) confirming the presence of severe exocrine pancreatic insufficiency. He remains well using regular Creon, however, when he omits it, his symptoms return.

DISCUSSION

The risk of PD-1 induced pancreatic insufficiency is not widely recognised but the wide spectrum of troublesome symptoms it causes are easily treated if diagnosed correctly, and treatment significantly improves

Table 2 Suggested treatment guidelines for checkpoint inhibitor induced diarrhoea (these may differ slightly between authorities)[3]

	Severity of symptoms			
CTCAE severity	Grade 1	Grade 2	Grade 3–4	Grade 3–4 (steroid resistant)
Management approach	Symptomatic management including loperamide	Oral prednisolone 40 mg od	Hospital admission Intravenous rehydration Intravenous hydrocortisone 100 mg four times a day or methylprednisolone 1 mg/kg	Infliximab 5 mg/kg (maximum three infusions)
Length of treatment	Escalate therapy if symptom persistence at >1 week or increasing severity	Treat for 8 weeks Escalate therapy if symptom persistence or increasing severity	Reassess after 3–5 days, switch to oral reducing steroid regimen when stable Escalate therapy if symptom persistence or increasing severity	No response, consider: ► Vedolizumab ► Mycophenolate mofetil ► Calcineurin inhibitors Failed medical therapy: consider surgery

Patients may require venous thromboembolism prophylaxis and calcium supplementation while on corticosteroid therapy.
CTCAE, Common Toxicity Criteria for Adverse Events.

Table 3 Patient characteristics

Past medical history	Hypothyroidism
Medication	Thyroxine 100 µg Fluoxetine 40 mg daily Vitamin-D supplements Metoclopramide 10 mg prn
Alcohol Intake	None
Gall stone disease	None
Hyperlipidaemia	None
Weight/height/body mass index	105 kg/180 cm/32.41
Tumour :	Stage 4 (pT3a,cN0, M1) Clear Cell renal cancer. rhabdoid morphology Heng/International Metastatic Renal-Cell Carcinoma Database Consortium score: Poor[3]—expected median survival 7.8 months 1. <1 year from time to diagnosis to systemic therapy. 2. Haemoglobin <lower limit normal (120 g/L). 3. Platelets>upper limit of normal.
Cancer therapies	Right cytoreductive nephrectomy, May 2019. Ipilimumab and Nivolumab, July–November 2019. Nivolumab (single agent) November 2019–December 2020
Symptoms	Bowels open 3–6 times a day with type 5–7 stool Intermittent steatorrhoea Pain helped by having his bowels open Nocturnal defecation once a week Urgency of defecation Bright red rectal bleeding Borborygmi weight

Table 4 A suggested approach to the investigation of Checkpoint inhibitor diarrhoea; if delayed diagnosis of the cause(s) of diarrhoea potentially compromises cancer therapy, our approach is to arrange all the investigations at the same time, and not wait for the results of first line investigations before arranging others

Test recommended	Reason for test
Comprehensive blood screen including full, blood count, renal function, liver function, inflammatory markers, blood sugar, coeliac screen, 9:00 hour cortisol and thyroid function tests	Risk of previously unrecognised pre-existing conditions, predisposing to toxicity or newly induced conditions especially affecting the endocrine system.
Stool for culture	Assess for infective diarrhoea
Stool for faecal elastase	Assess for Pancreatic Insufficiency
Stool for faecal calprotectin	To assess the potential severity of GI inflammation
Glucose hydrogen methane breath test	To exclude the development of small bowel bacterial overgrowth
Upper GI endoscopy with small bowel aspirate, duodenal and gastric biopsies	To exclude small bowel overgrowth To exclude the presence of villous atrophy despite normal tissue transglutaminase To look for characteristic histological changes in the gastric biopsies of autoimmune effects in the GI tract
Lower GI endoscopy—in the first instance we perform flexible sigmoidsocopy as it can be performed at the same time as upper GI endoscopy.	To assess for colonic macroscopic or microscopic inflammation and the presence of pathogens such as *Clostridium difficile* and cytomegalovirus infection
SeHCAT scan	'To exclude the presence of bile acid malabsorption

Case reports and clinical experience suggest that small bowel bacterial overgrowth, pancreatic insufficiency, bile acid diarrhoea, immunotherapy-induced gluten intolerance (serology negative duodenal villous atrophy responsive to a gluten free diet), microscopic colitis and infectious colitis are causes for diarrhoea in some of these patients.
GI, gastrointestinal .

quality of life. Pancreatic insufficiency is frequently missed as a possible cause for symptoms in the oncological setting.[7]

Our patient had no predisposing reason to develop pancreatitis other than nivolumab. Our patient had no change over time in the appearance of the pancreas on multiple scans. There are brief case reports of possible autoimmune pancreatitis resulting from nivolumab therapy; however, these universally report diffuse enlargement of the pancreas. A well conducted, case-control series of 356 patients has suggested that 7.7% of patients treated with nivolumab developed pancreatic atrophy and (1.1%) patients developed pancreatic insufficiency responsive to pancreatic supplements. The presence of atrophy did not correlate (p=0.87) with the development of pancreatic insufficiency.[8] Pancreatic insufficiency has previously been reported to occur with another checkpoint inhibitor, pembrolizumab.[9]

A very few authorities have suggested that the guidelines which assume that diarrhoea occurring after immunotherapy, is an immune-mediated colitis are over simplistic because the majority of patients not responding to treatment with immunosuppression.[5] This report illustrate why this may be the case.

If diarrhoea during immunotherapy threatens optimal treatment of the cancer as it did in our patient, we recommend early, rapid and systematic assessment for the cause(s) of diarrhoea (table 4) particularly if empirical treatment for an immune colitis is not rapidly effective.[5]

Gastroenterologists need to be aware that surprisingly, the underlying mechanisms whereby most modern biological therapies for cancer cause toxicity have been poorly researched. However, most symptomatic patients are found to have simple, treatable diagnoses if carefully investigated and in some patients, this approach may profoundly improve long-term outcomes.

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