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# Chemoimmunotherapy-related enteritis resulting in a mechanical small bowel obstruction – A case report

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## ABSTRACT

**INTRODUCTION AND IMPORTANCE:** Mechanical small bowel obstruction (SBO) is amongst the commonest diagnoses encountered in surgical departments. Although the aetiology is frequently post-surgical adhesions, the condition can arise in a virgin abdomen and we now know several of these cases do not require acute operative management. Here we report one such case where a small bowel obstruction transpired due to enteritis in the setting of chemoimmunotherapy with no prior abdominal surgery.

**CASE PRESENTATION:** A 62 year old male presented to our department with 2 days of vomiting and obstipation. This is on a background of metastatic non-small cell lung cancer for which he was due for his 4<sup>th</sup> cycle of carboplatin, pemetrexed and pembrolizumab. Computed Tomography (CT) of the abdomen demonstrated a segment of thickened distal small bowel without any mass lesion, along with upstream dilatation. The findings were consistent with a mechanical SBO due to enteritis. Infective causes were excluded. The patient successfully recovered with non-operative intervention in the coming days.

**CLINICAL DISCUSSION:** Enteritis is an established adverse effect of various chemoimmunotherapy agents, though a case severe enough to produce a mechanical bowel obstruction is exceptionally rare. We demonstrate through this case that the condition may resolve through conservative measures.

**CONCLUSION:** The diagnosis of chemoimmunotherapy-related enteritis producing an SBO although uncommon, should be considered in the relevant population. A non-operative approach may be appropriate under some circumstances.

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## 1. Introduction

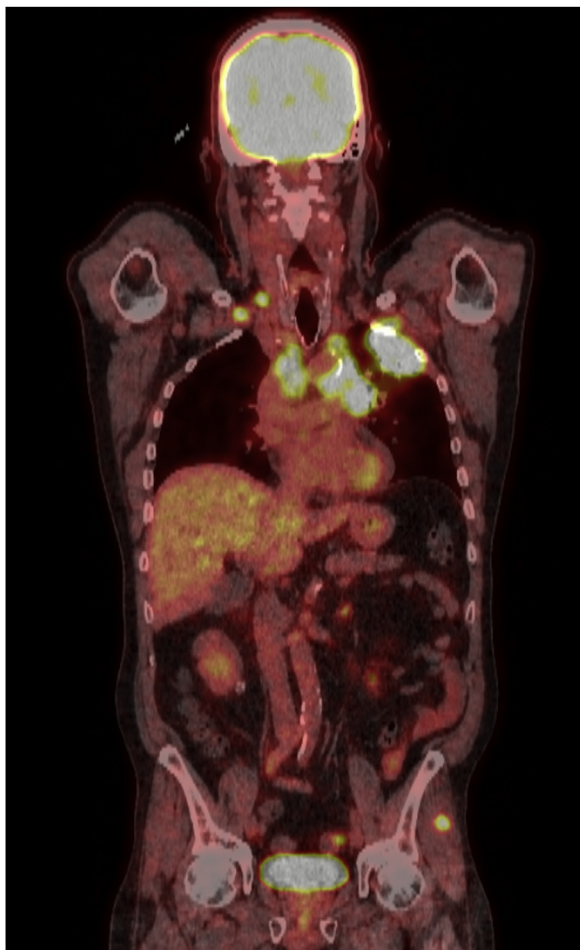
Mechanical small bowel obstruction (SBO) is one of the more common diagnoses encountered in surgical units globally. The causes are diverse and can be classified as those extrinsic, intrinsic or within the intestinal lumen. Up to 75% of cases are attributable to post-surgical adhesions [1]. Under these circumstances, treatment usually encompasses a trial of conservative therapy in the form of nasogastric decompression and gut rest prior to considering surgical intervention [2]. Although the traditional doctrine dictated an SBO in a virgin abdomen mandates operative intervention, a shift in practice has occurred in recent years [3]. Management is guided by the underlying aetiology, and a non-operative approach is appropriate in some circumstances. We present an unusual case encountered at a tertiary hospital whereby a mechanical SBO ensued due to chemoimmunotherapy-related enteritis, without a prior history of surgery. Although the enterotoxicity of these agents is well established, a case severe enough to disrupt gastrointestinal

(GI) continuity is atypical [4]. This case has been reported in line with the SCARE 2020 criteria [5].

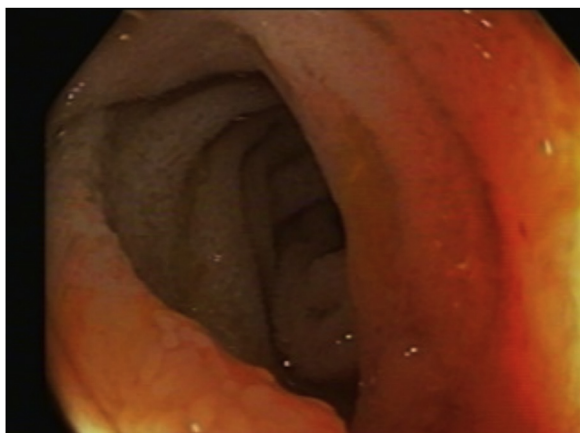
## 2. Presentation of case

A 62 year old male self-presented to his local emergency department with a 2-day history of anorexia, vomiting, lower abdominal pain and obstipation. This is on a background of stage IV metastatic non-small cell lung cancer diagnosed 4-months previously. At the time of his initial diagnosis, there was evidence of bilateral hilar disease alongside skeletal and adrenal metastatic deposits, but sparing the alimentary tract (Fig. 1). He had completed 3-cycles of systemic therapy in the form of 3-weekly carboplatin, pemetrexed and pembrolizumab; with the 4<sup>th</sup> cycle scheduled on the day of presentation. Imaging performed 2-weeks prior demonstrated a good response to treatment with a reduction in the burden of disease. The patient's additional systemic comorbidities included coronary artery disease, dyslipidaemia, hypertension and a 35 pack-year ex-smoking history. His medications included low dose aspirin, telmisartan and rosuvastatin. Background was also relevant for no prior intraabdominal surgery or pelvic radiotherapy. There was no personal or family history of inflammatory bowel

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**Fig. 1.** Positron Emission Tomography (PET) scan at the time of initial diagnosis. There is evidence of uptake at the left upper lobe primary lesion along with hilar, cervical node and musculoskeletal metastatic deposits. Note sparing of the alimentary tract throughout.



**Fig. 2.** Surveillance lower gastrointestinal endoscopy 16 months prior to presentation. Image is of the caecum with the ileocaecal valve visible. The ileocolonic mucosa appears normal.

disease and surveillance colonoscopy performed 16-months prior demonstrated normal ileocolonic mucosa (Fig. 2).

On arrival, his temperature was 37.5 degrees Celsius and he was tachycardic to a heart rate of 140. The latter normalised quickly with intravenous fluid resuscitation. On examination his abdomen was distended and tender in the lower regions without signs of

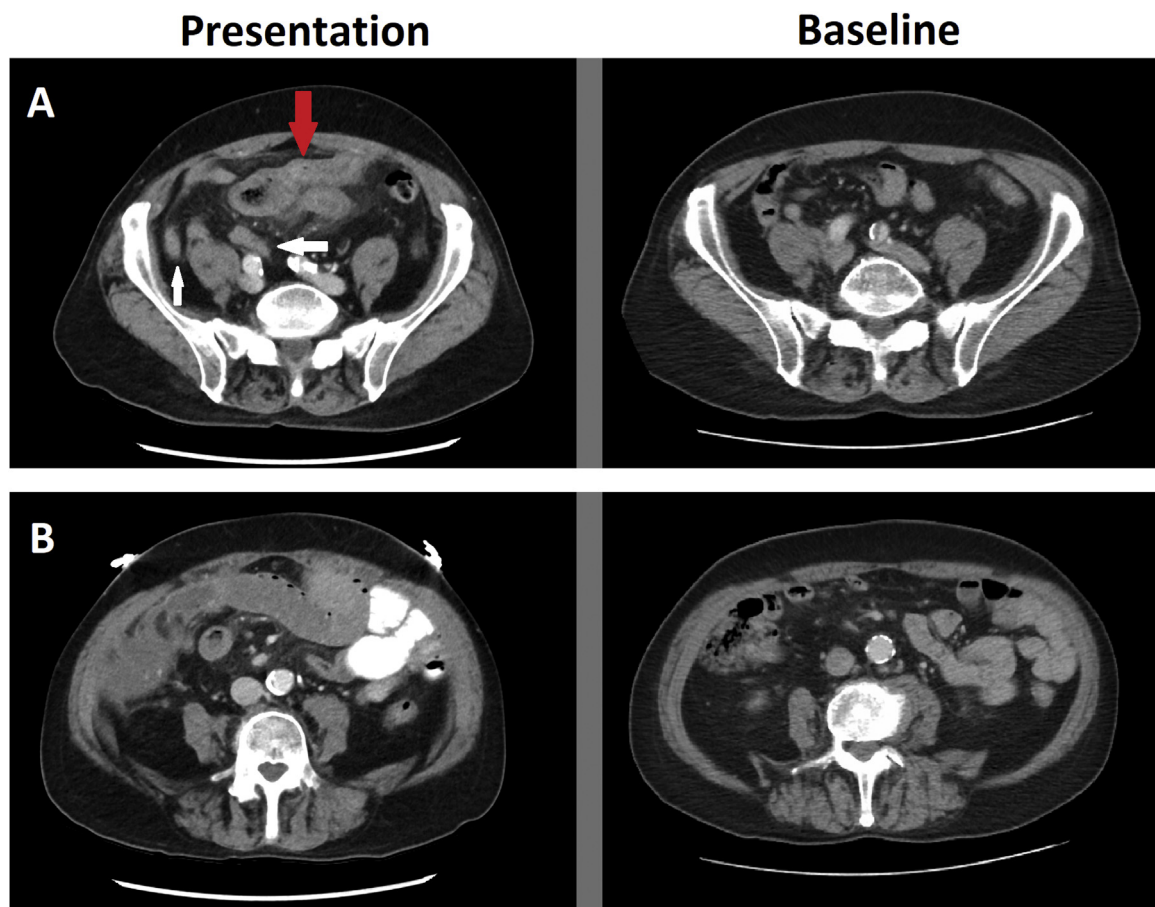
peritonism. No masses or cough impulses were palpated in the inguinal regions. Haematology and biochemistry showed a white cell count of  $7 \times 10^9/L$ , neutrophils of  $5 \times 10^9/L$  and C-reactive protein (CRP) of 294 mg/L. A computed tomography (CT) scan of the abdomen was performed demonstrating a long segment of thickened distal small bowel with surrounding induration of the mesentery (Fig. 3A). Small bowel dilatation was evident upstream to this point and was collapsed distally (Fig. 3B). Notably, no obstructing mass was visualised and there was sparing of the entire colon. The findings were consistent with a distal mechanical small bowel obstruction due to enteritis and were new when compared to the most recent imaging 2 weeks prior. On further questioning, the patient described alternating constipation and diarrhoea in the week preceding his presentation. There were no known sick contacts, no recent travel history and no notable exposure to under-cooked foods.

He was admitted under the care of the surgical team, kept fasted and a nasogastric tube was inserted. As the working diagnosis was enteritis related to chemoimmunotherapy, the medical oncology team was consulted with a view to consider directed treatment options. Upon their review less than 24 h later, he began to show signs of improvement in the form of improved pain, reduced nasogastric output, passage of small amounts of flatus and a CRP that was down-trending. The scheduled treatment cycle for his malignancy was delayed. He continued to improve in the coming days, with his diet gradually upgraded and eventuated in the passage of stool. Faeces culture and PCR returned negative for viral, bacterial and parasitic causes. He was discharged 72 h into his admission tolerating a full diet. At 2 weeks follow up in the outpatient oncology department, his symptoms remained improved and CRP was down to 10 mg/L. In light of his clinical stability, the 4<sup>th</sup> cycle of chemoimmunotherapy was administered a week later although unfortunately he experienced a recurrence of intermittent abdominal pain, eventuating in a small bowel perforation the following month. All antineoplastic agents were subsequently withheld to allow for his recovery.

### 3. Discussion

Despite recent advancements, enterotoxicity remains a challenging adverse effect to manage amongst antineoplastic agents used in a variety of cancers [4]. Chemotherapy and immunotherapy related enteritis usually manifests as abdominal pain, diarrhoea and paradoxically constipation under some circumstances. Its severity is graded according to the frequency of stools and the presence of alarm signs such as fevers or bloody diarrhoea, which ultimately guides treatment and the requirement for inpatient management [6,7]. In some cases, the condition can progress to severe surgical complications such as a spontaneous small bowel perforation [8]. Although it is not uncommonly associated with the presence of a paralytic ileus, chemoimmunotherapy-induced enteritis severe enough to result in a mechanical bowel obstruction is an extremely rare occurrence [9]. To our knowledge, only one such case has previously been described related to capecitabine in metastatic colorectal cancer [10].

Some of the more commonly described culprits of this phenomenon are 5-fluorouracil and irinotecan, both used in combination in colorectal cancer. With regards to our patient's regimen, selected reports have implicated pemetrexed [11]. Although, it should be noted that cases of pemetrexed-related enterocolitis are more frequently accompanied by neutropenia. In the KEYNOTE-189 phase III trial, there were notably higher rates of GI toxicity in the Pembrolizumab-chemotherapy arm compared with chemotherapy alone in the absence of an increased risk of neutropenia [12]. This



**Fig. 3.** Computed tomography (CT) scan of the abdomen performed at the time of presentation to hospital (left column) when compared to the patient's most recent surveillance imaging two weeks prior (right column). A: Axial CT slice at the level of the S1 vertebra demonstrating a thickened segment of small bowel with surrounding induration of the mesentery. A narrowed transition point is evident (red arrow). Collapsed small bowel distally is seen in the right lower quadrant (white arrows). B: Axial CT slice at the level of L4 with evidence of dilated loops of small bowel upstream to the segment of enteritis. The findings are new when compared to baseline imaging two weeks prior.

raises the possibility of Pembrolizumab as the potential causative agent in the setting of concurrent chemotherapy.

The mechanism in which chemo- and immunotherapeutic agents induce intestinal inflammation can be explained through first principles. One of the biggest challenges in antineoplastic therapy has been to selectively halt proliferation of rapidly dividing tumour cells. Adverse effects frequently stem from their non-selective effects on high turnover host cells, which includes elements of the GI mucosa [4,7]. A mucositis may subsequently develop, characterised by lymphocytic infiltrate and bowel wall oedema. This may manifest as mouth ulcers, enteritis or colitis depending on the region of GI tract involved. Histological features in the small bowel include villous atrophy and glandular destruction [10]. In the case we describe, it is likely that wall oedema was to the extent such that the intestinal lumen was obscured, ultimately preventing passage of gastrointestinal contents.

We recognise that the diagnosis of chemoimmunotherapy-related enteritis producing a SBO is difficult to make in the absence of histological sampling at the time of the obstruction. The segment of bowel affected in our patient was not accessible endoscopically, and a surgical resection could not be justified given the patient initially improved with conservative measures. Accordingly, we considered other plausible causes under the given circumstances. The rapid evolution of the bowel wall changes on imaging, absence of a mass lesion together with the spontaneous resolution of symptoms effectively excluded a malignant cause of SBO. Negative faeces culture/virology and lack of epidemiological risk factors meant that

a communicable cause was unlikely. Additionally, in a study that looked to differentiate chemotherapy-related enterocolitis from an infective cause, radiological evidence of small bowel involvement favoured the former [13]. Absence of a strong family history alongside a normal recent colonoscopy study rendered inflammatory bowel disease less likely. Thus the clinical and radiological features are most in keeping with a drug-induced enteritis with a resultant SBO.

In addition to the usual supportive measures with any SBO, management in this case involved withholding the suspected offending agents. Thereafter, treatment is directed depending on the nature, duration and severity of symptoms [7]. Severe cases of chemotherapy related gastrointestinal toxicity have been managed with octreotide alongside fluid resuscitation and antimotility agents, though the latter is evidently inappropriate in the presence of obstructive features as in this case [14]. Antibiotics are usually reserved where there is accompanying neutropenia or fevers [7,14]. Where immunotherapy is believed to be the causative agent, corticosteroids and anti-TNF alpha therapy have proven successful in refractory cases [6]. However, little information is available on the best practice when a mechanical SBO ensues as a result of enteritis owing to the rarity of the condition. Our patient's symptoms initially resolved with supportive measures and he was referred for ongoing management of his malignancy. It should be noted that acute toxicity does not preclude reinstating chemoimmunotherapy at a later point and there have been cases where this was implemented with a successful outcome [6,8].

#### 4. Conclusion

Chemotherapy-related enteritis is an unfortunate adverse effect of various antineoplastic agents. In the rare event that this progresses to a mechanical SBO, we demonstrate through this case that withholding the offending agents alongside the appropriate supportive care can effectively resolve the condition. Despite its rarity, the diagnosis should be considered in the appropriate population as the condition can be successfully managed without operative intervention.

#### Declaration of Competing Interest

The authors Ali P. Mourad and Marie Shella De Robles declare no conflict of interest.

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#### Ethical approval

Ethics approval is not required for the writing of case reports at our facility.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### Registration of research studies

researchregistry 6307 available at: <https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5fc2f6df704425001b6e41ca/>.

#### Guarantor

Ali P. Mourad.

#### Patient perspective

The patient was grateful of the care he received during his time in our unit. He was strongly supportive of the writing of this case if it could help others in a similar scenario.

#### Provenance and peer review

Not commissioned, externally peer-reviewed.

#### CRediT authorship contribution statement

**Ali P. Mourad:** Conceptualization, Investigation, Resources, Writing - original draft, Writing - review & editing. **Marie Shella De Robles:** Conceptualization, Writing - original draft, Writing - review & editing.

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