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SHORT COMMUNICATION

Risk of bowel obstruction in patients with colon cancer responding to immunotherapy: an international case series

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Background: Immunotherapy is used routinely for treating deficient mismatch repair (dMMR) colon cancer (CC). This case series highlights an emerging safety issue, where patients develop bowel obstruction associated with immunotherapy response.

Patients and methods: Patients with dMMR CC who developed bowel obstruction while responding to immunotherapy were retrospectively identified. Data on patient, disease, treatment, and response-specific factors were explored for potential risk factors. Overall treatment numbers were used to estimate incidence.

Results: Nine patients from eight European centres were included. Common features were hepatic flexure location (5/9), T4 radiological staging (6/9), annular shape (8/9), radiological stricturing (5/9), and endoscopic obstruction (6/9). All received pembrolizumab and obstructed between 45 and 652 days after starting treatment. Seven patients underwent surgical resection; one was managed with a defunctioning stoma; and one was managed conservatively. One patient died from obstruction. Radiological response was seen in eight patients, including two complete responses. Pathological response was seen in all seven who underwent resection, including four complete responses. The overall incidence of immunotherapy response-related obstruction in these centres was 1.51%.

Conclusions: Bowel obstruction associated with immunotherapy response may represent a rare treatment-related complication in dMMR CC. Clinicians must recognise this safety signal and share experience to maintain patient safety.

Key words: colon cancer, immunotherapy, regression, bowel obstruction, case series

INTRODUCTION

Colon cancer (CC) is the most common abdominal malignancy and a major cause of cancer-related death.[1] Localised disease typically requires surgical resection with or without additional chemotherapy, whereas metastatic CC is usually treated with systemic anticancer therapies alone.[2,3] For deficient mismatch repair (dMMR) metastatic CC specifically, immunotherapy is now the established first-line treatment.[3]

Neoadjuvant chemotherapy (NAC) for locally advanced CC has been shown to be safe and effective in randomised trials, but lesser benefit has been observed for dMMR tumours.[4] Immunotherapy for dMMR localised colon and rectal cancers has been investigated in phase II trials with consistently remarkable rates of pathological complete response (pCR).[5,6]

In CC, bowel obstruction is a major complication and the most common indication for emergency surgery, with

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significant morbidity and mortality.[7,8] While obstruction risk is well recognised in the metastatic setting, the emergence of neoadjuvant therapies has placed a broader population at risk. In the international Fluorouracil, Oxaliplatin and Targeted Receptor pre-Operative Therapy (FOxTROT) trial, 4.3% of participants developed bowel obstruction during a short course of NAC; endoscopic obstruction and radiological or endoscopic stricturing were identified as independent baseline risk factors for bowel obstruction.[9] Interestingly, there was no association between obstruction risk and pathological regression, suggesting tumour phenotype may be more relevant in this setting than treatment response.

This case series was collated following observations from clinicians internationally that patients with dMMR CC were unexpectedly developing bowel obstruction after treatment with immunotherapy. However, rather than being associated with disease progression, they were associated with excellent immunotherapy response, an unusual phenomenon in CC.

PATIENTS AND METHODS

Cases were identified retrospectively by clinicians across our international research network. While a specific period for inclusion was avoided to ensure maximal case identification, all instances of obstruction occurred within the past 3 years. Patients who developed bowel obstruction within a primary colonic tumour showing evidence of immunotherapy response (radiological and/or pathological) were included.

The following data were collected for each patient: age, sex, tumour site, radiological staging [according to the American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) system, version 8], sites of metastases, tumour annularity, the presence of radiological stricturing, details of endoscopic evaluation, molecular biomarker testing results (*RAS*, *BRAF*, and MMR), tumour histology, type and duration of immunotherapy, clinical presentation, radiological response, relevant clinical outcomes (including surgical resection and/or defunctioning, colonic stenting, and adverse events), interval from starting immunotherapy to bowel obstruction, pathological staging (according to the AJCC TNM system, version 8), tumour regression score (TRS), and the total number of patients given immunotherapy for colorectal cancer within that centre.[10] One case was selected to provide greater detail, including imaging and histology.

Common features were explored for potential risk factors. The incidence of bowel obstruction associated with immunotherapy response was estimated by dividing the number of cases by the total number of patients given immunotherapy for colorectal cancer within these centres.

Written consent was obtained from all patients or next of kin. Local information governance policies were followed at each centre.

RESULTS

Detailed case

A 76-year-old woman presented with 8 months of abdominal pain, fatigue, and weight loss. After being found to have iron-deficiency anaemia, a computed tomography (CT) scan, colonoscopy, histological assessment of biopsies, and molecular testing diagnosed a dMMR, *BRAF V600E*-mutant, moderately differentiated hepatic flexure adenocarcinoma (Figure 1). The radiological staging was reported as T4b N1 M0 with predicted invasion of the peritoneum and duodenum. A specialist colorectal multidisciplinary team (MDT) confirmed that the tumour was unresectable and recommended attempted downstaging with immunotherapy.

The patient tolerated 3 months of pembrolizumab well with toxicity limited to grade 1 immune-related dermatitis. A CT scan at this point showed a partial response within the primary tumour and no new disease (Figure 1). The treating team and patient agreed to complete a further 3 months of pembrolizumab before reassessing resectability with the MDT.

Seventeen days after the most recent CT scan, the patient presented acutely with severe abdominal pain and vomiting. She also described a nonspecific change in bowel habit. On examination, she was haemodynamically stable but had obvious abdominal distension, with diffuse tenderness on palpation and absent bowel sounds. An urgent CT scan showed a significant reduction in the size of the hepatic flexure tumour, causing luminal stricturing and obstruction with gross distension of the ascending colon, caecum, and terminal ileum (Figure 1).

Following a sudden deterioration, the patient underwent an emergency laparotomy and right hemicolectomy. As a result of persistent intraoperative haemodynamic instability, damage control surgery with a laparostomy and delayed primary closure was carried out with the patient taken to intensive care for immediate organ support. She returned to theatre the following day for the formation of an end ileostomy and closure of the abdomen.

Macroscopic histopathological assessment of the surgical specimen confirmed the presence of a fibrotic stricture with a lumen diameter of 8 mm, surrounded by areas of necrosis and mucin. Microscopically, islands of residual adenocarcinoma were present and associated with an intense lymphoplasmacytic inflammatory reaction and large pools of acellular mucin (Figure 2). Residual cancer accounted for $<$20% of the tumour volume, indicating a good response to immunotherapy with a TRS of 2. The final pathological staging was ypT1 ypN1a ypR0.

Other cases

A further eight cases were identified across seven European centres (Table 1). The primary tumour was located at the hepatic flexure in five patients, sigmoid in three patients, and descending colon in one patient. On radiological

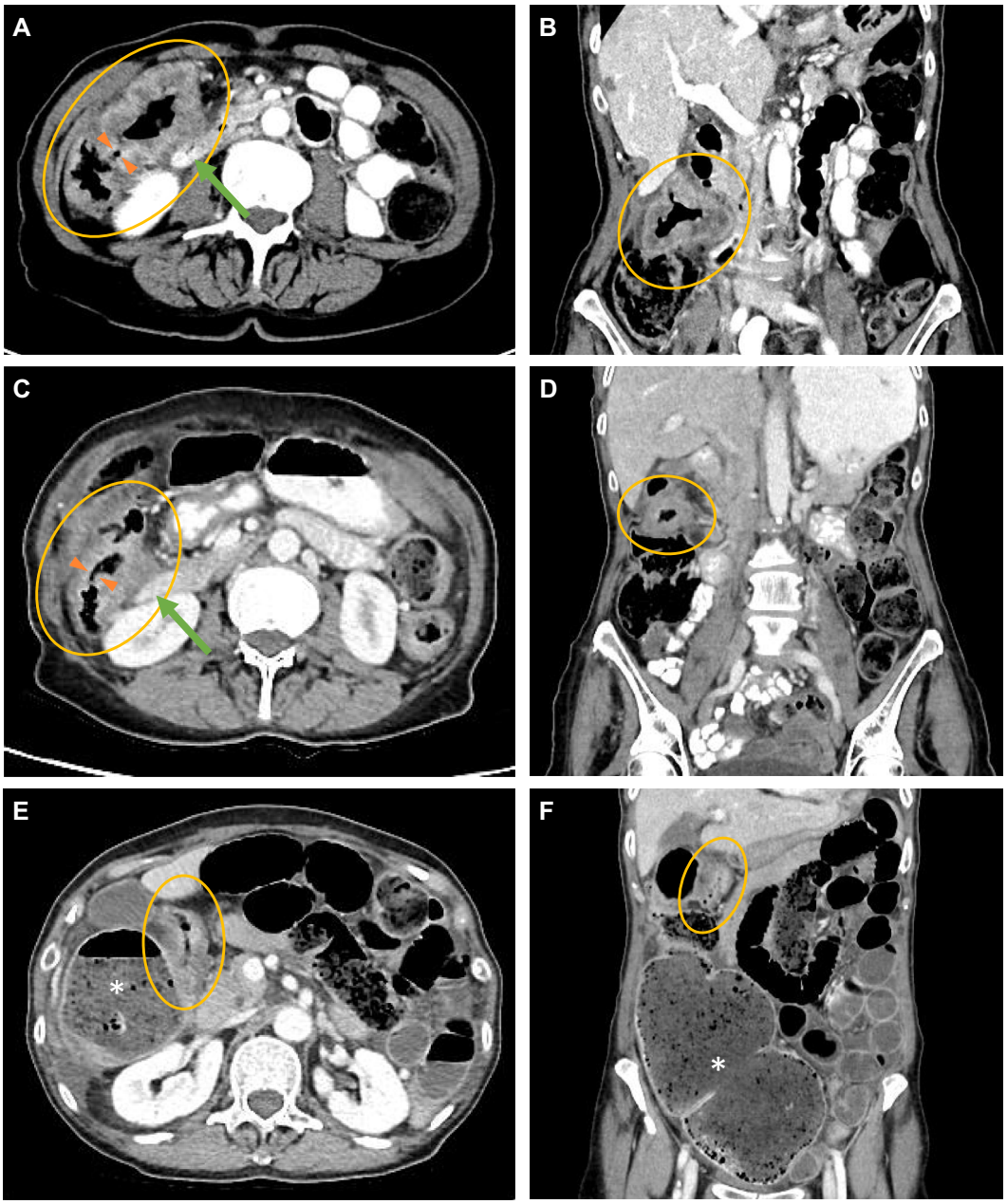

Figure 1. Evolution of the primary tumour on computed tomography. (A and B) Baseline images showing a cT4b tumour at the hepatic flexure with suspected involvement of the duodenum. Luminal narrowing is observed in the centre of the tumour. (C and D) Images following 3 months of pembrolizumab showing a partial response within the primary tumour and persistent luminal narrowing. (E and F) Images after a further 17 days showing an accelerated radiological response, with stricturing causing acute large bowel obstruction. Green arrows, duodenum; orange triangles, narrowed colonic lumen; yellow rings, area of primary tumour. The asterisk (*) indicates the dilated right colon.

assessment, six tumours were staged as T4 and three as T3; eight were described as annular; and five were described as having radiological stricturing. Six tumours were not traversable at endoscopy.

All patients received pembrolizumab and developed bowel obstruction between 45 and 652 days (median 79 days; interquartile range 47-394 days) after starting treatment (Table 1). Seven patients underwent surgical resection of their tumours, including four who were initially defunctioned (Figure 3). Another patient was defunctioned and, at the time of writing, continues to receive immunotherapy. One patient was managed conservatively. Radiological response was seen in eight patients, including two radiological complete responses. Pathological response was seen in all seven who underwent resection of their tumour, including four pCRs. One patient died from bowel obstruction. At the time of writing, eight of these cases (one excluded due to unknown treatment numbers in this centre) occurred out of 529 (1.51%) similarly treated patients in these centres.

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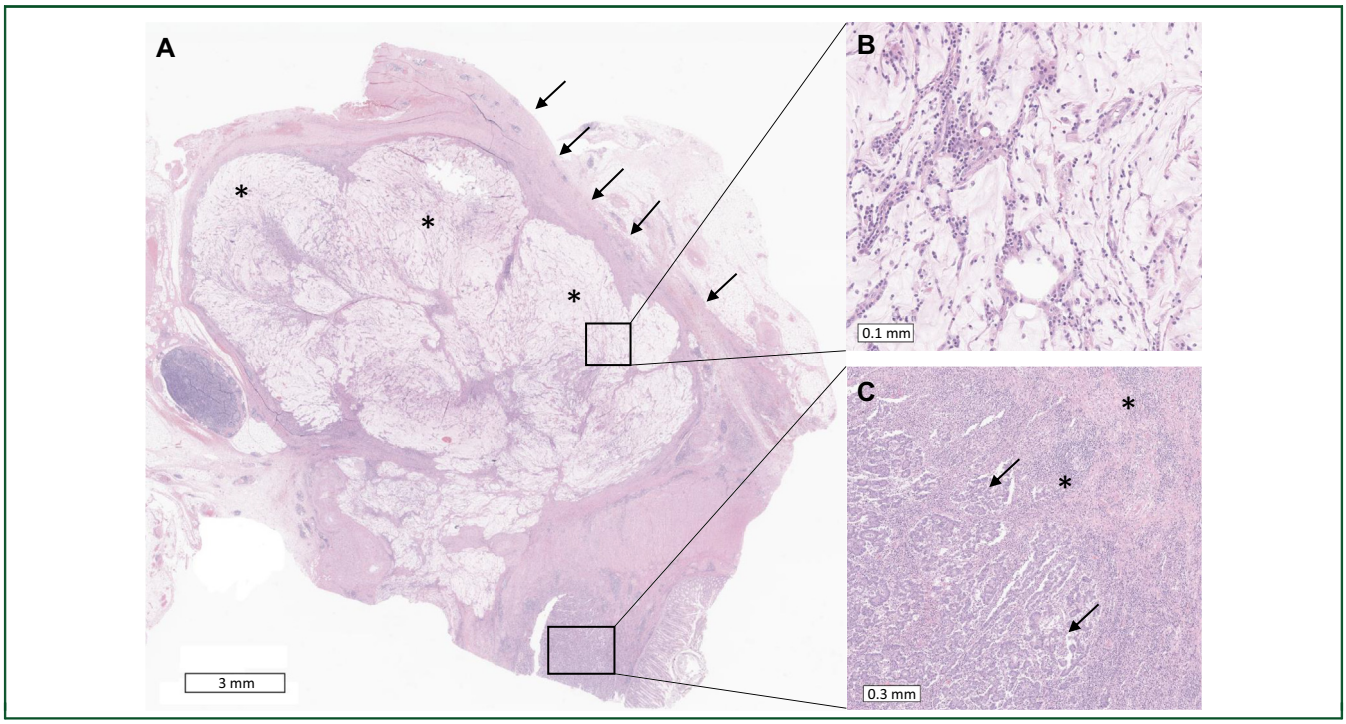

Figure 2. Microscopic features of response to immunotherapy. Images were taken during the histological assessment of the right hemicolectomy specimen after immunotherapy. Residual cancer remains with evident tumour regression (tumour regression score of 2) and final staging of ypT1 ypN1a ypR0. (A) Haematoxylin and eosin overview showing tumour regression with fibrosis extending beyond the bowel wall and into the subserosal fat (black arrows), large pools of mucin without viable tumour cells (black stars), an intense lymphocytic reaction, and a small region of residual moderately differentiated tumour (C). (B) Acellular mucin pools with inflammatory cells but no viable tumour cells. (C) A small area of residual moderately differentiated adenocarcinoma (black arrows) that is confined to the submucosa (ypT1) and surrounded by aggregates of lymphocytes (black asterisks).

DISCUSSION

Immune checkpoint inhibitors are used routinely for dMMR metastatic CC and are emerging as a transformative treatment in the neoadjuvant setting for localised disease.[3,5,6] As new indications for immunotherapy in CC are confirmed, it is critical to recognise all treatment-related complications to support decision making and safe patient stratification. In this series, we have reported nine cases of bowel obstruction associated with immunotherapy response, an important safety signal not previously described. Identifying risk factors for obstruction must become a priority for the clinical community.

Bowel obstruction is a persistent risk for patients with metastatic CC. During periods of disease progression, patients may require acute intervention with surgical resection and/or defunctioning with a stoma or a colonic stent.[11] For rectal cancer, slowly evolving symptoms may be treated with radiotherapy.[12] With the development of neoadjuvant therapies, the risk of bowel obstruction also applies to localised CC.

In this case series, we have identified several themes: first, the primary tumour was located at the hepatic flexure in five out of nine cases, which is disproportionate to the wider dMMR CC population[13]; second, radiological stricturing, endoscopic obstruction, and annular tumour shape were reported in most cases; and third, obstruction appeared to occur more quickly in those with localised, compared with metastatic, disease (Figure 3). In FOxTROT, obstruction was most common in tumours of the hepatic and splenic flexures and transverse colon.[4,9] As dMMR CCs predominantly arise in the right colon, hepatic flexure tumours may represent a specific group at high risk of obstruction associated with immunotherapy response.[13] Endoscopic obstruction and radiological or endoscopic stricturing were identified as independent risk factors for bowel obstruction in FOxTROT. As these features were also common in this series, they may represent risk factors applicable to either NAC or immunotherapy.

In contrast to the FOxTROT data, for each patient in this series, bowel obstruction was associated with a response to treatment, including four with a pCR.[9] dMMR and proficient MMR (pMMR) CCs are increasingly recognised as distinct entities, which may include patterns of response and associated complications.[14] While immunotherapy response in CC has not been well characterised, a recent report introduced the concept of an 'inside-out' pattern, where tumour regression transitions from serosa to mucosa with residual tumour most likely to remain on the luminal surface.[15] There is also evidence for differing radiological appearances between dMMR and pMMR tumours.[16] These distinctions may underpin the emergence of new treatment-related complications. Characterising tumour appearance and treatment response, according to MMR status, is therefore an important avenue of research.

Lynch syndrome accounts for ~20% of dMMR CCs.[14] In this case series, six patients had initial molecular testing which raised the possibility of Lynch syndrome and required

Table 1. Summary of cases

Case	Age (years) and sex	Tumour site	Baseline TNM[a]	Annular tumour shape	Rad stricture[b]	Able to pass endoscope[c]	Molecular biomarkers	Lynch syndrome work-up	Histology	Rad response	Time to obstruction (days)	Key outcomes	Pathological TNM and TRS[a]
1	66 F	Hepatic flexure	T4b N1 M1 (liver)	Yes	No	No	MLH1, PMS2 loss *BRAF* wild type *KRAS A146T* *NRAS* wild type	Awaiting somatic MLH1 promoter hypermethylation testing	Adenocarcinoma	PR	183	Defunctioning stoma, immunotherapy ongoing.	N/A
2	77 F	Hepatic flexure	T4a Nx M1 (peritoneum and lymph nodes)	Yes	Yes	No	MSI-H *BRAF V600E* *KRAS* wild type *NRAS* wild type	N/A	Adenocarcinoma	PR	604	Emergency surgery[d]	ypT0 ypN0 R0 TRS0
3	48 F	Descending colon	T4b N2 Mx	Yes	No	No	PMS2 loss *BRAF* unknown *KRAS* unknown *NRAS* unknown	Awaiting germline testing	Adenocarcinoma	PR	48	First episode: managed conservatively. Second episode: defunctioning stoma, planned surgery.	ypT3 ypN0 R0 TRS1
4	45 M	Sigmoid	T3 Nx M1 (liver)	Yes	No	Yes	PMS2 loss *BRAF* wild type *KRAS G12A* *NRAS* wild type	Awaiting germline testing	Mucinous adenocarcinoma	SD	47	Defunctioning stoma, planned surgery.	ypT0 ypN0 R0 TRS0
5	49 M	Sigmoid	T4b N2 M0	Yes	Yes	No	MSH2, MSH6 loss *BRAF* wild type *KRAS* wild type *NRAS* wild type	Unknown	Adenocarcinoma	CR	53	Defunctioning stoma, planned surgery.	ypT0 ypNx R0 TRS0
6 (detailed case)	76 F	Hepatic flexure	T4b N1 M0	Yes	Yes	Yes	MLH1, PMS2 loss *BRAF V600E* *KRAS* wild type *NRAS* wild type	N/A	Adenocarcinoma	PR	81	Emergency surgery[d], re-operation (within 30 days), death (within 30 days).	ypT1 ypN1 R0 TRS2
7	64 F	Hepatic flexure	T3 N1 M1 (liver, peritoneum)	No	No	No	MSI-H *BRAF* wild type *KRAS* wild type *NRAS* wild type	Unknown	Adenocarcinoma	PR	79	Expedited surgery[d]	ypT0 ypN0 R0 TRS0
8	71 F	Hepatic flexure	T4a N1 M0	Yes	Yes	No	MLH1, PMS2 loss *BRAF V600E* *KRAS* wild type *NRAS* wild type	N/A	Adenocarcinoma	PR	45	Defunctioning stoma, expedited surgery[d]	ypT1 ypN0 R0 TRS2
9	24 F	Sigmoid	T3 N2 M1 (lymph nodes)	Yes	Yes	Yes	MLH1, PMS2 loss *BRAF* wild type *KRAS* wild type *NRAS Q61R*	No abnormality on germline testing	Adenocarcinoma	CR	652	Managed conservatively without complication.	N/A

The interval from starting immunotherapy to developing bowel obstruction, in days.

CR, complete response; F, female; M, male; M0/M1/Mx, metastasis stage; MSI-H, microsatellite instability-high; N0/N1/N2/Nx, lymph node stage; N/A, not applicable; PR, partial response; R, residual tumour classification; Rad, radiological; SD, stable disease; T0/T1/T3/T4, primary tumour stage; TNM, tumour-node-metastasis; TRS, tumour regression score; yp, pathological stage following neoadjuvant treatment.

[a]According to AJCC TNM version 8.[10] Sites of metastatic disease are stated in brackets.

[b]Defined as clear luminal narrowing without upstream obstruction on baseline CT.

[c]Defined as a nontraversable tumour on endoscopy.

[d]Expedited surgery is defined as taking place sooner than initially planned but not within 48 h of obstruction. Emergency surgery defined as taking place within 48 h of obstruction.

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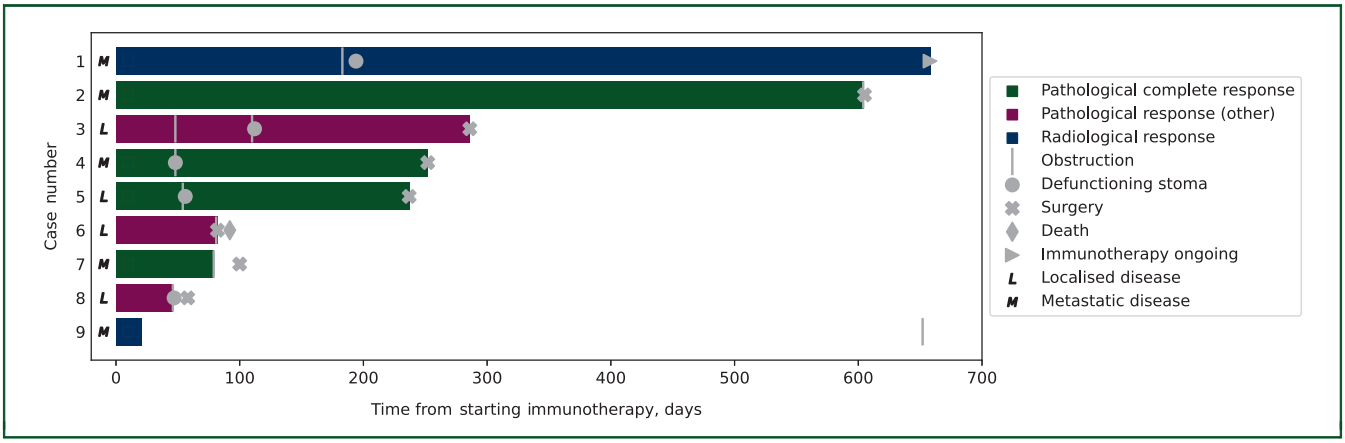

Figure 3. Timing of obstruction and interventions. Swimmer plot showing the timeline for developing obstruction and interventions, according to treatment response categories. Bar length represents time receiving immunotherapy. In case 3, bowel obstruction was initially managed with conservative measures before reobstructing and requiring a defunctioning stoma. In case 9, immunotherapy was stopped after two cycles due to toxicity but bowel obstruction did not occur until much later.

further germline testing. At the time of writing, only one patient had undergone germline testing, which showed no evidence of germline variants in the mismatch repair genes. For the other five, the underlying aetiology remains unclear. There is some evidence for better treatment response and prognosis in Lynch syndrome-associated, compared with sporadic, dMMR CC, although this is not conclusive.[17] Given the potentially disproportionate representation of Lynch syndrome-associated tumours in this case series, it is possible that stricturing responses are more likely in this patient group.

It is challenging to illustrate the incidence of a rare complication in a relatively novel treatment area. Nevertheless, as an approximation, 8 of 529 (1.51%) patients given immunotherapy for colorectal cancer in these centres developed bowel obstruction associated with immunotherapy response. These numbers should be interpreted with significant caution; only centres where a case was identified were included, which may overestimate incidence; yet, many patients with metastatic disease will no longer have a primary tumour *in situ*, resulting in an underestimate. However, these data suggest that obstruction may be more common, and occur earlier, in patients with localised, compared with metastatic, disease and may explain the lack of cases seen in large metastatic trials (Figure 3).[18] In a phase II trial of neoadjuvant toripalimab for dMMR localised colorectal cancer, one patient developed bowel obstruction but this was considered unrelated to study treatment.[19]

While ongoing trials of neoadjuvant immunotherapy may provide additional insight into obstruction risk, this is unlikely to be definitive. Therefore, the pooling of clinical experience and existing cases is important to support the identification of patients at risk. For example, a retrospective review of the detailed case in this series identified luminal narrowing on CT, which may represent a risk factor for obstruction (Figure 1). Multidisciplinary input is likely to be essential for risk prediction on an individual level. Translational molecular research may also uncover patterns of immunological response specifically associated with obstruction risk. Furthermore, we must consider changes to established practice, which may include more frequent imaging, bowel motility assessments, or greater use of upfront surgical defunctioning and colonic stenting.

We propose that clinicians recognise the potential risk factors described in this case series, including hepatic flexure location, radiological stricturing, endoscopic obstruction, and annular tumour shape, and actively disseminate this information within local MDTs. While these data do not provide robust criteria for risk assessment on an individual level, routine radiological evaluation will include several of the aforementioned risk factors and may also demonstrate subtle signs of evolving obstruction, such as upstream colonic wall thickening. It is critical for patients and acute services to be aware of this phenomenon, necessitating clear safety-netting advice, informative documentation (e.g. alert cards) to indicate when a primary tumour is *in situ* and the provision of effective educational resources. Furthermore, until we better understand this treatment-related complication, it may be reasonable to adopt a lower threshold for upfront defunctioning or more frequent imaging during treatment.

There are several limitations to this case series: the lack of a systematic approach to case identification may have resulted in an under-representation of the true affected population; bowel obstruction is poorly defined and may have impacted case identification[20]; original local data was used without central review of imaging or pathology; and limited outcome data was available to illustrate the impact of bowel obstruction. Nevertheless, the value of highlighting an important safety signal in this rapidly evolving treatment area should not be understated.

Bowel obstruction in CC secondary to a stricturing immunotherapy response, rather than progressive disease, is a novel phenomenon which has not been previously described. This case series provides a clear signal for a potential safety issue, which requires further evaluation to identify specific high-risk factors. Immunotherapy continues to transform the treatment of dMMR CC, but it is critical that progress is made while ensuring patient safety remains paramount.

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