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Overview of studies of the vitamin D/vitamin D receptor system in the development of non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. NAFLD is known to be associated with obesity, type 2 diabetes, metabolic syndrome and increased cardiovascular events: for these reasons, it is becoming a global public health problem and represents an important challenge in terms of prevention and treatment. The mechanisms behind the pathogenesis of NAFLD are multiple and have not yet been completely unraveled; consequently, at moment there are not effective treatments. In the past few years a large body of evidence has been assembled that attributes an important role in hepatic aberrant fat accumulation, inflammation and fibrosis, to the vitamin D/vitamin D receptor (VD/VDR) axis, showing a strong association between hypovitaminosis D and the diagnosis of NAFLD. However, the data currently available, including clinical trials with VD supplementation, still provides a contrasting picture. The purpose of this editorial is to provide an overview of recent advances in the pathogenesis of NAFLD in relation to VD/VDR. Based on recent data from literature, we focused in particular on the hypothesis that VDR itself, independently from its traditional ligand VD, may have a crucial function in promoting hepatic fat accumulation. This might also offer new possibilities for future innovative therapeutic approaches in the management of NAFLD.

Key words: Vitamin D; Vitamin D receptor; Non-alcoholic fatty liver disease; Type 2 diabetes

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Core tip: In the last years, many evidences attribute to the vitamin D/vitamin D Receptor axis an important role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). The purpose of this editorial is to provide an overview of recent advances in the pathogenesis of NAFLD in relation to vitamin D/vitamin D receptor (VD/VDR). We focused in particular on the hypothesis that VDR itself, independently from its traditional ligand VD, may play a crucial function in promoting hepatic fat accumulation, also offering new possibilities for innovative therapeutic approaches in the management of NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is currently considered the most common chronic liver disease worldwide^[1]. Recent epidemiologic studies report that the prevalence of NAFLD is increasing, starting from the currently estimated 25% in the general population^[2,3], and rising dramatically in obese individuals^[4], in subjects with type 2 diabetes (T2D)^[5] and those with metabolic syndrome^[6]. NAFLD is becoming a global public health problem^[7]. In many countries the number of patients affected by the disease is rapidly growing, so that in the last years the disease has reached epidemic proportions. Moreover, several studies have shown increased cardiovascular events in NAFLD patients and demonstrated that NAFLD is an independent risk factor for cardiovascular mortality^[8-10].

VITAMIN D AND NAFLD

In spite of the alarming prevalence and the clinical implications of NAFLD, the mechanisms underlying its development and progression are still not fully understood, and currently there are no effective treatments. Over the years many different pathophysiological theories have been put forward, leading to the most widely accepted hypothesis, "multiple parallel hits"^[11]. According to this model the steps conducive to hepatic fat accumulation, inflammation and fibrosis are orchestrated by a delicate interplay of factors^[11], and in this context the role of the vitamin D/vitamin D receptor (VD/VDR) axis has become an active area of research. Indeed, apart from its central role in bone and mineral homeostasis, VD is a molecule that exerts various effects on a number of biological systems; active VD in particular has been shown to regulate the immune system and to modulate insulin sensitivity in experimental models of metabolic diseases^[12-14].

Numerous studies have demonstrated that low VD circulating levels are associated with obesity^[15], metabolic syndrome^[16-19], and T2D^[20-22]. Investigations conducted in several adult populations also showed a strong association between hypovitaminosis D and the diagnosis of NAFLD^[23-30]. This association was also confirmed in children, in which low VD levels were found to correlate with the histological severity of NAFLD independently from metabolic characteristics^[31,32].

Data from animal studies further support the notion that the impairment of VD balance plays a role in the development of NAFLD. Roth and colleagues showed that in obese rats the lack of VD intake allowed the onset and progression of NAFLD, which was evaluated through liver histology demonstrating a higher NAFLD activity score and increased lobular inflammation^[33]. Likewise, under experimental conditions, VD has been shown to have an anti-inflammatory effect, accompanied by a significant inhibition of the hepatic expression of pro-fibrotic mediators, such as platelet-derived growth factor and transforming growth factor. The anti-inflammatory effect was also demonstrated by the suppression of the production of collagen, α -smooth muscle actin and tissue inhibitors of metalloproteinase-1 β ^[34-37]. In addition, in a study conducted on mice with nonalcoholic steatohepatitis (NASH), phototherapy reduced hepatocyte inflammation and fibrosis and improved insulin resistance by increasing the serum active form of VD^[38].

On the basis of these evidences and of both experimental and epidemiological data, VD has attracted the interest for a potential therapeutic option during NAFLD. However, up until now results from randomized clinical trials have failed to demonstrate the efficacy of VD supplementation in improving either fatty liver content, or the histological parameters of inflammation and fibrosis, or transaminases in the course of NAFLD and NASH^[39-45].

The clinical significance of VD in NAFLD is thus still controversial. A critical examination of the results from trials conducted so far may provide reasonable grounds for conducting further appropriately designed investigations (for example, personalized supplementation regimes in relation to VD levels at baseline and stage of liver damage, higher VD supplementation doses, longer periods of supplementation) before reaching any final conclusions on this topic. However, at present it is not possible to recognize which real benefits can be obtained from restoring optimal VD values in the case of chronic hepatic damage as a result of NAFLD.

ROLE OF VDR

In addition to the question of vitamin D, the role of VDR *per se* has been investigated in metabolic diseases, focusing in particular on its effect/expression in insulin sensitive tissues and organs, such as adipose tissue and the liver. In 2012, Barchetta *et al*^[46] demonstrated for the first time in humans the expression of VDR in different hepatic cell types and reduced VDR expression in the hepatic cells of patients with NASH. Since that time many studies have shown that in the liver VDR regulates necro-inflammation and fibrosis^[47-50]. Moreover, Arai *et al*^[51] recently demonstrated that, in patients with biopsy-proven NAFLD, polymorphisms of the VDR gene are associated with the severity of liver fibrosis.

Interestingly the data showed that not only VD, but also secondary hydrophobic bile acids, such as lithocholic acid, activate VDR in human hepatocytes^[52,53]. Bozic *et al*^[50] demonstrated that in animal models, the development of liver steatosis was blunted in the presence of VDR deletion. Notably, data obtained in mice exposed to a high fat diet showed an early induction of hepatic VDR expression in the presence of a fatty liver, followed by a trend towards VDR reduction in the long term, whereupon more severe inflammation and fibrosis occurred^[50]. In that same research, an expression analysis of genes related to lipid metabolism in mouse livers indicated that VDR might exert a pro-steatotic activity in the hepatocytes as results of both the activation lipogenic pathways and the inhibition of fat oxidation. Moreover, García-Monzón *et al*^[54] very recently demonstrated that hepatic angiopoietin-like protein 8 (ANGPTL8) expression is increased upon VDR activation. It is known that ANGPTL8 is a key regulator of triglycerides metabolism and that higher circulating ANGPTL8 levels are associated with the presence of NAFLD^[55-57]. These data suggest that VDR induction is more prominent in simple steatosis than in advanced liver damage, which is likely to indicate that VDR is induced at the early stages of the disease and does not require liver injury or fibrosis to have become established.

The overall data appear to support the hypothesis that, in the course of metabolic diseases, VDR itself, independently from its traditional ligand VD, may have a crucial function in promoting hepatic fat accumulation. Further studies should be oriented in this direction with a view to fully understanding the processes behind hepatic VDR activation and evaluating its role as a new target for innovative therapeutic approaches to the early management of NAFLD.

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Immune checkpoint inhibitor-induced diarrhea/colitis: Endoscopic and pathologic findings

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Abstract

The indications of immune checkpoint inhibitors (ICPIs) for cancer treatment have rapidly expanded, and their use is increasing in clinical settings worldwide. Despite the considerable clinical benefits of ICPIs, frequent immune-related adverse events (irAEs) have become nonnegligible concerns. Among irAEs, ICPI-induced colitis/diarrhea is frequent and recognized not only by oncologists but also by gastroenterologists or endoscopists. The endoscopic findings show similarity to those of inflammatory bowel disease to a certain extent, particularly ulcerative colitis, but do not seem to be identical. The pathological findings of ICPI-induced colitis may vary among drug classes. They show acute or chronic inflammation, but it may depend on the time of colitis suggested by colonoscopy, including biopsy or treatment intervention. In the case of chronic inflammation determined by biopsy, the endoscopy findings may overlap with those of inflammatory bowel disease. Here, we provide a comprehensive review of ICPI-induced colitis based on clinical, endoscopic and pathologic findings.

Key words: Immune checkpoint inhibitor; Colitis; Diarrhea; Endoscopic; Pathologic

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Core tip: Immune checkpoint inhibitor (ICPI)-induced colitis/diarrhea is frequent and recognized not only by oncologists but also by gastroenterologists or endoscopists. The endoscopic findings resemble those of inflammatory bowel disease to a certain extent, particularly ulcerative colitis, but are not identical. The pathological findings of ICPI-induced colitis may vary among drug classes. The findings show acute or chronic phases

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but may depend on the diagnostic timing or treatment intervention. Colonoscopy with biopsy is necessary to confirm ICPI-induced colitis, and early evaluation may avoid exacerbating or prolonging colitis due to treatment resistance.

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INTRODUCTION

In 1992, Ishida *et al*^[1] identified a protein on activated T lymphocytes called programmed cell death protein 1 (PD-1), a key player in tumor immunology. In 1996, Leach *et al*^[2] identified a protein called cytotoxic T-lymphocyte antigen-4 (CTLA-4), another major blocking pathway for the human immune system that was similar to PD-1. Since then, their discoveries have led to the development of immune checkpoint inhibitors (ICPIs) as anticancer drugs and have brought about a major revolution in cancer treatment strategy. Both CTLA-4 and PD-1 deliver negative signals to T-cell-mediated excessive immune activation, known as checkpoints, and ICPIs disrupt the signals mediated by CTLA-4 and PD-1 to prevent T cells from blocking pathways. By inhibiting immune checkpoints, activation of T cells is maintained, thereby helping cancer cells to induce cytotoxic T cell-mediated death. In 2018, Professor Honjo and Professor Allison won the Nobel prize in Physiology or Medicine for their work.

Presently, there are six ICPIs available and approved by the United States Food and Drug Administration for different cancers. Despite the significant clinical benefits of ICPIs, frequent immune-related adverse events (irAEs) in the skin, endocrine organs, gastrointestinal (GI) tract, liver, and lungs and in the musculoskeletal, renal, nervous, hematologic, cardiovascular, and ocular systems have become nonnegligible concerns. Most irAEs have a delayed onset and prolonged duration compared with those from chemotherapy^[3]. The incidence of irAEs appears to be similar across tumor types^[4]. Among irAEs, ICPI-induced colitis/diarrhea is frequent and recognized not only by oncologists but also by gastroenterologists or endoscopists. In this review, we provide a comprehensive review of ICPI-induced colitis based on clinical, endoscopic and pathologic findings.

ONSET TIMING OF ICPI-INDUCED DIARRHEA/COLITIS

ICPI-induced diarrhea occurs after an average of three infusions^[5], although it can occur immediately after the first infusion. Recent reports suggest that the onset timing of ICPI-induced diarrhea/colitis may differ by ICPI type. ICPI-induced diarrhea/colitis induced by ipilimumab (anti-CTLA-4) usually occurs 6 to 7 wk after the initiation of ipilimumab^[6]. The median time from last the ipilimumab treatment to diarrhea onset is 11-14 d (range 0-59 d)^[7,8]. On the other hand, Wang *et al*^[9] reported that 3.2% of patients (30/973) receiving anti-PD-1 developed ICPI-induced colitis at a median of 25.4 wk (range 0.6-120 wk). ICPI-induced diarrhea/colitis induced by anti-PD-1 seems to occur later than that induced by anti-CTLA-4. After the combined use of ipilimumab and nivolumab or pembrolizumab, 24.4% of patients (79/324) developed ICPI-induced diarrhea/colitis significantly earlier, at a median of 7.2 wk (range 0.7-51 wk)^[9]. Because the ranges of its onset timing are widely distributed, it is difficult to predict the development of ICPI-induced diarrhea/colitis. In addition, it may be influenced by other drugs, including NSAIDs, antibiotics, or previous anticancer drugs. Moreover, it seems difficult to predict the development of colitis before patients have symptoms^[10]. We should keep in mind that ICPI-related colitis can occur at any point, even after discontinuation of ICPIs.

LOCATION

Geukes Foppen *et al*^[11] reported total colonoscopy in 62 of 92 patients (67%) suspected of ICPI-induced colitis. Of these patients, 68% showed pancolitis (> 3 affected

segments), and the ascending colon had more severe colitis than the descending colon. In cases where a total colonoscopy was not performed, patients with colitis in the ascending colon can be underestimated by sigmoidoscopy alone. Abdominal computed tomography (CT) findings may be useful not only to evaluate perforation, obstruction, and toxic megacolon but also to evaluate inflamed lesions due to ICPIs. The common CT findings of 16 patients treated with ipilimumab showed that 75% of patients had diffuse colitis patterns, and 25% had segmental colitis^[12]. CT was not sufficient to diagnose colitis when using endoscopic evaluation as the gold standard because it has a high false-negative rate and low sensitivity^[13]. In contrast, Garcia-Neuer *et al*^[14] reported that CT was useful for predicting ICPI-induced colitis with a positive predictive value of 96% and a negative likelihood ratio of 0.2 in 34 diarrhea patients who underwent both CT and colonoscopy with biopsy. Early sigmoidoscopy without bowel preparation has merit to assess ICPI-induced colitis because it can be performed more easily and earlier than total colonoscopy. Therefore, the combined use of sigmoidoscopy and CT may be useful to evaluate ICPI-induced colitis at an earlier stage.

ENDOSCOPIC EVALUATION AND FINDINGS

There are several reports about the endoscopic findings of ICPI-induced colitis. Wang *et al*^[13] observed that endoscopic inflammatory findings were found in more than 80% of patients with ICPI-induced diarrhea/colitis. Common endoscopic inflammation findings are reported as exudates, loss of vascular pattern, granular or edematous mucosa, patch or diffuse erythema, aphtha and ulcerations (Figure 1)^[15,16]. Most of the inflammatory changes, including pathological changes, are dominantly more diffuse than patchy^[10], but patchy distribution was endoscopically observed in half of the patients with diarrhea^[17]. These endoscopic findings resemble those of inflammatory bowel disease (IBD) to a certain extent, particularly with ulcerative colitis (UC)^[16,18], but sometimes look different from a UC-like pattern (Table 1).

Wang *et al*^[13] reported in 53 patients with diarrhea, clinical symptoms did not always correlate with other endoscopic findings except for the presence of ulceration, which had a strong relationship with higher colitis. Similarly, another retrospective study showed that there was no significant correlation between diarrhea/colitis symptoms and endoscopic findings in 92 patients who developed diarrhea.

They also reported that pancolitis and the presence of ulceration are indicators for steroid-refractory colitis^[11]. Geukes Foppen *et al*^[11] reported that the Mayo score was associated with the presence of ulceration. Abu-Sbeih *et al*^[19] categorized endoscopic findings as low-risk and high-risk for steroid-responsiveness. High-risk findings included either ulcers deeper than 2 mm and/or larger than 1 cm in surface area or endoscopically extensive colitis from the proximal colon to the splenic flexure. These patients require frequent use of infliximab or vedolizumab and more frequent and longer hospital stays than non-high-risk patients^[19]. They also reported that timely early colonoscopy decreased the duration of steroid treatment^[19]. If the colonoscopy shows normal mucosal findings, we are not always able to exclude the presence of ICPI-induced colitis, as cases of isolated ileitis^[20] or enteritis without colitis^[21] can also occur. We can also rule out microscopic colitis or other infectious diseases such as *Clostridioides difficile* or cytomegalovirus^[7]. Therefore, early colonoscopy with mucosal biopsy from colorectal and ileum-end mucosa is necessary not only to evaluate the severity and distribution of colitis^[11] but also to ensure shorter and less intense treatment^[19].

PATHOLOGY

The histologic features of ICPI-associated colitis may vary among drug classes, *i.e.*, CTLA-4 inhibitors and PD-1/PDL1 inhibitors. Although they are nonspecific, some findings can be helpful clues to diagnose and speculate about the class of inhibitors. On the other hand, there is significant overlap between ICPI-associated colitis and other types of colitis, making the differential diagnosis difficult.

The histologic findings of CTLA-4-associated colitis are relatively consistent across most studies. The previously reported histologic features of CTLA-4 associated colitis are similar to those of autoimmune colitis^[22]. They include lamina propria expansion due to dense lymphoplasmacytic infiltrate, increased intraepithelial lymphocytosis, and apoptosis in the crypts. Neutrophilic cryptitis and crypt abscess are also found. At times, there is prominent eosinophilia in the lamina propria. Although dense lymphoplasmacytic lamina propria expansion is reminiscent of other mimics, the lack

Table 1 Summary of endoscopic and pathological findings of immune-related diarrhea and colitis

Endoscopic and pathological findings of immune-related diarrhea and colitis	
Endoscopic findings	
Endoscopic features	(1) Exudates; (2) loss of vascular pattern; (3) granular or edematous mucosa; (4) patch or diffuse erythema; (5) aphtha; (6) ulceration
Inflammatory distribution	(1) Diffuse; (2) patchy (dominantly more diffuse than patchy)
Risk factors for steroid-refractory colitis	(1) Extensively inflamed area (<i>e.g.</i> , pancolitis); (2) deeper ulceration
Pathological findings	
Anti-CTLA-4 associated colitis	Like autoimmune colitis: (1) lamina propria expansion due to dense lymphoplasmacytic infiltrate; (2) increased intraepithelial lymphocytosis; (3) apoptosis in the crypts; (4) neutrophilic cryptitis and crypt abscess; (5) occasional prominent eosinophilia in the lamina propria; (6) the lack of findings of basal plasmacytosis, crypt distortion, or granulomas
Anti-PD1/anti-PDL1-associated colitis	(1) Expansion of lamina propria by lymphoplasmacytic infiltrate; (2) the increase in intraepithelial neutrophils and neutrophilic crypt abscess; (3) crypt distortion; (4) increased crypt cell apoptosis

CTLA-4: Cytotoxic T-lymphocyte antigen-4; PD1: Programmed cell death protein 1; PDL1: Programmed cell death receptor ligand 1.

of findings of basal plasmacytosis, crypt distortion, or granulomas can help the differentiation.

The most common findings of anti-PD1/anti-PDL1-associated colitis are the expansion of the lamina propria by lymphoplasmacytic infiltrate and features of active colitis^[23-27]. The latter are characterized by an increase in intraepithelial neutrophils and neutrophilic crypt abscess (Figure 2A). Other findings include crypt distortion, increased crypt cell apoptosis, features of ischemic colitis, and collagenous colitis (Figure 2B). Although, in the study by Gonzalez *et al*^[26], there were no cases with increased intraepithelial lymphocytosis commonly observed in CTLA-4-associated colitis, Chen *et al*^[23] and Bavi *et al*^[27] described features of lymphocytic colitis in a minority of their cases with anti-PD1/anti-PDL1. In the latter studies, a PD-1 inhibitor and CTLA-4 inhibitor were prescribed for their patient population either in combination or sequentially. Therefore, it is unlikely that this finding is related to PD-1 inhibition alone.

As mentioned, the histologic features of ICPI-associated colitis are nonspecific and can mimic other type of colitis, including infectious colitis, IBD, graft versus host disease (GVHD), and other drug-induced colitis. Although infectious colitis typically shows features of active colitis, increased apoptosis and crypt atrophy/dropout are not typical features^[28]. ICPI-associated colitis lacks the features of chronicity that characterize IBD^[29]. The lamina propria expansion by lymphoplasmacytic infiltrate can discriminate from GVHD although increased crypt apoptosis is the *sine qua none* of the diagnosis of GVHD^[30]. Despite the histopathological differential diagnostic points, clinical correlation and medical history are indispensable for discrimination between ICPI-associated colitis and mimics (Table 1).

MORBIDITY ASSOCIATED WITH ICPI-INDUCED DIARRHEA/COLITIS AND TREATMENT

IrAEs involving the GI tract range from mild to severe events^[31] and are well reported for anti-CTLA4 but less well reported for anti-PD-1 and anti-PD-L1 and for combined anti-CTLA4 plus anti-PD-1. Most clinical trials distinguish diarrhea from colitis even though they overlap in most practical cases. Diarrhea is evaluated based on an increase in stool per day or ostomy output. Colitis is evaluated based on clinical symptoms (abdominal pain, mucus or blood in stool) or diagnostic observations based on radiographic and/or colonoscopy findings. The severity is usually classified based on the Common Terminology Criteria for Adverse Events^[32] (Table 2).

Moderate to severe ICPI-related colitis may lead to severe deterioration in organ function and quality of life and life-threatening events. Diarrhea and colitis occurred in 8% to 22% of patients treated with anti-CTLA4^[15]. A recent systemic review reported that 613 fatal ICPI toxic events were found from 2009 through January 2018 searched by Vigilyze, which included 135 anti-CTLA-4 deaths and 32 combination anti-CTLA-4 plus anti-PD-1 deaths from colitis (27%)^[33]. Colonic perforation was reported to occur in 1-5% of melanoma patients treated with ipilimumab (anti-CTLA-4)^[7,15,34], and 0.6% of patients treated with ipilimumab died due to ICPI-induced

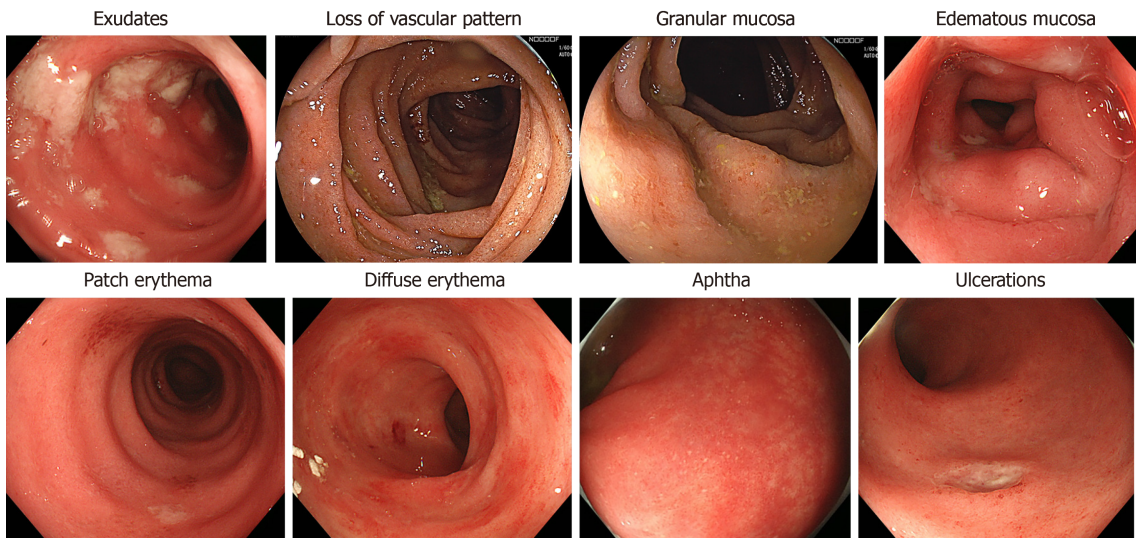


Figure 1 Endoscopic findings caused by an immune checkpoint inhibitor.

colitis^[35].

Anti-CTLA4-related colitis is reportedly associated with mouth ulcers, anal lesions and extraintestinal irAEs^[17]. A recent meta-analysis of 34 studies that included 8863 patients in clinical trials revealed that, for anti-CTLA4 alone (ipilimumab), all grades of colitis occurred in 9.1% (95% confidence interval (CI), 6.6%-12.5%) of participants, grade 3/4 colitis occurred in 6.8% (95% CI: 5.3%-8.6%) of participants, and grade 3/4 diarrhea occurred in 7.9% (95% CI: 5.5%-11.4%) of participants. Similarly, for anti-PD-1 alone (nivolumab or pembrolizumab), the rates were 1.4% (95% CI: 1.1%-1.8%), 0.9% (95% CI: 0.7%-1.3%), and 1.3% (95% CI: 1.0%-1.7%), respectively. For anti-PD-L1 alone (atezolizumab), the rates were 1.0% (95% CI: 0.4%-2.2%), 0.6% (95% CI: 0.2%-1.6%), and 0.3% (95% CI: 0.1%-1.1%), respectively^[36]. For anti-CTLA4 (Ipilimumab) plus anti-PD-1 (nivolumab), the rates were 13.6% (95% CI: 7.7%-22.9%), 9.4% (95% CI: 4.8%-117.4%), and 9.2% (95% CI: 6.8%-12.3%), respectively. ICPI-induced diarrhea/colitis induced by anti-CTLA-4 can develop more often and more severely than ICPI-induced diarrhea/colitis induced by anti-PD-1. Combined anti-CTLA4 plus anti-PD-1 treatment is also more strongly associated with diarrhea/colitis than single-drug treatment^[36]. Ipilimumab is commonly used at either 10 mg/kg or 3 mg/kg. There were similar rates of severe colitis at these doses, but severe diarrhea was more frequent at a dose of 10 mg/kg than at 3 mg/kg^[36]. Recently, Marthey *et al*^[17] showed that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with an increased risk of ICPI-induced colitis induced by CTLA-4 (2/38, 5% *vs* 11/35, 31%, $P = 0.003$). Therefore, the use of NSAIDs may affect the incidence of ICPI-induced diarrhea/colitis. Table 3 shows a summary of the incidence of immune-related diarrhea or colitis based on representative clinical trials.

In the case of grade 1 diarrhea/colitis, antidiarrheal drugs and/or oral hydration with electrolyte substitution can be initiated. In cases of persistent or grade 2 or higher diarrhea or rectal bleeding, it is necessary to confirm colitis or to rule out GI infection by testing for stool leukocytes, stool cultures, IBD, or tumor-related GI symptoms. In particular, *Clostridioides difficile* toxin and/or antigen test, cytomegalovirus DNA polymerase chain reaction, and tests for stool ova and parasites should be carried out in every patient with diarrhea treated with ICPIs. Sigmoidoscopy or colonoscopy combined with mucosal biopsy needs to be performed to evaluate the presence of colitis and to rule out GI metastasis because it is not uncommon in lung cancer or melanoma. If ICPI-induced colitis is diagnosed, an oral steroid is recommended. In the case of grade 3/4 diarrhea/colitis or persistent symptoms after oral steroids for several days, changing the treatment to intravenous steroids should be considered, and an infusion solution with electrolytes should be given. If patients respond to intravenous steroids within several days, they should be switched to oral steroids and tapered. However, if they fail to respond to steroid infusion, treatment with anti-TNF- α should be considered^[15,37]. Recently, a case series reported that vedolizumab was a safer and more theoretic alternative than anti-TNF in patients with steroid-dependent or partially refractory ICPI-induced enterocolitis^[38]. In the near future, vedolizumab may be effective and safe because it inhibits the migration of mucosal-associated T lymphocytes without inducing immune suppression and does not show an increased risk of serious infections in patients with UC or Crohn's disease^[39,40].

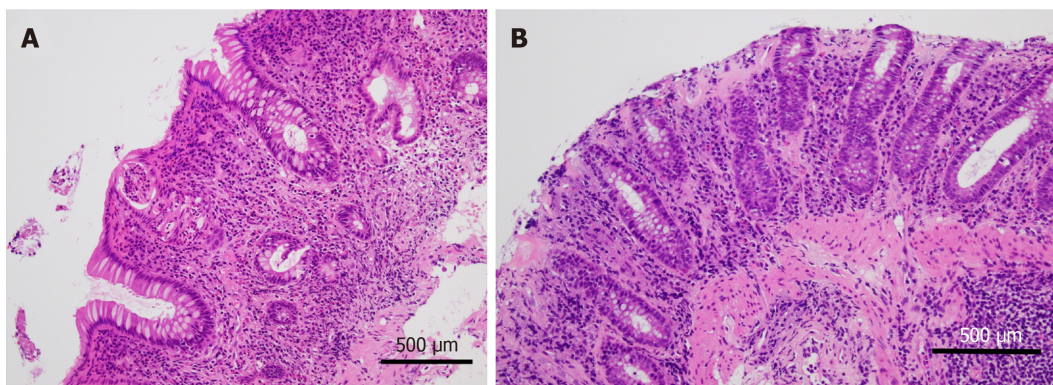


Figure 2 Programmed cell death protein 1 inhibitor-associated colitis. A: This colon biopsy reveals lamina propria expansion by lymphoplasmacytic infiltrate. Crypt distortion, crypt abscess, and cryptitis are prominent in the mucosa. In the stroma, a significantly increased eosinophilic infiltrate is observed; B: In another case of immune checkpoint inhibitors-related colitic mucosa, a subluminal collagen band thickening is prominent as observed in collagenous colitis. (Hematoxylin and eosin original magnification $\times 20$, a scale bar represents 500 μm).

CONCLUSION

The combination of endoscopic and pathological findings may help diagnose ICPI-induced colitis as well as exclude infectious colitis, including *Clostridioides difficile* or cytomegalovirus, ischemic colitis, other drug-induced colitis, or segmental diverticular colitis. However, there are no specific findings because the endoscopic and pathological findings can depend on the time of colitis proven by biopsy or treatment intervention. In cases of persistent or grade 2 or higher diarrhea or rectal bleeding, colonoscopy evaluation is necessary to confirm ICPI-induced colitis and to rule out other diseases. Early evaluation and intervention may avoid exacerbating or prolonging colitis.

Table 2 Definition of diarrhea and colitis based on Common Terminology Criteria for Adverse Events v5.0^[32]

CTCAE Term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v5.0 Change
Diarrhea	A disorder characterized by an increase in frequency and/or loose or watery bowel movements	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death	Clarification: Grade 2, 3, Definition
Colitis	A disorder characterized by inflammation of the colon	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death	Addition: Navigational note; Clarification: Grade 3

ADL: Activities of daily living; CTCAE: Common Terminology Criteria for Adverse Events.

Table 3 Summary of incidence of immune-related diarrhea and colitis

ICPI	Target	Author	Year	Plus other drugs	n	Cancer type	Any graded diarrhea/colitis, n (%)	Grade 3-5 diarrhea/colitis, n (%)
Nivolumab	PD-1	Topalian <i>et al</i> ^[41]	2012	None	296	Solid cancer	33 (11)/ND	3 (1)/ND
		Weber <i>et al</i> ^[42]	2013	None	34	Melanoma	13 (38.2)/0 (0)	Not observed ¹
				Ipilimumab-naïve	56		11 (19.6)/0 (0)	
		Weber <i>et al</i> ^[43]	2015	None	268	Melanoma ²	30 (11.2)/ND	1 (0.4)/ND
		Larkin <i>et al</i> ^[44]	2015	None	315	Melanoma	60 (19.2)/4 (1.3)	7 (2.2)/2 (0.6)
		Ferris <i>et al</i> ^[45]	2016	None	236	SCCHN	16 (6.8)/0 (0)	0 (0)/0 (0)
		Kang <i>et al</i> ^[46]	2017	None	330	GC/GEJC	23 (7)/2 (1)	2 (1)/1 (< 1)
		Hamid <i>et al</i> ^[47]	2013	None	135	Melanoma	27 (20)	1 (1)
		Garon <i>et al</i> ^[48]	2015	None	495	NSCLC	40 (8.1)/ND	3 (0.6)/ND
		Ribas <i>et al</i> ^[49]	2015	None	361	Melanoma ²	32 (8.9)/5 (1.4)	2 (0.6)/2 (0.6)
Pembrolizumab	PD-1	Herbst <i>et al</i> ^[50]	2016	None	690	NSCLC	46 (6.7)/6 (0.9)	2 (0.3)/4 (0.6)
		Ribas <i>et al</i> ^[51]	2016	None	655	Melanoma	115 (18)/11 (2)	6 (1)/7 (1.1)
		Mok <i>et al</i> ^[52]	2019	None	636	NSCLC	34 (5)/7 (1)	5 (< 1)/4 (< 1)
		Weber <i>et al</i> ^[53]	2008	None	88	Melanoma	ND	5 (5.6)/4 (4.5)
		Weber <i>et al</i> ^[54]	2009	None	57	Melanoma	20 (35)/ND	10 (18)/ND
				budesonide	58		19 (33)/ND	8 (14)/ND
		Wolchok <i>et al</i> ^[55]	2010	None	214	Melanoma	58 (27)/ND	11 (5.1)/ND
		Hodi <i>et al</i> ^[56]	2010	None	131	Melanoma	43 (32.8)/10 (7.6)	7 (5.3)/7 (5.3)
				gp100	380		146 (38.4)/20 (5.3) ³	17 (4.5)/12 (3.2) ³
		Robert <i>et al</i> ^[57]	2011	Dacarbazine	247	Melanoma	81 (32.8)/11 (4.5)	10 (4.0)/5 (2.0)
Ipilimumab	CTLA-4	Margolin <i>et al</i> ^[58]	2012	None	72	Melanoma	30 (42)/ND	6 (8.3)/ND
		Kwon <i>et al</i> ^[59]	2014	None	399	Prostate cancer	199 (51)/27 (7)	64 (16)/18 (5)
		Larkin <i>et al</i> ^[44]	2015	None	311	Melanoma	103 (33.1)/36 (11.6)	19 (6.1)/27 (8.7)
		Eggermont <i>et al</i> ^[35]	2016	None	471	Melanoma	194 (41.2)/73 (15.5)	46 (9.8)/39 (8.2)

Ipilimumab plus nivolumab	CTLA4 and PD1	Wolchok <i>et al</i> ^[60]	2013	None	53	Melanoma	18 (34.0)/5 (9)	3 (6)/2 (4)
		Larkin <i>et al</i> ^[44]	2015	None	315	Melanoma	138 (44.1)/37 (11.8)	29 (9.3)/24 (7.7)
		Schadendorf <i>et al</i> ^[61]	2017	None	407	Melanoma	30 (7.4)/40 (9.8)	25 (6.1)/32 (7.9)
		Wolchok <i>et al</i> ^[62]	2017	None	313	Melanoma	142 (45)/40 (13)	29 (9)/26 (8)
		Hellmann <i>et al</i> ^[63]	2017	None	77	NSCLC	16 (21)/4 (5.2)	1 (1.3)/3 (3.9)
		Motzer <i>et al</i> ^[64]	2018	None	547	Renal cell carcinoma	145 (27)/ND	21 (4)/ND
Durvalumab	PD-L1	Antonia <i>et al</i> ^[65]	2017	None	473	NSCLC	87 (18.3)/ND	3 (0.6)/ND
		Motzer <i>et al</i> ^[66]	2018	None	475	NSCLC	88 (18.5)/ND	3 (0.6)/ND
		Loibl <i>et al</i> ^[67]	2019	None	92	Breast cancer	26 (28.3)/ND	3 (3.3)/ND
Atezolizumab	PD-L1	Herbst <i>et al</i> ^[68]	2014	None	277	Solid tumors or hematological malignancies	29 (10.5)/ND	0 (0)/ND
		Rosenberg <i>et al</i> ^[69]	2016	None	311	Urothelial carcinoma	24 (8)/3 (1)	1 (0.3)/2 (1)
		Fehrenbacher <i>et al</i> ^[70]	2016	None	142	NSCLC	ND	ND/2 (1)
Avelumab	PD-L1	Socinski <i>et al</i> ^[71]	2018	ABCP	393	NSCLC	70 (17.8)	11 (2.8)
		Chung <i>et al</i> ^[72]	2019	None	150	GC/GEJC	ND/2 (1.3)	ND/1 (0.7) ⁴
		Barlesi <i>et al</i> ^[73]	2019	None	396	NSCLC	24 (6)/ND	0 (0)/ND

¹Dose-limiting colitis was not observed in this trial;

²Progressed after ipilimumab;

³Immune-related event;

⁴No atezolizumab-related grade 4 but adverse events were reported, but only one patient showed Grade 5 cardiac failure. SCCHN: Squamous cell carcinoma of the head and neck; NSCLC: Non-small-cell lung cancer; ABCP: Atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; GC/GEJC: Gastric/gastroesophageal cancer; ND: Not described.

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Successful management of adhesion related small bowel ischemia without intestinal resection: A case report and review of literature

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Abstract

BACKGROUND

Intraabdominal adhesions develop spontaneously or after an inflammatory process or surgical procedure in the abdomen. They are the most common cause of small bowel obstruction (SBO). SBO occasionally leads to intestinal ischemia (InIs) which can be a life-threatening condition that requires management as soon as possible. We herein report a case of SBO with InIs presented in our institution and treated without intestinal resection.

CASE SUMMARY

A 34-year-old man presented at the emergency department after a 12-h-onset diffuse abdominal pain, bloating and nausea. He had a history of traumatic right hepatectomy 11 years ago as well as adhesiolysis and resection of a long part of small bowel 2 years ago. An abdominal computed tomography (CT) showed dilated loops that led to the diagnosis of SBO. Due to deteriorating lactic acidosis, the patient was operated. Torsion of the small bowel around an adhesion led to 2.30 m of ischemic ileum. After the application of N/S 40 °C for 20 min, the intestine showed signs of improvement and it was decided to avoid resection and instead temporary close the abdomen with vacuum-pack technique. At the second-look laparotomy 48 h later, the intestine appeared normal. The patient was discharged on the 8th post-op day in excellent condition.

CONCLUSION

In case of SBO caused by adhesions, extreme caution is needed if InIs is present, as the clinical signs are mild and you should rely for diagnosis in CT findings and lactate levels. Conservative surgical approach could reverse the effects of InIs, if performed quickly, so that intestinal resection is avoided and should be used even when minimum signs of viability are present.

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Core tip: Intraabdominal adhesions are the most common cause of small bowel obstruction which occasionally leads to intestinal ischemia (InIs). InIs can be a life-threatening condition that requires high index of suspicion because the clinical signs are mild and you should rely for diagnosis in computed tomography findings and lactate levels. Lactate, if present is a good indicator of the progress or regression of the disease. Diagnosis of InIs leads to immediate operation. Conservative surgical approach avoiding resection of ischemic bowel, could lead to reversal of InIs and should be used even when minimum signs of viability are present.

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INTRODUCTION

Small bowel obstruction (SBO) is a major cause of hospital admissions (15% in United States) and is associated with significantly high rates of patients' morbidity and even mortality^[1,2]. Post-operative abdominal adhesions play a pivotal role in SBO detection while 10% of affected patients are attributed to peritonitis and only 5% of SBO cases remain of unknown origin^[2]. Generally, abdominal adhesions are created either spontaneously, by an inflammatory process or after a surgical procedure in the abdomen and pelvis^[3,4]. Moreover, adhesive SBO (aSBO) occurs in 3% of all laparotomies and 1% during the first postoperative year. Recurrence rate after aSBO is 19%-53%^[5]. Patients with SBO usually present with colicky abdominal pain, distention, nausea, vomiting, constipation and obstipation^[1,6,7]. Laboratory findings include in the majority of the cases mild leukocytosis and possibly electrolyte disturbances^[1,8]. Abdominal computed tomography (CT) remains the gold-standard diagnostic procedure for aSBO^[9,10].

Initial management of aSBO is conservative including nasogastric tube for intestinal decompression with parallel administration of intravenous fluids and analgesics and electrolyte correction on occasion^[5,11,12]. In accordance with recent investigations 70% of aSBO cases resolve without operative intervention^[5]. However, one of the possible outcomes of SBO is intestinal strangulation which eventually leads to ischemia^[5,13]. Intestinal ischemia (InIs) is a potentially lethal complication as it presents without specific symptoms and it requires high index of suspicion for establishment of the diagnosis^[14]. Elevated lactate levels and acidosis are indicative of an upcoming ischemia and should also be taken into account during the patient's management^[13,15-17]. Additional CT findings implying InIs are mesenteric edema, free peritoneal fluid and a transitional point, while parietal pneumatosis is a sign of irreversible bowel wall necrosis^[2,13]. Thus, in case of evidence of small bowel strangulation, subsequent laparotomy is mandatory. We here present a case of aSBO with signs of intestinal strangulation and ischemia due to torsion around a dense adhesion at mid-ileum in a young male patient successfully treated without intestinal resection. Relevant literature is briefly reviewed. Clinical features and imaging findings are discussed, while the role of current diagnostic and therapeutic management of this nosologic entity is emphasized.

CASE PRESENTATION

Chief complaints

A 34-year-old man was admitted due to a 12-h-onset increasing diffuse abdominal pain.

History of present illness

The patient also appeared to our emergency department with general malaise and reported bloating and nausea.

History of past illness

He also reported similar clinical symptoms in the past. He was a 20 pack-year smoker. Moreover, the patient had a history of partial right hepatectomy due to liver trauma in 2007 and 1.5 m of small bowel resection due to aSBO in 2016.

Physical examination

On meticulous physical examination, he presented mild tachycardia, tachypnea as well as distended abdomen with guarding and diminished bowel sounds.

Laboratory testing

Apart from elevated lactate levels (Lac = 2.2 mmol/L), common laboratory blood and urine examinations were within normal limits.

Imaging examination

Subsequent ultrasonography was not indicative of pathologic findings. Erect abdominal X-rays depicted limited small bowel fluid levels, indicating intestinal obstruction. Subsequent CT scan identified the presence of bowel dilation and wall edema with parallel winding of the major vessels of gastrointestinal (GI) tract at the transitional zone, assessing InIs without signs of vascular obstruction or thrombosis.

FINAL DIAGNOSIS

Therefore, the final diagnosis was aSBO (**Figure 1**). Additional CT angiography as well as low molecular heparin administration was not implemented as signs of thrombosis were absent and intestinal strangulation was verified.

TREATMENT

Six hours after admission and fluid resuscitation, the patient was submitted to exploratory laparotomy, due to deteriorating lactic acidosis (Lac = 8 mmol/L) raising strong suspicion of evolving InIs. Surgical operation was performed via a midline incision while the presence of normal bowel from the ligament of Treitz to a length of 1.30 m of jejunum was verified. On the contrary, the rest of the small bowel including ileocolic junction was ischemic and congested due to twirling around an adhesion created at the location of an intestinal anastomosis. A diminutive sign of peristalsis was apparent at the most distal ischemic bowel loops (**Figure 2**). Resection was reserved as last treatment option due to the short length of the remaining healthy bowel. Rewarming with N/S (40 °C) was applied for 20 min. The intestine, slightly but clearly, improved in color and peristalsis in about half of its ischemic length. Lactic acidosis was also reduced (Lac = 6 mmol/L) during this operation allowing us to postpone resection. The abdomen was temporarily closed with vacuum-pack technique, searching for a second look laparotomy in forty-eight hours. During this period, lactate was normalized (Lac = 0.8 mmol/L).

OUTCOME AND FOLLOW-UP

Subsequent second look operation elucidated that the bowel was perfused in all its length and peristalsis was present (**Figure 3**). The abdomen was closed permanently. Hospital stay was uneventful and he was discharged from the surgical department 8 d postoperatively. Twenty-four hours later, the patient complained for bloody diarrheas, which was expected due to the mucosal apoptosis. Finally, the last 6 mo, the patient remains under intense monitoring without signs of relapse.

DISCUSSION

Intra-abdominal adhesions are fibrous bands between organs or tissues that are usually formed after an abdominal or pelvic operation, an inflammatory process, or an abdominal trauma^[18]. In fact, it has been elucidated, that they may develop after abdominal surgeries in about 67% of the cases and in 97% of patients undergoing



Figure 1 Abdominal computed tomography indicative of the torsion of the ileum around the adhesion at the center of the picture.

gynecological procedures^[19,4]. However, the formation of adhesions varies among patients and depends on the severity and type of the initial surgery, potential post-operative complications as well as the presence of intra-peritoneal foreign bodies^[3]. In general, according to a recent survey, the overall incidence of aSBO is 4.6%^[20]. More specifically, aSBO complicates 19.3% among ileal-anal pouch anastomoses, while affects 11.1% of patients submitted to gynecological surgical operations. Nonetheless, the technique of the procedure affects significantly the development of SBO^[20,21]. Consequently, aSBO prevalence was 9.5% in open colectomy versus 4.3% in laparoscopic one and 7.1% in open cholecystectomy vs 0.2% in relevant laparoscopic operation. Contrariwise, there was no difference in the development of aSBO after open or laparoscopic appendectomies (1.4% vs 1.3%)^[20]. Finally, laparotomy due to abdominal trauma, was complicated by aSBO in 2.5% of the cases, whereas the incidence of early post-op SBO (within 30 days after surgery) was 24.2%^[20,22]. Our case involves a 34-year-old man with a history of partial hepatectomy due to liver trauma 11 years ago, which was followed by a SBO and 1.5 m intestinal resection 2 years ago and now presented with aSBO and subsequent InIs.

Although the clinical presentation of aSBO depends on the location and duration of the obstruction, it usually involves colicky abdominal pain, abdominal distention, nausea and vomiting related to the site of intestinal strangulation^[1,23]. Most patients report a history of prior abdominal surgery^[24]. In case of ischemia though, intermittent abdominal pain becomes more severe and located while fever should always raise suspicion of InIs and sepsis^[1,6]. Meticulous physical examination usually reveals a restless patient with signs of dehydration, poor skin turgor and abdominal distention^[1,23]. During inspection visible peristalsis is sometimes observed. In subsequent auscultation, bowel sounds are initially increased and high-pitched, but diminish with advanced SBO^[1]. Signs that SBO has resulted in InIs or perforation (peritonitis) include affected vital signs such as tachycardia, tachypnea and pyrexia as well as rebound tenderness, guarding and abdominal rigidity. Our patient presented with a 12-h-onset increasing diffuse abdominal pain, bloating and nausea and on examination mild tachycardia, tachypnea, distended abdomen with guarding and diminished bowel sounds were documented.

Laboratory findings suggestive of SBO more often include mild leukocytosis and possibly electrolyte disturbances due to dehydration and third space volume loss^[8]. Elevated lactate levels and acidosis should be also considered through the patient's management as they strongly indicate intestinal strangulation^[13]. In fact, lactate although not universally present at ischemia, when apparent is a good indicator of the progress or regression of the disease^[25]. Imaging techniques that are proposed for aSBO vary according to the initial clinical signs, but mostly abdominal CT can contribute to the diagnosis of this condition as it may often accurately identify strangulation in aSBO^[26,27]. Imaging findings may also include reduced bowel wall enhancement and mesenteric fluid detection indicative of strangulation as well as small bowel wall thickening associated with aSBO^[28,29]. Ideally, only patients who develop strangulation should undergo surgery, and these operations should be performed promptly to avoid transmural necrosis and perforation. Early recognition of SBO strangulation is thus pivotal to help improve the patient outcome by preserving the involved bowel loops and avoiding needless surgical resection^[30].



Figure 2 Dilated ischemic small bowel loops at the exploratory laparotomy.

Nevertheless, regardless of the cause, obstructed bowel eventually becomes edematous, leading to bowel ischemia, inflammation and necrosis. Strangulation is usually verified if at least one of the following criteria is fulfilled including bluish discoloration, loss of arterial pulsation, subserosal and mesenteric hemorrhage, lack of peristalsis and frank infarction. In our patient, abdominal CT scan revealed bowel dilation and wall edema with winding of the major vessels of GI tract predicting InIs.

Our case concerns a young man with aSBO and resultant ischemia of a 2.30 m long intestinal loop which involved the ileocecal valve. Thus, even though initial management of aSBO is usually conservative and the majority of aSBO cases resolve without surgical intervention, given the signs of InIs, laparotomy was mandatory^[2,5,11]. The standard procedure for this condition involves resection of the ischemic bowel and primary anastomosis^[31]. However, in the present case, resection would lead to short bowel syndrome; a mal-absorptive state caused by massive intestinal resection^[32,33]. It usually occurs when the small bowel is less than 2 m long, so that its absorptive function is diminished and the patient cannot maintain its nutritional status and homeostasis by the enteral route alone. These patients are initially dependent on total parenteral nutrition which could progressively lead to liver insufficiency^[32,34]. In order to avoid this outcome, taking into consideration that the physiologic consequences of ischemia are still reversible within six hours from onset, and based on diminutive sign of peristalsis at the ischemic ileum, it was decided initially a more conservative approach without intestinal resection^[16]. The option of surgical excision was reserved for the second look laparotomy in case that the bowel became necrotic. Fortunately, at the second-look operation the small bowel appeared normal and the resection wasn't warranted. In this way and even though the intestinal loop at first seemed marginally viable judging from its color and size, the ischemia was reversed, and the patient improved quickly without complications.

CONCLUSION

The treatment of aSBO should be, at the beginning, conservative excluding cases presented with clinical signs or CT findings predictive of surgical intervention or peritonitis requiring an urgent laparoscopic or laparotomic exploration^[2]. On occasion, conservative surgical approach avoiding resection of ischemic bowel, could lead to reversal of InIs and should be initiated even when minimum signs of viability are present and also when less than six hours have passed from the onset of ischemia, time limit allowing reversal of ischemic damage. The second look laparotomy in 24-48 h is an alternative that allows, under the condition of close monitoring (vital signs, clinical evaluation for acute abdomen, lactate levels), the reperfusion and resolution of ischemic impairment of a marginally viable bowel, or deterioration and early resection based on the close monitoring.

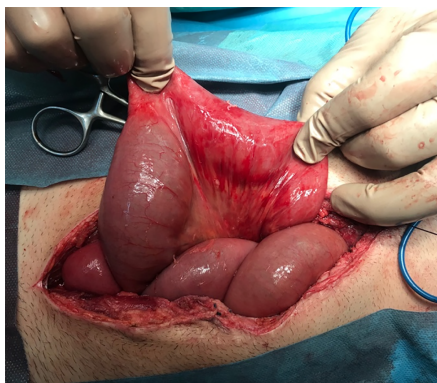


Figure 3 The small bowel at second look laparotomy 48 h later. Location of most severe ischemia: On the left side of the image the surgeon holds the bowel at the location of previous anastomosis where the adhesion that led to torsion and ischemia was formed.

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