Case Report

Haemorrhagic shock secondary to a diffuse ulcerative enteritis after Ipilimumab and Nivolumab treatment for metastatic melanoma: a case report

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Abstract: We provide a unique case of haemorrhagic shock complicating a corticosteroid-resistant diffuse ulcerative enteritis in a patient treated with a combination of an anti cytotoxic T-lymphocyte antigen-4 (CTLA4) and an anti programmed cell death protein 1 (PD-1) for metastatic melanoma. Immunotherapy has changed the perspective for the management of patients with metastatic melanoma but are also responsible for digestive complications mainly represented by immunomediated colitis. Digestive bleeding is common in patients with extensive colonic lesions but has never been described in enteritis independent of colitis. The patient with acute intestinal obstruction related ileitis without evidence of stricture on imaging and then had a gastro-intestinal bleed. In the absence of haemorrhagic lesions on upper gastrointestinal endoscopy, colonoscopy and computed tomography (CT) angiography, a surgical exploration with enteroscopy was performed. This revealed an extensive ulcerated jejunoileitis, with active bleeding, within a Meckel's diverticulum. Management included resection of the Meckel diverticulum with a transient double barrel ileostomy. Two infliximab infusions were given due to persistent bleeding. We observed a dramatic improvement after infliximab treatment with complete cessation of bleeding and no further need for transfusions. A complete mucosal healing has been achieved on enteroscopy at 3 months with disappearance of histological inflammatory lesions. This observation suggests that infliximab represents a therapeutic option in severe enteritis and may be as effective as in more moderate immune-mediated enterocolitis.

Keywords: Metastatic melanoma; immune checkpoint inhibitors; immune-mediated enterocolitis; gastrointestinal haemorrhage; case report

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Introduction

Immune checkpoint inhibitors can induce immune-mediated intestinal toxicities. A recent meta-analysis of melanoma trials has shown that the incidence of all-grade diarrhea and colitis induced by the cytotoxic T-lymphocyte antigen-4 monoclonal antibody (Anti CTLA4) Ipilimumab was 35.4% and 8.8% respectively (1). In Melanoma phase III trials, the digestive toxicity induced by Ipilimumab is dose dependent and accounts for up to 1% of treatment-related deaths mainly related to Grade 3-4 diarrhea and colonic perforation (2). In melanoma trials, the intestinal toxicity of anti-programmed deaths receptor-1 antibodies (anti-PD1) is less frequent (relative risk of all-grade diarrhea and colitis of 0.58 and 0.16 compared to anti CTLA4 respectively) and associated with less severe complications (1). The addition of anti PD1 to anti CTLA4 increases the likelihood of severe gastrointestinal toxicity. Enteritis may be associated with colitis mainly with anti CTLA4. There are very few

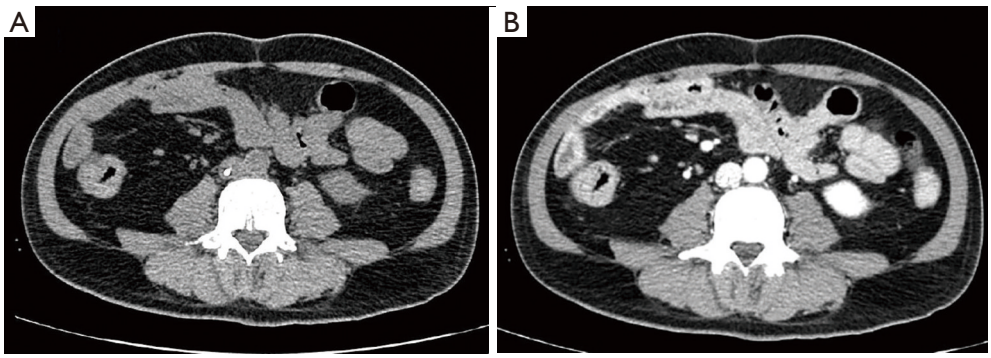

Figure 1 Axial CT images without (A) and after (B) injection of contrast material. After injection (B), there is a diffuse mural thickening and parietal enhancement of the small bowel loop. CT, computed tomography.

cases of enteritis independent of colitis described. One patient was admitted in our intensive care unit for massive intestinal bleeding attributed to an immuno-mediated enteritis, reported as follows. We present the following case in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-58/rc).

Case presentation

A 62-year-old man followed for occipital melanoma T1aN0M0 who had been treated by surgery in October 2017 had an isolated metastatic lymph node relapse in March 2019. The molecular status of a cervical adenopathy revealed a V559A mutation of exon 11 of C-KIT without BRAF and NRAS mutations. The patient was offered a combination therapy including an anti programmed cell death protein 1 (PD-1) (Nivolumab 1 mg/kg) with an anti CTLA-4 (Ipilimumab 3 mg/kg) every three weeks. Three weeks after the second infusion, the patient was hospitalized for fever, frontal syndrome and intestinal obstruction. The clinical examination showed an abdominal meteorism with no palpable mass or signs of peritoneal irritation. Both complete infectious and neurological work-up were negative. The contrast-injected abdominopelvic computed tomography (CT) revealed discrete parietal thickening of the cecum and extensive ileitis with distension of the upper small bowel and no evidence of stricture (*Figure 1A,1B*). A diagnosis of immune-mediated enteritis was given. After administration of 250 mg intravenous methylprednisolone for three consecutive days combined with gastric aspiration and broad-spectrum antibiotherapy, he promptly improved. He presented on day 2 of oral steroids at a dose of 1 mg/kg/day a spontaneously resolutive gastro-intestinal bleed with acute reduction in haemoglobin level required the transfusion of 4 units of red blood cells. As the upper gastrointestinal endoscopy was normal, the bleeding was attributed to ileitis and no further explorations were performed. Steroids were maintained at full dose. At day 18, the patient was admitted to intensive care for haemorrhagic shock with melena and blood loss at 7.2 g/dL. A new upper gastrointestinal endoscopy was normal. Colonoscopy showed a congestive aspect of the cecum with patchy obliteration of the vascular pattern, and ulcerated ileitis with frank blood in the lumen. A CT angiography did not show active arterial bleeding. A stool specimen was cultured including a search for clostridium difficile infection and a virological stool analysis to investigate for the presence of adenovirus, cytomegalovirus or human herpes virus by transcriptase polymerase chain reaction were negative. The blood test did not show cytomegalovirus, Epstein-Barr virus and human herpes 6 viremia. It was decided at day 22 to perform an exploratory laparotomy with intra-operative enteroscopy because of persistent hypovolemic shock that required multiple transfusions (19 red blood cells, 10 fresh-frozen plasma, 2 platelets concentrates). Two and a half meters of the jejunoileum were examined. There were multiple deep ulcers without active bleeding predominating over the last 150 centimeters with an upper limit of lesions not seen (*Figure 2*). A Meckel diverticulum was found 60 cm from the ileocecal valve. This was invaginated into the lumen, which revealed a deep ulceration with visible bleeding. It was decided a bowel-sparing option to avoid the risk of short bowel syndrome. The Meckel diverticulum was resected along with 5 cm of ileum proximal and distal to its base with a double barrel ileostomy. Pathological analysis showed

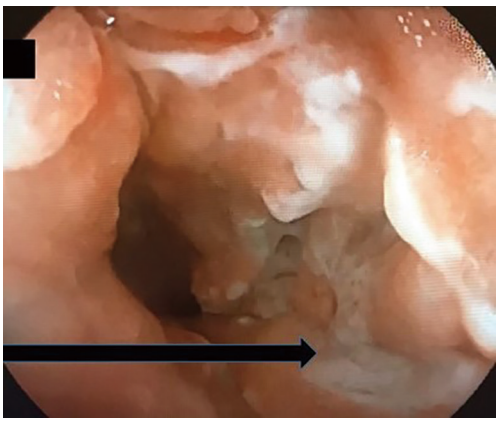

Figure 2 Enteritis with deep ulcers.

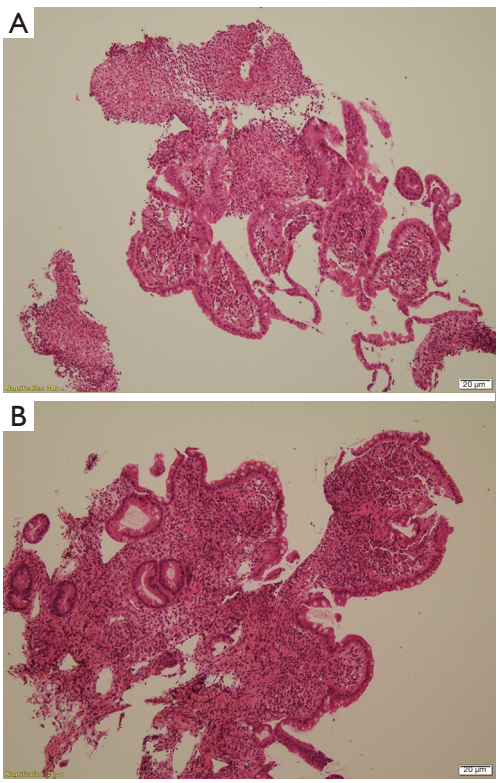

Figure 3 Pathological findings with hematoxylin and eosin (H&E) stained procedure. (A) H&E, ×100 magnification. Ileitis with mucosae showing thickened villi and architectural changes of the underlying glands. The lamina propria contains an increased number of lymphocytes as well as a few polymorphonuclears. (B) H&E, ×100 magnification. Ileitis with architectural distorsion. Erosion with inflammatory exudates can be seen on the top and lower-left parts of the picture.

signs of ileitis with architectural distortion and inflammatory infiltrate (*Figure 3A,3B*). However, the patient continued to have hematochezia postoperatively, requiring the transfusion of 4 more units of red blood cells. There was no evidence of an anastomotic leakage. The presence of deep ulcers likely to bleed and not accessible to an endoscopic procedure led us to propose a salvage medical treatment. This life-threatening bleeding led us to start an intensified Infliximab regimen. He received two infusions of Infliximab (IFX) at a dose of 10 mg/kg (baseline at day 6 after surgery and 2 weeks later). He showed a dramatic improvement after the first injection with complete cessation of bleeding and no further need for transfusions. An enteroscopy performed one month after the first injection of Infliximab showed re-epithelialization of jejunoileal ulcerations. At three months after the second injection of Infliximab, a new enteroscopy revealed a complete mucosal healing with no histopathological abnormalities, and a CT scan revealed a stable disease according to RECIST V.1.1 criteria with complete remission of enteritis. Elective closure of the ileostomy was done after steroids tapering six months after the initial surgery. The timeline of this patient's history and current information is provided in *Figure 4*. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

Discussion

Enterocolitis is the most frequent intestinal immune-related adverse effect induced by immune checkpoint inhibitors. Diarrhoea and abdominal pain represent the leading symptoms and their severity is evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE). Clinical symptoms are poorly correlated with the severity of lesions. In a series of 39 patients receiving anti-CTLA-4, it was reported that endoscopic lesions were mainly in the colon and characterized by ulcers (79%), erosions (13%), and erythema (8%) (3). Among patients receiving anti-PD1, the gastrointestinal toxicity seems more heterogeneous, including acute colitis, microscopic colitis, upper gastrointestinal tract inflammation and

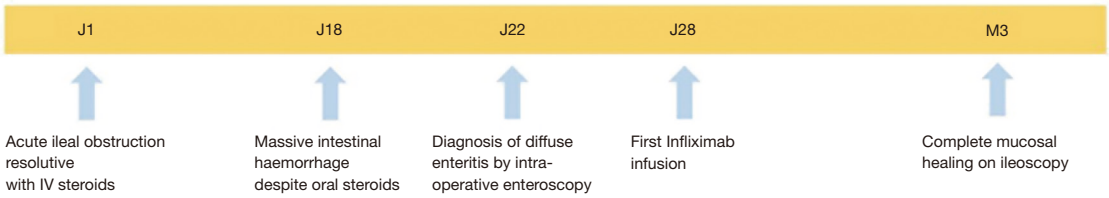

Figure 4 The timeline of the patient's historical and current information of care.

intestinal pseudo-obstruction (4). Although the term enterocolitis is frequently used in the literature, few studies have documented lesions of the ileum seen on endoscopic examination. Histologic abnormalities were described mainly for colon: acute mucosal inflammation with neutrophils and cryptitis or chronic features including mucosal infiltration with lymphocytes and plasma cells, as well as crypt abnormalities (distortion, branching, and apoptotic cells). PD-1 and CTLA-4 blockade generate toxicity that mimics autoimmune diseases, which explains why the macroscopic and microscopic lesions observed are close to those of inflammatory bowel diseases with the exception of apoptosis lesions (5). It has been shown that pancolonic involvement and presence of endoscopic ulcers were predictive markers of worsening clinical evolution (6). The CT scan often performed in clinical practice is of interest only to eliminate a perforating complication but does not reveal the topography and severity of endoscopic lesions.

Patients with bloody diarrhoea require immediate hospitalization for endoscopic evaluation at least by flexible sigmoidoscopy and the introduction of intravenous steroids in the absence of acute surgical abdomen. It has been shown that digestive bleeding is correlated with the severity of endoscopic lesions and was mainly observed in cases of extensive colonic ulcerations. The incidence of intestinal bleeding is uncertain and varies from 10% to 64% (3,4,6). To our knowledge, this is an unusual case of massive digestive bleeding attributed to iatrogenic diffuse enteritis. The intraoperative findings suggest that luminal Meckel diverticulum ulcerations, as well as other small bowel lesions were active bleeding sites. Visualization of the Meckel diverticulum can be difficult at the CT scan. As in severe colitis, our report suggests that Infliximab can be used as a salvage therapy in steroid refractory immune-mediated enteritis (7). The absence of colitis led to doubts about the mechanism of bleeding explaining the late introduction of Infliximab. An induction treatment with no more than 3 infusions of Infliximab at a dose of 5 mg/kg (baseline, days 14 and 42) is recommended, this derives from randomised trial of Infliximab in severe ulcerative colitis. However, the optimal regimen remains challenging. Inflammatory bowel disease patients with more severe disease at baseline have been shown to have higher faecal loss of Infliximab, contributing to primary non-response. We decided to use a dose of 10 mg/kg because of the disease severity and data suggesting that an accelerated salvage Infliximab regimen improves the prognosis in acute severe ulcerative colitis (8). Our case does not allow us to validate the indication for an optimised Infliximab in severe steroids-resistant immuno-mediated enterocolitis.

A recent paper showed that patients with advanced melanoma experiencing severe immune check point inhibitor toxicity have a significantly prolonged survival compared with patients who do not (9). However, in this subgroup of patients, anti TNF use was associated with decreased survival. These results should be analysed with caution as there were more patients treated with Ipilimumab in the anti TNF group which is a less efficient treatment than Nivolumab. These data suggest that Infliximab should be used sparingly for the patients with metastatic melanoma. Vedolizumab has been suggested to be an option in patients refractory to steroids and/or Infliximab, but there are no data suggesting that this treatment can be used as a first-line treatment after steroids failure (10).

Surgical indications are variously appreciated in the literature and seem to occur in less than 5% of cases. The most common indications for emergency surgery are colonic perforation, toxic megacolon or severe flare refractory to both steroids and Infliximab. Precise description of a patient cohort operated on for immune-mediated digestive complications has not been reported. Although the stomach and small bowel may be involved, a colectomy or a loop ileostomy are the most frequently reported surgical procedures, the colon usually being the predominant inflamed area (11). We found only one study mentioning a case of emergency colectomy for persistent

rectal bleeding out of 198 patients treated by Ipilimumab for metastatic melanoma or renal cell carcinoma (12). We report the first case of intestinal surgery for a severe and isolated immune-mediated small bowel complication. Although the combination of the two check point inhibitors potentiated the severity of digestive disorder, the toxicity profile of Ipilimumab led us to definitively contraindicate the subsequent administration of an anti CTLA-4. A retreatment with an anti PD1 appears to be a possible option in the event of subsequent tumour progression.

Our observation illustrates that location of intestinal bleeding can present a diagnostic challenge in patients treated with immunotherapy. Emergency upper and lower endoscopy are mandatory to obtain histological evidence of immune-mediated complications and an endoscopic hemostasis therapy. In case of heavy bleeding, salvage treatment with Infliximab may be as effective as in more moderate immune-mediated enterocolitis and should be preferred to surgery or radiological embolization in case of haemodynamically stable patients. This case report suggests that Infliximab can induce clinical, endoscopic and histologic remission in immuno-mediated enteritis.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-58/rc

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-58/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-58/coif). TA received payment during the Presentations for MSD. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

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