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Case Report

The Role of Abdominal Surgery in Refractory Immune Checkpoint Inhibitor Enterocolitis: A Case Report

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Abstract
This article describes the case of a 73-year-old patient with grade 3 immune checkpoint inhibitor (ICI)-induced enteritis. Five different immunosuppressive agents (glucocorticoids, high-dose infliximab, methotrexate, mycophenolate mofetil, and vedolizumab) were administered, however, with no clinical or radiographical benefit. A laparotomy was performed, as the patient showed signs of intestinal obstruction, with a segmental resection of the ileal loop. Biopsy results showed multiple fibrotic strictures. The current treatment guidelines for ICI enterocolitis only include drugs as a treatment option. Nevertheless, it remains important to consider early surgical intervention in order to avoid serious complications due to persistent and pronounced inflammation. The current case highlights the importance of surgery as a treatment modality in the multidisciplinary approach for ICI-induced enteritis, which should be taken into consideration after second- or third-line treatment.

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Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that enhance the hosts' tumor response by blocking inhibitory ligand/receptor interactions essential for both immunological homeostasis and self-tolerance. CD8+ and CD4+ T-lymphocytes are activated together with inflammatory macrophages which both produce cytokines, e.g., interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha and in turn lead to cell dysfunction, apoptosis, and cytotoxicity [1, 2].

Nevertheless, the enhancement of T-cell activity can lead to a systemic loss of tolerance, and result in immune-related adverse events (irAEs). The most commonly noted irAEs include dermatitis, pneumonitis, thyroiditis, hepatitis, and colitis. Most irAEs can be managed effectively if found and treated early. Cardiovascular, pulmonary, hematological, renal, and neurological irAEs are less frequently seen, though they are of great clinical importance [1–4].

The reported overall incidence of ICI enterocolitis ranges between 1 and 25 percent and varies based on the specific agent, dose, and combination of ICIs used. As an example, cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors or combination regimens (e.g., nivolumab plus ipilimumab) are associated with increased risk of developing ICI enterocolitis and of progressing to severe colitis compared with single-agent programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1). In addition, studies have suggested that higher doses of CTLA-4 therapy are associated with a greater risk of developing colitis. Most patients have left colon involvement, though the incidence of isolated right-sided colitis or ileitis is approximately 10 percent. Also, the complete gastro-intestinal tract can be affected and is probably underreported [5–13]. As both TNF-alpha and IFN-gamma play an important role in the pathogenesis of this irAE, they are used as targets for current treatment modalities [1–4].

The increasing use of ICIs in the treatment of both advanced and early stages of various malignancies has resulted in a substantial increase in incidence of irAEs. Initially, immunotherapy was only used as monotherapy. Currently, there are different treatment regimens wherein ICIs are being combined with chemotherapy and/or targeted therapy. Nevertheless, data regarding the long-term complications and consequences of ICIs are still lacking [1].

This article focuses on a case with grade 3 ICI enteritis refractory to immunosuppression. An overview of different treatment guidelines of ICI enterocolitis is presented, and the role of abdominal surgery is discussed.

Case Report

A 73-year-old male patient, with no relevant medical history, had recently been diagnosed with stage IV urothelial cancer. The patient's diagnosis was discussed with a multidisciplinary tumor board, and enfortumab vedotin (1.25 mg/kg body weight on day one and eight of a three-weekly regimen) together with pembrolizumab (200 mg, every 3 weeks) was initiated. After three cycles, the patient developed a checkpoint inhibitor-related pneumonitis [14, 15]. Steroid therapy was initiated, i.e., prednisolone 1 mg/kg body weight/day. The pneumonitis resolved and treatment was rechallenged by only the admission of enfortumab vedotin during the last three cycles.

Following six cycles, the patient was hospitalized due to acute abdominal pain, nausea, vomiting, and diarrhea. An abdominal computed tomography (CT) scan was performed and revealed a diffuse edematous wall thickening of the level of the ileal loops (maximum 1 m in length) and of the rectosigmoid (shown in Fig. 1). Repetitive cultures were positive for *Campylobacter*-induced enterocolitis. Subsequently, cytomegalovirus (CMV)-induced colitis

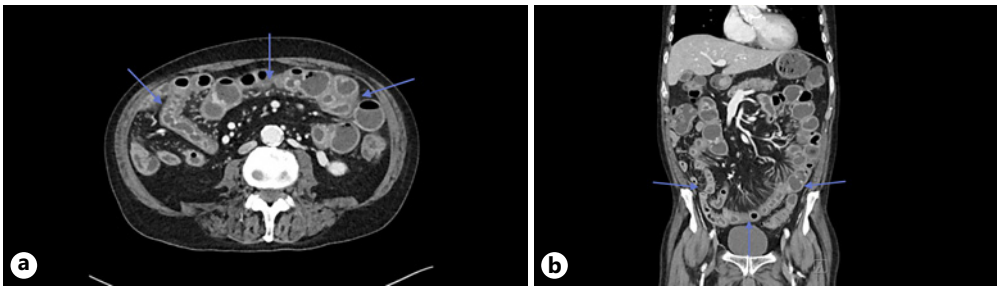

Fig. 1. Axial (**a**) and coronal (**b**) CT images with contrast: edematous wall thickening at the level of the ileal loops.

was also suspected due to fever spikes and high CMV viremia. Nevertheless, no CMV inclusions were noticed on histology of the colon and ileum. Treatment with azithromycin, 500 mg/day, and ganciclovir, 5 mg/kg body weight/12 h, was initiated.

Despite adequate treatment of these infectious complications, the patient deteriorated with persistent high-output diarrhea. Radiological reassessment showed unchanged edematous wall thickening at the level of the preterminal ileal loops. Extensive gastro-intestinal checkup was executed with infectious workup (multiplex PCR panel, CMV PCR), laboratory evaluation (TBC, HIV testing among other), fecal pancreatic elastase, total IgA and tissue transglutaminase IgA, repeat ileocolonoscopy, enteroscopy and esophagogastroduodenoscopy with multiple biopsies. Interestingly, the ileocolonoscopy and enteroscopy showed no mucosal changes in the ileum. Histopathology findings at the level of the colon were normal, while the ileal biopsies showed an enteritis, characterized by a marked inflammatory cellular infiltrate in the lamina propria consisting of neutrophils, lymphocytes, and plasma cells. During this period, blood tests showed a normal renal function, thyroid function, and liver tests.

At this point, grade 3 ICI enteritis (in casu ileitis) was identified, according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). The patient was treated with high-dose corticosteroids without any clinical and radiographic improvement. The following 6 months, he received multiple high doses of infliximab (10 mg/kg body weight), methotrexate, mycophenolate mofetil, and vedolizumab. Different opportunistic infections, such as catheter-related infections and sepsis secondary to bacterial translocation, were treated with antibiotics. A combination of enteral and parenteral nutrition was initiated because of cachexia. Eventually, surgical resection was considered due to persistent signs of obstruction. A presurgery CT enterography still showed extensive ileitis involving multiple segments but also suspected fibrotic strictures with significant prestenotic dilatations (shown in Fig. 2). These fibrotic areas were characterized by abnormally thickened loops with minimal enhancement, no adjacent mesenteric inflammation and demonstrated upstream small bowel dilatation.

During the laparotomy, an 80-cm pathological thickened and inflammatory-appearing ileum segment was resected and an entero-enterostomy was constructed. There were no immediate or late complications following surgery. Histopathology findings of the resected ileum showed a chronic, extensive, ulcerative, and active ileitis with transmural lymphocytic infiltration. Following surgery, the patient was included in a rehabilitation program where he made a full recovery and regained a normal level of exercise capacity.

The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530832).

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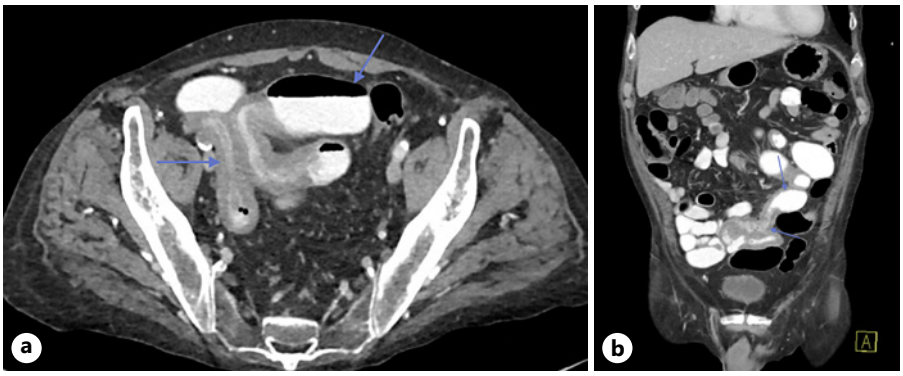

Fig. 2. Axial (**a**) and coronal (**b**) CT images with contrast: fibrotic area with thickened loop and only minimal enhancement, no adjacent mesenteric inflammation, and prestenotic dilation.

Discussion

ICIs are approved for the treatment of various types of cancers; however, irAEs are a major problem associated with ICI treatments. Most irAEs can be managed effectively if found and treated early. Nevertheless, severe cases can be very challenging and life-threatening [1].

Currently, four consensus guidelines on the management of irAEs (ESMO 2017, ASCO 2021, SITC 2021, and NCCN 2022) exist. However, these recommendations are based on a limited amount of evidence and expert opinions. Furthermore, guidelines can be found for ICI-induced colitis; specific guidelines for ICI-induced enteritis cannot be found because of its rare occurrence and/or underreporting. Therefore, guidelines recommend the same management as ICI-induced colitis [4, 16–18].

The current guidelines mandate a prompt initiation of corticosteroids. Treatment should be assessed early to determine the need for second-line therapy with biologic agents such as infliximab or vedolizumab [4, 16–18]. Very limited data are available for patients with refractory disease; a handful of case series suggest a possible benefit of an association with a Janus kinase inhibitor (tofacitinib), interleukin-12-blocking antibody (ustekinumab), or fecal microbiota transplantation [19–21]. Surgery is only suggested for patients with complications, i.e., toxic megacolon, intra-abdominal abscesses, or perforation [4, 16–18].

ICI enterocolitis was initially considered to be an "inflammatory bowel disease (IBD)-like" irAE because of the same pathophysiology and clinical presentation. However, recent data have shown that there is a clear distinction in both histologic features and pathophysiological pathways. Despite these differences, all therapeutic decision algorithms in ICI enterocolitis are still based on and very similar to those in IBD, i.e., incremental immunosuppression with or without suspension of ICI therapy [3, 22].

Therefore, it might be interesting to compare certain IBD-specific strategies to the ICI management. For example, patients with severe Crohn's disease and life-threatening conditions may require surgical intervention. Also, mild and severe Crohn's patients, who are refractory to medication, may benefit from surgery. Especially for hospitalized IBD patients who fail to respond to medical rescue therapy within 7 days, surgery is likely warranted. Switching to another rescue therapy can induce remission, but the risk of serious adverse events rises and early surgical treatment is one option to consider in selected patients (especially with short segment disease where resection of all macroscopic disease is feasible). The optimal timing of surgery in the management algorithm of Crohn's disease will always be a matter of debate. Arguments in favor of early surgical intervention instead of an emergency

procedure for complications are a better nutritional status and general condition of the patient. Long-term use of corticosteroids leads toward more surgical complications and a higher risk of infectious problems and severe sepsis [23–25].

Some of these concepts can be interesting in the management of ICI enterocolitis. According to the current clinical practice ICI guidelines, surgery is only recommended in patients with complicated disease [4, 16–18]. There might be a window for surgery before a chronic more fibrotic phenotype occurs. Unfortunately, no ideal biomarkers are available to guide the clinician in this decision and the combination of persisting symptomatology, imaging criteria for fibrosis on CT/magnetic resonance imaging enterography, length of resected bowel segment, failure of previous medical treatments are arguments that can legitimize surgery. The balance between medical therapy and surgery might be achieved in a multidisciplinary setting involving gastroenterologists, oncologists, surgeons, and radiologists.

Of note, while the factors governing the pathophysiological manifestations in ICI enterocolitis are only beginning to be studied in depth, it is reasonable to consider the lack of histologic chronicity at the presentation of ICI enterocolitis since these patients undergo rapid investigations once symptom onset occurs, resulting in endoscopic examination followed by initiation of anti-inflammatory treatment and suspension of ICI therapy. This time course is in contrast with the usual pattern of new-onset IBD presentation, in which patients are often ill for weeks/months prior to undergoing endoscopy, allowing more chronic inflammatory mucosal changes to occur.

Looking back at the current case, we could question whether a surgical intervention should have been executed earlier in line with the therapy for the hospitalized severe Crohn's patient because persistent and pronounced inflammation augments the risk for serious complications (such as perforation, obstruction, fibrotic strictures, abscesses). As described above, our patient suffered from severe complications during the different medical treatments (catheter-related infections, sepsis by a bacterial translocation) and no further benefit was expected from immunosuppressive therapy. In contrast, the poor general nutritional status, the long-lasting use of corticosteroids, and the resection of the long bowel segment hampered our decision for earlier surgery [26].

We do not argue that based on this case report, surgery should be an upfront treatment modality given the fact that most patients will respond to immunosuppressive therapy. In line with the guidelines, a second-line immunosuppressive therapy should be initiated promptly if there is no improvement after 3 days of steroid initiation, but in our case, surgery should be considered if there is no adequate response after 6 weeks of second-line immunosuppressive therapy instead of only considering surgery in the case of complications. A management algorithm of ICI enterocolitis is proposed in Figure 3.

Learning Points/Take Home Messages

- More scientific research is needed to gain a better understanding of the incidence, clinical presentation, and treatment of ICI enteritis.
- Surgery can be an important treatment modality in the multidisciplinary approach for ICI enterocolitis and should be considered after second- or third-line treatment.
- Surgical intervention should be included in the current treatment guidelines.
- To avoid life-threatening complications, surgical intervention should be considered in patients with a severe presentation of ICI enterocolitis (grade 3–4), hospitalized patients, and those who do not respond to first- and second-line therapy.
- Persistent inflammation in refractory disease will eventually increase the growth of fibrous tissue in the bowel, in which case surgery becomes inevitable.

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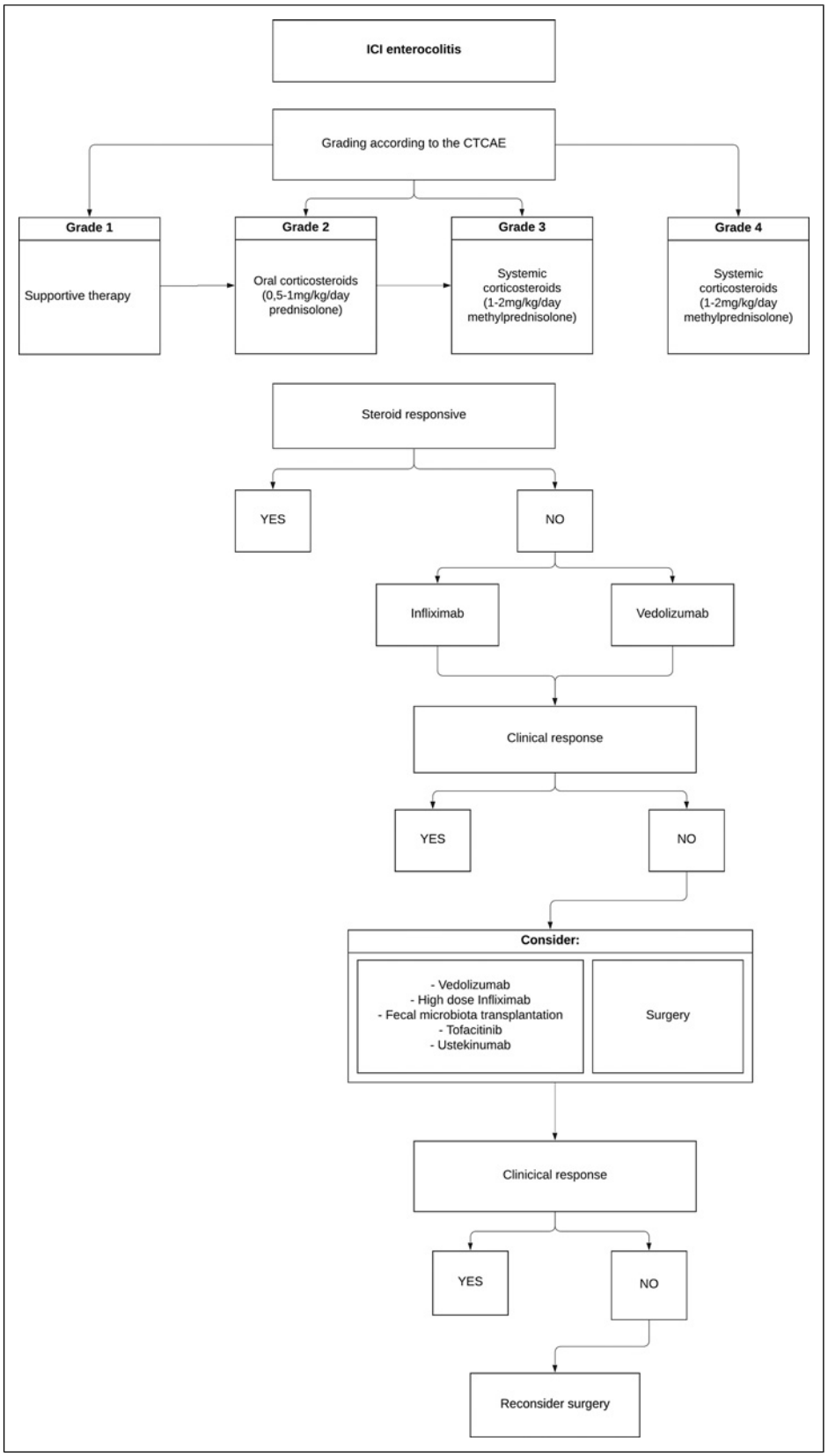

Fig. 3. Proposal for a management algorithm of ICI enterocolitis.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. A written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Manon Verhé, Thomas De Somer, Barbara Defoort, Erik Vanderstraeten, Els Monsaert, Vincent Bouderez, Christof Vulsteke, and Christophe Van Steenkiste treated the patient and contributed to the writing of this case report. Dias Stefanie and Delombaerde Danielle contributed to the writing of this case report.

Data Availability Statement

All data that support the findings of this case report are included in the article and its supplementary materials. Further inquiries can be directed to the corresponding author.

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