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Authors:
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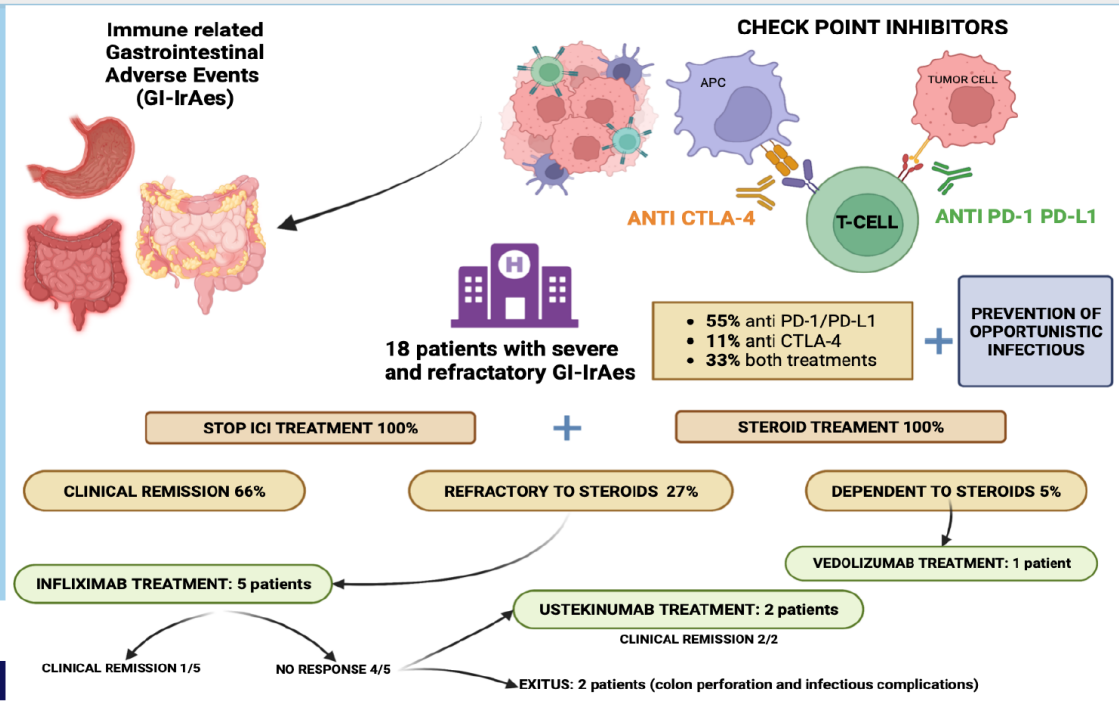
SEVERE AND REFRACTORY GASTROINTESTINAL TOXICITY DUE TO IMMUNE CHECKPOINT INHIBITORS: CLINICAL EXPERIENCE IN A TERTIARY REFERRAL HOSPITAL



- Create multidisciplinary committees to aid the clinicians
- Oncologists should refer patients to an experienced Gastroenterology Unit
- Prevent treatment related complications (Prophylactic antibiotics and antifungal)
- IBD patients under ICI treatment should be monitored

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Severe and refractory gastrointestinal toxicity due to immune checkpoint inhibitors: clinical experience in a tertiary referral hospital

Elena Céspedes-Martínez[1,2], Virginia Robles-Alonso[1,2], Claudia Herrera-De Guise[1,2], Luis Fernando Mayorga[1,2], Francesc Casellas[1,2], María Roca-Herrera[3], Natalia Borruel[1,2]

[1]Crohn's-Colitis Unit (UACC). Digestive System Research Unit. Hospital Universitari Vall d'Hebron. Barcelona, Spain. [2]CIBER of Hepatic and Digestive Diseases (CIBEREHD). Barcelona, Spain. [3]Medical Oncology Department. Hospital Universitari Vall d'Hebron. Barcelona, Spain

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Correspondence: Elena Céspedes Martínez. Crohn's-Colitis Unit (UACC). Digestive System Research Unit. Hospital Universitari Vall d'Hebron. Passeig de la Vall d'Hebron, 119. 08035 Barcelona, Spain

e-mail: elena.cespedes@vallhebron.cat

Author contributions: Elena Céspedes-Martínez: study concept and design, data collection and manuscript preparation. Virginia Robles-Alonso: data collection, manuscript preparation and revision. Luis Fernando Mayorga: data collection and manuscript draft. Claudia Herrera-De Guise: data analysis and manuscript draft. Francesc Casellas: critical revision of the manuscript for important intellectual content. María Roca-Herrera: data collection and manuscript preparation. Natalia Borruel: critical revision of the manuscript for important intellectual content and revision.

Conflict of interest: VR has research funding from Takeda and has received consulting fees from Janssen. NB has received consulting fees from Takeda, Janssen, Pfizer and Tillots. LM

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and CH have received consulting fees from Janssen. The authors have no other disclosures to report in the last 12 months.

ABSTRACT

Introduction: immune checkpoint inhibitors (ICI) are increasingly used to treat several types of cancer. These drugs lead to a wide range of toxicities. Immune-related gastrointestinal adverse events are common and potentially severe. In this manuscript, we recount the real clinical experience in a tertiary center.

Methods: a retrospective and observational study was conducted in adult patients under ICI treatment. Included patients had been referred to the Gastrointestinal Service of Hospital Universitario Vall d'Hebron for evaluation of severe toxicities, from January 2017 to January 2020, for whom the clinical, epidemiological and evolutive data were collected.

Results: a total of 18 patients were included. Fifty-five percent received anti-programmed cell death protein 1 (PD-1)/anti-programmed death-ligand 1 (anti PD-L1), 11 % received anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) and 33 % received both treatments. The toxicities were manifested as enterocolitis, microscopic colitis and gastritis. Upper gastrointestinal endoscopy was performed in seven patients; all were proved to have histological changes on duodenum biopsies. Treatment was stopped in all patients and steroids were initiated. Sixty-six per cent achieved clinical remission with steroids. Five patients received anti-TNF treatment (infliximab). Only one of the five had responded. Two anti-TNF refractory patients received ustekinumab, with an appropriate clinical response. One patient received apheresis granulocyte as concomitant treatment. A patient with a steroid-dependent course started vedolizumab. Three patients had other immune-related adverse events.

Conclusion: gastrointestinal immune-related adverse events are acquiring a higher profile in daily practice and gastroenterologists play an even greater role in the management of these patients.

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Keywords: Gastrointestinal immune-related adverse events. Immune checkpoint Inhibitors. Management. Enterocolitis.

INTRODUCTION

Immune checkpoint inhibitors (ICI) are a new group of monoclonal antibodies with an increasing number of clinical indications for cancer (1). These drugs enhance the immune response against tumor cells by blocking signaling via either cytotoxic T lymphocyte antigen 4 (CTLA-4) or programmed cell death protein 1 (PD-1), which are responsible for immune tolerance pathways.

The development of new types of ICI have increased rapidly over the last few years. The use of anti CTLA-4 (ipilimumab and tremelimumab), anti PD-1 (nivolumab or pembrolizumab) and anti-programmed death-ligand 1 (anti PD-L1 [atezolizumab, avelumab or durvalumab]) are indicated in several types of cancer and in many ongoing clinical trials in tertiary hospitals. Currently, the main indications for the use of these agents approved by the European Medicines Agency and the Food and Drug Administration are melanoma, non-small-cell carcinoma, solid tumors with high microsatellite instability, Merkel cell carcinoma, hepatocellular carcinoma, gastric cancer or cervical cancer, although yielding promising results in more indications (2).

Despite the well-known effectiveness of these novel treatments, their use is associated with a wide range of toxicities, as a consequence of blocking the immune tolerance, causing a hyperactivation of the immune system in the body. The immune-related adverse events (IrAE) are very heterogeneous, even with the same agent, with few prognostic factors involved in their development.

The gastrointestinal (GI) IrAE are some of the most common and potentially severe (3,4). Enterocolitis, microscopic colitis and gastritis are described as the most common clinical presentations, an important cause of medical consultation and ICI treatment discontinuation. Other GI-IrAE reported are enteric neuropathy or esophagitis (4). The inflammation caused by the ICI shares certain clinicopathological features with inflammatory bowel disease (IBD) (5). Patients under anti CTLA-4 treatment develop GI-

IrAE more frequently than those with anti-PD1/PD1L (5.7-9.1 % *vs* 0.7-1.6 % [4]). The anti CTLA-4 toxicity is related to the most severe GI events, being worse if the patient is treated with the combination treatment (anti CTLA-4 plus anti PD-1).

Due to the increasing use of these agents, the IrAE emerges as a new field of study and analysis. The creation of multidisciplinary committees, including gastroenterology specialists, are especially relevant in tertiary centers, helping to make the best clinical decisions when treating patients (1). In this article we recount the real clinical experience in a tertiary center with a multidisciplinary IrAE committee. We also include our experience with IBD patients under ICI treatment. The current recommendations are not based on clinical trials; we describe the effectiveness of the different treatments and the potential complications observed within their use in daily practice.

MATERIALS AND METHODS

A retrospective, descriptive and observational study was conducted in adult patients under treatment with ICI. Subjects included were those who developed severe GI-IrAE (according to Common Terminology Criteria for Adverse Events [CTCAE]), requiring referral to the Gastrointestinal Unit for treatment or hospitalization, or refractory to the first line of treatment with steroids. We do not differentiate between patients treated with ICI under strict indication or in clinical trials. IBD patients under treatment with ICI were analyzed, with independence of severity of the disease, to evaluate this specific population.

The IrAE included were those affecting the GI tract by demonstrating inflammation in the upper or lower tract. Microbiological, endoscopic and histological investigations were set up for all the patients to confirm the diagnosis and to exclude other possible causes, independently of the presence or not of macroscopic lesions. An upper endoscopy was performed during the diagnostic process after the Gastroenterology Unit decided to create a common protocol for all patients. All patients included in the study before that moment did not undergo upper endoscopy, since during the first part of the study it was not implemented as a diagnostic protocol.

All patients between January 2017 and January 2020 were included, and their clinical, epidemiological and evolutionary data were collected. Ethical approval for this study was obtained by the Ethics Committee of Hospital Universitario Vall d'Hebron (UAC-ICI-2020-02). Informed consent was not sought specifically for the present study because it is an observational study, and data was retrospectively collected from patients that had already consented to use their clinical information for future studies.

Statistical analysis

Descriptive statistics were used to study the frequency of the demographic and clinical characteristics of our subjects and the average of clinical and treatment outcomes related to the GI-IrAE. Descriptive data were presented with STATA as percentages for discrete variables, and as median with interquartile range (IQR) for continuous variables.

RESULTS

Characteristics of patients

A total of 18 patients (Table 1) were included. The median age was 55 (30-82), 50 % were female (9/9). Thirty-three per cent (n = 6) had lung cancer and 16 % (n = 3) had melanoma, 11 % (n = 2) had esophagus cancer, 11 % (n = 2) had cervix cancer, and the remaining had urothelial cancer, colorectal cancer, Hodgkin's lymphoma, hepatocellular carcinoma and breast cancer. Fifty-five per cent (n = 10) were active smokers and 33 % (n = 6) had quit smoking before the onset of the GI-IrAE. Fifty-five per cent had been under chemotherapy and 22 % (n = 4) were receiving both treatments concomitantly. Carboplatin is the shared chemotherapy in all those patients, and this drug is associated with non-severe diarrhea, playing no role in the immune-related path of GI-IrAE. Fifty-five per cent (n = 10) were under anti PD-1 or PD-L1 treatment, 11 % (n = 2) under anti CTLA-4 and 33 % (n = 6) were receiving combination treatment (Table 2). All patients received the treatment in a clinical trial setting.

One of the patients had a previous diagnosis of ulcerative colitis (UC). A 77-year-old UC patient, with extended UC, developed enterocolitis after the introduction of ICI. He was in

clinical and endoscopic remission when previously under treatment with salicylates and adalimumab, which was withdrawn after the oncological diagnosis of melanoma.

Immune related adverse event

All patients (n = 18) developed a severe GI-IrAE (diarrhea G3-G4, dyspepsia G3) (6). The first clinical manifestation was diarrhea G2 (6) in 94 % (n = 17) of patients and the first symptom was dyspepsia G2 in one patient. The median onset of adverse event from the first ICI dose was 171 days. After a histological diagnosis, 77 % (n = 14) patients had enterocolitis as GI-IrAE, 16 % (n = 3) had microscopic colitis and 5 % (n = 1) had gastritis (Table 3).

Fibrogastroscopy was performed in seven patients, six of them without upper GI symptoms. Four patients had endoscopic lesions (two duodenal atrophy and two erosive duodenitis). All seven patients had histological proven inflammatory changes on the duodenum biopsies (all had inflammatory infiltrate and two also had epithelial atrophy). One patient's first symptom was epigastric pain, with gastric inflammation on fibrogastroscopy and an inflammatory infiltrate on biopsies.

Treatment

All patients stopped ICI treatment and started systemic steroids treatment, prednisone or methylprednisone, with weight-adjusted doses. One patient with microscopic colitis used a local action steroid (oral budesonide, 9 mg). Twelve patients (66 %) achieved clinical remission, five (27 %) were steroid refractory and one had a steroid-dependent course. All five patients with a steroid refractory course received anti-TNF treatment with infliximab. The IBD standard doses of 10 mg/kg were used. One patient (20 %) had complete clinical remission after one single induction dose. The remaining four patients received three consecutive doses (10 mg/kg at week 0, 1 and 3) (7), without clinical response. Plasma levels of infliximab were used in one patient to adjust the treatment, using the recommended target levels for IBD (8,9). Two of those patients died due to complications, as detailed below.

The two remaining patients received Ustekinumab, using 6mg/kg doses iv. One patient had a complete response after one infusion. The other patient received Granulocyte-apheresis treatment concomitantly to Ustekinumab, achieving complete clinical remission (Fig. 1).

Inflammatory bowel disease patients

Only one of three of the IBD patients under ICI treatment developed an IrAE. The UC patient had a steroid-dependent course, starting vedolizumab treatment with adequate response. ICI treatment was reintroduced and maintained to avoid clinical relapse. The patient is still in remission at the time of publication.

Complications

All the complications during follow-up were collected. Six patients died, four of them because of oncologic progression of primary disease. Others from disease-related or treatment complications: one of *Aspergillus* spp. lung-related disease and one of colon perforation. Infectious complications were observed in four patients. Two subjects had cytomegalovirus (CMV) related colitis and one had *Clostridioides difficile* infection. Other events related to the high doses of steroids were *Aspergillus* spp. lung disease, adrenal insufficiency secondary to steroids or steroid myopathy.

Other immune-related adverse events

Concomitantly to GI ones, three IrAE were diagnosed: hepatitis (n = 2), adrenalitis and interstitial nephritis. All patients had a good response to steroids and ICI discontinuation, including patients with both immune-mediated hepatitis and enterocolitis, with normalization of hepatic function and clinical remission of colitis. However, one of those patients had a previous diagnosis of UC, with a steroid-dependent course and adequate response to vedolizumab, without hepato-toxicity relapse.

DISCUSSION

Cancer immunotherapy is a major expanding field nowadays (1). In parallel to growing indications, IrAE incidence is increasing. The GI-IrAE are one of the most frequent and severe (4), which is why treatment development could improve the prognosis in these patients. Gastroenterologists play an important role in the management of these patients, and it is necessary to create multidisciplinary committees.

Our study illustrates the clinical experience with severe and refractory GI-IrAE in a tertiary referral hospital. It is a single center, retrospective experience study, with a low number of patients. Sample size analysis was not performed because all the severe GI-IrAE patients that required specific management by our Gastroenterology Unit were collected. However, our clinical experience could be useful for other centers due to the lack of evidence in this area.

Our patients are a heterogeneous sample because they were collected from ongoing clinical trials, with different advanced tumor indications and newly developed agents. In other studies, anti CTLA-4 and combination treatments cause most of the GI-IrAE and also those with major severity (10). The difference in the prevalence observed in our group is because the majority of our patients were receiving anti PD1/PD-L1, which overestimated the frequency of GI events in those. However, the most extensive and severe clinical manifestations coincide in patients treated with anti CTLA-4 or combination treatment, while microscopic colitis seems to be more common in those with anti PD-1/PD-L1 treatment.

The affectation of the upper GI tract is a constant in our patients, supporting the hypothesis of GI inflammatory infiltration all along the digestive tract (11). There are reported cases of acute immune-related gastritis due to nivolumab treatment (12,13), but we consider almost all ICI treatments capable of causing upper GI manifestations. The potential onset of macroscopic lesions makes it necessary to perform upper endoscopy studies with biopsies to complete the diagnostic process. Further studies are needed to learn the role of these effects on prognosis.

The treatment used is based on IBD treatment (14,15). Current consensus guidelines are based upon clinical experience, without any strong evidence-based data (6,15-17). The

first-line treatment for patients with severe adverse events is immunotherapy discontinuation. A recent review found that 65 % of patients with GI-IrAE diagnosis underwent permanent discontinuation of the treatment (18). Steroids are the first line agent, being a rationally safe and effective treatment in these patients (6,15-19). However, adverse effects due to high steroid doses and long-time exposure must be sought by clinicians and prevented. Moreover, steroids have a role against antitumor response, which makes steroid-free treatment strategies likely to be clinically relevant (15,19).

Refractory response to steroids was reported in between 30 % and 60 % of the patients (6). Infliximab (IFX) is the best-known second-line agent with this indication given the experience in severe UC's patients (20). IFX is associated with faster symptom resolution, mostly in patients with high-grade colitis, avoiding long time exposure to steroids and improving prognosis, with a lower rate of perforation or death (14,15). Currently, the literature supports the use of one to three single early doses (5-10 mg/kg) to provide symptoms control, with an average of 50-100 % of response to the first dose in previous studies (17,21-24). Only in the event of non-response, consecutive doses of infliximab might be necessary 14 days after the first infusion (20). In our experience, clinical remission with the first IFX infusion was achieved only in one of five patients. The difference between our experience and the previously described data was probably because of the unfavorable clinical situation and pharmacokinetics in our subjects, with drug losses due to the pro-inflammatory status.

Other monoclonal antibodies agents like ustekinumab could be used if there was no response to anti-TNF, drawing on extensive IBD experience (25). Our experience is favorable for its use as a third line agent, although there is a lack of studies about this drug in Gi-IrAE (18). Vedolizumab has been shown to be effective in steroid-refractory enterocolitis, with an excellent clinical evolution in our patient. However, this monoclonal antibody has no place in severe clinical enterocolitis (26). Granulocyte-apheresis may be useful as a combination treatment to help achieve remission, since it does not provoke any immunological impairment, but there are no studies available to support clinical use.

Ustekinumab and vedolizumab are considered as safe treatments, and IFX has also been reported to be safe when only a few doses are needed (14,15).

Furthermore, infectious complications are frequent. Steroid and anti-TNF agents are believed to be risk factors for developing opportunistic infections (27). Due to the complications observed in our patients, we started using antibiotic and antifungal treatments in a prophylactic way. The Infectious, Oncology and IBD units decided to develop a prophylactic infectious protocol with cotrimoxazole and fluconazole at the same time as starting steroids. In addition, we set up regular controls for over-infection with CMV and *Clostridioides difficile.*

Concomitant IrAE are frequently found in the literature. The most common events are those affecting the skin or endocrine organs (thyroiditis or adrenalitis) and those that affect GI organs (hepatitis o enterocolitis) (6,28-30). Nine per cent of patients in ICI treatment develop multisystem IrAEs (28), but frequency of non-GI IrAE has not been reported to be higher in patients with enterocolitis than in other IrAEs (31). In our experience, vedolizumab is a safe treatment in those patients with previous immune-mediated hepatitis and good response to ICI discontinuation and steroids. However, in those patients with liver disease, we should consider other treatments (31,32).

Patients with IBD are believed to be at a greater risk of developing GI-IrAE with ICI treatment. However, these patients are generally excluded from clinical trials so there is a lack of clinical information (33). This supposed predisposition necessitates a closer follow-up by the GI and IBD-units. IBD patients discontinue treatments when they are diagnosed with cancer. Prior to halting IBD treatment, it should be recommended to assess the intestinal inflammatory activity through biomarkers or endoscopy performance (34). Afterwards, patients should be monitored, with an early identification of clinical relapse or treatment-related events. However, differentiation between an IBD flare and a GI-IrAE is sometimes difficult for clinicians. A prospective clinical trial is now enrolling patients with ICI treatment indication and previous diagnosis of IBD (AIM-NIVO, ClinicalTrials.gov ID NCT03816345).

CONCLUSIONS

In conclusion, our manuscript may help in the treatment of the GI-IrAE. It is essential to create multidisciplinary committees to aid clinicians. When a severe GI-IrAE is suspected in a subject under ICI treatment, the oncologist should refer the patient to an experienced Gastroenterology Unit to tailor the treatment and prevent related complications or death.

REFERENCES

1. Collins M, Soularue E, Marthey L, et al. Management of patients with immune checkpoint inhibitor-induced enterocolitis: a systematic review. Clin Gastroenterol Hepatol 2020;18(6):1393-403.e1 DOI: 10.1016/j.cgh.2020.01.033

2. European Medicines Agency. Science Medicines Health. Opdivo. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo

3. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016;13(8):473-86. DOI: 10.1038/nrclinonc.2016.58

4. Soularue E, Lepage P, Colombel JF, et al. Enterocolitis due to immune checkpoint inhibitors: a systematic review. Gut 2018;67(11):2056-67. DOI: 10.1136/gutjnl-2018-316948

5. Khoja L, Day D, Wei-Wu Chen T, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol 2017;28(10):2377-85. DOI: 10.1093/annonc/mdx286

6. Haanen J, Obeid M, Spain L, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(12):1217-38. DOI: 10.1016/j.annonc.2022.10.001

7. Hindryckx P, Novak G, Vande Casteele N, et al. Review article: dose optimization of infliximab for acute severe ulcerative colitis. Aliment Pharmacol Ther 2017;45(5):617-30. DOI: 10.1111/apt.13913

8. Zhang B, Wu Q, Zhou YL, et al. Immune-related adverse events from combination immunotherapy in cancer patients: a comprehensive meta-analysis of randomized

controlled trials. Int Immunopharmacol 2018;63:292-2. DOI: 10.1016/j.intimp.2018.08.014

9. Papamichael K, Van Stappen T, Vande Casteele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2016;14(4):543-9. DOI: 10.1016/j.cgh.2015.11.014

10. Chen JH, Pezhouh MK, Lauwers GY, et al. Histopathologic features of colitis due to immunotherapy with anti-PD-1 antibodies. Am J Surg Pathol 2017;41(5):643-54. DOI: 10.1097/PAS.0000000000000829

11. Boike J, Dejulio T. Severe esophagitis and gastritis from nivolumab therapy. ACG Case Rep J 2017;4:e57. DOI: 10.14309/crj.2017.57

12. Nishimura Y, Yasuda M, Ocho K, et al. Severe gastritis after administration of nivolumab and ipilimumab. Case Rep Oncol 2018;11(2):549-56. DOI: 10.1159/000491862

13. Abu-Sbeih H, Faleck DM, Ricciuti B, et al. Immune checkpoint inhibitor therapy in patients with preexisting inflammatory bowel disease. J Clin Oncol 2020;38(6):576-83. DOI: 10.1200/JCO.19.01674

14. Johnson DH, Zobniw CM, Trinh VA, et al. Infliximab associated with faster symptom resolution compared with corticosteroids alone for the management of immune-related enterocolitis. J Immunother Cancer 2018;6(1):103. DOI: 10.1186/s40425-018-0412-0. Erratum in: J Immunother Cancer 2019;7(1):107. DOI: 10.1186/s40425-018-0412-0

15. Abu-Sbeih H, Wang Y. Management considerations for immune checkpoint inhibitor-induced enterocolitis based on management of inflammatory bowel disease. Inflamm Bowel Dis 2020;26(5):662-8. DOI: 10.1093/ibd/izz212

16. Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother 2021;9(6):e002435. DOI: 10.1136/jitc-2021-002435

17. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 2007;5(1):103-10. DOI: 10.1016/j.cgh.2006.09.033

18. Ma C, MacDonald JK, Nguyen TM, et al. Pharmacological interventions for the prevention and treatment of immune checkpoint inhibitor-associated enterocolitis: a systematic review. Dig Dis Sci 2022;67(4):1128-55. DOI: 10.1007/s10620-021-06948-w

19. Dougan M. Checkpoint blockade toxicity and immune homeostasis in the gastrointestinal tract. Front Immunol 2017;8:1547. DOI: 10.3389/fimmu.2017.01547

20. Samaan MA, Pavlidis P, Papa S, et al. Gastrointestinal toxicity of immune checkpoint inhibitors: from mechanisms to management. Nat Rev Gastroenterol Hepatol 2018;15(4):222-34. DOI: 10.1038/nrgastro.2018.14

21. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol 2015;33(28):3193-8. DOI: 10.1200/JCO.2015.60.8448

22. O'Connor A, Marples M, Mulatero C, et al. Ipilimumab-induced colitis: experience from a tertiary referral center. Therap Adv Gastroenterol 2016;9(4):457-62. DOI: 10.1177/1756283X16646709

23. Verschuren EC, van den Eertwegh AJ, Wonders J, et al. Clinical, endoscopic, and histologic characteristics of ipilimumab-associated colitis. Clin Gastroenterol Hepatol 2016;14(6):836-42. DOI: 10.1016/j.cgh.2015.12.028

24. Luque Carmona AM, Ontanilla-Clavijo G, Leo Carnerero E. Severe enterocolitis secondary to ipilimumab and nivolumab with an excellent response to a single dose of infliximab. Rev Esp Enferm Dig 2020;112(11):889-90. DOI: 10.17235/reed.2020.6886/2020

25. Hillock NT, Heard S, Kichenadasse G, et al. Infliximab for ipilimumab-induced colitis: a series of 13 patients. Asia Pac J Clin Oncol 2017;13(5):e284-90. DOI: 10.1111/ajco.12651

26. Bergqvist V, Hertervig E, Gedeon P, et al. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. Cancer Immunol Immunother 2017;66(5):581-92. DOI: 10.1007/s00262-017-1962-6

27. Karam JD, Noel N, Voisin AL, et al. Infectious complications in patients treated with immune checkpoint inhibitors. Eur J Cancer 2020;141:137-42. DOI:

10.1016/j.ejca.2020.09.025

28. Maher VE, Fernandes LL, Weinstock C, et al. Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. J Clin Oncol 2019;37(30):2730-7. DOI: 10.1200/JCO.19.00318

29. Shankar B, Zhang J, Naqash AR, et al. Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. JAMA Oncol 2020;6(12):1952-6. DOI: 10.1001/jamaoncol.2020.5012

30. Beck KE, Blansfield JA, Tran KQ, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. J Clin Oncol 2006;24(15):2283-9. DOI: 10.1200/JCO.2005.04.5716

31. Fernández-Gordón Sánchez FM, Gómez-Domínguez E, Paredes Ruiz D, et al. Ustekinumab for corticodependent immune-mediated colitis by pembrolizumab, an alternative for patients with concomitant liver injury. Rev Esp Enferm Dig 2022;114(6):356-7. DOI: 10.17235/reed.2022.8618/2022

32. Queiroz NSF, Regueiro M. Safety considerations with biologics and new inflammatory bowel disease therapies. Curr Opin Gastroenterol 2020;36(4):257-64. DOI: 10.1097/MOG.0000000000000607

33. Grover S, Ruan AB, Srivoleti P, et al. Safety of immune checkpoint inhibitors in patients with pre-existing inflammatory bowel disease and microscopic colitis. JCO Oncol Pract 2020;16(9):e933-42. DOI: 10.1200/JOP.19.00672

34. Dougan M, Wang Y, Rubio-Tapia A, et al. AGA clinical practice update on diagnosis and management of immune checkpoint inhibitor colitis and hepatitis: expert review. Gastroenterology 2021;160(4):1384-93. DOI: 10.1053/j.gastro.2020.08.063

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Table 1. Demographic characteristics

Sex (women/men)	9/9
Age (median)	52
Tobacco history	
Current smokers	10 (55 %)
Ex-smokers	6 (33 %)
Never smokers	2 (11 %)
Type of cancer	
Lung	6 (33 %)
Melanoma	3 (16 %)
Esophagus (adenocarcinoma/squamous)	2 (1/1)
Cervix	2 (11 %)
Urothelial	1 (5 %)
Colorectal	1 (5 %)
Hodgkin's Lymphoma	1 (5 %)
Breast	1 (5 %)
Chemotherapy	
Concomitantly	4 (22 %)
Previously	10 (50 %)
IBD	1 (5 %)

IBD: inflammatory bowel disease. Number of patients (%).

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Table 2. Immune checkpoint inhibitors

Anti PD1	**Anti PD1L**	**Anti CTLA4**
Tislelizumab Pembrolizumab Nivolimumab	Atezolizumab Durvalumab	Ipilimumab *Tremelimumab*

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Table 3. Type of disease according to immunotherapy

Disease	Subjects (%)	Immunotherapy
Enterocolitis	14 (77 %)	Anti PD-1/Anti PD-1L: 8 – Tislelizumab – Atezolizumab – Pembrolizumab – Unknown (CT) – Nivolumab – Durvalumab Anti CTLA-4: 2 – Ipilimumab – *Tremelimumab* Combined treatment: 4
Microscopic colitis	3 (16 %)	Anti PD-1/Anti PD-1L: 3 – Atezolizumab – Durvalumab – Nivolumab
Gastritis	1 (5 %)	Combined treatment

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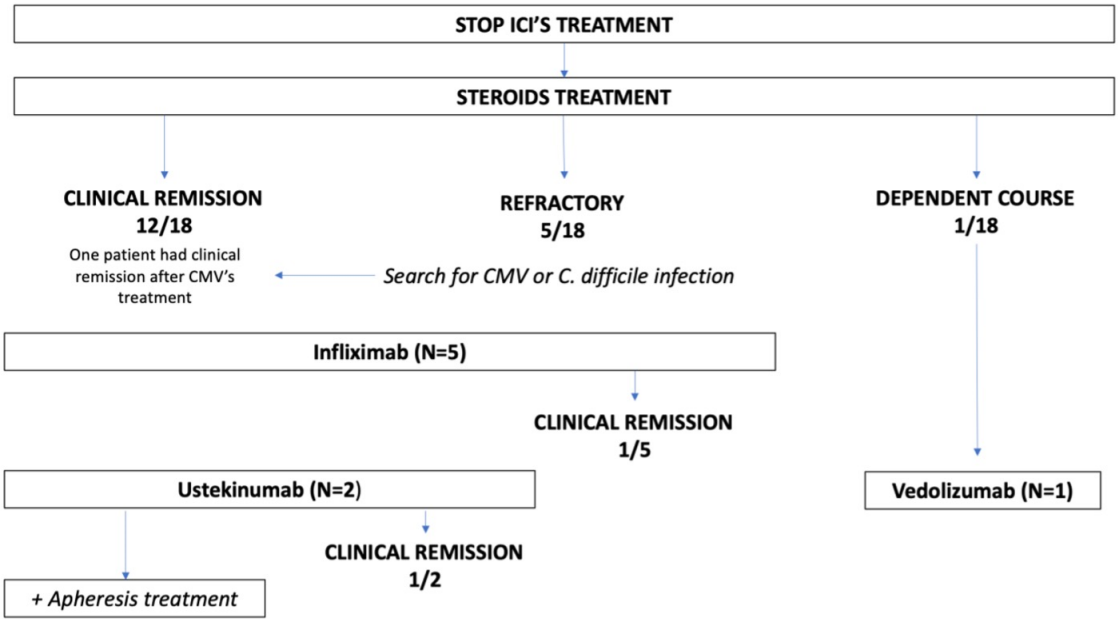

Fig. 1. GI-IrAE management in our patients based on the European Society for Medical Oncology (ESMO) guidelines. ICI: immune checkpoint inhibitors; CMV: cytomegalovirus.

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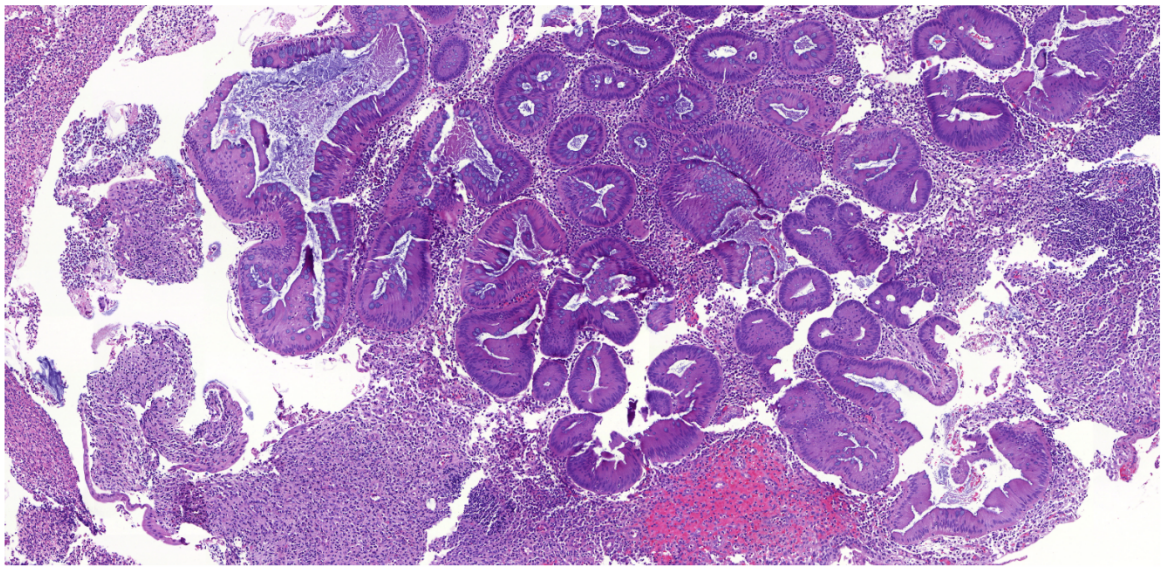

Fig. 2. Histological alterations suggestive of immune mediated enterocolitis.