Immune checkpoint inhibitor refractory colitis leading to total colectomy in a melanoma patient

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Abstract

Immunotherapy is becoming more and more relevant in the treatment of advanced melanoma. Proper management of its side effects can prevent severe complications. We describe the case of a 73-year-old patient with severe refractory colitis secondary to immunotherapy. The patient has been treated for 6 months with Nivolumab, an anti-PD-1, as adjuvant therapy for locally advanced melanoma. He was admitted to the hospital with a deteriorating general condition associated with severe diarrhea and rectal bleeding for 3 weeks. Despite three lines of treatment (high dose corticosteroids, infliximab, mycophenolate mofetil), the patient still presented clinical and endoscopic colitis, with additional infectious complications. The patient required surgical management for total colectomy. In this article we present one of the rare cases of autoimmune colitis that did not respond to various immunosuppressive treatments and required surgery. (Acta gastroenterol. belg., **2023,** 86, **371-373**).

Key words : melanoma, immune checkpoint inhibitor, colitis, colectomy.

Introduction

In the treatment of advanced or metastatic melanoma, anti-PD1 monoclonal antibodies have improved total patient survival with reduced toxicity in comparison to standard chemotherapy and anti-CTLA4 monoclonal antibodies (1). Nivolumab binds to the PD-1 receptor on regulatory T cells to induce an anti-tumor response consisting of increased T cell activation, expansion and infiltration into the tumor microenvironment (2).

Nevertheless, immunotherapies (including nivolumab) are associated with significant adverse events related to overactivation of the immune system. These reactions can affect any organ with a prevalence of the skin, endocrine glands and digestive tract (3).

The guideline of treatment for the management of these side effects recommend corticosteroid as the first line therapy. In refractory cases, treatment with anti TNF-a (e.g. infliximab) or mycophenolate mofetil can be initiated as a second line therapy (4). We report a case of severe colitis refractory to infliximab and mycophenolate mofetil, which required a surgical intervention.

Case report

We present the case of a 73 year old patient followed in oncology for a dorsal melanoma, with left axillary lymph node invasion. This melanoma was staged pT4bN2a (IIIc) in September 2020, without BRAF mutation. He underwent tumor resection and adjuvant immunotherapy with nivolumab was started in December 2020.

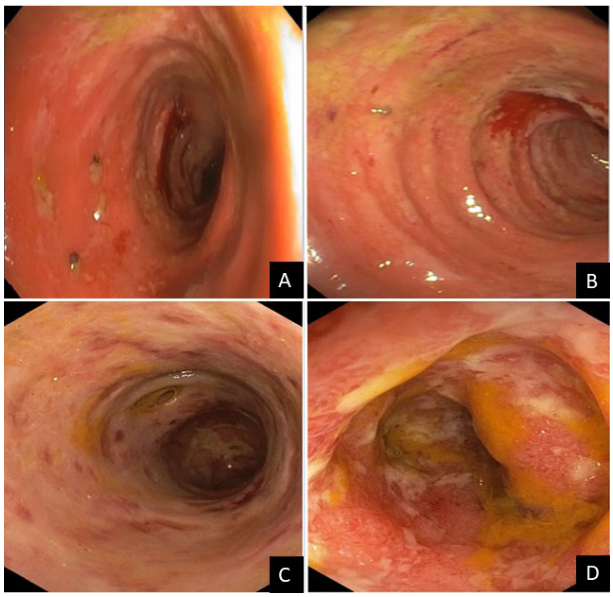

Figure 1. — Endoscopy.
A,B: before treatment; C,D: after treatment.

The patient was admitted to gastroenterology in May 2021 with severe diarrhea (World Health Organization grade III) associated with hypogastric pain and rectal bleeding. On admission, the patient had a soft but tender abdomen in the hypogastric region and increased bowel sounds. Blood tests showed an inflammatory syndrome (CRP 101 mg/L, normal values < 5 mg/L), grade III normocytic anaemia and negative CMV serology and PCR. A CT scan with IV contrast showed thickening of the rectal and sigmoid colon walls, with infiltration of the surrounding fat. Admission sigmoidoscopy revealed severe ulcerated colonic mucosa (MAYO score 3) (Figure 1, image A and B). Anatomopathological study showed a

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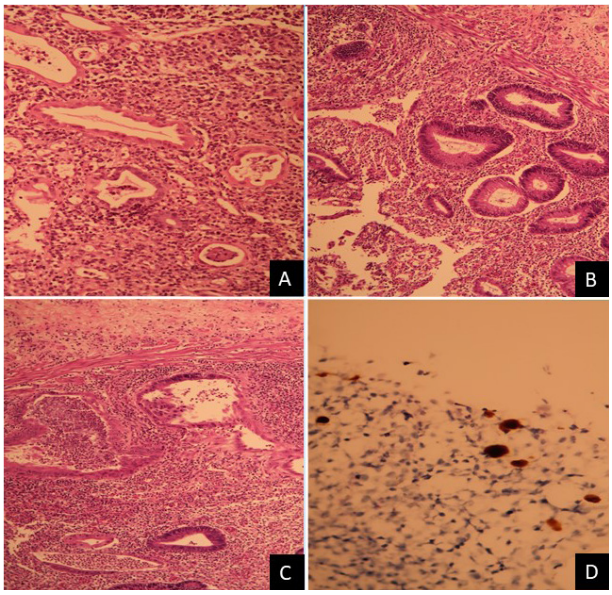

Figure 2. — Biopsy.
A,B: Coloniculceration, residual regenerative colonic glands and severe inflammatory infiltrate; C: acute inflammatory infiltrate with cryptitis; D: immunostaining detection for CMV.

severe, ulcerated, destructive acute colitis with massive neutrophilic infiltration of the mucosa, destruction of the glands and a distinctly regenerative appearance of the mucosa (Figure 2, image A, B and C). A nivolumab-related colitis was diagnosed.

Nivolumab was immediately discontinued as recommended. After an infectious assessment excluding Clostridium difficile, Salmonella, Shigella and Yersinia, high-dose systemic corticosteroid therapy was started (methylprednisolone 1mg/kg IV). The patient's general condition was, at this stage, preserved. At day 7 after admission, the patient still had clinical grade 3 colitis, so infliximab 5mg/kg IV was started in combination with the corticosteroid. The patient's general condition deteriorated with an increase in diarrhea. In this context, a second identical dose of infliximab was given at day 10 despite the ESMO guidelines recommends a second dose after 2 weeks. At day 14, in consideration of a new sigmoidoscopy showing the persistence of severe rectosigmoiditis (Mayo 3), the dose of systemic corticosteroid therapy was increased (methylprednisolone 1.5mg/Kg IV) and a topical corticosteroid (beclometasone 5mg twice a day) was started.

From day 19 to day 35, the patient developed two septic episodes with a Staphylococcus aureus bacteremia and another Enterococcus faecium bacteremia, treated with a total of 24 days of antibiotic therapy. The main hypothesis of the infectious origin is a bacterial translocation in the digestive tract. In view of the infectious context and in the absence of clinical response of the colitis, a third line of treatment was started at day 20 with mycophenolate mofetil (500mg twice daily PO) for 18 days, still associated with topical and systemic corticoids in degressive doses. At day 38, a third sigmoidoscopy was performed showing the persistence of severe pancolitis. A last chance treatment was given based on high dose mycophenolate mofetil (1000mg twice daily PO) combined with methylprednisolone 64mg PO for 5 days.

At the time of this third sigmoidoscopy, the patient had clinical and laboratory evidence of mononucleosis syndrome. This was confirmed by CMV reactivation in the plasma and on anatomopathological analysis (Figure 2, image D). Treatment with ganciclovir was given for a total of 21 days until the CMV PCR became undetectable.

At day 45, a fourth sigmoidoscopy was performed showing cicatricial pancolitis with moderate to severe active inflammatory involvement regardless of the various drug attempts (Figure 1, image C and D). In view of the infectious complications and the lack of endoscopic and clinical response, and after medical and surgical discussion, the indication for total coloprotectomy by laparotomy with terminal ileostomy was made. This was performed at day 52. The patient was discharged after 84 days in hospital in good physical condition. He did not require revalidation. Immunotherapy was not continued and the patient did not develop tumor recurrence.

Discussion

We present a case of severe and refractory autoimmune colitis secondary to immunotherapy with nivolumab.

The incidence of digestive toxicity is higher with anti-CTLA-4 than with anti-PD-1, mainly manifesting as colitis. The incidence of colitis in patients treated with anti-PD-1 or PD-L1 agents is 0.0-1.4%, and grade 3 or higher colitis occurs in 0.0-0.9% of cases. With CTLA-4 therapy, the rate of colitis is reported to be 5.7-9.1%, with an incidence of grade 3 colitis of 4.1-6.8% (5,6,7).

The upper gastrointestinal tract is only rarely involved in ICI toxicity, as shown by Vandepapelière et al (1-2% of the cases with anti -PD1) (8).

In our case, the colitis was complicated by two septicaemias, the first with Staphylococcus aureus and the second with Enteroccocus faecium, as well as CMV reactivation during immunosuppressive therapy. Viral infection may occur as consequence of treatment-induced immunosuppression. It is imperative to investigate CMV infection before augmenting the immunosuppressive therapy. Positive immunohistochemical stainings of colon biopsies and detecting CMV-DNA could explain the resistance to immunosuppressive treatments and induce severe complications if not detected early and treated correctly. CMV screening should be incorporated into current treatment algorithms (9,10).

In our patient, three lines of treatment were tried without clinical or endoscopic improvement. Our case illustrates severe clinical (WHO grade III) and endoscopic (Mayo score 3) colitis that does not respond to the recommended treatment algorithm. According to the recommendations, in case of WHO grade 3 or 4 colitis, immunotherapy should be discontinued and initial management should be

initiated with (methyl)prednisolone 1-2mg/kg (5,11,12). Our patient was admitted with grade 3 colitis with good general condition and very good clinical tolerance. After multidisciplinary discussion, we decided to start with 1mg/kg of methylprednisolone due to the patient's good clinical condition. There was a very transient period of improvement in symptoms from 10 diarrheas per day to 5 diarrheas per day. Then the patient had deteriorated clinically and recurred with grade 3 diarrhea which prompted us to increase the dose of methylprednisolone in a second step.

According to Brahmer JR, et al. and Tang L, et al. they suggest a dose of 1-2 mg/kg, but the subsequent dosing of corticosteroids is unfortunately not clear (11, 12). Furthermore, the literature review by Tang et al. shows that 1mg/kg is often used in grade 3-4 colitis and paradoxically 2mg/kg is used in grade 2 colitis with no significant difference in effectiveness (12).

If there is no improvement, treatment with Infliximab 5mg/kg should be given, which may be repeated a second time if necessary. If there is no endoscopic or clinical response to previous treatments, recommendations for further management are unclear. Mycophenolate mofetil is a third-line treatment option as well as Vedolizumab. Studies do not show significant differences between these two molecules in terms of efficacy (5,13). In our patient, given the reactivation of CMV, vedolizumab did not seem a reasonable treatment option.

Due to the multiple complications, a total colo-protectomy had to be performed. It should be noted that, based on the endoscopic appearance, and in line with known complications in immunotherapy-induced colitis, there was a risk of colonic perforation. Only one case of autoimmune colitis requiring total colectomy without perforation has been reported in the literature, in a colitis secondary to ipilimumab. This patient had severe colitis treated with infliximab which was complicated by necrotic fasciitis of the arm. Due to persistent diarrhea and lack of improvement of endoscopic lesions, colectomy was performed (14). In the literature, we have not found similar cases following treatment with nivolumab. This procedure is only described in cases of colonic perforation. In the literature review by Portenkirchner et al. it is recommended to perform an offloading ileostomy as a first-line procedure in drug-refractory colitis in order to rest the colon and improve the healing rate with the aim of avoiding radical surgery (5). Given the rarity of this procedure in colitis, the number of patients who have undergone an offloading ileostomy in this setting is not sufficient to draw conclusions.

Conclusion

Immunotherapy is becoming more and more relevant in the treatment of cancer, particularly advanced melanoma. We will be confronted with these side effects more and more frequently in our clinical practice. We describe a patient whose colitis secondary to immunotherapy was refractory to 3 lines of treatment. He also presented with CMV reactivation in the colon. In this context, a colectomy had to be performed.

Conflict of interest

I declare any conflict of interest, including any financial activities, additional affiliations, personal or other relationships with other people or organizations that could influence, or be perceived to influence, their work, such as employment, consultancies, stock ownership, honoraria, patent applications/registrations, grants or other funding.

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