World Journal of Health and Medicine
Case Presentation
Volume 1 | Issue 1 (Jun-Aug 2023) | Pages: 01-08
Published Date: June 30, 2023

The Nivolumab Induced Ulcerative Colitis, Case Report and a Literature Review

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Received Date: June 08, 2023; Accepted Date: June 21, 2023; Published Date: June 26, 2023

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Citation: Harsh Kapoor, Rakesh Kumar Jagdish, PuneetGupta and Charul Dabral. The Nivolumab Induced Ulcerative Colitis, Case Report and a Literature Review. W J Heal Med. 2023;1(1):1001.

Abstract

Use of immunotherapy is common in malignancy in these days with encouraging results, but this also comes along with some serious adverse events, and utmost cautions, and high index of suspicion should be kept in the same. We have seen a case that developed severe biopsy proven ulcerative colitis like diseases, post nivolumab therapy, and responded to treatment with steroids, melamine and other supportive treatment for ulcerative colitis.

Introduction

In recent time the treatment of various malignant conditions have been markedly benefited with the use of immunotherapy with encouraging results. However, cautions should be executed while using these for their specific but rare serious adverse events. Immunotherapy-related colitis is similar to ulcerative colitis in many aspects with only few differences and moreover management is also somewhat similar. Early diagnosis should be done with high index of suspecting this. We discuss one of our cases we have encountered with nivolumab induced ulcerative colitis.

Case Report

Mr. HKR, 49-year old male, known case of the Ca Esophagus (post-surgery 2020), post chemotherapy and immunotherapy, he is on Nivolumab therapy, completed 4 doses, last taken, 2 months back, completed four doses only. Nivolumab was given for his residual distress on the PET CT scan in lymph nodes. He was admitted with complaints of the history of melena of four days duration and blood in stool, bleeding per rectum with increased frequency of loose stools. There was no history of alcoholism, tobacco or substance abuse and no significant family history. He came to emergency in hypotension (BP 90/60 mmHg), with severe anemia. He received blood transfusion for anemia correction. His Stool for occult blood was positive. He underwent Upper GI Endoscopy which was normal, except for mild esophagitis, no growth

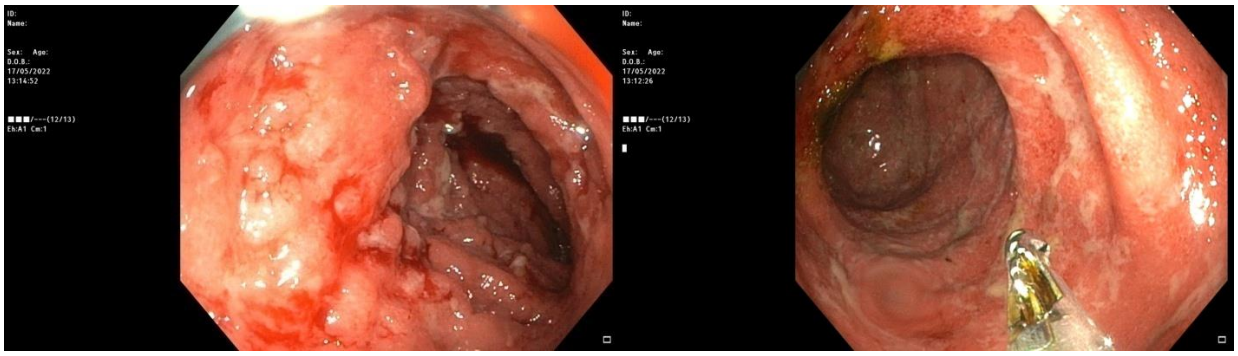
noted, anastomotic site was normal. Colonoscopy was done which showed severe pan colitis, severe disease, biopsies taken, grade-II-III internal and external hemorrhoids, colonic biopsies were suggestive of ulcerative colitis.

For iron deficiency anemia, he received IV iron 1 gm infusion, and for severe pan colitis, he was started on Methylprednisolone Injection 40 mg once daily with weekly taping of 10 mg, he switched to oral steroids once his symptom resolution stated. Mesalamine was also given in doses of 1.2 gm three times daily along with other supportive treatment with antibiotic and probiotics. On follow up steroids were tapered 10 mg every weekly decreased and he has symptomatic improvement, with normalization of stool colour, texture and frequency. Colonoscopy was repeated which showed significant improvement in his diseases and biopsies were also taken which also confirm the clinical improvement was seen along with chemical, pathological improvement as shown in Table 1 and Figure 1 to 3. Moreover, the progression, remission and other long term outcome will be seen on long term follow up, whether it is similar to UC or behaves differently.

Table1:

Investigations	**15/05/22**	**19/05/22**	**24/05/22**	**25/05/22**	**Investigations**	**15/05/2022**	**24/05/2022**	**Investigations**	**15/05/2022**
Hemoglobin	9.4	8.5	9	9.5	**S. Bili. T/D**	0.74/0.20	0.3/0.15	**HBsAg/ Anti-HCV**	Non-reactive
TLC	11100	7500	10200	11200	**AST/ ALT**	42.9/18.0	22.6/16.0	**HIV**	Non-reactive
P. Counts	350	278	314	290	**ALP**	82.8	143.1	**RBS**	80.9
Urea / Creat	15.3/0.66	10.2/0.66	15.0/0.52		**T. Prot/ S. Albumin**	4.8/1.82	4.8/2.14		
Na / K	124/5.4	127/3.44	129/3.90		**INR**	1.3			

Abbreviations: Na: Sodium, K: Potassium, P. Count: Platelets count, TLC: Total Leukocyte Count, Crete: Creatinine, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, INR: International Normalized ratio, HIV: Human Immunodeficiency Virus.



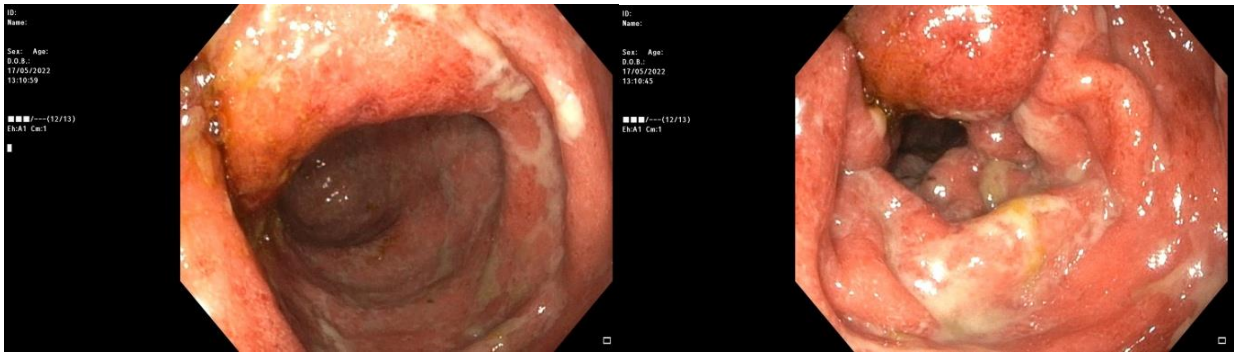


Figure 1: Initial Colonoscopy Images: Severe pan colitis with ulcerative diseases, friable mucosa, loss of vascular pattern, biopsy taken.

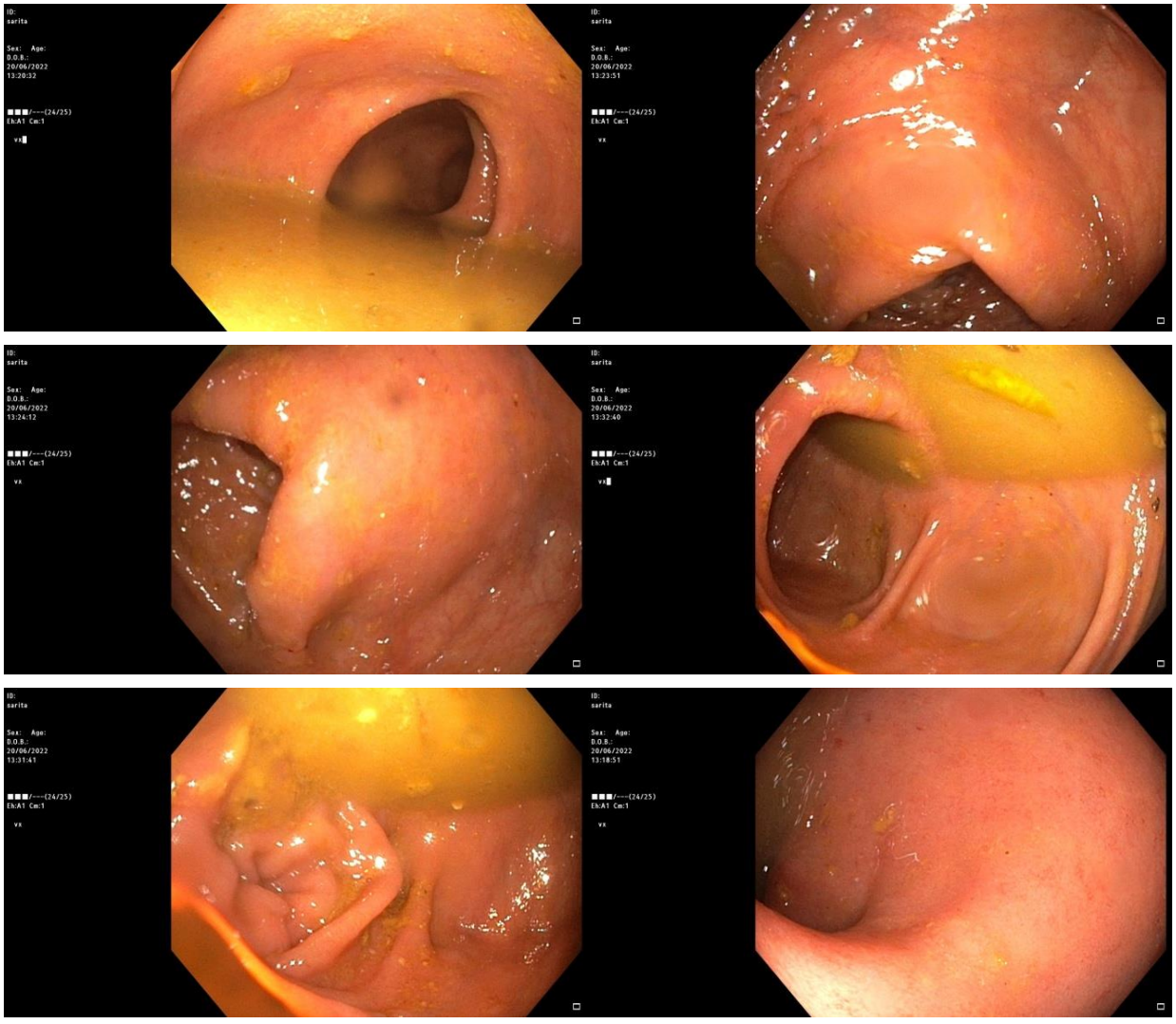


Figure 2: Colonoscopy images after treatment: mild disease activity, with resolution of ulcerative features, with mild erythema present.

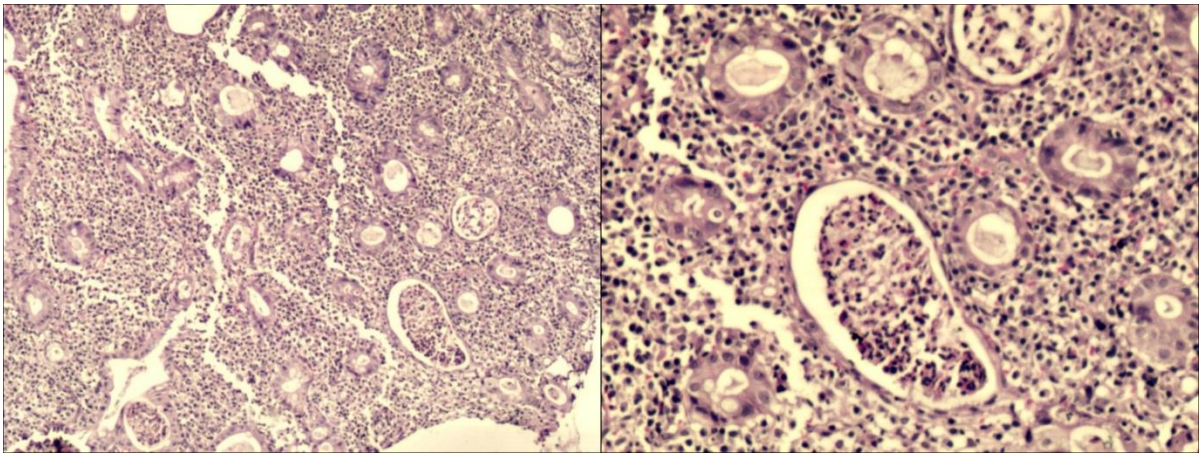


Figure 3: Biopsy Images: suggestive of ulcerative colitis with crypt abscess, creptitis and inflammatory infiltrates.

Review of Literature: Background

Nivolumab and other Immune Checkpoint Inhibitors (ICIs) are found to have efficacy in prolonging survival and in some cases, even recovery is seen, for a variety of malignancies like HCC, Ca Esophagus, Ca lung, etc.

Immune-checkpoint inhibitors can be classified as an anti-PD-1 antibody, anti PD-L1 antibody, and anti-CTLA-4 antibody, and all of these have been shown to prolong the survival of cancer patients in studies [1-3].

The PD-1 pathway controls autoimmunity and suppresses inflammation. Furthermore, inhibition of the PD-1 pathway in mice leads to various autoimmune diseases [4]. The basic mechanism of these agents is to increase the immune response to kill the tumor cells, which is by blocking the inhibitory signal through binding to the inhibitory receptor or its ligand. However, enhanced immunity can trigger the autoimmune process and can result in the precipitation of autoimmune diseases. Therefore, autoimmune diseases are considered as contraindications for their use. Blockade of immunity checkpoints is also associated with inflammatory side effects which are known as immune-related adverse events. These are considered as unique adverse events related to these agents who are different from the conventional chemotherapy adverse events. Similar to autoimmune diseases, these immune-inflammatory adverse events can affect any organ system but typically target the gastrointestinal, hepatic, skin, and endocrine systems [5].

The incidence of Common Terminology Criteria for Adverse Events (CTCAE) has shown that CTLA-4 inhibitors result in more adverse events as compared to PD-1/PD-L1 inhibitors. Grade 3/4 diarrhea is 1% to 2% with PD-1/ PD-L1 inhibitors treatment compared to 3% to 6% with CTLA-4 inhibitors treatment. Grade 3/4 colitis accounts for 1% to 3% among patients treated with PD-1/PD-L1 inhibitors compared to 7% to 9% among patients treated with CTLA-4 inhibitors. These findings suggest that colitis is less frequent during treatment with PD-1/PD-L1 inhibitors than during treatment with CTLA-4 inhibitors [6,7].

Moreover, the literature and data is scarce in this area about the endoscopic features of PD-1/PD-L1 inhibitors as the data which is available is only in the form of case reports [8-11].

Yamauchi R, et al. [12] has reported nivolumab-induced colitis which was similar to UC in both colonoscopy and histological images. Treatment was also similar to that for UC and was largely successful [12].

Studies on basic pathophysiology by Nancey S, et al. [13] on evaluation of these patients have found T-cell imbalance with the decrease in regulatory T-cells and the increase in effect or T-cells [13].

A similar T-cell imbalance was obtained from UC samples in a study by Hanai H, et al [14]. In mice models, Chikuma S, et al. [5] have found that in PD-1-deficient mice, excessive cytokines are produced from T cells and are reported to cause autoimmune disease onset [15]. In summary, in basic studies, excessive cytokine production from activated T cells may partly play an important role in the morphological and pathogenic similarity between the two diseases.

Immune Related Adverse Events of Nivolumab Therapy

Nivolumab and other Immune Checkpoint Inhibitors (ICIs), which have shown high efficacy against a variety of cancers in recent years, promise long-term survival and even recovery. ICIs are also associated with unique adverse events that are different from those associated with conventional chemotherapy [3,16]. Immune-related Adverse Events (irAEs) are attributed to various autoimmune responses that can occasionally become severe and may even be fatal [17-19]. Among them, irAE-associated colitis is reported to closely resemble Ulcerative Colitis (UC) in endoscopic features and treatment responses [12,20-22]. A recent report confirmed the efficacy of concurrent administration of infliximab and ICIs [23].

Ulcerative colitis is conventionally a disease of young patients and recently, the number of elderly-onset UC patients has been rising [24]. In elderly patients, the proportion of comorbidities including malignancy unrelated to Inflammatory Bowel Disease (IBD) is high [25].

For these reasons, the number of IBD patients with a co-morbid malignancy requiring ICI treatment is expected to increase. However, patients with autoimmune diseases such as IBD have historically been excluded from clinical trials of ICIs, and there are few reports of programmed cell death Protein-1 (PD-1) inhibitors administered to patients with a pre-existing form of IBD [26,27]. Herein, we report an elderly patient with remission of a worsening UC flare-up after nivolumab administration.

Treatment

If immune-related colitis is suspected, a gradual approach according to severity is recommended [28]. The National Cancer Institute's CTCAE has typically been used to define grades of diarrhea and colitis during clinical treatment. According to previous reports [29,30], if grade 1 diarrhea/colitis is diagnosed, Immune-Checkpoint Inhibitors (ICI) can be continued and symptomatic treatment for the adverse event should be given and careful follow-up should be conducted, but If the diarrhea/Colitis is of grade 2, with increased stool frequency, abdominal pain, mucous or blood in stool, ICI (Immune-Checkpoint Inhibitors) needs to be stopped and symptomatic treatment for the adverse event should be given, along with oral systemic corticosteroids, equivalent to 0.5 mg/kg/day to 1 mg/kg/day methylprednisolone for >3 days should be given, which are gradually tapered over 4-8 weeks, if improvement is seen. Moreover, if the improvement is not observed within 3-5 days or worsening occurs, then the adverse event should be managed as a grade 3 adverse event. For grade 3 diarrhea/colitis, Intravenous (IV) high-dose systemic steroids, equivalent to 1 mg/kg/d to 2 mg/kg/d methylprednisolone should be given.

In steroid-refractory cases, immunosuppressive treatment should be escalated along with risks of steroid-related adverse events or severe colitis-related complications like gastrointestinal perforation. Infliximab therapy (anti-TNF therapy) has shown promising results in some cases that do not respond to steroids [12] but anti-TNF cannot be used in gastrointestinal perforation or sepsis.

Similar to the treatment of ulcerative colitis, treatment with mesalazine is shown to reduce the severity of immune-checkpoint inhibitor-induced colitis symptoms along with the decrease in the frequency of diarrhea and improvement in the

endoscopic findings [30]. The basic mechanism behind this is similar to UC, where mesalazine functions as an inhibitor of inflammatory cytokines as well as prostaglandin-related substances [31,32]. In this way, mesalazine may improve patient outcomes following nivolumab-induced colitis. Moreover, the progression, remission and other long-term outcomes will be seen in the long-term follow-up, whether it is similar to UC or behaves differently.

Conclusion

The use of immunotherapy is common in malignancy these days with encouraging results, but this also comes along with some serious adverse events, and the utmost caution and high index of suspicion should be kept for the same. Management of immunotherapy-related colitis is similar to ulcerative colitis but these needs to be identified early for best results before further life-threatening complications set in. It needs to be seen if drug-induced ulcerative colitis has the same risk of recurrence as intrinsic UC.

References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.
2. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455-65.
3. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.
4. Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. Nat Immunol. 2013;14(12):1212-8.
5. Postow MA. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book. 2015:76-83.
6. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013;369(2):134-44.
7. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515(7528):563-7.
8. Kubo K, Kato M, Mabe K. Nivolumab-associated colitis mimicking ulcerative colitis. Clin Gastroenterol Hepatol. 2017;15(9):A35-6.
9. Takayama M, Ohara Y, Hata K, Kinoshita D, Okuda H, Kawasaki T, et al. A case of acute colitis mimicking ulcerative colitis during nivolumab infusion therapy for advanced melanoma. Gastrointest Endosc. 2017;59(4):450-5.
10. Takenaka T, Yamazaki K, Miura N, Harada N, Takeo S. Osimertinib reactivated immune-related colitis after treatment with anti-PD1 antibody for non-small cell lung cancer. Invest New Drugs. 2017;35(6):848-50.
11. Yanai S, Nakamura S, Matsumoto T. Nivolumab-induced colitis treated by infliximab. Clin Gastroenterol Hepatol. 2017;15(4):e80-1.
12. Yamauchi R, Araki T, Mitsuyama K, Tokito T, Ishii H, Yoshioka S, et al. The characteristics of nivolumab-induced colitis: an evaluation of three cases and a literature review. BMC Gastroenterol. 2018;18(1):135.
13. Nancey S, Boschetti G, Cotte E, Ruel K, Almeras T, Chauvenet M, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab is associated with a profound long-lasting depletion of Foxp3+ regulatory T cells: a mechanistic explanation for ipilimumab-induced severe enterocolitis? Inflamm Bowel Dis. 2012;18:E1598-1600.

14. Hanai H, Iida T, Ikeya K, Abe J, Maruyama Y, Shimura T, et al. A new paradigm in ulcerative colitis: regulatory T cells are key factor which induces/exacerbates UC through an immune imbalance. Mol Immunol. 2013;54(2):173-80.
15. Chikuma S, Terawaki S, Hayashi T, Nabeshima R, Yoshida T, Shibayama S, et al. PD-1-mediated suppression of IL-2 production induces CD8+ T cell anergy in vivo. J Immunol. 2009;182(11):6682-89.
16. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. JAMA Oncol. 2019;5(10):1411-20.
17. Yoshino K, Nakayama T, Ito A, Sato E, Kitano S. Severe colitis after PD-1 blockade with nivolumab in advanced melanoma patients: potential role of Th1-dominant immune response in immune-related adverse events: two case reports. BMC Cancer. 2019;19:1019.
18. Gupta A, De Felice KM, Loftus EV, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. Aliment Pharmacol Ther. 2015;42(4):406-17.
19. Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, 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.
20. Canete F, Manosa M, Lobaton T, Mesonero F, Rodriguez-Lago I, Cabre E, et al. Nivolumab-induced immune-mediated colitis: an ulcerative colitis look-alike-report of new cases and review of the literature. Int J Colorectal Dis. 2019;34(5):861-5.
21. Thompson JA, Schneider BJ, Brahmer J, Armand P, Davies M, Ernstoff MS, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), management of immunotherapy-related toxicities, Version 1. 2020. J Natl Compr Canc Netw. 2020;18(3):231-41.
22. Abu-Sbeih H, Ali FS, Wang X, Mallepally N, Chen E, Altan M, et al. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis. J Immunother Cancer. 2019;7(1):93.
23. Badran YR, Cohen JV, Brastianos PK, Parikh AR, Hong TS, Dougan M. Concurrent therapy with immune checkpoint inhibitors and TNFalpha blockade in patients with gastrointestinal immune-related adverse events. J Immunother Cancer. 2019;7(1):226.
24. Shi HY, Chan FK, Leung WK, Li MK, Leung CM, Sze SF, et al. Natural history of elderly-onset ulcerative colitis: results from a territory-wide inflammatory bowel disease registry. J Crohns Colitis. 2016;10(2):176-85.
25. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. Inflamm Bowel Dis. 2009;15(2):182-9.
26. Leonardi GC, Gainor JF, Altan M, Kravets S, Dahlberg SE, Gedmintas L, et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and pre-existing autoimmune disorders. J Clin Oncol. 2018;36(19):1905-12.
27. Gutzmer R, Koop A, Meier F, Hassel JC, Terheyden P, Zimmer L, et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and pre-existing autoimmunity or ipilimumab-triggered autoimmunity. Eur J Cancer. 2017;75:24-32.
28. Eigentler TK, Hassel JC, Berking C, Aberle J, Bachmann O, Grunwald V, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev. 2016;45:7-18.

29. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30(21):2691-7.
30. Marthey L, Mateus C, Mussini C, Nachury M, Nancey S, Grange F, et al. Cancer immunotherapy with anti-CTLA-4 monoclonal antibodies induces an inflammatory bowel disease. J Crohns Colitis. 2016;10(4):395-401.
31. Rousseaux C, Lefebvre B, Dubuquoy L, Lefebvre P, Romano O, Auwerx J, et al. Intestinal anti-inflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. J Exp Med. 2005;201(8):1205-15.
32. Ikeda I, Tomimoto A, Wada K, Fujisawa T, Fujita K, Yonemitsu K, et al. 5-aminosalicylic acid given in the remission stage of colitis suppresses colitisassociated cancer in a mouse colitis model. Clin Cancer Res. 2007;13(21):6527-31.