*Wang D, et al. Iran J Immunol. 2020; 17(2):167-171*
https://doi.org/10.22034/iji.2020.85507.1717.

## CASE REPORT

# Immune-Related Adverse Events Mimicking Behcet's Disease in a Gastric Cancer Patient Following Camrelizumab Treatment

Dong Wang[1,¥], Shasha Zhang[2,¥], Pingan Ding[1], Yufei Zhao[2], Xiaoyun Zhang[2], Qun Zhao[1*]

[1]Department of Surgery, [2]Department of Immunology and Rheumatology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, P.R. China

## ABSTRACT

**Background:** Anti-programmed cell death 1(anti-PD-1) antibodies are immune checkpoint inhibitors (ICIs) used as a treatment option for a number of cancers to expand lifespan. However, the toxicity caused by ICIs is often unpredictable and can be occasionally life-threatening. **Objective:** To evaluate the immune-related adverse events (irAEs) induced by Camrelizumab, an anti-PD-1 antibody in a patient with gastric cancer. **Case:** The patient was a 32-year-old man who was diagnosed with stage IIIA gastric adenocarcinoma (cT4aN1M0) in pre-operative evaluation. However, pancreatic invasion and peritoneal metastasis were found during surgery. He received a three-week cycle of 200 mg Camrelizumab combined with systemic chemotherapy. After the fifth administration of Camrelizumab, the patient displayed irAE mimicking Behcet's disease with oral and penile ulcers, skin and abdominal incision lesions. Camrelizumab was permanently discontinued, but systemic chemotherapy was continued. The symptoms were improved with discontinuation of Camrelizumab and administration of glucocorticoid and immunosuppressive agents for 8 weeks, but suspicious liver metastases occurred and carbohydrate antigen 19-9 showed an increasing trend in the meantime. Given the significant improvement in the patient's symptoms after discontinuation of Camrelizumab and administration of corticosteroids and immunosuppressants, we assumed that these treatments may play a role in the rehabilitation of patients. **Conclusion:** Severe irAEs occur at a low frequency when anti-PD-1 antibodies are used as monotherapy. Whether anti-PD-1 antibodies combined with systemic chemotherapy increase the incidence of irAEs is not certain.

*Received: 2020-03-02, Revised: 2020-06-13, Accepted: 2020-06-17.*
**Citation:** Wang D, Zhang S, Ding P, Zhao Y, Zhang X, Zhao Q. Immune-Related Adverse Events Mimicking Behcet's Disease in a Gastric Cancer Patient Following Camrelizumab Treatment. *Iran J Immunol*. 2020; 17(2):167-171. doi: 10.22034/iji.2020.85507.1717.

**Keywords: Anti-PD-1 antibodies, Gastric Adenocarcinoma, Immune-Related Adverse Events, Ulcers**

---

*Corresponding author: Dr Qun Zhao, Department of Surgery, The Fourth Hospital of Hebei Medical University, 12 Jiankang Road, Shijiazhuang 050011, P.R. China, e-mail: zhaoqun@hebmu.edu.cn
¥These authors contribute equally to this work.

## INTRODUCTION

Anti-Programmed Cell Death 1 (anti-PD-1) antibodies enhance antitumor immunity by blocking negative regulators of T-cell function, which had a great impact on cancer immunotherapy (1). However, immune checkpoint inhibitors (ICIs) have their own distinctive adverse events commonly described as immune-related adverse events (irAEs) (2,3). Even though any organ or tissue could be affected, irAEs most commonly affect the skin, gastrointestinal tract, endocrine glands, liver, and lung. In most cases, the irAEs occur within the first 3-4 months of therapy, occasionally after a single dose, but can also occur long after drug discontinuation (4,5). Although the irAEs are generally mild and could be controlled medically, interruption of ICI, high dose corticoids and immunosuppressive are needed when severe irAE occurs (6,7). Camrelizumab (AiRuiKa™), a programmed cell death 1 (PD-1) inhibitor and monoclonal antibody humanized IgG4, inhibited the binding interaction of PD-1 and PD-L1 so as to activate T cells for immune killing to tumor cells (8,9,10).

## CASE REPORT

A 32-year-old man was diagnosed with stage ⅢA gastric adenocarcinoma (cT4aN1M0) preoperatively and underwent palliative surgery on 28 December 2018. Pancreatic invasion and peritoneal metastasis were found during the operation (pT4aN2M1). The expression level of the PD-L1 was detected by immunohistochemistry and the positive rate of PD-L1 staining was 5% with a monoclonal antibody (clone 22C3, DAKO). Therefore, he started a three-week cycle of 200mg camrelizumab combined with systemic chemotherapy of intravenous infusion of paclitaxel liposome (Nanjing luye Medicine Co.Ltd) 135mg/$m^2$ and orally administration of Weikangda (a combined Tegafur, Gimeracil and Oteracil Potassium Capsules, Shandong new times Medicine Co.Ltd) 60mg twice a day after intraperitoneal injection of paclitaxel liposome 60mg postoperatively. The patient's condition improved and stabilized within the first four cycles of the treatment based on CT and tumor biomarker examination. However, after the fifth administration of camrelizumab, two small, irregular, painful ulcers developed on the medial side of the upper lip, which healed itself after a few days (Figure 1A, Figure 2A). Meanwhile, lesions appeared on the glans of the penis with scab and erosion intermittently (Figure 1B), and the erosion developed on the abdominal incision with yellow purulent secretion occasionally (Figure 1C, Figure 1D). Initially, topical use of glucocorticoid for 4 weeks without camrelizumab discontinuing did not improve the patient's symptoms of erosion on the glans and abdominal incision. In addition, he suffered from small intestinal obstruction at that time, which was relieved after being treated with intestinal obstruction catheter. The skin lesions, initially small blisters, later resembling folliculitis or acne with mild itching on the back of both hands and feet appeared after he was treated with camrelizumab druing the sixth cycles (Figure 1E, Figure 1F). The patient had no previous history of immune-related disease. The laboratory analysis indicated the normal antinuclear antibody spectrum and immunoglobulin. Cytokine examination at that time indicated that IL-8 was promoted as 25.92 pg/mL. He refused the biopsy of skin lesions or other invasive physical examination. We diagnosed him as immune-related adverse event mimic Behcet's disease based on the clinical manifestation and laboratory analysis.

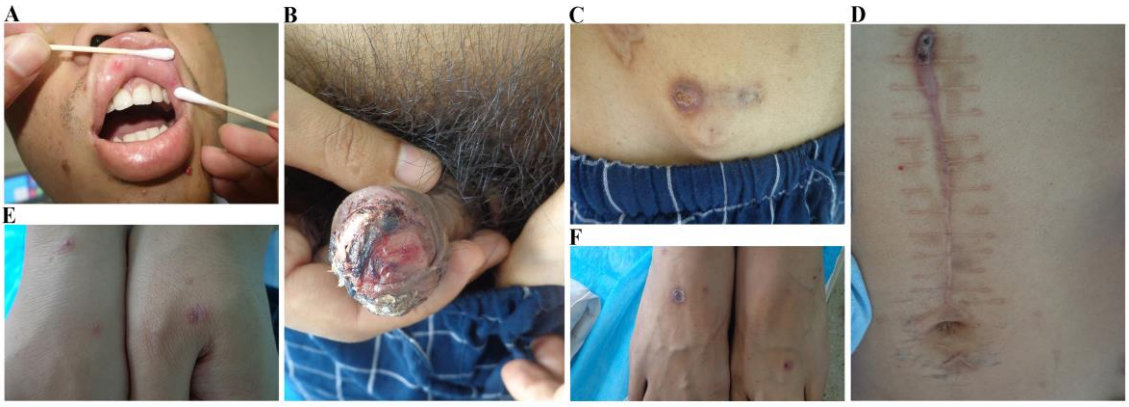


**Figure 1. Clinical manifestations before treatment.** Two small, irregular, painful ulcers on the medial side of the upper lip (A). Lesions on the glans of the penis with scab and erosion intermittently (B). Erosion on the right lower abdominal incision (C) and median abdominal incision (D) with yellow purulent secretion occasionally. Skin lesions, initially small blisters, later resembling folliculitis or acne with mild itching on the back of both hands (E) and feet (F).

Thus, camrelizumab was terminated and he was then treated with prednisone acetate tablets 40mg and thalidomide tablets 50mg daily. The original systemic chemotherapy continued with a three-week cycle. Two months later, the symptoms of the glans and skin lesions significantly improved, and pigmentation was left on the back of both hands and feet (Figure 2B, Figure 2E, Figure 2F). The abdominal incision was not fully healed because it was sutured again when the venous port acess was removed (Figure 2C, Figure 2D). After discontinuing the prednisone acetate and thalidomide, no irAE was observed.

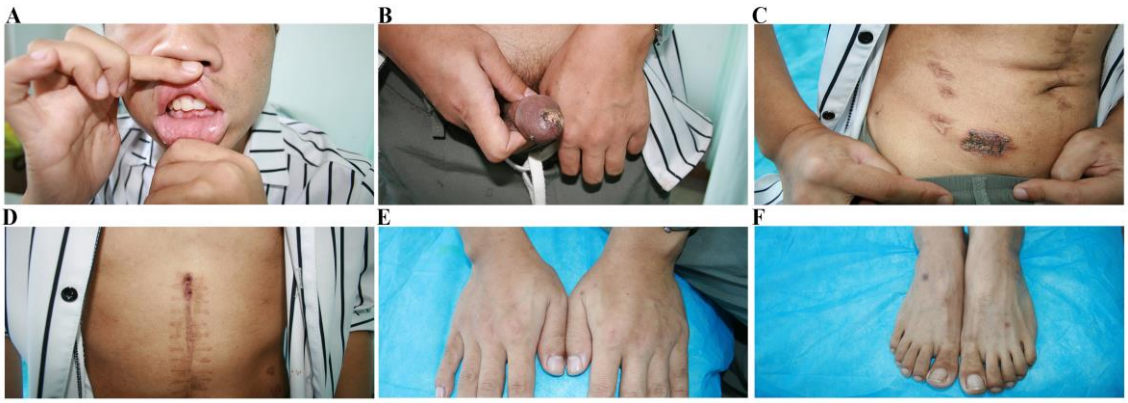


**Figure 2. Self-healing oral ulcers a few days later and other clinical manifestations after two months of administration of prednisone acetate and thalidomide.** Oral ulcers healed up after a few days without any treatment (A). Scab on the glans of the penis without erosion (B). Scab with purulent secretion on the right lower abdominal incision since it was sutured again when the venous port acess was removed (C). Scab without purulent secretion on the median abdominal incision (D). Pigmentation left on the back of both hands (E) and feet (F).

## DISCUSSION

Anti-PD-1 antibodies which enhance antitumor immunity by blocking negative regulators of T-cell function has been recommended for third-line treatment of patients with advanced gastric cancer (11). Camrelizumab is known to be a PD-1 inhibitor and monoclonal antibody humanized IgG4, which binds to PD-1. Clinical trial for anti-PD-1 antibodies camrelizumab plus systemic chemotherapy was well tolerated with noteworthy responses as the first-line therapy in advanced gastric cancer patients (Clinical trial No: NCT03472365). We reported that a gastric cancer patient developed the delayed immune-related adverse event with camrelizumab. The irAE mimics Behcet's disease with oral ulcers, erosion of glans, skin lesions, and abdominal incision lesions is similar to positive reaction of pathergy skin test. This might be the first case of irAE mimicking Behcet's disease after PD-1 antibody treatment in gastric cancer patient. Most gastric cancer patients treated with camrelizumab experienced an adverse event, among which 24% were ≥grade 3 and 2.7% were ≥grade 4. The prevailing irAEs occurring at a rate of ≥ 10% include reactive cutaneous capillary endothelial proliferation, anaemia, fever, fatigue, hypothyroidism, proteinuria, and cough. Most irAEs are reversible and can be controlled by interrupting camrelizumab treatment or corticosteroids (12). The patients with grade 4 and some serious grade 3 irAEs need permanent discontinuation of ICI. The irAEs of the gastric cancer patient could be classified as severe grade 3, according to the symptoms including the skin and abdominal incision lesions, multi-site ulcers and the depth of the ulcers. The irAEs are unique adverse events caused by ICIs with which all organs can be affected, yet the mechanisms of irAEs still remain elucidated (13). Camrelizumab is a humanized high-affinity IgG4-kappa anti-PD-1 monoclonal antibody for treatment of various malignancies (12). The heavy chain complementary-determining regions 2 (CDRsH2) of camrelizumab bind to the 58 N-glycosylated asparagine of PD-1, thereby blocking the interaction of PD-1 to PD-L1 allowing T cells to be activated (10). The abnormal activation of T cells could increase T cell activity against antigens presented in tumors and healthy tissues as well as inflammatory cytokines levels to initiate autoimmune diseases (14). The promotion of IL-8 might increase the activity of neutrophils and neutrophil infiltration around the blood vessels that mimic the possible pathogenesis of Behcet's disease in this case (15,16). Several studies have found that patients with irAEs respond better to ICI compared to those without irAEs (17,18). We will observe the following process of the patient to check whether irAE respond better to camrelizumab.

In conclusion, we reported immune-related adverse event mimic Behcet's disease in a gastric cancer patient with camrelizumab treatment.

## ACKNOWLEDGEMENTS

The present study was supported by the Science and Nature Project of Hebei (Grant No. H2019206428).

## REFERENCES


1. Kadono T. Immune-related adverse events by immune checkpoint inhibitors. Japanese J Clin Immunol. 2017; 40:83-9.
2. Obara K, Masuzawa M, Amoh Y. Oral lichenoid reaction showing multiple ulcers associated with anti-programmed death cell receptor-1 treatment A report of two cases and published work review. J Dermatol. 2018; 45:587-91.
3. Cappelli LC, Shah AA, Bingham CO. Immune-Related Adverse Effects of Cancer Immunotherapy— Implications for Rheumatology. Rheum Dis Clin North Am. 2017; 43:65-78.
4. Suarez-Almazor ME, Kim ST, Abdel-Wahab N, Diab A. Review: Immune-Related Adverse Events With Use of Checkpoint Inhibitors for Immunotherapy of Cancer. Arthritis Rheumatol. 2017; 69:687-99.
5. Johnson DB, Friedman DL, Berry E, Decker I, Ye F, Zhao S, et al. Survivorship in immune therapy: assessing chronic immune toxicities, health outcomes, and functional status among long term ipilimumab survivors at a single referral center. Cancer Immunol Res. 2015; 3:464–69.
6. Cohen Tervaert JW, Ye C, Yacyshyn E. Adverse events associated with immune checkpoint blockade. N Engl J Med. 2018; 378:1164-65.
7. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28:119–42.
8. Finlay WJJ, Coleman JE, Edwards JS, Johnson KS. Anti-PD1 'SHR-1210′ aberrantly targets pro-angiogenic receptors and this polyspecificity can be ablated by paratope refinement.MAbs. 2019; 11:26-44.
9. Mo H, Huang J, Xu J, Chen X, Wu D, Qu D, et al. Safety, anti-tumour activity, and pharmacokinetics of fixed-dose SHR-1210, an anti-PD-1 antibody in advanced solid tumours: a dose-escalation, phase 1 study. Br J Cancer. 2018; 119:538–45.
10. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. Front Pharmacol. 2017; 8:561.
11. Markham A, Keam SJ. Camrelizumab: First Global Approval. Drugs. 2019; 79:1355-61.
12. Postow MA, Sidlow R, Hellmann MD. Adverse events associated with immune checkpoint blockade. N Engl J Med. 2018; 378:158-68.
13. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med. 2016; 375:1767-78.
14. Charo IF, Ransohoff RM. The Many Roles of Chemokines and Chemokine Receptors in Inflammation. N Engl J Med. 2006; 354:610-21.
15. Zimmermann HW, Sebastian S, Gassler N, Nattermann J, Luedde T, Trautwein C, et al. Interleukin-8 is activated in Patients with chronic liver diseases and associated with hepatic macrophage accumulation in human liver fibrosis. PLoS One. 2011; 6:e21381.