MEDS Clinical Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2023.040701
ISSN 2616-1907 Vol. 4 Num. 7

Lynch Syndrome-Associated Colorectal Cancer with Tumor Disappearing after Toripalimab Injection Treatment: A Case Report

Lu Lyu[1], Yali Yan[2], Guofang Gao[3,*]

[1]Department of Allergy, Hohhot First Hospital, Hohhot, 010030, China
[2]Department of Allergy and General Surgery, Hohhot First Hospital, Foundational and Translational Medical Reseach Center, Hohhot, 010030, China
[3]Department of Pediatric Outpatient, Beijing Jishuitan Hospital, National Center for Orthopaedics, Beijing, 102208, China
[*]Corresponding author

Keywords: Lynch syndrome; Colorectal cancer; Immune checkpoint inhibitor; Immune-related adverse events

Abstract: This study aims to investigate the effect of immune checkpoint inhibitors in Lynch syndrome-associated colorectal cancer patients and provide a reference for treatment. A retrospective analysis of a case with multiple recurrences in colorectal cancer. The immune-related adverse effects and effect of Toripalimab Injection treatment is a case series study with a 2-year follow-up. The patient showed stable disease with immunotherapy for ten months. The tumor disappeared along with the download trend of blood tumor marker measurement. The immune-related adverse events were in remission during the treatment and eventually disappeared upon discontinuation of the medication. We believe our report can provide some references for treating this case and treating immune-related adverse reactions.

1. Introduction

Lynch syndrome (LS) is an autosomal dominant genetic disease caused by a germ-line mutation of 4 kinds of DNA mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) or the EPCAM gene by epigenetic inactivation of the respective MSH2 allele[1]. Cancer of the colon and rectum is the third most common cancer and the second leading cause of death worldwide, approximately 5-16% of disease patients are associated with cancer-related gene mutation, and Lynch syndrome accounts for 3-5%[2]. Subtotal/total colectomy is the preferred treatment for Lynch syndrome-associated colorectal cancer(CRC), however, immunotherapy for microsatellite-instability-high advanced colorectal cancer is uprising, and the efficiency has proven with the development of LS's disease research[3-4]. We report a 2-year follow-up of a 57-year-old male patient with Lynch syndrome-associated colorectal cancer, who was referred for Toripalimab Injection, one of the immune checkpoint inhibitors (ICI) mainly used in melanoma. The tumor in the colon is disappeared after regular treatment.

2. General Information

A 57-year-old man visited the hospital with obstructive defecation and lumbago and was diagnosed with advanced descending colon cancer. From the age of 30 years, he had two episodes of colorectal cancer and experienced surgeries for rectal cancer and subtotal colectomy. Contrast-enhanced computed tomography (CECT) showed a sigmoid colonic mass lesion with few enlarged perilesional lymph nodes. Colonoscopy demonstrated circumferential ulceration with an irregular margin associated with luminal narrowing noted 17 cm from the anal verge, and scope could not negotiate beyond; biopsies took. Later, the biopsy(Figure 1) came with moderately differentiated adenocarcinoma of the colon, along with anastomotic mucosa necrosis and chronic inflammation. The serum tumor markers were as follows: carcinoembryonic antigen was 3.65ng/ml, carbohydrate antigen 19-9 (CA 19-9) was 21.82U/ml, carbohydrate antigen 72.4 (CA72.4) was 24.17U/ml，and carbohydrate antigen 125 (CA125) is 4.28U/ml. On abdominal contrast-enhanced CT, remnant thickened intestinal wall performed postoperative morphological changes, a 63 mm x49mm mass shadow. And the surrounding fat layer was turbid. Lymph nodes (LNs) were multiple; the larger was an 8mm mass shadow. It was considered a colorectal cancer recurrence and may be cancer metastasis. Further detection of screening of genetic bowel disease-associated colorectal cancer showed microsatellite instability-high tumors and MLH1 mutation, confirming Lynch Syndrome.

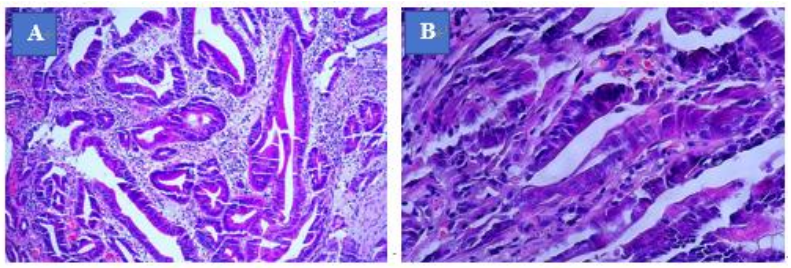

Figure 1: Histopathological Section of the Colon (Hematoxylin & Eosin; A: ×10; B: ×40).

3. Family History

In this family, even cases of colorectal cancer in four generations have been diagnosed (Figure. 2). The onset of age is between 30 and 62 years old. The median age is 40 years old. Two of these cases died of colorectal cancer. Four diagnosed with colon cancer and accepted surgery; half died later. One out of seven became ill three times, treated surgically and nonsurgically, with various clinical diagnoses of two colons and one colorectal cancer, then recovered after immunotherapy. This patient is proband to understand the Lynch syndrome, screening for gene loci.

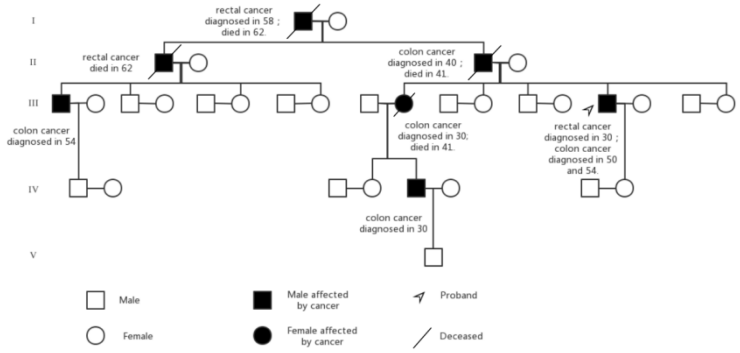

Figure 2: Patient Family Map.

4. Treatment and Outcome

This patient received two cycles of Capecitabine plus oxaliplatin (XELO) regimen at the beginning of tumor recurrence. Following genetic test results regarding the diagnosis, the patient was referred for immunotherapy, using Toripalimab Injection 240mg/q21d ivgtt for two years, after screening for hereditary colorectal cancer gene loci. Assessing tumor changes by abdominal contrast-enhanced CT and detection of serum tumor markers during drug treatment (Table 1), a sharp reduction in tumor size was reported as assessed on abdominal contrast-enhanced CT imaging(Figure 3), as well as in the detection of serum tumor markers over one month. He was free of tumor progression at ten months. At the time of writing-two years later, he was still in remission. However, the cervical lymph nodes did not shrink after 5 months of treatment.

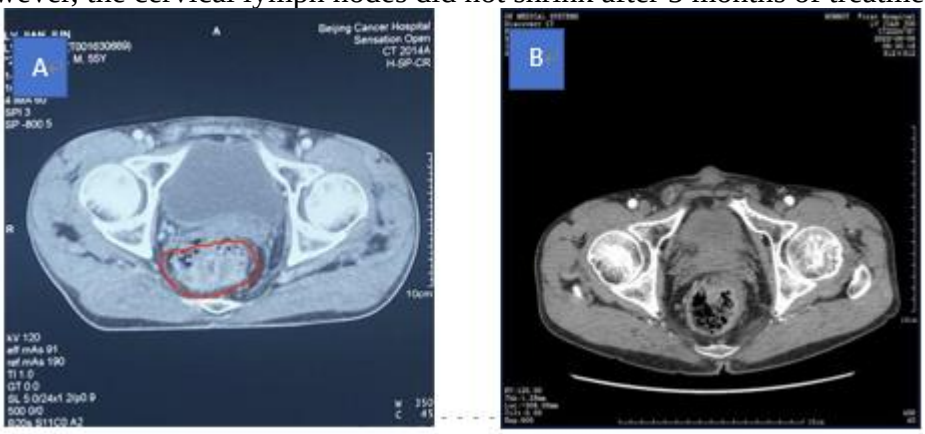

Figure 3: Contrast-enhanced abdominal CT images of the patient before and after 42 months of discontinuation of the medication.

Table 1: The tumor and lymph node changes by abdominal contrast-enhanced CT and detection of serum tumor markers during drug treatment.

Time(month)	The long diameter of the tumor(mm)	The short diameter of the tumor(mm)	The short axis of the largest lymph node(mm)	CEA(ng)	CA199(U/ml)	CA72.4(U/ml)	CA125(U/ml)
0	63	49	8	3.65	21.82	24.17	4.28
2	59	44	6	4.82	21.04	50.83	4.52
3	47	26	7	5.1	14.18	8.46	3.53
5	43	23	5	4.68	13.99	10.18	3.86
8	0	0	5	——	——	——	——
11	0	0	5	——	——	——	——
20	0	0	5	——	——	——	——
25	0	0	5	7.35	12.83	2.44	7.2
48	0	0	5	——	——	——	——

5. The immune-related adverse events

The immune-related adverse events were adverse cutaneous reactions, affecting mainly the back and the back of the hands with maculopapular rashes. On the back, these papules rushed rapidly when medication therapy disappeared without any measure some hours or one week later. It was perhaps related to sweating, so thinning coveries could relieve symptoms. Skin rash and induration came out on the back of the hands, sometimes the scaly skin. Topical corticosteroids were administered less effectively. However, skin moisturizer did work. Appropriate application of a moisturizer attempts to improve dryness and the skin's natural barrier function to protect the skin

from internal and external irritants to keep the skin healthy. The smaller the tumor was, the lower the adverse cutaneous reaction was, but it did not cure. After treatment, the skin reaction was spontaneous remission.

6. Conclusion

We experienced a case of Lynch syndrome for advanced descending colon cancer in the patient. He had been treated with Toripalimab Injection since 57 years old. The effectiveness of ICI is reliably established, but this medication is not reliably established due to colorectal cancer following diagnosis, especially since durable remission is rare. The mechanism of action of it is discussed[5] that programmed death-ligand 1 (PD-L1), a critical immune checkpoint ligand, is a transmembrane protein synthesized in the endoplasmic reticulum of tumor cells and transported to the plasma membrane to interact with programmed death 1 (PD-1) expressed on T cell surface. Expression of programmed death ligand 1 in tumor microenvironments is a primary immune checkpoint for tumor-specific T cell responses as it binds to programmed cell death protein-1 on activated and dysfunctional T cells1. As well as, the adverse cutaneous reaction is one of the immune-related adverse events (irAEs)[6], and the mechanism is that the tumor and normal tissue offers the same tumor-specific target for the treatment of cancer, indicating its potential in the therapy of chronic inflammation and autoimmunity. Normal tissue directly acted or combined by activated T cells are functionally defective as antigen-presenting cells to start complement mediating inflammation.

Similarly, the up-regulation of the inflammatory cytokines caused by T-cell activation indicated a normal tissue inflammatory response. The maculopapular eruption, treated with PD-1/PD-L1 as monotherapy is about 10.0%-21.5%, was the most typical type of adverse cutaneous reaction due to ICI. The skin is a physical barrier, and irAEs reflect a high level of immune activation since the skin is highly immunogenic and concludes immune cell subsets to perform different immune functions[7]. Lynch syndrome, in other words, is hereditary nonpolyposis colorectal cancer (HNPCC); the relative risk of colorectal cancer is higher and younger, and the risk of other cancers is uprising compared to the general population[2]. Thus, it is essential to screen and detect Lynch syndrome and Lynch-like syndrome cancer to decrease the mortality and morbidity of the related disease. The NCCN guidelines recommend universal screening for MMR/MSI status among patients with LS, and the identification of LS carriers is currently based on germ-line testing of subjects with MMR-deficient (dMMR) tumors or fulfilling clinical criteria, matched germ-line DNA was analyzed for mutations in LS-associated mismatch repair genes (MLH1, MSH2, MSH6, PMS2, EPCAM). If the people were diagnosed with LS, they should be screened the early colorectal cancer with colonoscopy at regular intervals and removal of colorectal polyps in time[8]. For MLH1, MSH2, or EPCAM mutation carriers, current guidelines recommend colonoscopy every 1 to 2 years starting in their 20s-25s; for MSH6 or PMS2 mutation carriers, every 5 years beginning in their 30-35s; severity and age at onset of excessive alcohol consumption were documented with a structured lifetime drinking history questionnaire and with selected alcoholism screening questionnaires (CAGE and Michigan Alcoholism Screening Test); furthermore, a family history of cancer increased the risk of age at onset of diseases, so screening starting in 5 years before early-onset age[1].

In conclusion, clinical results of Toripalimab Injection treatment for Lynch syndrome-associated colorectal cancer with tumor screening and DNA testing, recovered using Toripalimab Injection. It is provoked whether using an immune checkpoint inhibitor is an alternative strategy to surgery in LS-associated cancer. It is an optimal measure for improving the rate of disease detection while minimizing the risk of LS-associated cancer overall. Serum markers such as CEA and CA 19-9

significantly assess disease prognosis and response to treatment[9]. These findings translate into a superior long-term efficacy remaining in remission. All in all, there was considerable progress in screening, diagnosis, surveillance, prevention, and treatment of LS-associated cancer. The more, the better investigation of Toripalimab Injection as the Lynch syndrome-associated cancer immune checkpoint inhibitor, followed by improving the happiness of the patients and their family.

References

[1] Bhattacharya P, McHugh TW. Lynch Syndrome [J]. Treasure Island (FL): StatPearls Publishing, 2023. PMID: 28613748.

[2] Rebuzzi F, Ulivi P, Tedaldi G. Genetic Predisposition to Colorectal Cancer: How Many and Which Genes to Test? [J]. Int J Mol Sci. 2023, 24(3):2137. Doi: 10. 3390/ijms24032137. PMID: 36768460; PMCID: PMC9916931.

[3] Weng J, Li S, Zhu Z, Liu Q, Zhang R, Yang Y, Li X. Exploring immunotherapy in colorectal cancer. J Hematol Oncol. 2022 Jul 16; 15(1):95. doi: 10. 1186/s13045-022-01294-4. PMID: 35842707; PMCID: PMC9288068.

[4] Ofshteyn, A., Jiang, B., Bingmer, K., Nakayama, J. M, Gallego, C., Giglia, M., Stein, S. L, & Steinhagen, E. (2020). Prophylactic Gynecologic Surgery at Time of Colectomy Benefits Women with Lynch Syndrome and Colon Cancer: A Markov Cost-Effectiveness Analysis. Diseases of the colon and rectum, 63(10), 1393-1402. https://doi. org/10. 1097/DCR. 0000000000001681

[5] Shui L, Cheng K, Li X, Shui P, Zhou X, Li J, Yi C, Cao D. Study protocol for an open-label, single-arm, phase Ib/II study of combination of toripalimab, nab-paclitaxel, and gemcitabine as the first-line treatment for patients with unresectable pancreatic ductal adenocarcinoma. BMC Cancer. 2020 Jul 9; 20(1):636. doi: 10. 1186/s12885-020-07126-3. PMID: 32646394; PMCID: PMC7346390.

[6] Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin. 2020 Mar;70(2):86-104. doi: 10. 3322/caac. 21596. Epub 2020 Jan 16. PMID: 31944278.

[7] Shah NJ, Lacouture ME. Dermatologic immune-related adverse events to checkpoint inhibitors in cancer [J]. J Allergy Clin Immunol, 2023, 151(2):407-409. doi: 10. 1016/j. jaci. 2022. 11. 015. Epub 2022 Dec 2. PMID: 36463979.

[8] Møller P, Seppälä T, Dowty JG, et al. Colorectal cancer incidences in Lynch syndrome: a comparison of results from the prospective lynch syndrome database and the international mismatch repair consortium [J]. Hered Cancer Clin Pract, 2022, 20(1):36. doi: 10. 1186/s13053-022-00241-1. PMID: 36182917; PMCID: PMC9526951.

[9] Desai S, Guddati AK. Carcinoembryonic Antigen, Carbohydrate Antigen 19-9, Cancer Antigen 125, Prostate-Specific Antigen and Other Cancer Markers: A Primer on Commonly Used Cancer Markers. World J Oncol. 2023 Feb;14(1):4-14. doi: 10. 14740/wjon1425. Epub 2023 Feb 26. PMID: 36895994; PMCID: PMC9990734.