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CASE REPORT

# Immunotherapy induced hypothyroidism with hyperlipidemia: a case report and literature review

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## Abstract

In recent years, immune checkpoint inhibitors have been increasingly used in clinical practice. While considering the efficacy of immunotherapy, it is also necessary to be alert to immune-related adverse effects (irAEs). These include skin, gastrointestinal, liver, endocrine, and pulmonary toxicities. Here, we report a case of irAEs of hypothyroidism with marked hyperlipidemia during sintilimab administration.

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**Key words:** immune-related adverse effects (irAEs); hyperlipidemia; hypothyroidism; immune checkpoint inhibitors (ICIs); sintilimab; immunotherapy

Sintilimab injection is an immune checkpoint inhibitor (ICI) and a recombinant, fully human immunoglobulin G-type programmed cell death protein 1 (PD-1) inhibitor. It has been approved since December 2018 for the treatment of relapsed or refractory classical Hodgkin lymphoma. Extensive clinical trials have been carried out in solid tumors such as lung, liver, gastric, and esophageal cancers, but few reports of related adverse reactions are available. Hyperlipidemia caused by immunotherapy is even rarer. Here, we report a case of immune-related adverse effects (irAEs) of hypothyroidism with marked hyperlipidemia during sintilimab administration and discuss its occurrence, characteristics, and treatment options to provide a reference for the follow-up of clinical safe application of ICIs ( immune checkpoint inhibitors).

## Case presentation

A 48-year-old female patient was treated in the outpatient department of Tianmen Traditional Chinese Medicine Hospital on March 18, 2020. Her chief complaints were intermittent dizziness and fatigue for more than 2 months, with no significant past medical history. Tumor markers investigation showed 60 4 ng/mL carcinoembryonic antigen (CEA) and 171 U/mL cancer antigen 199 (CA199). Abdominal ultrasound showed a space-occupying lesion (6.1 × 5.1 cm) in the right lobe of the liver.

She was treated at the Hubei Cancer Hospital on March 20, 2021. Abdominal computed tomography (CT) showed enlarged peripheral mesenteric lymph nodes and an invasion of the superior mesenteric artery by colon (hepatic flexure) cancer; the adjacent abdominal wall and pancreatic head may be involved. On April 1, 2020, the patient underwent radical resection for right colon cancer. Postoperative pathology revealed (right colon) mucinous adenocarcinoma (approximately 60%), moderately differentiated common type adenocarcinoma (approximately 40%), with large areas of necrosis that involved all muscularis to extramuscularis fibroadipose tissue (pT3). No vascular tumor thrombus or nerve invasion was noted. The superior and inferior resection margins, the mesorectum's root resection margins, the mesangial resection margins, and the omentum were nets. No cancer metastasis was observed in any of the 14 mesenteric lymph nodes. Immunohistochemistry: MSH2 (–), MSH6 (–), MLH1 (3 +, 90%), PMS2 (3 +, 70%), BRAF (V600E) (–), CD56 (–), CGA (+/–), syn (–), Ki67 (Li: 95%). Immunohistochemistry showed loss of mismatch repair proteins MSH2 and MSH6, suggesting possible microsatellite instability-high. Further confirmation by polymerase chain reaction was recommended, but the patient refused. After surgery, the patient was treated with one cycle of the XELOX regimen. On May 24, 2020, she was re-admitted to the Hubei Cancer Hospital with increased levels of tumor markers. Abdominal magnetic resonance imaging showed that there were still neoplastic lesions in the hepatic flexure of the colon, which may involve the adjacent abdominal wall and pancreatic head; the lymph nodes around the lesion may

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contain metastatic cells. Multiple metastases to the liver: Multiple lymph nodes were found in the hepatic hilar and retroperitoneal areas. The curative effect was evaluated by PD. Subsequently, two cycles of the XELIRI regimen plus bevacizumab targeted therapy were administered.

On July 13, 2020, the patient was admitted to our hospital's oncology department. Tumor marker CA125 was normal, CA724 > 300.00U/mL, CA199 17598.00U/mL, CEA 265.84 ng/mL; Fig. 1). Abdominal CT showed that after resection of colon cancer, metastatic tumors of the head of the pancreas and invasion of the superior mesenteric artery, superior mesenteric vein and multiple liver metastases were found. Since the patient's postoperative immunohistochemical findings suggested deficient mismatch repair, immunotherapy was possible. Fourteen cycles of immunotherapy with sintilimab were performed from July 17, 2020 to May 30, 2021. During the review, CA199 and CA724 showed a progressive decline to the normal range (Fig. 1), and the imaging review efficacy evaluation was a partial response (PR) (Fig. 2). On May 28, 2021, the tumor marker CA724 81.96 U/L significantly increased (Fig. 1). Therefore, fruquintinib-targeted therapy was added based on immunotherapy with sintilimab. On January 25, 2021, the imaging review efficacy evaluation was PR (Fig. 2).

Secondary hypothyroidism and hyperlipidemia developed during immunotherapy. The patient began to have hypothyroidism after 2 cycles of immunotherapy; thyroid-stimulating hormone (TSH) increased to 39.64 mIU/L, thyroxine (FT4) decreased to 2.85 pmol/L, and (tri-iodothyronine) FT3 decreased to 1.92 pmol/L, at which time levothyroxine was administered orally at a dose of 50 μg daily. A review after 21 days showed TSH 42 mIU/L, FT4 7.63 pmol/L, and FT3 2.81 pmol/L, and the dose of levothyroxine was increased to 75ug daily. Since then, FT3 and FT4 levels have risen to normal, but TSH is still elevated; hence, the patient continued to have subclinical hypothyroidism. By May 26, 2021, hypothyroidism recurred, evident by TSH 8.1 mIU/L, FT4 11.63 pmol/L, and FT3 3.2 pmol/L, while the patient developed very marked hyperlipidemia with triglycerides (TG) 30.89 mmol/L and total cholesterol (TC) 8.84 mmol/L. Fenofibrate Capsules (II) (Guangdong Xian Qiang), 0.1 g was given orally daily for lipid-lowering therapy. A review on August 10, 2021, revealed TSH 34 mIU/L, FT4 10.87 pmol/L, FT3 2.2 pmol/L. Consequently, the daily oral dose of levothyroxine was raised to 100ug, while the lipid-lowering therapy proved effective with TG 2.94 mmol/L, TC 5.81 mmol/L; fenofibrate treatment was continued. On November 16, 2021, a recheck revealed TSH, FT4, FT3, TC, and TG levels were within normal ranges. The daily oral dose of levothyroxine was 100ug, and fenofibrate was changed to atorvastatin. The last review date was March 13, 2022, and all of the above indicators were in the range, and the oral administration of levothyroxine and atorvastatin was continued.

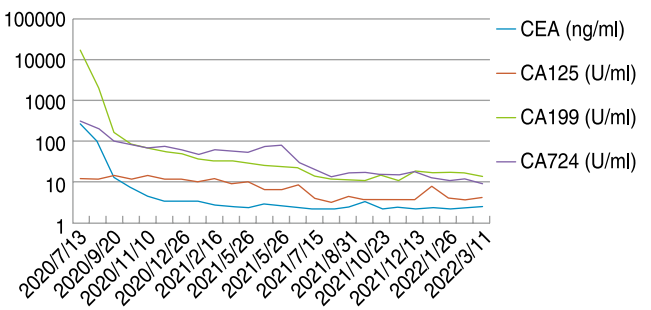


**Fig. 1** The chart shows the trends of tumor markers during the course of immunotherapy in our hospital

## Discussion

Colorectal cancer (CRC) is one of the most common cancers of the digestive tract in China. Its incidence and mortality rates have increased significantly over the past 30 years. A retrospective study showed that CRC has risen from sixth in common tumors to fourth [1]. Although its treatment is still based on fluorouracil and its derivatives, such as oxaliplatin and irinotecan, the long-term survival of patients remains to be improved. With the development of immunology and precision medicine, new immunotherapy drugs targeting programmed death-1 (PD-1) and its ligands (PD-L1 and PD-L2) have

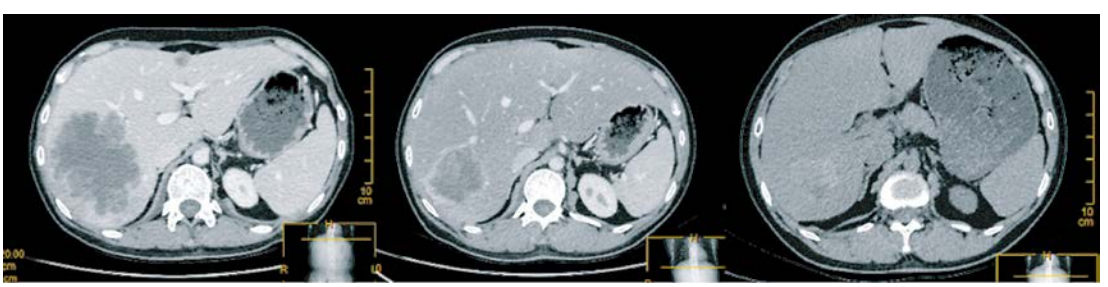


**Fig. 2** CT revealed tumor masses at different times of the disease

been put into a new stage of tumor therapy. In recent years, PD-1 has achieved good results in treating solid and non-solid tumors, such as lung, breast, and liver cancers, and lymphoma [2-6].

Nivolumab and pembrolizumab, which were first marketed abroad in 2015, are the first PD-1 inhibitors to be marketed with remarkable clinical efficacy, but they also have adverse drug reactions (ADRs) such as immune-related pneumonitis, enteritis and rash. Sintilimab, a new class of drug developed independently in China, potently blocks the PD-1 / PD-L1 pathway and binds with a 50 fold higher affinity to the receptor than nivolumab, is durable and stable, can increase effector T cell infiltration in tumor tissues, and induces stronger antitumor immune responses [7]. Sintilimab, in combination with chemotherapy, can improve the short-term outcomes of patients with advanced CRC and has become an important option for prolonging patient survival.

However, while PD-1 inhibitors have significant therapeutic effects, there are also ADRs, such as fatigue, itching, diarrhea, erythema, nausea, myocarditis, and neurotoxicity [7-10]. Endocrine toxicity includes thyroid dysfunction and an acute hypophysis. The incidence of thyroid dysfunction is 5–10% (unrelated to tumor type) [11, 12]. PD-1 inhibitor single-agent-related endocrine toxicity often occurs within 10–24 weeks [13-15]. After 2 months of treatment, FT3 and FT4 levels decreased, and TSH levels increased. The treatment duration was consistent with the time of ADR.

Hyperlipidemia is a common clinical disease that can cause atherosclerosis. It is a high-risk factor for critical diseases such as coronary heart disease and pancreatitis. Hyperlipidemia is divided into two types: primary and secondary. Primary hyperlipidemia is a disorder caused by genetic or environmental factors, while secondary hyperlipidemia is caused by other factors, such as hypothyroidism. Clinical studies have shown that thyroid hormones can enhance the sensitivity of tissue to direct lipolytic hormones, reduce TG synthesis, and improve its clearance rate. Meanwhile, hypothyroidism and hyperlipidemia comorbidities are very easy. Hypothyroidism is generally associated with decreased myocardial contractility, decreased heart rate, reduced blood volume, and cardiac output and is also associated with elevated serum lipid levels.

Hypothyroidism-induced hyperlipidemia and decreased expression of low-density lipoprotein (LDL) receptors on the liver surface are associated with LDL particle oxidation. The role of FT4 in the human body is to enhance LDL activity by promoting mRNA secretion by LDL receptors in hepatocytes. In patients with hypothyroidism, the in vivo activity of LDL decreases, and damage to liver cells leads to a prolonged clearance time of LDL particles in serum, resulting in an increase in TC and TG levels [16]. Moreover, the binding of FT4 to the ApoB100 locus on LDL particles inhibits their oxidation of LDL particles. However, FT4 levels are too low for patients with hypothyroidism to provide sufficient antioxidant capacity, oxidizing LDL particles to form modified LDL, which cannot be recognized by LDL receptors, resulting in a large amount of low-density lipoprotein cholesterol accumulation [17].

Levothyroxine is a FT4 replacement therapy commonly used in clinics. This drug regulates thyroid function by improving thyroid hormone levels in patients. By exerting the effect of elevated serum TSH levels, it promotes an increase in blood lipid metabolism, thereby affecting blood lipid levels. Therefore, hyperlipidemia occurrence in this patient was related to long-term hypothyroidism.

Immune-related ADRs caused by PD-1 inhibitors sometimes appear later, even after the end of immunotherapy; therefore, regular monitoring and follow-up of thyroid function, lipid profile, renal function, and pituitary function are necessary after treatment. Most patients with hypothyroidism require long-term hormone replacement therapy and long-term monitoring and follow-up. Hypothyroidism and hyperthyroidism may occur during the treatment of hypothyroidism. Patients are currently recommended to be monitored for symptoms for at least 1 year after the end of PD-1 inhibitor therapy.

## Conclusion

More immune-related toxicity may occur with the popularization of PD-1/PD-L1 inhibitors in clinical practice. The incidence of hyperlipidemia in this patient was related to long-term hypothyroidism. Monitoring toxicity is as important as evaluating efficacy during the course of PD-1/PD-L1 inhibitor monotherapy or combination therapy. The monitoring contents include biochemical tests and imaging studies, especially the indicators of renal function, thyroid function, lipid profile, and pituitary function, which are generally monitored once every 4 to 6 weeks. Due to partial toxicity's late-onset, monitoring symptoms for at least 1 year is recommended after treatment.

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## Conflicts of interest

The authors indicated no potential conflicts of interest.

### Author contributions

All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## References


1. Zheng Y, Wang ZZ. Interpretation of global colorectal cancer statistics. Zhonghua Liu Xing Bing Xue Za Zhi. 2021;42(1):149-152.
2. Sun J, Zheng Y, Mamun M, et al. Research progress of PD-1/PD-L1 immunotherapy in gastrointestinal tumors. Biomed Pharmacother. 2020;129:110504.
3. Sun L, Zhang L, Yu J, et al. Clinical efficacy and safety of anti-PD-1/PD-L1 inhibitors for the treatment of advanced or metastatic cancer: a systematic review and meta-analysis. Sci Rep. 2020;10(1):2083.
4. Ni X, Xing Y, Sun X, et al. The safety and efficacy of anti-PD-1/anti-PD-L1 antibody therapy in the treatment of previously treated, advanced gastric or gastro-oesophageal junction cancer: A meta-analysis of prospective clinical trials. Clin Res Hepatol Gastroenterol. 2020;44(2):211-222.
5. Suzuki S, Haratani K, Hayashi H, et al. Association of tumour burden with the efficacy of programmed cell death-1/programmed cell death ligand-1 inhibitors for treatment-naïve advanced non-small-cell lung cancer. Eur J Cancer. 2022;161:44-54.
6. Fedorova LV, Lepik KV, Mikhailova NB, et al. Nivolumab discontinuation and retreatment in patients with relapsed or refractory Hodgkin lymphoma. Ann Hematol. 2021;100(3):691-698.
7. Wang J, Fei K, Jing H, et al. Durable blockade of PD-1 signaling links preclinical efficacy of sintilimab to its clinical benefit. MAbs. 2019;11(8):1443-1451.
8. Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. JAMA Oncol. 2019;5(7):1008-1019.
9. Man J, Ritchie G, Links M, et al. Treatment-related toxicities of immune checkpoint inhibitors in advanced cancers: A meta-analysis. Asia Pac J Clin Oncol. 2018;14(3):141-152.
10. Ruggiero R, Fraenza F, Scavone C, et al. Immune Checkpoint Inhibitors and Immune-Related Adverse Drug Reactions: Data From Italian Pharmacovigilance Database. Front Pharmacol. 20209;11:830.
11. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 2018;4(2):173-182.
12. Chang LS, Barroso-Sousa R, Tolaney SM, et al. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev. 2019;40(1):17-65.
13. Puzanov I, Diab A, Abdallah K, et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95.
14. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158-168.
15. Khan Z, Hammer C, Guardino E, et al. Mechanisms of immune-related adverse events associated with immune checkpoint blockade: using germline genetics to develop a personalized approach. Genome Med. 2019;11(1):39.
16. Tassi R, Baldazzi V, Lapini A, et al. Hyperlipidemia and hypothyroidism among metastatic renal cell carcinoma patients taking sunitinib malate. Related or unrelated adverse events? Clin Genitourin Cancer. 2015;13(2):e101-e105.
17. Su X, Peng H, Chen X, et al. Hyperlipidemia and hypothyroidism. Clin Chim Acta. 2022;527:61-70.


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