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RETIFANLIMAB-INDUCED THYROID GLAND DYSFUNCTION AND COLITIS (CASE REPORT)

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Abstract. Immunotherapy is a modern and effective method of treating malignant neoplasms. Retifanlimab is a humanized and stabilized immunoglobulin G4κ monoclonal antibody that binds to PD-1. The drug has been proven to effectively treat cervical cancer and squamous cell tumors of the anal canal caused by the human papillomavirus. Phase III studies of the effectiveness and safety of this monoclonal antibody in patients with non-small cell lung cancer is currently underway.

Patients treated with immunotherapy have an increased risk of developing immune-related adverse events. The most common immune-related side effects in the patient after taking retifanlimab were thyroid gland disorders, itching, pneumonitis and skin rash. In this article, we would like to present a case report of a combined immune-related thyroid and colon dysfunction induced by retifanlimab.

Materials and methods. We collected clinical data and laboratory results of a patient with advanced stage of non-small cell lung cancer. A 59-year-old male patient had disease progression after first-line chemotherapy. He received retifanlimab as second-line therapy at 375 mg intravenously every three weeks.

The results. The first laboratory symptoms of thyroid gland dysfunction began after 36 weeks of taking retifanlimab. After 42 weeks, a laboratory picture of hyperthyroidism was observed with a critically low level of TSH and a high level of T4. In addition, the patient reported diarrhea 7–8 times a day for the last seven days. Immune-related adverse events (colitis grade 3 and hyperthyroidism grade 1) were suspected. The administration of retifanlimab was temporarily discontinued. 750 mg of methylprednisolone was administered once over 60 minutes. The patient's general condition was significantly improved the next day, and prednisolone was prescribed orally at a dose of 2 mg/kg/day. On the second day, diarrhea recurred twice; on the third, the stool returned to normal. Hormone levels were gradually normalized until week 46.

Discussion. Immune-related adverse events may occur as a result of taking any monoclonal antibodies. Early diagnosis and therapy of immune-related adverse reactions is the key to the safe and effective use of PD-1/PD-L1-blocking antibodies.

Immune-related colitis occurred in 1.6% of patients treated with retifanlimab. Hyperthyroidism was observed in 4.3%.

Thyroid disorders that correspond to 1 or 2 grades of severity are common. Therefore patients do not require any medication therapy, or endocrine therapy can be used. However, 13% of patients required systemic corticosteroid therapy. Antihyperthyroidism therapy or corticosteroids (oral prednisolone 1–2 mg/kg/day) are prescribed only when clinical symptoms appear and, accordingly, the severity of the disease is 2 or 3. It is possible to prescribe high-dose steroid therapy.

The appointment of loperamide is sufficient for the initial symptoms of colitis. Therefore, monoclonal antibodies are not discontinued. However, more severe cases require systemic corticosteroids and temporary drug withdrawal. When life-threatening conditions develop, immunotherapy is permanently discontinued.

Conclusions. Immunotherapy is always associated with risk of developing immune-related side effects. Depending on the grade of severity, they require different treatment options. Targeted monitoring of laboratory results and clinical symptoms is the key to safe treatment with immune checkpoint inhibitors.

Keywords: retifanlimab, thyroid gland, colitis, immunotherapy, cancer.

Introduction. Immunotherapy is a modern and effective method of treating malignant neoplasms. The Food and Drug Administration (FDA) continues actively approving monoclonal antibodies for treating different solid tumors. One of the latest representatives of this type of drug is retifanlimab.

Retifanlimab is a humanized and stabilized immunoglobulin G4κ monoclonal antibody that binds to PD-1. This drug blocks the interaction between PD-1 and its ligands. Therefore, it can cause activation of the antitumor function of T cells [1]. In phase I clinical trials in advanced solid tumors, retifanlimab demonstrated clinical activity and low toxicity. The drug has been used to effectively treat cervical cancer and squamous cell tumors of the anal canal caused by the human papillomavirus [2].

Research rationale. In March 2023, the FDA approved retifanlimab for treating Merkel cell carcinoma [3]. Phase III studies of the effectiveness and safety of this monoclonal antibody in patients with locally advanced and metastatic squamous cell anal carcinomas,

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gastroesophageal adenocarcinomas, and non-small cell lung cancer are currently underway [4, 5].

The primary function of immune checkpoint molecules is protection against autoimmune reactions and inflammation, so patients treated with immunotherapy have an increased risk of developing immune-related adverse events. The most common immune-related side effects in the patient after taking retifanlimab were thyroid gland disorders, itching, pneumonitis, skin rash, etc. [4, 5, 6].

In this article, we would like to present a case report of a combined immune-related thyroid and colon dysfunction induced by retifanlimab.

Materials and methods. We collected clinical data and laboratory results of a patient with advanced stage of non-small cell lung cancer participating in a clinical trial. A 59-year-old male patient had disease progression after first-line chemotherapy. He received retifanlimab as second-line therapy at 375 mg intravenously every three weeks. The Ethics Committee of the Sumy Regional Clinical Oncology Center approved the study. Written informed consent for participation in the study was collected.

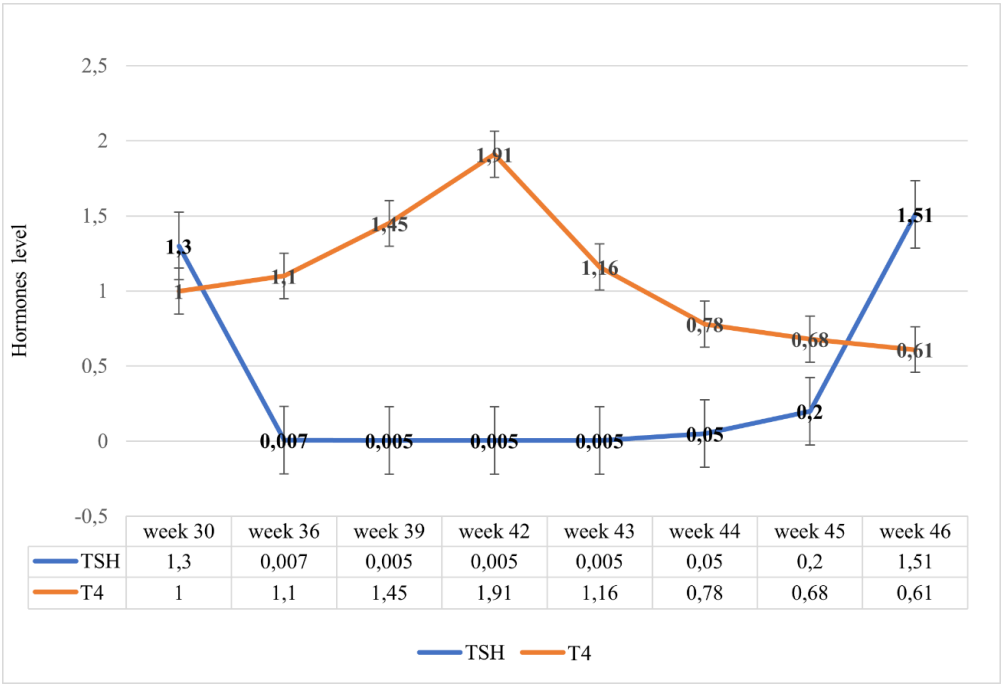
The function of the thyroid gland (the level of thyroid-stimulating hormone - TSH and tetraiodothyronine - T4) was assessed before the treatment began, then every six weeks. In case of detection of abnormalities - according to the doctor's decision. The severity of the thyroid gland and colon dysfunction was determined according to CTCAE 5.0 criteria [7].

The results. The first laboratory symptoms of thyroid gland dysfunction began after 36 weeks of taking retifanlimab. So that you know, the patient did not take any other medications that could lead to thyroid dysfunction. According to the laboratory test results, the TSH level was low, and T4 was within the normal range. This condition had no clinical symptoms, so no treatment was prescribed.

Thirty-nine weeks after the start of retifanlimab therapy, the TSH level became critically low (<0.005, reference range 0.4–4.85 μU/mL), but T4 was within the normal range. After 42 weeks, a laboratory picture of hyperthyroidism was observed with a critically low level of TSH and a high level of T4. In addition, the patient reported diarrhea 7–8 times a day for the last seven days. The family doctor prescribed loperamide 2 mg 4 times daily, but it did not help. The patient lost 12% of his baseline weight. The general condition was moderate. Immune-related adverse events (colitis grade 3 and hyperthyroidism grade 1) were suspected. The administration of retifanlimab was temporarily discontinued. Intensive rehydration therapy and steroid hormones were prescribed. 750 mg of methylprednisolone was administered once over 60 minutes.

The patient's general condition was significantly improved the next day, and prednisolone was prescribed orally at a dose of 2 mg/kg/day. On the second day, diarrhea recurred twice, and on the third, it stopped completely, and the stool returned to normal. A gradual decrease in the dose of steroid hormones lasted for four weeks.

Blood tests for monitoring thyroid hormones level were repeated every week. Four weeks later (at week 46), TSH and T4 levels were within normal ranges. Figure 1 shows changes in TSH levels concerning T4.



	week 30	week 36	week 39	week 42	week 43	week 44	week 45	week 46
TSH	1,3	0,007	0,005	0,005	0,005	0,05	0,2	1,51
T4	1	1,1	1,45	1,91	1,16	0,78	0,68	0,61

Fig. 1. Changes in TSH and T4 levels during treatment with steroid hormones.

Figure 1 shows that at week 30, TSH and T4 levels were normal. After that, laboratory symptoms of hyperthyroidism increased, which reached their maximum value at week 42. After the steroid therapy, hormone levels were gradually normalized until week 46.

After altogether discontinuing steroid hormones, the patient continued treatment with retifanlimab. Manifestation of immune-related colitis or disorders of thyroid function were no longer observed.

Discussion. Immune-related adverse events may occur as a result of taking any monoclonal antibodies. They can be severe or even fatal. Disorders can occur in any system of organs or tissues. Most often, immune-related adverse reactions develop during treatment with PD-

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1/PD-L1 blocking antibodies. However, autoimmune complications may occur when the treatment is completed. In some cases, checkpoint inhibitors cause disturbances in the work of more than one system or organ.

Early diagnosis and therapy of immune-related adverse reactions is the key to the safe and effective use of PD-1/PD-L1-blocking antibodies. Particular attention should be paid to liver transaminases, creatinine, thyroid hormones, skin, and mucous membranes. It is always necessary to analyze alternative causes of side effects (infection, food allergy, reaction to taking other drugs).

According to the study by Rao et al. [4], immune-related colitis occurred in 1.6% of patients treated with retifanlimab. Among them, grade 4 was registered in 0.2%, grade 3–0.2%, and grade 2–0.7%. Systemic corticosteroids were required by 71% of patients.

Immune-related thyroid gland disorders due to retifanlimab are the most common and occur in 12.8% of patients. Hypothyroidism is observed in 8.5%, and hyperthyroidism in 4.3%.

Thyroid disorders that correspond to 1 or 2 grades of severity are common. Therefore patients do not require any medication therapy, or endocrine therapy can be used. However, 13% of patients required systemic corticosteroid therapy. A peculiarity of the effect of retifanlimab is the possibility of developing hypothyroidism after hyperthyroidism [4].

In our case, the patient required systemic corticosteroid therapy due to the development of grade 3 immune-mediated colitis. This treatment had a positive effect not only on the colon but also on the function of the thyroid gland. According to Kimbara et al. [8], early prescription of steroid hormones prevents the transition from hyperthyroidism to hypothyroidism. That may be why the level of hormones normalized quite quickly.

To monitor thyroid function, TSH and T4 levels should be assessed before starting treatment with immune checkpoint inhibitors and every 6–8 weeks during therapy [9]. Immunotherapy can be continued if there are side effects in the 1st grade.

Antihyperthyroidism therapy (propylthiouracil, carbimazole, or methimazole) or corticosteroids (oral prednisolone 1–2 mg/kg/day) is prescribed only when clinical symptoms appear and, accordingly, the severity of the disease is 2 or 3. According to the doctor's decision, it is possible to prescribe high-dose steroid therapy [10]. It is necessary to stop taking immune checkpoint inhibitors until the normalization of laboratory indicators or reduction of symptoms to 1 grade of severity, and in the case of 4 grade - to stop permanently.

The appointment of loperamide is sufficient for the initial symptoms of colitis. Therefore, monoclonal antibodies are not discontinued. However, more severe cases require systemic corticosteroids and temporary drug withdrawal. When life-threatening conditions develop, immunotherapy is permanently discontinued.

Conclusions. Immunotherapy is always associated with the risk of developing immune-related side effects. Depending on the grade of severity, they require different treatment options. Targeted monitoring of laboratory results and clinical symptoms is the key to safe treatment with immune checkpoint inhibitors.

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ДИСФУНКЦІЯ ЩИТОПОДІБНОЇ ЗАЛОЗИ ТА КОЛІТ, ВИКЛИКАНІ РЕТИФАНЛІМАБОМ (КЛІНІЧНИЙ ВИПАДОК)

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Резюме. Ретифанлімаб - це гуманізоване та стабілізоване моноклональне антитіло до імуноглобуліну G4κ, яке зв'язується з PD-1. Пацієнти, які отримують імунотерапію, мають підвищений ризик розвитку імуноопосередкованих побічних ефектів. У цій статті представлено випадок комбінованої імунозалежної дисфункції щитоподібної залози та товстої кишки, викликаної ретифанлімабом.

Матеріали і методи. Ми зібрали клінічні дані та результати лабораторних досліджень пацієнта з пізньою стадією недрібноклітинного раку легені. Він отримував ретифанлімаб як терапію другої лінії по 375 мг внутрішньовенно кожні три тижні.

Результати. Через 42 тижні від початку лікування ретифанлімабом спостерігалася лабораторна картина гіпертиреозу з критично низьким рівнем ТТГ і високим рівнем Т4. Крім того, протягом останніх семи днів хворий скаржився на діарею 7–8 разів на добу. Були запідозрені імуноопосередковані коліт 3 ступеня та гіпертиреоз 1 ступеня. Введення ретифанлімабу було тимчасово припинено. 750 мг метилпреднізолону вводили одноразово протягом 60 хв. На наступний день призначено преднізолон перорально в дозі 2 мг/кг/добу.

Обговорення. Дисфункція щитоподібної залози 1–2 ступеня тяжкості не потребує медикаментозної терапії. Кортикостероїди призначають лише при 2–3 ступеню тяжкості захворювання. При початкових симптомах коліту достатньо призначення лоперамід. Однак більш важкі випадки потребують системних кортикостероїдів і тимчасової відміни препарату. При розвитку загрозливих для життя станів імунотерапію припиняють остаточно.

Висновки. Імунотерапія завжди пов'язана з ризиком розвитку імунозалежних побічних ефектів. Цілеспрямований моніторинг є запорукою безпечного лікування інгібіторами імунних контрольних точок.

Ключові слова: ретифанлімаб, щитоподібна залоза, коліт, імунотерапія, рак.

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