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Case Report

Diabetes Mellitus Induced by Nivolumab plus Regorafenib in a Patient with Esophageal Cancer

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Abstract

Nivolumab is now preferred as first-line and second-line treatment for advanced esophageal cancer, while regorafenib improves survival in refractory gastroesophageal cancer. The combined use of nivolumab and regorafenib has shown promising results. Nivolumab-induced thyroid dysfunction is a common immune-related adverse event (irAE), while type 1 diabetes mellitus induced by immune checkpoint inhibitors is rare and usually permanent. It is unclear whether the combination of regorafenib and nivolumab increases the risk of irAEs. We report a patient with recurrent esophageal squamous cell carcinoma who was treated with nivolumab plus regorafenib and developed thyroiditis and diabetic ketoacidosis. The rechallenge was successful, and the patient achieved a good treatment response.

Keywords: Combine therapy, diabetes mellitus, immune-checkpoint inhibitor, immune-related adverse event, nivolumab, regorafenib, target therapy, thyroiditis

Introduction

Nivolumab combined therapy is now preferred to chemotherapy alone as first-line and second-line treatment for advanced esophageal cancer for longer overall survival.[1] The combined use of nivolumab and regorafenib has shown promise in the treatment of advanced refractory colorectal cancer.[2,3] Diabetes mellitus induced by immune checkpoint inhibitors (ICI-DM) is a rare immune-related adverse event (irAE) that initially presents with diabetic ketoacidosis (DKA) in most cases and sometimes with fulminant episodes. The median time to onset of endocrine toxicities is 14.5 weeks (range: 1.5–130 weeks), and the onset time is even shorter when combining anti-PD (L) 1 with anti-cytotoxic T-lymphocyte associated protein-4 (CTLA-4) antibodies.[4] In the REGONIVO, EPOC1603 trial, 55 patients with gastric or colorectal cancer were treated with nivolumab plus regorafenib. Among them, one patient developed DKA after 9 months of combination treatment and was the only

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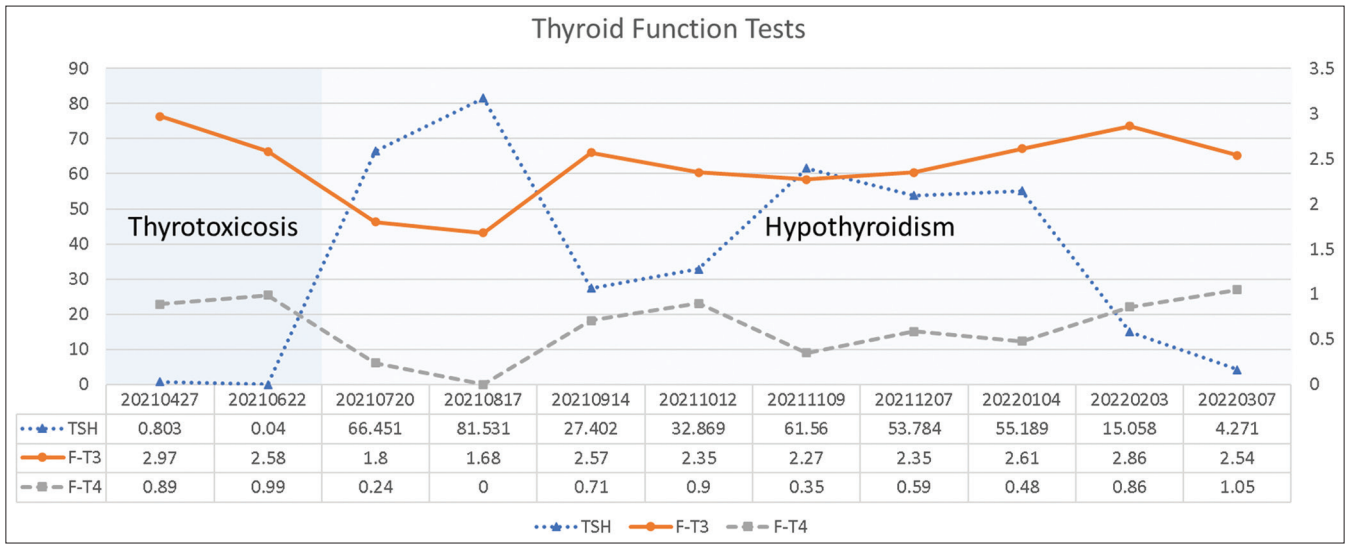
treatment-related death in the trial.[2] It is unclear whether combining immune and target therapy would increase the incidence or severity of ICI-DM. We report a patient with recurrent esophageal cancer treated with nivolumab plus regorafenib who suffered from thyroiditis and DKA.

Case Report

A 57-year-old painter with hypertension and peptic ulcers without a family history of DM was diagnosed with middle-third esophageal squamous cell carcinoma (ESCC), cT3N2M0, stage IIIB (AJCC 8th). He received 1 month of neoadjuvant chemoradiotherapy with weekly cisplatin 30 mg/m^2 and fluorouracil 1000 mg/m^2 (PF). The radiation dose was 4500 cGy/25 fx. Esophagectomy and gastric tube reconstruction were arranged on August 5, 2020, pT3N0cM0, stage group IIB. After surgery, concurrent chemoradiotherapy with PF and radiation 2160 cGy/12 fx were performed. However, lung metastasis developed, and he was enrolled in the NCT04704154 trial on April 29, 2021, with nivolumab 480 mg every 4 weeks, along with regorafenib 90 mg daily. He experienced grade II hand-foot syndrome, so the dosage of regorafenib was reduced to 60 mg once daily. However, he developed transient subclinical hyperthyroidism, followed by subclinical hypothyroidism [Figure 1]. Moreover, the initially normal blood sugar level (80–120) started to increase gradually after nivolumab and regorafenib treatment. On October 30, 2021, he was diagnosed with DKA, accompanied by symptoms of shortness of breath, diarrhea, and body weight loss. At the time of DKA diagnosis, laboratory tests revealed glycated hemoglobin (HbA1c) 13.2%, glutamic acid decarboxylase autoantibody (GAD-Ab) 8.02 U/mL (<10.0), insulin 37.81 mU/L (1.9–23), C-peptide 1.56 ng/mL (1.1–5.0), urine ACR 6.74 ug/mg (0.6–1.3), creatinine 0.94 mg/dL,



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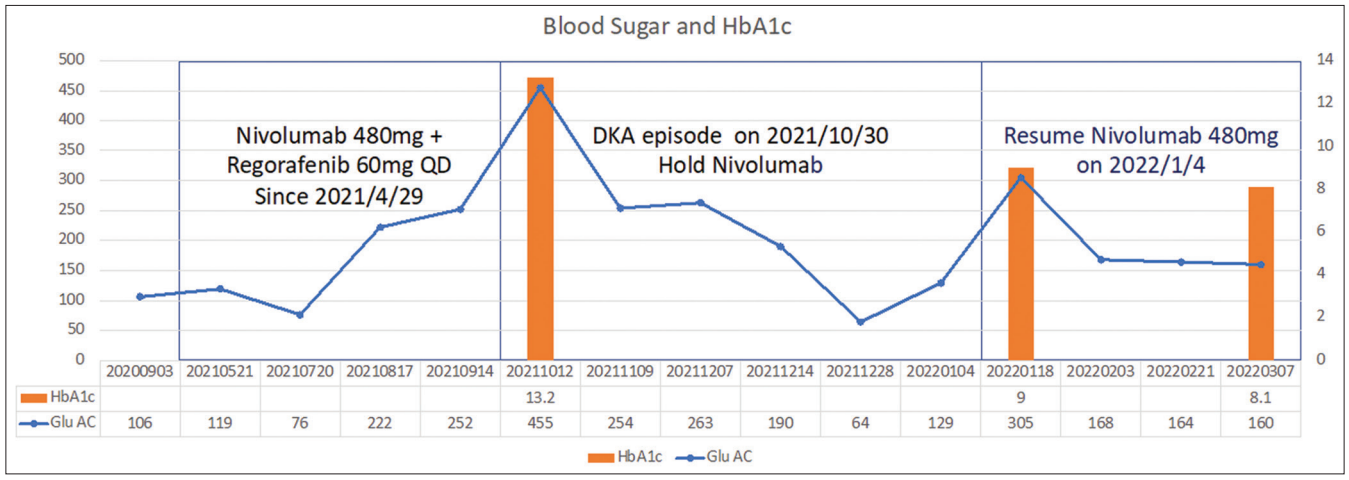
TSH	0.803	0.04	66.451	81.531	27.402	32.869	61.56	53.784	55.189	15.058	4.271
F-T3	2.97	2.58	1.8	1.68	2.57	2.35	2.27	2.35	2.61	2.86	2.54
F-T4	0.89	0.99	0.24	0	0.71	0.9	0.35	0.59	0.48	0.86	1.05

Figure 1: The patient developed transient thyrotoxicosis followed by hypothyroidism 3 months after starting treatment of nivolumab plus regorafenib. TSH: Thyroid-stimulating hormone. FT3: Free triiodothyronine. FT4: Free thyroxine



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HbA1c						13.2						9			8.1
Glu AC	106	119	76	222	252	455	254	263	190	64	129	305	168	164	160

Figure 2: The patient had diabetic ketoacidosis (DKA) about 6 months after starting treatment of nivolumab plus regorafenib. Nivolumab was held while regorafenib was continued. Nivolumab treatment was resumed 2 months later after remission of DKA. HbA1c: Glycated hemoglobin. Glu AC: Blood glucose before meals, DKA: Diabetic ketoacidosis

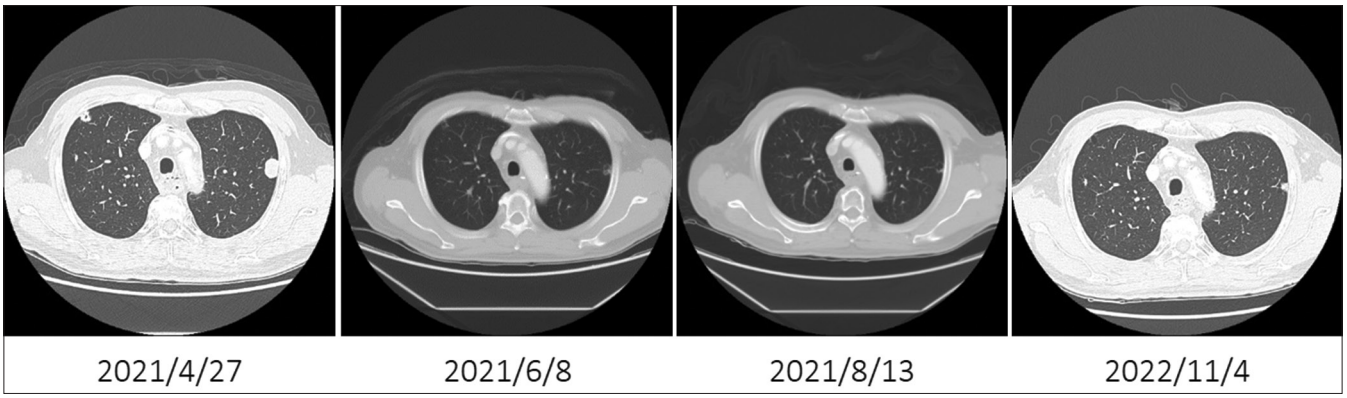

Figure 3: Follow-up chest computed tomography scan showed complete remission of lung metastasis

and GFR 82 mL/min/1.73 m^2 (>90). Under the diagnosis of ICI-DM and hypothyroidism, insulin treatment and thyroxine sodium 150 μg were given while nivolumab was halted. After treatment, there was an improvement in the clinical symptoms and HbA1c level [Figure 2]; however, the C-peptide level decreased (<0.1 ng/mL). Two months later, on January 4, 2022, nivolumab was resumed. He demonstrated good tolerance to the treatment and remained in a state of cancer remission throughout follow-up until the last visit on January 30, 2023 [Figure 3].

Discussion

This patient had relapsed ESCC with lung metastasis and underwent treatment with nivolumab plus regorafenib. After the combination treatment, he developed transient hyperthyroidism 1 month later, hypothyroidism 3 months later, and DKA 6 months later. He had a low C-peptide level but was negative for GAD-Ab. Nivolumab was held while regorafenib was continued. After receiving insulin treatment, he recovered from DKA and resumed nivolumab treatment 2 months later. Complete tumor remission was achieved for at least 2 years.

Phase II trials have investigated the treatment effect and safety of nivolumab combined with regorafenib with or without chemotherapy in esophagogastric cancer patients (NCT04757363,[5] NCT04704154), and the results have been promising, with 71% of the patients achieving progression-free survival at 6 months. About 46% of the patients developed irAEs, including arthralgias (15%), dermatitis (13%), acute interstitial nephritis (8%), hepatitis (8%), and hypothyroidism (5%), but no treatment-related deaths were noted. Based on these results, other phase II and phase III trials (INTEGRATEIIb) are ongoing.

Limited data are available regarding the onset time of DM induced by combined targeted therapy and immunotherapy. In our patient, the onset time of ICI-DM did not appear to be shorter compared to other cases of ICI-DM. No clinical trials have focused on comparing irAEs in patients receiving nivolumab plus regorafenib combined therapy to those receiving nivolumab monotherapy. Among the 50 patients in the REGONIVO EPOC1603 trial, six developed hyperthyroidism and six developed hypothyroidism. In addition, one patient developed DKA after 9 months of combination treatment, which resulted in the only treatment-related death in the trial.[2]

Mechanisms underlying the synergistic effect of regorafenib and immunotherapy are being investigated. Possible mechanisms include reduction and reprogramming of tumor-associated macrophages, enrichment in M1 macrophage phenotype, and suppression of interferon-induced PD-L1. Regorafenib also inhibits vascular endothelial growth factor receptor and its signaling pathway, leading to tumor blood vessel normalization and improving T-cell infiltration. Furthermore, regorafenib has been studied for its potential to enhance immune responses and improve the efficacy of immunotherapy in microsatellite-stable tumors.[6] Diagnosing ICI-DM involves conducting antibody, insulin, and C-peptide examinations. However, unlike other types of type 1 DM, where islet antibodies are present in over 90% of patients, only 49% of ICI-DM patients have islet antibodies, primarily GAD65. Therefore, the diagnosis of ICI-DM is not solely based on antibody screening but rather on clinical suspicion, including low insulin C-peptide levels, dependence on insulin, and the exclusion of type 2 DM and other causes of insulin resistance.[7-10] Ongoing research is focused on the early detection of B cell destruction in ICI-DM through the analysis of cytokines and autoantibodies. HLA-DR4 has been associated with ICI-DM and may aid in identifying high-risk patients. Other potential predictors, including single-nucleotide polymorphisms related to PD-1/PD-L1 sensitivity, CTLA-4, interleukin (IL)-2, and IL-2 receptors, are being investigated.[7,11] While there is some evidence of a correlation between ICI-DM and a better treatment response to immune therapy, the data are still conflicting.[10] In cases of ICI-DM, more than 95% of patients have previously received PD-1/PD-L1 inhibitors. Studies in mice have shown that PD-1 inhibitors can induce DM more rapidly than CTLA-4 inhibitors. The inhibition of PD-1/PD-L1 can disrupt long-term energy in the islets, leading to ICI-DM. In addition, blocking PD-1/PD-L1, but not CTLA-4, prompts antigen-specific CD4+ T cells to swarm dendritic cells (DCs), resulting in decreased cellular velocity and prolonged engagement between T cells and DCs in the pancreatic lymph

nodes. The accumulation of insulin-specific autoreactive CD4+ T cells in the pancreatic lymph nodes has also been demonstrated in PD-1-deficient nonobese diabetic mice. Furthermore, the expression of PD-L1 has been observed in the islets of patients with type 1 DM.[6] In most cases, ICI-DM is considered to be a permanent condition that poorly responds to steroids and requires lifelong insulin therapy. Treatment with anti-IFN-γ and anti-TNF-α seemed to prevent CPI-DM in anti-PD-L1–treated NOD mice in one study, although few studies have reported on the use of anti-TNF-alpha in human patients. However, rare cases recovered from ICI-DM, and some reports have mentioned the use of infliximab as a treatment option.[6-9] There are ongoing investigations into alternative treatments for ICI-DM besides insulin. Teplizumab, a humanized anti-CD3 monoclonal antibody, has shown a trend in delaying the onset of type 1 DM in high-risk individuals. Other therapies, such as rituximab, imatinib, and tocilizumab have been reported to extend C-peptide production.

In conclusion, ICI-DM is a rare and potentially severe irAE often characterized by DKA. While most cases can be managed with insulin and resume immunotherapy, the correlation between ICI-DM and treatment response is under debate. As the combination use of immune therapies and target therapies increases, further research is necessary to understand the mechanisms of ICI-DM and improve the management of ICI-DM. Blood sugar monitoring and early interventions are crucial for the timely detection and prevention of ICI-DM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

Dr. Li-Yuan Bai, an editorial board member at *Journal of Cancer Research and Practice*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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