CASE REPORT

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Pembrolizumab Associated Autoimmune Diabetes Mellitus: Case Series

Pembrolizumab İlişkili Otoimmun Diabetes Mellitus: Olgu Serisi

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ABSTRACT

The use of immune checkpoint inhibitors is increasing every day. With such frequent use, the side effects and management associated with these treatments are becoming difficult. One of rare side effects is autoimmune diabetes mellitus. In this review, we will discuss two cases of pembrolizumab-associated diabetes mellitus treated in our clinic and those reported in the literature. Most of the reported cases presented with diabetic ketoacidosis and they were on insulin therapy. The relationship between diabetes and immune checkpoint inhibitors needs to be clarified.

Keywords: Autoimmune diabetes, intensive insulin therapy, immunotherapy-related adverse events, cancer immunotherapy, pembrolizumab induced diabetes mellitus

ÖZ

İmmün kontrol noktası inhibitörlerinin kullanımı gün geçtikçe artmaktadır. Bu sık kullanım göz önüne alındığında bu tedavilere bağlı yan etkiler ve yönetimi zorlaşmaktadır. Nadir görülen bir tanesi otoimmün diyabettir. Bu derlemede kliniğimizde tedavi edilen pembrolizumab ilişkili iki diyabet olgusundan ve literatürde bildirilen olgulardan bahsedeceğiz. Bildirilen olguların çoğu diyabetik ketoasidoz ile başvurmuştur ve insülin tedavisine ihtiyaç göstermektedir. Diyabet ile immün kontrol noktası inhibitörleri arasındaki ilişkinin açıklığa kavuşturulmasına ihtiyaç vardır.

Anahtar Kelimeler: Otoimmün diyabet, intensif insülin tedavisi, immünoterapi ilişkili advers olaylar, kanser immünoterapisi, pembrolizumabın indüklediği diyabetes mellitus

INTRODUCTION

Pembrolizumab and other checkpoint inhibitors are increasingly being used to treat various cancers. Pembrolizumab, a programmed cell death 1 (PD-1) inhibitor, has the ability to overstimulate the immune system, leading to the activation of a large number of hematopoietic cells, macrophages, dendritic cells, and pancreatic cells that express its ligand[1,2]. As such, it may interfere with cell function in other non-cancer tissues during treatment. This results in a collection of immune-related adverse events (irAEs), the most common of which is the hypofunction of the pituitary, thyroid and adrenal glands.

Type 1 diabetes mellitus (T1DM) is an autoimmune disease due to absolute insulin deficiency related to islet β cell death[3-5]. PD-1 inhibitors may indirectly damage islet β cells through excessive activation of the autoimmune system, leading to the development of T1DM.

Among relatively common autoimmune adverse events associated with pembrolizumab, including pneumonia, colitis, hepatitis, hypophysitis, hyperthyroidism, hypothyroidism and nephritis, diabetes was rarely observed in only 0.1-1.4% of patients in clinical trials. In the few case reports of checkpoint inhibitor associated T1DM, no correlation between the number

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of administered cycles and the development of diabetes was outlined.

In this case report, we present two patients with triple-negative breast cancer who developed checkpoint inhibitor associated autoimmune diabetes after receiving (neo) adjuvant pembrolizumab therapy. Written consent was obtained from the patients for the presentation of the cases.

CASE REPORT

The patient was a 25-year-old premenopausal female with a history of thalassemia minor, who presented with a right breast mass measuring 4 cm on breast MRG. A tru-cut biopsy was performed of the right upper quadrant mass, revealing metaplastic breast carcinoma and ductal carcinoma in situ.

The ki-67 was 50%; estrogen-receptor, progesterone-receptor and Cerbb2 were negative in immunohistochemistry staining. A staging positron emission tomography/computed tomography (PET/CT) scan did not detect any evidence of distant metastases. No evidence of axillary lymph node involvement was noted. Neoadjuvant chemotherapy consisting of 4 cycles of adriamycin plus cyclophosphamide (AC) followed by weekly carboplatin plus paclitaxel for a total of 12 weeks simultaneously with pembrolizumab administered every 21 days was initiated.

Following neoadjuvant chemotherapy, the patient underwent bilateral subcutaneous mastectomy, right sentinel lymph node sampling, and immediate breast reconstruction. The postoperative pathology showed a complete pathological response. The removed 2 sentinel lymph nodes were benign as well. Adjuvant treatment with pembrolizumab was continued for a total of 17 cycles. Due to worsening fatigue at 11 months after surgery, an adrenocorticotropic hormone stress test was performed, which was consistent with adrenal insufficiency. Treatment with hydrocortisone was started with near resolution of symptoms. Over a course of 3 months, hydrocortisone was tapered and eventually discontinued.

Approximately 3 months after the discontinuation of hydrocortisone treatment and 8 months after the end of adjuvant pembrolizumab, the patient presented with nausea. A random plasma glucose was found to be 500 mg/dL (baseline fasting plasma glucose at diagnosis was 84 mg/dL); There was no ketone in the urine and no acidosis in the arterial blood gas. Anti-GAD and anti-insulin antibodies requested to identify the etiology of diabetes were negative. The C-peptide level was found to be low (HbA1c value 11.8% and C-peptide value 0.2 ng/mL). HLA haplotypes, which have been shown to be closely associated with T1DM, requested from the tissue type laboratory were negative. After consultation with the endocrinology clinic, the diagnosis of classical T1DM was ruled out because of the patient's advanced age at onset of diabetes, negative autoantibodies, absence of HLA haplotypes and the reported development of autoimmune diabetes after the end of immunotherapies in the literature. Diagnosis of checkpoint inhibitor related autoimmune T1DM was made and intensive insulin treatment was started. Education on diabetes, diabetic nutrition and lifestyle was given and blood sugar levels were closely monitored. After 2 years of follow-up, the patient still remains on insulin therapy.

The second patient was a 56-year-old postmenopausal female who underwent further evaluation and testing after detecting a 2.8 cm mass in the right breast. Tru-cut biopsy was found to be compatible with triple negative invasive ductal carcinoma. PET/CT revealed no metastases to distant organs. Axillary imaging performed at the time of diagnosis was negative. The patient was treated with pembrolizumab every 21 days in combination with neoadjuvant four cycles of AC followed by weekly carboplatin plus paclitaxel for 12 weeks, per Keynote 522 study. After neoadjuvant treatment, the patient underwent sentinel axillary lymph node biopsy and partial mastectomy. Pathology revealed a 2 mm in situ ductal carcinoma, but no viable invasive tumor was found. There was no evidence of metastasis in the sentinel lymph node specimens.

At the postoperative month 3, while pembrolizumab treatment was ongoing, fasting blood sugar was detected as 330 mg/dL (pre-treatment fasting plasma glucose was 97 mg/dL) and HbA1c was 7.7%. Autoantibody tests performed after referral to the endocrinology clinic revealed that anti-GAD antibodies were 0.70 IU/mL (less than 10 IU/mL) and anti-insulin antibodies were 2.30 U/mL (less than 10 IU/mL). The C-peptide was 0.31 ng/mL (normal 0.9-1.8 ng/mL). The patient was started on intensive insulin therapy and put on a diabetic diet after being diagnosed with checkpoint inhibitor related T1DM. Since blood sugar regulation was not accomplished with intermittent insulin therapy, an insulin pump was installed, which improved blood sugar management. The patient completed 1-year course of pembrolizumab and remains on insulin therapy. She has been disease-free for four years.

DISCUSSION

T1DM caused by PD-1 inhibitors is extremely rare. Diabetic ketoacidosis (DKA) is the most frequent form of presentation in most cases reported in the literature[6,7]. Although T1DM in general is not as common among irAEs, PD-1 inhibitor-associated T1DM can rapidly worsen to the point that patients may not survive if not identified and treated in a timely manner[8]. Physicians should inform patients receiving checkpoint inhibitors about the possibility of treatment induced diabetes and educate them about the related clinical symptoms. Nivolumab, another immune checkpoint inhibitor, has been

Table 1. Comparison-of-T1DM-and-IO-related-DM

	IO related autoimmune DM	Type 1 DM
Risk factors	*Anti PD-1/PDL-1 checkpoint inhibitors	*Unclear
Presentation	*More frequent DKA	*DKA mostly in childhood
Clinical course	*Median 12 weeks after IO treatment, *C-peptide mostly low.	*Honeymooning
Autoantibodies	*Generally negative (60%)	*Present in 90%
Genetik	*Rare	*Almost 90% haplotypes
Exocrine pancreatic involvement	*Amylase lipase simultaneously high	*Reduced pancreatic volumes but enzymes generally normal

T1DM: Type 1 diabetes mellitus IO: Immunotherapy, PD-1: Programmed cell death 1, PDL-1 programmed cell death ligand, DKA: Diabetic ketoacidosis, DM: Diabetes mellitus

associated with a higher risk of T1DM in studies[9]. The primary pathogenesis-related processes proposed are: t cell activation and proliferation-induced damage to pancreatic beta islet cells; increased autoantibodies to insulin; predisposition due to HLA genotype; and an increase in proinflammatory cytokines.

Studies show that the incidence of autoimmune diabetes increases with combination immunotherapy (anti-PD-1, anti-CTLA-4)[10]. There have been reports of cases of diabetes mellitus (DM) with a fulminant course and DKA presentation, particularly in combination treatment settings[11]. By reviewing previous case reports[12,13], the features of diabetes associated with PD-1 inhibitors can be summarized as follows: late-onset diabetes [Based on the literature reviewed, the time from administration of immunotherapy (IO) to hyperglycemia ranged from 5 days to 23 months], rapid islet cell destruction, and initially low C-peptide levels. In cases reported in the literature, frequent complaints include polydipsia, polyuria, nausea, vomiting, dizziness, fatigue, upset stomach, diarrhea, progression to coma and other diseases of the endocrine glands. Table 1 summarizes the significant clinical differences between patients with IO-related DM and patients with conventional T1DM.

Our results validate previous correlations in case series, showing that 50% of patients will manifest within 12 weeks of starting IO treatment and that IO-associated DM is almost exclusively linked to anti-PD1 and anti-PD-L1 medication. Both of our patients had no family history of DM and had no additional risk factors that might predispose to diabetes mellitus. Although concomitant elevated amylase lipase levels have been reported in the literature, the amylase lipase levels of our patients were found to be within the normal range. With a high incidence of DKA and a rapid decrease in the synthesis of endogenous insulin, the disease not only manifests itself more quickly but also more fulminantly. In contrast, in general, no precipitating factor is identified in classic T1DM, and the disease typically has a much slower onset, with a lower prevalence of DKA and autoantibodies occurring years before the onset of clinical symptoms[14,15]. The exact criteria that put pembrolizumab users at risk for autoimmune diabetes remain unknown in today's setting.

CONCLUSION

Although IO related T1DM is uncommon, it can have fatal consequences. Therefore, it is important to educate patients and their families about the warning signs and symptoms of DKA and hyperglycemia. Because of the rapid loss of pancreatic β-cell function and the significant risk of DKA, clinical oncologists and endocrinologists should be aware of this condition and offer appropriate treatment. In addition, further studies are needed to determine the precise mechanism of underlying IO-related T1DM. It would also be useful to investigate novel strategies or islet cell and insulin nanoformulations for the treatment of diabetes. To best monitor and manage this rare adverse event, it is necessary to identify possible predisposing variables and update existing guidelines.

Ethics

Informed Consent: Written informed consent was obtained from the patient to present this case.

Authorship Contributions

Surgical and Medical Practices: O.Ö., A.G., E.G., Concept: O.Ö., A.G., E.G., Design: O.Ö., A.G., E.G., Data Collection or Processing: O.Ö., A.G., E.G., Analysis or Interpretation: O.Ö., A.G., E.G., Literature Search: O.Ö., A.G., E.G., Writing: O.Ö., A.G., E.G.

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KAYNAKLAR

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