Case Report

Occurrence of Type 1 Diabetes in A Patient Enrolled in An Immunotherapy Combination Phase 1 Clinical Trial: A Case Study

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ABSTRACT

Advances in cancer immunotherapy treatments have shown promising results in patients with metastatic malignancy who have been refractory to prior treatments. Immune checkpoint inhibitors such as pembrolizumab in combination with other systemic agents may unleash immune-related adverse events (irAEs). Immunotherapy-induced Type 1 diabetes is rare; however, if left undiagnosed, it may cause life-threatening metabolic endocrinopathies. Advanced practice registered nurses are in a unique position to recognize and identify this irAE and in doing so can provide pathways for early diagnosis and treatments, thus leading to improved clinical and patient outcomes.

Key words: Immune checkpoint inhibitors, immunotherapy, Type 1 diabetes

Introduction

The primary objective of Phase 1 clinical trials is to establish the optimal dose of a novel drug, treatment, or drug combination while identifying its toxicity profile.[1] Clinical trials with immune checkpoint inhibitors (ICIs) such as pembrolizumab in combination with targeted therapies have shown promising effects in improving survival rates in patients with advanced cancer.[2] These immunomodulating agents have contributed to immune-related adverse events (irAEs) such as insulin-dependent Type 1 diabetes (IDDM) which may be life-threatening, if not promptly recognized by advanced practice registered nurses (APRNs).[3]

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Case Report

A 50-year-old female with metastatic duodenal cancer began experiencing worsening control of her diabetes after exposure to an immunotherapy combination Phase 1 clinical trial. Her prior medical history included a new-onset Type 2 diabetes 6 months before her cancer diagnosis. She underwent a Whipple procedure after which she was initiated on lantus insulin that continued for 4 months and then transitioned to oral therapy with metformin 500 milligrams twice daily thereafter. She was followed by her local endocrinologist initially; however, due to worsening glucose control, a referral was placed to the endocrinology department for assistance with diabetes management.

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Her hemoglobin A1c (HbA1c) was 6.8% before initiation with pembrolizumab, which increased to 8.5% after five cycles and 9.2% after nine cycles of treatment. She began experiencing extreme fasting blood sugars in the 300's and occasional hypoglycemic episodes in the low 50's at night, along with tachycardia and diaphoresis. Polyuria and polydipsia were also present during the episodes with hyperglycemia. During the time of the consult, the endocrinology team found that her HbA1c was 10.4% with a connecting peptide (C-peptide) of less than 0.02; however, her islet cell antibodies were nonexistent in the blood work. These laboratory data along with the pattern of her presentation were highly suggestive that she had developed IDDM secondary to immunotherapy. She was initiated on tandem insulin pump, Tresiba and metformin 1000 milligrams twice daily in addition to using a premeal insulin sliding scale. She was taken off Phase 1 clinical trial after 15 cycles secondary to disease progression and was transitioned to standard of care treatment.

Discussion

The development of ICI has provided a platform of newly emerging anticancer therapies that has helped raise hope for many cancer patients.[4] Although highly effective, these immunomodulating agents have contributed to a unique spectrum of irAEs that resembles autoimmune responses.[5] Metabolic endocrinopathies have appeared as one of the most common irAEs and their manifestations are often irreversible, and their underlying mechanism is mostly undefined. IDDM is an autoimmune disorder that is caused by the destruction of insulin-producing pancreatic beta cells secondary to thymus cell mediated destruction.[6] It is eminent that ICI disrupts the metabolic homeostasis by causing interruption of the signaling of these thymus cells.[7]

Although this patient had a history of Type 2 diabetes, the pattern of presentation suggested development of autoimmune IDDM induced by exposure to immunotherapy. Laboratory data demonstrated that she did not show any presence of islet cell antibodies; however, her C-peptide was almost undetectable. In cases with immunotherapy-associated IDDM, C-peptide levels were unsuitably low soon after diagnosis, suggesting that the human body is not making enough insulin.[2] A substantial decrease in the levels of C-peptide was suggestive of destruction of pancreatic beta cell function as the cause of IDDM.[2] It is understood that the absence of islet cell autoantibodies does not eliminate the emergence of immunotherapy-induced IDDM.[8]

The associated symptoms of IDDM are hyperglycemia along with polyuria, polydipsia, and polyphagia with increasing physical weakness or lack of energy with total body weight loss.[8] A patient with IDDM will require an implanted insulin device or long-acting subcutaneous insulin; however, there are no established guidelines for patients who develop IDDM secondary to ICI.[5] Since this glycemic impairment has been seen in patients receiving immunotherapy, it comes with significant importance that APRNs are challenged to identify this irAE for improved clinical outcomes. The APRNs should assess for clinical signs of IDDM such as weight loss and immediate onset of polyuropolydipsic syndrome.[9] A baseline fasting blood glucose and HbA1c should be performed if the patient has a history of diabetes before initiation and during treatment with immunotherapy.

The diagnosis of IDDM does not contraindicate the discontinuation of treatment with ICI but may interrupt therapy in severe cases.[10] This may cause stress and anxiety for the patients who are concerned about tumor growth. The APRN should make a prompt referral to the endocrinology team to assess for immunotherapy-related diabetes and decrease the potential morbidity associated with hyperglycemia or diabetic ketoacidosis.[10] Glycemic control can prove to be challenging with the instability of hyperglycemic or hypoglycemic episodes in these patients. Co-management and care coordination between the APRNs and the endocrinology service are essential to optimize patient outcomes.

Conclusions

Advances in cancer treatment with ICIs are promising; however, the incidence of autoimmune side effects such as IDDM will continue to rise if not promptly recognized. The APRN as part of the multidisciplinary team should be able to identify these irAEs and disseminate the information to other healthcare providers to improve the quality of care. Referrals to the appropriate discipline should be considered early in the management of this metabolic endocrinopathy. APRNs should counsel their patients on these potential irAEs to optimize patient outcomes, decrease treatment interruptions, and improve overall patient satisfaction.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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