



Rapid Development of Type 1 Diabetes Mellitus after Initiation of Anti-PD-1 Therapy

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Abstract

Programmed death protein 1 (PD-1) is a receptor on immune cells that serves as a checkpoint and plays an important role in preventing the activation of T-lymphocytes. Malignant cells are known to activate this receptor, thereby allowing them to evade immune surveillance. Programmed death 1 immune-checkpoint inhibitor antibodies (anti-PD-1), such as nivolumab, act to revamp the immune response against tumor cells by preventing activation of this PD-1 receptor. This manipulation of the immune system has been proven beneficial in the treatment of advanced cancers but can potentially precipitate life-threatening autoimmune conditions. We present a case of fulminant type 1 diabetes mellitus in a patient soon after beginning treatment of stage IV squamous cell carcinoma of the lung with nivolumab monotherapy. While all reports thus far have had positive autoimmune markers, thereby coinciding with the primary mechanism of the drug therapy itself, we present a patient with negative autoantibodies. This rare side effect has only been described in one case report and a case series to date. This paper will add to the sparse literature to better characterize this rare but serious side effect, as well as provide a case suggesting a mechanism outside the classic humoral mechanism previously described.

Keywords

Nivolumab, Programmed death 1, pd-1, Anti-pd-1, Autoimmune, Diabetes, Non-small-cell lung cancer

Introduction

Nivolumab is one of two immune based chemotherapeutic agents targeting programmed death protein 1 receptor (PD-1). By increasing tumor surveillance and host immune response, an unregulated or non-specific activation can result in damage and destruction of uninvolved organ systems. We report a case of rapidly developing diabetes, presenting as diabetic ketoacidosis, within 2-weeks of beginning treatment with nivolumab.

Case Presentation

A 77-year-old Caucasian woman presented to the emergency room complaining of abdominal pain and progressive weakness. Her symptoms started one-week prior with fatigue, lightheadedness, polyuria, and polydipsia. Initial laboratory testing showed a blood

glucose of 504 mg/dL, beta-hydroxybutyric acid of 3.5 mMoles/L, hemoglobin A1C (HbA1c) of 10.2%, and elevated lipase. She was an excellent historian and denied any previous personal or family history of diabetes or autoimmune conditions. HbA1c on record from one-year prior was 5.6%. She was diagnosed with new-onset type 1 diabetes mellitus and diabetic ketoacidosis treatment protocol was initiated. Further questioning revealed that the patient began treatment with anti-PD-1 agent, nivolumab, for stage IV squamous cell lung cancer 10-days prior to presenting to the hospital. C-peptide levels (0.81 ng/mL) were inappropriately low in response to her blood glucose levels and continued to downturn despite persistent hyperglycemia. Treatment was without complication and she was discharged from the hospital on long-acting insulin with additional prandial control. She was instructed to follow-up with her oncologist. Laboratory tests performed at her follow-up appointment revealed negative HLA-A2, HLA-DR4, glutamic acid decarboxylase 65 antibodies, insulin autoantibodies, islet antigen 2 antibodies, islet cell antibody screen, as well as an islet cell antibody titer. She continues to receive nivolumab infusions every two weeks and her blood glucose is poorly controlled with insulin.

Discussion

Nivolumab was first approved by the Food and Drug Administration (FDA) for the treatment of advanced melanoma in December of 2014 and received expanded approval for the treatment of non-small cell lung cancer in March of 2015 [1]. This drug works through inhibiting activation of the programmed death protein 1 (PD-1) which is found on immune cells and, when activated, serves as a checkpoint to prevent the activation of T-lymphocytes. Malignant cells are known to activate this receptor, thereby allowing them to evade immune surveillance. Programmed death 1 immune-checkpoint inhibitor antibodies (anti-PD-1), such as nivolumab, prevent activation of this PD-1 receptor thereby revamping the immune response. Due to preliminary trials showing improved overall survival using anti-PD-1 medications [2], the use of these drugs is becoming more common among prescribing clinicians in the treatment of malignancies. Although two cases of diabetes were reported as side effects during initial clinical trials, one during monotherapy with nivolumab [3] and the other during combination therapy with nivolumab/ipilimumab [4], an autoimmune mechanism was not suggested until recently [5].

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Table 1: Summary of laboratory results from previously reported cases and current case.

Patient	Age	Anti-PD-1 Agent	Glucose Level at Presentation	C-peptide Level	GAD65 antibody positive?
1	54 F	Pembrolizumab	N/A	N/A	No
2	55 F	Nivolumab	532 mg/dL	< 0.1 ng/mL	Yes
3	58 M	Nivolumab	749 mg/dL	< 0.1 ng/mL	Yes
4	63 M	Nivolumab	247 mg/dL	1.3 ng/mL	Yes
5	64 M	Pembrolizumab	703 mg/dL	0.5 ng/mL	No
6*	77 F	Nivolumab	504 mg/dL	0.81 ng/mL	No
7	83 F	Nivolumab	350 mg/dL	< 0.1 ng/mL	Yes

*Patient 6 represents data obtained from the case reported in this manuscript.

Six cases of autoimmune diabetes due to anti-PD-1 therapy were found using a search of Google Scholar and Pubmed, either as a single or combination therapy [5,6]. Patients' presentation ranged from asymptomatic random elevations in serum or urine glucose tests to diabetic ketoacidosis, with the latter accounting for over half. Time from initiation of therapy to onset of event ranged from 1 week to 5 months. In all cases where C-peptide levels were reported, levels were inappropriately low or undetectable. Antibodies for anti-glutamic acid decarboxylase (GAD) were positive in 4 of the 6 [5,6]. Key findings from this case and previously reported cases are summarized in table 1 [5,6].

Both type 1 diabetes mellitus and latent autoimmune diabetes in adults (LADA) are characterized by low/undetectable C-peptide levels and the presence of GAD autoantibodies [7]. This has mirrored the laboratory findings of new onset diabetes due to nivolumab therapy to date [5,6]. Individuals with HLADQB1 have been shown to be at increased risk for type 1 diabetes and LADA [6]. Of note, all patients have been positive for this HLA A2 DR4 DQ8 genotype (HLA-A2 or HLA-DR4), which makes a relationship between these haplotypes and increased susceptibility to autoimmune diabetes after starting anti-PD-1 therapy likely [5,6].

The precise causality of autoimmune diabetes by nivolumab, although easily theorized by its anti-PD-1 immune modulation, has not been fully elucidated. And while type 1 diabetes mellitus is characterized by the presence of autoantibodies, whether to insulin, islet cells, or positive HLA subtypes, it has been shown that many patients may have autoantibody negative type 1 diabetes [8].

This new-onset diabetes mellitus secondary to anti-PD-1 therapy appears to respond to traditional treatment. It is persistent but remains stable despite continued dosing with anti-PD-1 medications [6]. As all reports have been recent, long-term outcomes and fluctuations among this population are yet to be fully determined.

Due to lack of prescriber awareness, as well as variable time of onset from treatment initiation, this severe side effect may go undocumented or misdiagnosed. It is important to recognize this early to initiate proper therapy as well as monitor for other organ systems becoming subsequently affected, as development of other autoimmune conditions including autoimmune thyroiditis has been identified in select patients [9]. While the exact mechanism of new-onset diabetes presenting as diabetic ketoacidosis in our patient is unknown, the lack of prior history of diabetes and clear correlation with the induction of monotherapy with nivolumab adds to the sparse literature on this topic. This case also demonstrates the unique possibility that new-onset diabetes, after treatment with anti-PD-1 antibodies, may not always correlate with traditional positive markers. Further studies would be required to investigate a possible cell-mediated autoimmune mechanism instead of the humoral autoimmune mechanism seen in classic type 1 diabetes mellitus.

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Ethical Statement

Title: Rapid Development of Type 1 Diabetes Mellitus After Initiation of Anti-PD-1 Therapy.

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We testify on behalf of all authors (listed above) that our article (title above) submitted to ClinMed International:

1. Is material that has not been published in whole or in part elsewhere;
2. Is not currently being considered for publication in another journal;
3. And that all authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly responsible for its content.
4. Date: March 26, 2016

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