

CLINICAL VIGNETTE

New Onset Type 1 Diabetes and Diabetic Ketoacidosis Induced by Nivolumab Therapy

Eric Stevens, M.D., and Shalini Bhat, M.D.

Introduction

The use of immunotherapy to treat a variety of cancers has significantly increased recently. Immunotherapy targets T-cell regulatory molecules and may be highly effective in multiple cancers which are refractory to chemotherapies. Nivolumab binds to and blocks the activation of PD-1, an Ig superfamily transmembrane protein, by programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen presenting cells. This results in the activation of T-cells and cell-mediated immune responses against tumor cells or pathogens. Blocking inhibitory molecules on activated T cells increases tumor cell destruction but also can breach tolerance, which enables pathological T cells to react with self-antigens.¹ Well-documented autoimmune endocrinopathies induced by immunotherapy include hypophysitis, hypopituitarism, and thyroiditis. The development of type 1 diabetes has been documented but has not been definitively linked to the agent nivolumab. We present a patient who developed immunotherapy induced type 1 diabetes.

Case Presentation

The patient is a 53-year-old male with a past medical history of ocular melanoma diagnosed in 2012. He was initially treated with ipilimumab and failed treatment. He had several unsuccessful rounds of chemotherapy before starting nivolumab. One week after the last of the three infusions with nivolumab, patient presented to the ED with fatigue, lethargy, increased thirst, and dry mouth. The patient had no past history of diabetes but had positive family history with diabetes in his mother. Current medications included levothyroxine, sertraline, mirtazapine, ranitidine, and bupropion.

His vitals were within normal limits and his physical exam was unremarkable. His labs were remarkable for glucose of 571, CO₂ 18, anion gap 35, small serum ketones, 2+ urine ketones, potassium 5.4. He was diagnosed with diabetic ketoacidosis and was treated with fluids and IV insulin. He was transitioned from insulin infusion when ketoacidosis resolved to a subcutaneous basal bolus insulin regimen. He received education about diabetes and teaching about insulin injections and was discharged home with a basal bolus regimen.

Further review of labs included a C-peptide <0.2 with Glucose of 260. Islet cell antibodies and glutamic acid decarboxylase (GAD) antibodies were negative. His A1c was 7.1%. A prior A1c six months earlier was 5.3% and glucose two weeks prior was 103.

The fact that he developed acute severe hyperglycemia with ketoacidosis and low/undetectable C-peptide levels was strong evidence for new insulin-deficient diabetes induced by immunotherapy. He was transitioned to subcutaneous glargine insulin at 16 units per day on day 2. His glucose level remained controlled, and on day 3 he was euglycemic. His glucose levels were stable on the insulin regimen at the 5 day follow up. He was discharged home with a glucose meter, and insulin. He has remained on basal-bolus insulin, which included 8 units/day of glargine insulin. He continued on the nivolumab treatment because of its effective anti-tumor action.

Discussion

With the increasing use of immunotherapy, physicians should be aware of the potential autoimmune side effects including type 1 diabetes. Immunotherapy induced type 1 diabetes has been documented in two patients with melanoma that happened to be antibody negative for GAD65, Insulin, and ICA antibodies.¹ The mechanism of diabetes caused by PD-1 inhibitors is unclear, but it may involve an excessive autoimmune response. Prior reports have described T cell-related autoimmunity is involved in the onset of autoimmune type 1 diabetes. This theory is supported by PD-1 expression decreases in peripheral CD4-positive T-lymphocytes in autoimmune type 1 diabetes.² Apoptosis and acute destruction of pancreatic β cells by T cells activated by nivolumab are thought to be involved in the development of diabetes.³ The onset of diabetes in these patients ranges from two weeks to five months after the first doses of immunotherapy.¹ At this time, development of type 1 diabetes after treatment of metastatic melanoma with nivolumab is just temporally associated¹. If diabetes development as a consequence of anti-PD1 treatment is shown to be definitively linked, these biologicals could be the first drugs to clearly induce type 1 diabetes in humans, which could open a new line of research in mechanisms of disease.⁴ Clinicians prescribing these drugs need to be aware of this life threatening adverse effect. Patient education and a glucose monitoring should be offered to patients who are started on this

medication. Currently, there are no official guidelines to screen patients started on this immunotherapy. It is suggested that all patients started on these medications should be screened for autoimmune diabetes with GAD65 antibody measurement, before and after the start of treatment. This case illustrates the importance of recognizing this potential precipitant of autoimmune diabetes in individuals receiving immunotherapy.

REFERENCES

1. **Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, Herold KC.** Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. *Diabetes Care*. 2015 Apr;38(4):e55-7. doi: 10.2337/dc14-2349. PubMed PMID: 25805871; PubMed Central PMCID: PMC4370325.
2. **Fujisawa R, Haseda F, Tsutsumi C, Hiromine Y, Noso S, Kawabata Y, Mitsui S, Terasaki J, Ikegami H, Imagawa A, Hanafusa T.** Low programmed cell death-1 (PD-1) expression in peripheral CD4(+) T cells in Japanese patients with autoimmune type 1 diabetes. *Clin Exp Immunol*. 2015 Jun;180(3):452-7. doi: 10.1111/cei.12603. PubMed PMID: 25682896; PubMed Central PMCID: PMC4449773.
3. **Fukui A, Sugiyama K, Yamada T, Tajitsu M, Cao X, Nagai J, Yambe Y, Imamura K, Nozawa K, Kitagawa C, Murase T.** A case of Nivolumab-induced fulminant type 1 diabetes with steroids and glucagon-like peptide 1 administration during the early onset. *J Clin Case Rep*. 2016;6:883.
4. **Hao J, Renno A, Imam S, Alfonso-Jaume M, Elnager N, Jaume JC.** Development of type 1 diabetes after cancer immunotherapy. *AACE Clinical Case Reports*. 2016; DOI:10.4158/EP161410.CR

Submitted May 29, 2017