Case Report

Breaking β Cell Tolerance After 100 Years of Life: Intratumoral Immunotherapy–Induced Diabetes Mellitus

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Abbreviations: AE, adverse events; GAD65, glutamic acid decarboxylase 65; HLA, human leukocyte antigen; HSV1, herpes simplex virus type 1; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; T1D, type 1 diabetes mellitus; T-VEC, talimogene iaherparepvec.

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Abstract

Cancer immunotherapies are changing the landscape of cancer care. Intratumoral talimogene iaherparepvec (T-VEC), an oncolytic viral vaccine, has been approved for treatment of unresectable melanoma with minimal toxicity. We describe the first case of a centenarian who developed autoimmune diabetes while on T-VEC immunotherapy. The patient’s high titer of glutamic acid decarboxylase 65 autoantibodies as well as insulin deficiency are consistent with autoimmune diabetes. Autoimmune diabetes has previously been seen following immune checkpoint inhibitor use; however, it has never been reported with T-VEC. This case highlights that autoimmune diabetes can be a rare but morbid complication of intratumoral T-VEC immunotherapy and can occur in the ultra-elderly.

Key Words: autoimmune diabetes, type 1 diabetes, intratumoral immunotherapy, T-VEC, immune toxicity, immune-related adverse events

Case Presentation

At over 90 years of age, this patient presented with metastatic melanoma involving lymph nodes and the small intestine. He was initially treated with surgery, including removal of cutaneous deposits, small bowel resection, and an inguinofemoral lymphadenectomy (Fig. 1).

Nine years after his initial diagnosis, at age 103 years, a positron emission tomography–computed tomography (PET/CT) scan revealed recurrent disease in his left leg. Given his history of multiple recurrences, further
resections were not advised and instead systemic treatment was recommended. He opted for intralesional talimogene laherparepvec (T-VEC, an oncolytic viral vaccine) over other immunotherapies, such as programmed death-1/programmed death-ligand 1 (PD1/PD-L1) inhibitors, due to a more favorable side effect profile and desire to avoid severe immune-related adverse events at his age.

T-VEC treatment consisted of 2 mL of $10^6$ PFU/mL injection into his new left leg lesions which were 1.8 cm and 2.5 cm in largest diameter. After his second intratumoral injection he developed severe fatigue, nausea, and vomiting, requiring administration of intravenous fluids. His blood glucose at that time was 165 mg/dL (Fig. 2). His symptoms resolved but his T-VEC dose reduced by half to 1 mL of $10^6$ PFU/mL for subsequent injections. At his fourth injection he was asymptomatic, but his blood glucose was elevated at 303 mg/dL. His next labs, which resulted the day after his fifth injection, showed a blood glucose of 612 mg/dL, which prompted a visit to urgent care. There, his glucose was again elevated at 300 mg/dL. There were no signs of diabetic ketoacidosis: his bicarbonate was 27 mmol/L (reference range, 21-32 mmol/L), his anion gap was 10 mmol/L, but urine and serum ketones were not checked. He had no evidence of pancreatic metastasis. He was given intravenous fluids and discharged with a plan for primary care follow-up. Three days later, having not reached his primary care physician, he presented to the emergency department. Blood

**Figure 1.** Timeline of the patient’s disease course. The series of events relating to development of previous autoimmunity, cancer diagnosis, and cancer treatment, leading up to the diagnosis with T-VEC–induced autoimmune, insulin-dependent diabetes. Dark blue-gray dots represent melanoma related events, blue dots represent melanoma treatment events, and light gray dots represent diabetes-related events.

**Figure 2.** Development of uncontrolled blood glucose in a T-VEC-treated patient. This represents the evolution of the patient’s hyperglycemia relative to his T-VEC injections. The solid circles represent blood glucose values and the diamonds represent T-VEC injections.
glucose was 534 mg/dL with a bicarbonate of 26 mmol/L and an anion gap of 12; again, ketones were not checked (Table 1).

Laboratory testing during the hospitalization revealed positive glutamic acid decarboxylase 65 (GAD65) autoantibodies (>250 IU/mL; normal <0.8 IU/mL); however, insulin autoantibody and islet antigen-2 antibody were both negative. His proinsulin was 17.7 pmol/L (normal <18.8 pmol/L) with a matched glucose of 478 mg/dL, suggesting relative insufficient insulin production. A C-peptide level was not checked at that time but 2 weeks after hospital admission, follow-up laboratory analysis revealed C-peptide to be inappropriately normal at 2.8 ng/mL (reference interval 0.8–3.1 ng/mL) with a matched serum glucose of 278 mg/dL. C-peptide levels were not rechecked.

He was discharged on 10 units insulin glargine daily and a carbohydrate-controlled diet.

Over the following weeks, glucoses ranged from 50 to 292 mg/dL. He was then switched from insulin to metformin and linagliptin due to his preference to avoid insulin. On oral antihyperglycemic medications alone, his fasting glucoses were between 140 and 200 mg/dL.

Follow-up CT scans performed 2 months after the fifth T-VEC dose showed progression of melanoma in the left leg and possible recurrence of small bowel metastasis at the anastomotic sites leading to T-VEC discontinuation. There was still no evidence of pancreatic metastasis. He was started on palliative radiation therapy, to which he responded. Throughout radiation treatment his blood glucose was elevated in the range of 200 to 300 mg/dL and he lost approximately 20 pounds while on metformin and linagliptin. A basal bolus insulin regimen was started 4 months after radiation completed.

He was alive and well 2 years following his T-VEC-induced diabetes diagnosis. Repeat islet autoantibodies performed 1 year following diabetes diagnosis were positive for anti-GAD65 autoantibody and insulin autoantibody. Zinc transporter 8 autoantibody, islet antigen-2 antibody, thyroperoxidase antibody, and thyroglobulin antibody were all negative. His human leukocyte antigen (HLA) type was identified as DR7-DQ2.2/DR7-DQ2.2 (homozygous for DRB07:01:01-DQA02:01-DQB02).

Pertinent past medical history includes vitiligo diagnosed about 20 years prior to his initial melanoma presentation, colon cancer treated with a partial colectomy, hypertension, and coronary artery disease. His family history includes a mother with a history of type 2 diabetes mellitus treated with oral medications and a father who died of anaphylaxis following penicillin. There were no other autoimmune diseases in the family.

Discussion

Here we describe induction of autoimmune diabetes in a patient over 100 years old coinciding with T-VEC therapy. His elevated anti-GAD65 autoantibody is consistent with autoimmune diabetes and his inappropriately normal C-peptide paired with insulin requirements are consistent with insulin-dependent diabetes. Annual risk for new onset autoimmune diabetes is highest in youth; in adulthood, there is an initial steep decline followed by a gradual increase in incidence in later decades of life. The incidence in Americans over 65 years of age is not known [1]. Notably, in Kronoberg, Sweden, cases have been noted through the ninth decade [2]. The oldest reported case of type 1 diabetes mellitus treated with oral medications and a father who died of anaphylaxis following penicillin. There were no other autoimmune diseases in the family.

Table 1. Laboratory Parameters Over Disease Course

|                        | Value     | Normal Range       |
|------------------------|-----------|--------------------|
| Labs at Emergency Department Presentation and During Hospitalization |           |                    |
| Glucose                | 378 mg/dL | 70-100 mg/dL       |
| HCO3                   | 26 mmol/L | 21-32 mmol/L       |
| Anion gap              | 12 mmol/L | 6-16 mmol/L        |
| Urine ketones          | Not Checked |                    |
| Hemoglobin A1c         | 11.2      | 4.8%-5.6%          |
| Free insulin           | 3.1 uU/mL | 1.5-14.9 uU/mL     |
| GAD65 autoantibody     | >250 IU/mL| <50 IU/mL          |
| Insulin autoantibody   | <0.4 U/mL | <0.4 U/mL          |
| IA-2 antibody          | <0.8 U/mL | <0.8 U/mL          |
| Labs 2 Weeks After Hospitalization                         |
| C-peptide              | 2.8 ng/ml | 0.8-3.1 ng/ml      |
| Matched serum glucose  | 278 mg/dL | 70-100 mg/dL       |
| Labs Approximately 1 Year After Hospitalization (different laboratory) |
| GAD65 autoantibody     | 771       | <20 DKU/mL         |
| Insulin autoantibody   | 0.746     | <0.010 index       |
| IA-2 antibody          | 0         | <5 DKU/mL          |
| Zinc transporter 8 autoantibody | -0.002 | <0.020 index       |
| Thyroperoxidase antibody| -0.006  | <0.03 index        |
| Thyroglobulin antibody  | 0.001     | <0.03 index        |

Abbreviations: GAD65, glutamic acid decarboxylase 65; IA-2 antibody, islet antigen 2 antibody; labs, laboratory values
the virus alongside local granulocyte macrophage colony-stimulating factor (GM-CSF) production to increase antigen presenting cell infiltration into the tumor microenvironment [5]. The mechanism of action is through two distinct pathways: direct oncolytic destruction of tumor cells locally as well as stimulation and maturation of antigen presenting cells with presumed subsequent priming of antigen-specific T cells causing induction of tumor-specific immunity [6]. Evidence of systemic immunity is well illustrated by an abscopal effect with regression of noninjected distant lesions [5, 7]. There is evidence of increased peripheral T regulatory cells (Tregs) and CD8+Foxp3+ suppressor T cells in melanoma patients compared with healthy donors, especially within the tumor microenvironment [6]. Notably, the CD8+Foxp3+ suppressor T cells appeared to be decreased in the periphery of T-VEC–vaccinated melanoma patients compared with unvaccinated patients. In another study [7], after a single injection of T-VEC, an increase in the number of both circulating CD8+ and CD4+ T cells in peripheral blood and the CD8+ T cell density in the tumor microenvironment was identified, which is often associated with therapeutic response.

T-VEC has been reported to produce an objective response in 26% of melanoma patients and a durable response in 16% of those treated [5]. The median time to response was 4.1 months and, importantly, more than a quarter of the patients that responded had a temporary increase in the size or number of new lesions before achieving a response. This increase may be attributable to pseudoprogression due to an increase of immune infiltrate into the tumor microenvironment. T-VEC is generally well tolerated. Grade 3 or higher adverse events (AEs) occurred in 36% of patients but cellulitis was the only severe AE common to more than 2% of patients. Low grade AEs were more common and included fever, chills, myalgias, and gastrointestinal symptoms similar to those described by our patient. This reflects that AEs occurring in response to T-VEC are not restricted to the local inflammation at the injection site; however, there are no previous reports of hyperglycemia.

This patient had no known autoimmune disease until the development of vitiligo 20 years prior to his diagnosis of clinically apparent melanoma, when he was already in his seventies. The antigen specificity of vitiligo in the setting of melanoma is often related to cross-reactivity between cancer cells and melanocytes, and is a positive prognostic marker of response to immune checkpoint inhibitors [8]. Development of vitiligo preceding melanoma diagnosis might suggest a smoldering immune response against melanocytic self-antigens through cancer immunoeediting, similar to that seen in systemic sclerosis [9, 10]. Interestingly, this patient was homozygous for a haplotype that is protective for T1D [11], suggesting that the T-VEC–generated immune response was significant enough to overcome his genetic protection after living over 100 years without a triggering event. Mechanistic studies would enable understanding of the modulation of the immune repertoire in response to T-VEC. For example, a study that profiles the tumor, site of AE (pancreas) and peripheral blood could identify whether there are antigen-specific cells that become clonally expanded in response to immunotherapies. In the setting of immune checkpoint inhibitors, it is becoming increasingly recognized that shared cancer and self-tissue antigens play a role in the AE response, even if from diverse organ systems [12, 13]. The development of T-VEC induced diabetes may therefore be due to shared antigens between melanoma and β cells that become expanded through T-VEC exposure. However, the rarity of these events and the limitations in accessing tissue makes these studies difficult, although they would be valuable to provide insight in to the development of AEs. T-VEC is also able to promote the CD8+ and CD4+ effector T cells while decreasing suppressive T-cell subsets. Altering this balance may permit a microenvironment in which autoreactive T cells against β cell antigens are promoted. This could be due to shared antigens between melanoma and β cells that are identified through T-VEC exposure and increases in CD8+ T cells or CD4+ T cells; but, could also be due to the decreases seen in suppressive T-cell subsets. Finally, it is possible but unlikely that HSV1 could have been a trigger. Viral exposures have long been thought to contribute to development of T1D, but HSV1 is not thought to be one such viral entity. Immune checkpoint inhibitors also can lead to development of autoimmune, insulin-dependent diabetes. In diabetes that develops in the setting of immune checkpoint inhibitors, it usually occurs following exposure to PD1 or PDL1 inhibitors, the onset of hyperglycemia is typically acute, islet cell autoantibodies are present only approximately half the time, and the genetic predisposition based on HLA type is likely similar to T1D [4]; however, there are also reports of immune checkpoint inhibitor–induced diabetes mellitus occurring in individuals with HLA types that are traditionally protective against T1D [11, 14], similarly observed in this case.

While T-VEC-induced diabetes is obviously rare, it is important to be aware of this highly morbid complication. Studies have shown an increased antitumor response in patients treated with combinations of T-VEC and immune checkpoint blockade [7, 15, 16], but also increases in AEs in some but not all trials. It will be important to monitor for differences in frequency and severity of AEs with the increasing number of patients exposed to T-VEC in addition to other immunomodulatory agents. Attention to changes in this patient’s blood glucose earlier in his presentation may have been able to prevent his hospital admission and would have expedited a referral to an endocrinologist,
suggesting that clinicians need to be aware of this AE and consider lab monitoring on a regular basis during T-VEC therapy, even if solely through use of a glucometer in clinic. Finally, it suggests that T-VEC or its downstream immunomodulatory effects could play a role in triggering autoimmune pancreatic islet cell destruction, as they did for this patient, who lived over 100 years without developing diabetes and had an HLA haplotype protective for T1D.

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