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LETTER TO THE EDITORS

A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome

Elizabeth Hansen[1] · Deepak Sahasrabudhe[1] · Lynn Sievert[1]

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Dear Editors,

The article entitled "Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report" provided an interesting perspective on the onset of insulin-dependent diabetes following anti-programmed cell death therapy [1]. While several recent reports cite the incidence of diabetes onset, little is mentioned on outcome or clinical course over time. Here we present a case of pembrolizumab-induced insulin-dependent diabetes, with insight on the clinical outcome following discontinuation of the offending agent.

Here we present a 58-year-old male, diagnosed with a 2.1-mm thick, Clark Level IV, non-ulcerated, cutaneous melanoma of the left upper arm in 2000. He underwent a wide excision and left axillary lymph node sampling, which revealed one of three lymph nodes to be involved. He was treated with interferon alpha 2B as adjuvant therapy for 1 year. In 2012, imaging revealed a right upper lobe lung nodule, left upper paramediastinal mass and lymphadenopathy in the aortopulmonary region. Biopsy of the right lung lesion showed metastatic melanoma. It harbored BRAF V600E mutation. He received vemurafenib, high-dose IL-2 and ipilimumab sequentially. Treatment with vemurafenib resulted in stable disease for 16 months.

In May 2014, repeat staging revealed multiple intra-abdominal and subcutaneous soft tissue masses, new liver lesions and an increase in the right upper lobe lesion, indicating progression of disease. In June 2014, treatment with anti-programmed cell death (PD-1) therapy with pembrolizumab at 2 mg/kg, every 3 weeks, was initiated on an expanded access program. Treatment-related side effects included hypothyroidism, fatigue, hair depigmentation, gastroesophageal reflux and weight gain. Initial restaging images showed an excellent response to PD-1 therapy, with a decrease in the majority of metastatic lesions. PD-1 therapy was continued. He received a total of 17 cycles.

In late June 2015 he presented with a fungal appearing inguinal rash, worsening fatigue, weight loss, polydipsia, polyuria and a non-fasting blood glucose level of 408 mg/dL. There was no abdominal pain or symptoms of pancreatic enzyme deficiency. Physical examination was unrevealing except for the rash. Serum amylase and lipase were normal. Hemoglobin A1c was 9.7 %, and serum titers of anti-glutamic acid decarboxylase antibodies were elevated confirming the diagnosis of insulin-dependent diabetes (Table 1).

Pembrolizumab was held, and the patient was started on a subcutaneous insulin regimen, consisting of both long-acting and short-acting insulin. No immunosuppressive agents or corticosteroids were administered.

In early July 2015 restaging images showed progressive disease with a new, large 4.3 × 3.3 cm mass in the liver. He was started on dabrafenib plus trametinib [2, 3].

Following pembrolizumab discontinuation, fasting blood glucose levels and total daily insulin requirements began to gradually decline. From insulin-dependent diabetes onset to 20 days post pembrolizumab discontinuation, median fasting blood glucose levels and total daily insulin requirements were 153 mg/dL (IQR 78.5 mg/dL) and

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✉ Elizabeth Hansen
Elizabeth_hansen@urmc.rochester.edu

[1] University of Rochester Medical Center, 601 Elmwood Avenue, Box 617, Rochester, NY 14642, USA

Table 1 Laboratory findings

	Baseline	Day 20	Day 55	Day 81
Islet autoantibodies				
Pancreatic islet cell antibodies	Negative (<1:4)			
Anti-GAD (U/mL)	>250			
Other results				
Blood glucose (mg/dL) (non-fasting)	408			
Fasting blood glucose median, IQR (mg/dL)		153 (78.5)[a]	108 (16)[b]	128 (13.5)[c]
Total daily insulin requirement, median (units), IQR		39 (8.75)[a]	23 (19)[b]	0[c]
C-peptide (ng/mL)		2.4	4.1	3.5
C-peptide (nmol/L)		0.799	1.365	1.166
Hemoglobin A1C (%)	9.7		7.1	
Creatinine (md/dL)	1.3			
Amylase (U/L)	53			
Lipase (U/L)	91			

[a] Median values from baseline until day 20

[b] Median values used day 21 until day 55

[c] Median values used day 56 until day 81

39 units (IQR 8.75 units), respectively (Table 1). By day 55 post insulin-dependent diabetes onset, median fasting blood glucose levels and total daily insulin requirements had decreased to 108 mg/dL (IQR 16 mg/dL) and 23 units (IQR 19 units), respectively. His hemoglobin A1c level decreased in parallel from 9.7 % to 7.1 % (Table 1).

C-peptide levels were obtained to ascertain residual β-cell function. Random C-peptide levels were drawn on day 20, 55 and 81 postinsulin-dependent diabetes onset. All C-peptide values were in the normal reference range, indicating endogenous insulin production. By day 54 after onset of insulin-dependent diabetes the patient was able to discontinue insulin.

To date, he continues to tolerate dabrafenib plus trametinib with restaging scans showing a response to therapy, as most lesions appear smaller in size or stable.

Discussion

It has been shown that after insulin-dependent diabetes onset, C-peptide levels decrease over time and ultimately become undetectable. In a study by Davis and colleagues, only 43 % of patients with insulin-dependent diabetes for 3–5 years had residual C-peptide levels ≥0.2 nmol/L [4]. Given that this patient has remained euglycemic after discontinuation of insulin and has detectable C-peptide levels, this likely indicates he has residual β-cell function post pembrolizumab-induced insulin-dependent diabetes onset. Furthermore, dabrafenib has been associated with all-grade hyperglycemia in 50 % of patients when used as a single agent. Given that his blood glucose levels normalized during treatment with this regimen, it is unlikely dabrafenib contributed to his hyperglycemia [3].

Overall, the use of anti-PD-1 antibody therapy has been associated with a number of autoimmune reactions. Generally, many of these adverse reactions can be managed with the use of corticosteroids and ultimately reversed. However, in less characterized reactions, such as insulin-dependent diabetes, the clinical course has not been well described. It is unknown whether corticosteroid administration would have provided benefit for this patient. In this case, it was chosen not to use corticosteroids as it was possible to control the hyperglycemia with insulin and due to the concern that steroid-induced hyperglycemia would have made it difficult to definitively ascertain recovery. Clinicians should also be aware that close monitoring of blood glucose is required during management of this unique autoimmune phenomenon, as insulin-induced hypoglycemia, a high-risk complication, may arise following recovery.

Recently, the US Food and Drug Administration-approved prescribing information was updated with a warning for the development of insulin-dependent diabetes following the use of pembrolizumab [5]. Patients undergoing treatment with anti-PD-1 therapy should be closely monitored for autoimmune reactions, including the rare reaction of insulin-dependent diabetes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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