



Case Report

Diabetic ketoacidosis induced by a single dose of pembrolizumab☆☆☆

Julian Maamari, BSc^a, Sai-Ching J. Yeung, MD PhD^b, Patrick S. Chaftari, MD^{b,*}^a School of Medicine, Lebanese American University, Byblos, Lebanon^b Department of Emergency Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ARTICLE INFO

Article history:

Received 11 October 2018

Accepted 18 October 2018

ABSTRACT

Immune checkpoint inhibitors are a new class of anticancer drugs recently approved by the US Food and Drug Administration (FDA) for the treatment of various malignancies. Pembrolizumab is an immune checkpoint inhibitor that targets the programmed cell death protein-1 (PD-1) receptor and blocks its interaction with programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2). Pembrolizumab was first approved by the FDA in 2014 for the treatment of advanced melanoma and is currently approved for use in non-small cell lung cancer and several other neoplasms. Immune checkpoint inhibitors such as pembrolizumab have been reported to induce immune-mediated side effects, including type 1 diabetes mellitus in very rare cases (0.1% in clinical trials). Here, we report the case of a woman with no known history of diabetes who presented to our emergency department in a state of diabetic ketoacidosis within 3 weeks of receiving only a single dose of pembrolizumab therapy, and without any previous exposure to immunotherapy. This case of abrupt adult-onset type 1 diabetes mellitus is an example of the undesirable side effects that can emerge after only a brief exposure to an immune checkpoint inhibitor. Close monitoring of patients receiving immune checkpoint inhibitors is warranted for the early diagnosis and management of imminent and potentially life-threatening complications.

© 2018 Elsevier Inc. All rights reserved.

1. Introduction

Immune checkpoint inhibitors (ICIs) are a new class of anticancer drugs. The ICI pembrolizumab was first approved by the US Food and Drug Administration (FDA) in 2014 to treat advanced melanoma and is now also approved for use in non-small-cell lung cancer and other neoplasms [1].

Type 1 diabetes mellitus (T1DM) is a rare immune-mediated side effect induced by ICIs, with an incidence rate of 0.1% in clinical trials [2]. Here, we report the case of a woman with sarcoma who presented to our emergency department (ED) with diabetic ketoacidosis (DKA) within 3 weeks of a single pembrolizumab treatment. This patient had no previous exposure to immunotherapy. We believe this is the first case of T1DM leading to DKA after only one dose of pembrolizumab.

2. Case report

A 47-year-old woman was diagnosed in November 2017 with cardiac angiosarcoma. She underwent neoadjuvant chemotherapy (doxorubicin/ifosfamide (5 cycles) and gemcitabine/docetaxel (2 cycles)), followed by surgical resection of the atrial mass in May 2018. Postsurgery, she was started on pembrolizumab.

When the patient presented for her second pembrolizumab dose, her blood glucose level was 452 mg/dL and she was sent to the ED for evaluation. She reported having extreme polydipsia during the past day and polyuria throughout the past 2 weeks, plus nausea, a soft lingering headache, and visual changes. Blood pressure was 99/62 mm Hg, heart rate 61 bpm, respiratory rate 19/min, temperature 36.8 °C, and oxygen saturation 96% at intake. She had no history of diabetes or use of diabetogenic medications, nor had she previously received ICIs. Further workup revealed: glucose 523 mg/dL (an increase), urine ketones 80 mg/dL, WBC count 4200, arterial blood gas pH 7.25 and partial pressure of carbon dioxide 33 mm Hg, potassium 4.6 mmol/L, bicarbonate 15 mEq/L, anion gap 26, and normal liver enzymes, creatinine, and chest X-rays. To check for hypophysitis, TSH, FT4, cortisol, FSH, and LH levels were measured [3]. Cortisol, FT4, and TSH were normal; FSH and LH were slightly elevated, consistent with the patient's perimenopausal age [4].

In the ED, the patient was rapidly treated for DKA with 8 units of insulin IV push and was started on insulin infusion with concurrent

☆ Grant or other financial support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

☆☆ Conflicts of interest: The authors declare that they have no conflicts of interest.

* Corresponding author at: Department of Emergency Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1468, Houston, TX 77030, USA.

E-mail address: pchaftari@mdanderson.org (P.S. Chaftari).

hydration and electrolyte replacement to avoid further deterioration. Endocrinology was consulted and the patient was admitted to the medical ICU. C-peptide was 0.1 ng/mL (<0.8, reference range 1.1–4.4 ng/mL), HbA1c 6.4%, serum β hydroxybutyrate 6.4 mmol/L (<0.4), anti- β -islet cell antibodies were negative, and anti-GAD antibodies were positive at 0.11 nmol/L (<0.02). In the ICU, nausea, malaise, and blurry vision resolved. By ICU day 2, her anion gap closed and she was able to tolerate oral intake. She was switched to insulin detemir 8 units subcutaneous BID and insulin lispro following a correctional scale.

On ICU day 3, she was transferred to a regular floor for close monitoring. Two days later, in stable condition, she was discharged home on insulin degludec 15 units subcutaneous every morning and insulin lispro following a correctional scale. She was to follow up with endocrinology as an outpatient.

3. Discussion

This case of abrupt adult-onset T1DM is yet another example of undesirable side effects that can emerge after only brief exposure to an ICI. Despite having no personal or family history of diabetes, the patient presented with symptoms indicative of DKA—a medical emergency seen in patients with T1DM [5]. Lack of any other trigger/history suggested pembrolizumab-induced T1DM. Unlike our patient, most (4 of 6) patients in the few published case reports received ipilimumab before starting pembrolizumab, and most were treated for melanoma [6]. The FDA has warned that pembrolizumab may cause immune-mediated endocrinopathies [7]. To our knowledge, this is the first case wherein T1DM-induced DKA occurred within a short 3-week timeframe, and after only one dose of pembrolizumab.

Anti-PD1 drugs such as pembrolizumab act by removing a negative regulatory signal on the cancerous cells, allowing T-cell activation and boosting immune function [8] but also reducing tolerance and, consequent, inducing autoimmune side effects. Case reports on anti-PD-1 immunotherapy describe some cases of anti-GAD antibodies and other cases of antibody-negative T1DM [9]. Our patient did not show signs of hypophysitis or any evidence of acute infection that may have triggered this event. She had normal blood glucose levels 3 weeks earlier

and did not exhibit any symptom of diabetes. Although a case of fulminant T1DM after 2 doses of pembrolizumab has been documented [10], we believe ours is the first case in which a patient developed DKA after a single dose of pembrolizumab. This is highly unusual, as most immune-related adverse events occur after ≥ 3 doses of immune checkpoint therapy.

New immunotherapies that may lead to serious unexpected adverse events are increasingly being used to treat a wide range of malignancies. Close monitoring of patients is warranted for early diagnosis and management of imminent and potentially life-threatening complications.

References

- [1] Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 2018.
- [2] Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One* 2016;29;11(7):e0160221. <https://doi.org/10.1371/journal.pone.0160221>.
- [3] Joshi MN, Whitelaw BC, Palomar MT, Wu Y, Carroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. *Clin Endocrinol (Oxf)* 2016;85(3):331–9. <https://doi.org/10.1111/cen.13063>.
- [4] Butler L, Santoro N. The reproductive endocrinology of the menopausal transition. *Steroids* 2011;76(7):627–35. <https://doi.org/10.1016/j.steroids.2011.02.026>.
- [5] Rose BD, Post TW. Hyperosmolar states – hyperglycemia. In: Rose BD, Post TW, editors. *Clinical physiology of acid-base and electrolyte disorders*. 5th ed. New York: McGraw-Hill; 2001. p. 794–821.
- [6] Cheema A, Makadia B, Karwadia T, Bajwa R, Hossain M. Autoimmune diabetes associated with pembrolizumab: a review of published case reports. *World J Oncol* 2018; 9(1):1–4. <https://doi.org/10.14740/wjon1085w>.
- [7] US Food and Drug Administration. Approved drugs: pembrolizumab (KEYTRUDA). <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm515627.htm>; 2016, Accessed date: 8 October 2018.
- [8] Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol* 2017;8:561. <https://doi.org/10.3389/fphar.2017.00561>.
- [9] Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, et al. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. *Diabetes Care* 2015;38(4): e55–7. <https://doi.org/10.2337/dc14-2349>.
- [10] Gaudy C, Clévy C, Monestier S, Dubois N, Préau Y, Mallet S, et al. Anti-PD1 pembrolizumab can induce exceptional fulminant type 1 diabetes. *Diabetes Care* 2015;38(11):e182–3. <https://doi.org/10.2337/dc15-1331>.