CASE REPORT

A Patient with Atezolizumab-Induced Autoimmune Diabetes Mellitus Presenting with Diabetic Ketoacidosis

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Abstract

Background: Atezolizumab, an immune checkpoint inhibitor, is a humanized monoclonal, anti-programmed death ligand 1 (PD-L1) antibody used for the treatment of metastatic urothelial carcinoma that has progressed after chemotherapy.

Case Presentation: We describe a patient with a known history of urothelial carcinoma who presented with diabetic ketoacidosis 6 weeks following his second cycle of atezolizumab. His serum lactate level was slightly elevated (2 mM) and his β-hydroxybutyrate level was elevated (3.9 mM). High anion gap metabolic acidosis secondary to diabetic ketoacidosis was diagnosed. Subsequent testing demonstrated hemoglobin A_{1c} level of 9.9%, positivity for anti-glutamic acid decarboxylase antibody (0.03 nM, reference range <0.02 nM), and suppressed C-peptide level (0.1 μg/L, reference range 0.9–7.1 μg/L) in the absence of detectable anti-islet antigen 2 (IA-2) or anti-insulin antibodies. His initial management included cessation of atezolizumab treatment, intravenous sodium chloride administration, and insulin pump infusion, after which metabolic acidosis gradually resolved. The insulin pump was subsequently switched to Protaphane at 18 units before breakfast and 8 units before dinner, together with metformin at 1000 mg twice daily. Four weeks later his medication was changed to human isophane insulin plus neutral insulin (70%/30%; Mixtard 30 HM; 26 units/4 units). Linagliptin at 5 mg was added 1 month later. His hemoglobin A_{1c} level declined to 8.1% 1 year later.

Conclusions: PD-L1 inhibitors can induce type 1 diabetes, and patients can present with diabetic ketoacidosis. Blood glucose levels should be regularly monitored in patients who are prescribed these medications.

Keywords: Atezolizumab; diabetic ketoacidosis; PD-L1 inhibitors; Type 1 diabetes

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Background

Atezolizumab, an immune checkpoint inhibitor, is a humanized monoclonal, anti-programmed death ligand 1 (PD-L1) antibody used for the treatment of metastatic urothelial carcinoma that has progressed after chemotherapy [1]. It was the first agent approved

by the US Food and Drug Administration as second-line treatment for advanced urothelial carcinoma [2]. Although immune checkpoint inhibitors are generally well tolerated compared with traditional chemotherapy, they can produce immune-related toxic effects [3]. PD-L1 inhibitors are recognized to cause thyroid problems but are now known to induce autoimmune diabetes. In this report, we describe a patient with a known history of urothelial carcinoma who presented with diabetic ketoacidosis 6 weeks following his second cycle of atezolizumab.

Case Presentation

A 75-year old man presented to the emergency department of our hospital with polydipsia, polyuria, nausea, vomiting, and reduced appetite associated with generalized malaise. He also reported increasing dyspnea and a productive cough. On inspection, the patient was dehydrated and showed signs of Kussmaul breathing. Physical examination revealed increased sputum sounds and crepitations on the lower chest bilaterally. His abdomen was soft and nontender.

The arterial blood gas and blood test results on admission are shown in Tables 1 and 2, respectively. Of note, his capillary glucose level was more than 27.8 mM (500.4 mg/dL). His fasting glucose level was 4.5 mM (81.0 mg/dL) 3 months before admission, and his random glucose level was 5.4 mM (97.2 mg/dL) 2 months before admission. Serum biochemistry showed hyponatremia (120 mM) and hyperkalemia (6.8 mM). His liver enzyme levels were normal but urea and creatinine levels were raised (6.8 and 14.2 mM, respectively). His arterial

Table 1 Arterial Blood Gas Parameters at Presentation.

Test (reference range)	Value on admission
pH (7.35–7.45)	7.03
P_{CO_2} (4.7–6.4 kPa)	3.0 kPa
P_{O_2} (11.0–14.4 kPa)	8.6 kPa
Bicarbonate (18–23 mM)	8.6 mM
Base excess (−2 to +2 mM)	−24 mM
O_2 saturation (94–98%)	82%
Chloride (102–114 mM)	88 mM
Lactate (<1.3 mM)	2.0 mM

Table 2 Laboratory Test Results at Presentation.

Test (reference range)	Value on admission
Hemoglobin (13.2–17.2 g/dL)	14.1 g/dL
Mean cell volume (83.0–98.0 fL)	93.9 fL
White blood cell count ($(4.0–9.7) \times 10^9$/L)	10.4×10^9/L
Platelet count ($(150–384) \times 10^9$/L)	380×10^9/L
Hemoglobin A_{1c} (≤6.5%)	9.9%
Serum osmolality (275–295 mOsm/kg)	316 mOsm/kg
Serum lactate (<2.2 mM)	1.8 mM
Sodium (137–144 mM)	120 mM
Potassium (3.5–5.0 mM)	6.8 mM
Urea (3.1–7.8 mM)	14.2 mM
Creatinine (65–109 μM)	143 μM
Total protein (66–80 g/L)	81 g/L
Albumin (35–52 g/L)	36 g/L
Total bilirubin (<19 μM)	7 μM
Alkaline phosphatase (43–105 IU/L)	136 IU/L
Alanine aminotransferase (<53 IU/L)	20 IU/L
Creatine phosphokinase (39–308 U/L)	52 U/L
β-Hydroxybutyrate (<0.6 mM)	3.9 mM
Thyroid-stimulating hormone (0.27–4.2 mIU/L)	1.59 mIU/L
Cardiac troponin (<14 ng/L)	18.6 ng/L
Sputum culture	Mucopurulent, large number of white blood cells seen, heavy growth of oral commensals identified

blood gas test results showed a severe metabolic acidosis. The uncorrected anion gap was 30 mM, but after correction for albumin (23 g/L) a significantly elevated anion gap of 34 mM was revealed. His serum lactate level was slightly elevated (2 mM) and his β-hydroxybutyrate level was elevated (3.9 mM). High anion gap metabolic acidosis secondary to diabetic ketoacidosis was diagnosed. Subsequent testing demonstrated hemoglobin A_{1c} (HbA_{1c}) level of 9.9%, positivity for anti-glutamic acid decarboxylase antibody (0.03 nM, reference range <0.02 nM), and suppressed C-peptide level (0.1 μg/L, reference range 0.9–7.1 μg/L) in the absence of detectable anti-islet antigen 2 (IA-2) or anti-insulin antibodies.

His initial management included cessation of atezolizumab treatment, intravenous sodium chloride administration, and insulin pump infusion, after which metabolic acidosis gradually resolved. Insulin pump was subsequently switched to Protaphane at 18 units before breakfast and 8 units before dinner, together with metformin at 1000 mg twice daily. Four weeks later his medication was changed to human isophane insulin plus neutral insulin (70%/30%; Mixtard 30 HM; 26 units/4 units). Linagliptin at 5 mg was added 1 month later. His HbA$_{1c}$ level declined to 8.1% 1 year later.

Discussion

Programmed cell death 1 (PD-1) is a coreceptor that is expressed predominantly by T cells in many cancers [4]. It interacts with PD-L1 and PD-L2 of antigen-presenting cells and tumor cells. Normally, binding of PD-1 to its effectors inhibit T cells and prevents immune activation. Blocking this binding leads to activation of cytotoxic T cells, thereby triggering an immune response to target tumor cells. Anti-PD-1 or anti-PD-L1 monoclonal antibodies have been increasingly used to treat different cancers, including urothelial cancers [5]. To date, 33 cases of diabetes have been reported as a result of anti-PD-1 or anti-PD-L1 antibody treatment [6–26]. Of these, only four cases were due to PD-L1 inhibitor treatment. The first case concerned a 70-year old man with adenocarcinoma of the lung without a history of diabetes who presented with hyperglycemia 15 weeks after treatment with an anti-PDL-1 antibody (the name of the drug was not reported) [13]. The second case concerned a 57-year old man with recurrent metastatic urothelial cancer who presented with incomplete diabetic ketoacidosis before his sixth cycle of the anti-PD-L1 antibody atezolizumab [18]. The third case involved a 63-year old woman with a history of hypothyroidism and iron-deficiency anemia with reactive thrombocytosis and leukocytosis who initially presented with hematuria and who subsequently underwent transurethral removal of a bladder tumor and was treated with atezolizumab but developed diabetic ketoacidosis after 6 weeks [25]. The fourth case concerned an 84-year-old woman with metastatic squamous cell carcinoma of the nasopharynx and no history of diabetes who was given the anti-PD-L1 antibody durvalumab and developed diabetic ketoacidosis 4 months later [26]. Here we report, to the best of our knowledge, the first case in an Asian male patient and the fifth case published thus far showing that atezolizumab can precipitate diabetic ketoacidosis. Our patient had a history of transitional cell carcinoma of the renal pelvis and presented with full diabetic ketoacidosis 6 weeks after his second cycle of atezolizumab. His C-peptide level was low, consistent with type 1 diabetes mellitus.

Of the previous 33 cases, 31 patients underwent autoantibody testing, of whom 18 showed positive results. Our patient was positive for anti-glutamic acid decarboxylase antibody, albeit only at a low level of 0.03 nM (reference range <0.02 nM). Previously, it was noted that the time between initiation of PD-1/PD-L1 inhibitor treatment and the onset of autoimmune diabetes was related to anti-glutamic acid decarboxylase antibody status [19]. Gauci et al. [19] calculated that the duration was shorter, with a median of 3 weeks, for positive status but was 12–13 weeks for negative status. These observations are in agreement with those of our patient, who had positive but low levels of anti-glutamic acid decarboxylase antibody, presenting 6 weeks after treatment. Although the use of PD-1 and PD-L1 inhibitors is mostly associated with type 1 diabetes, it can also worsen glucose control in those patients with established type 2 diabetes [27]. Moreover, it has been suggested that PD-1 and PD-L1 inhibitors may also predispose to type 2 diabetes [28].

The mechanisms underlying precipitation of diabetes mellitus by PD-1 or PD-L1 inhibitors remain incompletely understood. Type 1 diabetes mellitus involves autoimmune-mediated damage of the pancreas by the body's own immune system [29]. This can be triggered by different antigens, leading to reduced central or peripheral tolerance [30], and thus activation of the T lymphocytes. T lymphocytes can then infiltrate into the pancreatic islets and mediate destruction of the pancreatic β cells, leading to uncontrolled hyperglycemia. It is well established that coinhibitory PD-1/PD-L1 interactions provide the molecular signals that regulate autoreactive T-lymphocyte responses [31]. Indeed, the interaction between PD-1 expressed on autoreactive T cells and PD-L1 expressed on pancreatic islet cells

leads to the development of tolerance. By contrast, when either protein is inhibited, autoreactive T cells are relieved from inhibition and can induce cell death of the islet cells, leading to the development of autoimmune diabetes. Significantly, the available evidence suggests that even after discontinuation of immunotherapy, insulin therapy was required, which would indicate that the diabetes is irreversible [24]. In our case, the patient required long-term insulin therapy with adjunct hypoglycemic agents, which led to a decline of HbA_{1c} level from 9.9% to 8.1% 1 year later. These findings are in keeping with the notion of irreversible pancreatic damage.

The use of experimental animal models has provided some insights into possible mechanistic pathways. Thus, *Pdcd1$^{-/-}$* mice, which are deficient in PD-1, demonstrate an accelerated onset and frequency of type 1 diabetes [32]. These findings are consistent with the notion that PD-1/PD-L1 interactions are important for the regulation of autoreactive T-lymphocyte responses by mediating peripheral tolerance [33], which suppresses diabetes. Indeed, clinical studies have reported the association between PD-L1 gene haplotype [34], its polymorphisms, and low serum PD-L1 levels [35] and type 1 diabetes. Together these findings demonstrate the importance of PD-1/PD-L1 pathways in pancreatic cell function and that treatment modalities targeting these proteins can exert adverse effects on glucose control, thereby precipitating or inducing diabetes. Thus, activating the PD-1 pathway may help to induce immune tolerance and prevent type 1 diabetes but increase the risk of cancer or metastasis.

This is supported by experimental observations that PD-L1-driven tolerance reverses diabetes in nonobese diabetic (NOD) mice, a model for autoimmune type 1 diabetes [36]. There thus appears to be a balance of risk of cancer on the one hand and risk of diabetes on the other. Indeed, epidemiology studies clearly demonstrate the high rates of cancer and type 2 diabetes in developing areas where autoimmune type 1 diabetes is rare.

Conclusion

PD-L1 inhibitors, like PD-1 inhibitors, can induce type 1 diabetes, and patients can present with diabetic ketoacidosis. Blood glucose levels should be regularly monitored in patients who are prescribed these medications.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case.

Conflicts of Interest

None declared.

Author Contributions

Both authors drafted and critically revised the manuscript and approved the final version.

REFERENCES

1. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387: 1909–20.
2. Ning YM, Suzman D, Maher VE, Zhang L, Tang S, Ricks T, et al. FDA approval summary: atezolizumab for the treatment of patients with progressive advanced urothelial carcinoma after platinum-containing chemotherapy. Oncologist 2017;22:743–9.
3. Zhou J, Tse G, Wang X, Lakhani I, Lee S, Yang L, et al. Adverse cardiovascular complications following prescription of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. medRxiv 2020. https://doi.org/10.1 101/2020.12.21.20248648.
4. Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A. Programmed death-1 pathway in cancer and autoimmunity. Clin Immunol 2014;153:145–52.
5. Atkins MB, Clark JI, Quinn DI. Immune checkpoint inhibitors in advanced renal cell carcinoma: experience to date and future directions. Ann Oncol 2017;28: 1484–94.
6. Godwin JL, Jaggi S, Sirisena I, Sharda P, Rao AD, Mehra R, et al.

Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer. J Immunother Cancer 2017;5:40.

7. Aleksova J, Lau PKH, Soldatos G, McArthur G. Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma. BMJ Case Rep 2016;2016:bcr2016217454.

8. Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:190–209.

9. Okamoto M, Okamoto M, Gotoh K, Masaki T, Ozeki Y, Ando H, et al. Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. J Diabetes Investig 2016;7:915–8.

10. Teramoto Y, Nakamura Y, Asami Y, Imamura T, Takahira S, Nemoto M, et al. Case of type 1 diabetes associated with less-dose nivolumab therapy in a melanoma patient. J Dermatol 2017;44:605–6.

11. Munakata W, Ohashi K, Yamauchi N, Tobinai K. Fulminant type I diabetes mellitus associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma. Int J Hematol 2017;105:383–6.

12. 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:e55–7.

13. Mellati M, Eaton KD, Brooks-Worrell BM, Hagopian WA, Martins R, Palmer JP, et al. Anti-PD-1 and anti-PDL-1 monoclonal antibodies causing type 1 diabetes. Diabetes Care 2015;38:e137–8.

14. Martin-Liberal J, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. Cancer Immunol Immunother 2015;64:765–7.

15. Hansen E, Sahasrabudhe D, Sievert L. A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome. Cancer Immunol Immunother 2016;65:765–7.

16. Gaudy C, Clevy C, Monestier S, Dubois N, Preau Y, Mallet S, et al. Anti-PD1 pembrolizumab can induce exceptional fulminant type 1 diabetes. Diabetes Care 2015;38:e182–3.

17. Miyoshi Y, Ogawa O, Oyama Y. Nivolumab, an anti-programmed cell death-1 antibody, induces fulminant type 1 diabetes. Tohoku J Exp Med 2016;239:155–8.

18. Hickmott L, De La Pena H, Turner H, Ahmed F, Protheroe A, Grossman A, et al. Anti-PD-L1 atezolizumab-induced autoimmune diabetes: a case report and review of the literature. Target Oncol 2017;12:235–41.

19. Gauci ML, Laly P, Vidal-Trecan T, Baroudjian B, Gottlieb J, Madjlessi-Ezra N, et al. Autoimmune diabetes induced by PD-1 inhibitor-retrospective analysis and pathogenesis: a case report and literature review. Cancer Immunol Immunother 2017;66:1399–410.

20. Lowe JR, Perry DJ, Salama AK, Mathews CE, Moss LG, Hanks BA. Genetic risk analysis of a patient with fulminant autoimmune type 1 diabetes mellitus secondary to combination ipilimumab and nivolumab immunotherapy. J Immunother Cancer 2016;4:89.

21. Usui Y, Udagawa H, Matsumoto S, Imai K, Ohashi K, Ishibashi M, et al. Association of serum anti-GAD antibody and HLA haplotypes with type 1 diabetes mellitus triggered by nivolumab in patients with non-small cell lung cancer. J Thorac Oncol 2017;12:e41–3.

22. Ishikawa K, Shono-Saito T, Yamate T, Kai Y, Sakai T, Shimizu F, et al. A case of fulminant type 1 diabetes mellitus, with a precipitous decrease in pancreatic volume, induced by nivolumab for malignant melanoma: analysis of HLA and CTLA-4 polymorphisms. Eur J Dermatol 2017;27:184–5.

23. Chae YK, Chiec L, Mohindra N, Gentzler R, Patel J, Giles F. A case of pembrolizumab-induced type-1 diabetes mellitus and discussion of immune checkpoint inhibitor-induced type 1 diabetes. Cancer Immunol Immunother 2017;66:25–32.

24. Gauci M-L, Boudou P, Baroudjian B, Vidal-Trecan T, Da Meda L, Madelaine-Chambrin I, et al. Occurrence of type 1 and type 2 diabetes in patients treated with immunotherapy (anti-PD-1 and/or anti-CTLA-4) for metastatic melanoma: a retrospective study. Cancer Immunol Immunother 2018;67:1197–208.

25. Kapke J, Shaheen Z, Kilari D, Knudson P, Wong S. Immune checkpoint inhibitor-associated type 1 diabetes mellitus: case series, review of the literature, and optimal management. Case Rep Oncol 2017;10:897–909.

26. Way J, Drakaki A, Drexler A, Freeby M. Anti-PD-L1 therapy and the onset of diabetes mellitus with positive pancreatic autoantibodies. BMJ Case Rep 2017;2017:bcr2017220415.

27. Kotwal A, Haddox C, Block M, Kudva YC. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. BMJ Open Diabetes Res Care 2019;7:e000591.

28. Youssef N, Noureldein M, Daoud G, Eid AA. Immune checkpoint inhibitors and diabetes: mechanisms and predictors. Diabetes Metab 2020;30:101193.

29. Luo X, Herold KC, Miller SD. Immunotherapy of type 1 diabetes: where are we and where should we be going? Immunity 2010;32:488–99.

30. Fife BT, Pauken KE. The role of the PD-1 pathway in autoimmunity and peripheral tolerance. Ann N Y Acad Sci 2011;1217:45–59.

31. Schuster C, Brosi H, Stifter K, Boehm BO, Schirmbeck R. A missing PD-L1/PD-1 coinhibition regulates diabetes induction by preproinsulin-specific CD8 T-cells in an epitope-specific manner. PLoS One 2013;8:e71746.

32. Wang J, Yoshida T, Nakaki F, Hiai H, Okazaki T, Honjo T. Establishment of NOD-*Pdcd1*^{-/-} mice as an efficient animal model of type I diabetes. Proc Natl Acad Sci U S A 2005;102:11823–8.

33. Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, Albacker LA, et al. Tissue expression of PD-L1 mediates peripheral T cell tolerance. J Exp Med 2006;203:883–95.

34. Ni R, Ihara K, Miyako K, Kuromaru R, Inuo M, Kohno H, et al. PD-1 gene haplotype is associated with the development of type 1 diabetes mellitus in Japanese children. Hum Genet 2007;121:223–32.

35. Pizarro C, Garcia-Diaz DF, Codner E, Salas-Perez F, Carrasco E, Perez-Bravo F. PD-L1 gene polymorphisms and low serum level of PD-L1 protein are associated to type 1 diabetes in Chile. Diabetes Metab Res Rev 2014;30:761–6.

36. Li R, Lee J, Kim M-s, Liu V, Moulik M, Li H, et al. PD-L1–driven tolerance protects neurogenin3-induced islet neogenesis to reverse established type 1 diabetes in NOD mice. Diabetes 2015;64:529–40.