**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 86914

**Manuscript Type:** CASE REPORT

**Autoimmune diabetes from pembrolizumab: A case report and review of literature**

Bhanderi H *et al*. Pembrolizumab induced autoimmune diabetes mellitus

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**Received:** July 13, 2023

**Revised:** October 13, 2023

**Accepted:** October 30, 2023

**Published online:** November 24, 2023

**Abstract**

BACKGROUND

Immunotherapy, specifically the use of checkpoint inhibitors such as pembrolizumab, has become an important tool in personalized cancer therapy. These inhibitors target proteins on T-cells that regulate the immune response against tumor cells. Pembrolizumab, which targets the programmed cell death 1 receptor on T-cells, has been approved for the treatment of metastatic melanoma and non-small cell lung cancer. However, it can also lead to immune-related side effects, including pneumonitis, colitis, thyroid abnormalities, and rare cases of type 1 diabetes.

CASE SUMMARY

The case presented involves an adult patient in 30s with breast cancer who developed hyperglycemia after receiving pembrolizumab treatment. The patient was diagnosed with diabetic ketoacidosis and further investigations were performed to evaluate for new-onset type 1 diabetes. The patient had a history of hypothyroidism and a family history of breast cancer. Treatment for diabetic ketoacidosis was initiated, and the patient was discharged for close follow-up with an endocrinologist.

CONCLUSION

This literature review highlights the occurrence of diabetic ketoacidosis and new-onset type 1 diabetes in patients receiving pembrolizumab treatment for different types of cancer. Overall, the article emphasizes the therapeutic benefits of immunotherapy in cancer treatment, particularly pembrolizumab, while also highlighting the potential side effect of immune-related diabetes that can occur in a small percentage of patients. Here we present a case where pembrolizumab lead to development of diabetes after a few cycles highlighting one of the rare yet a serious toxicity of the drug.

**Key Words:** Pembrolizumab; Breast cancer; Autoimmune diabetes; Keytruda; Immunotherapy; Case report

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**Citation**: Bhanderi H, Khalid F, Bodla ZH, Muhammad T, Du D, Meghal T. Autoimmune diabetes from pembrolizumab: A case report and review of literature. *World J Clin Oncol* 2023; 14(11): 535-543

**URL**: https://www.wjgnet.com/2218-4333/full/v14/i11/535.htm

**DOI**: https://dx.doi.org/10.5306/wjco.v14.i11.535

**Core Tip:** Our review highlights an important and rare adverse effect of Pembrolizumab. We have also reviewed the number of cycles patients were treated with Keytruda before the onset of diabetes. Clinicians should be watchful for the signs and symptoms. Early discontinuation of immunotherapy is needed to prevent significant morbidity and mortality.

**INTRODUCTION**

Immunotherapy has become an essential tool in the treatment of cancers and represents therapeutic advancement in the individualized cancer therapy[1]. The role of immunotherapy is based on the ability to recognize abnormal tissue and enhance body’s immune system against tumor cells. Immune system has both stimulators and inhibitors for the immune response generation in order to maintain balance and avoid auto-immune response to self antigens by means of positive selection of T cells. But sometimes this positive selection leads to lack of required immune response against tumor cells, which leads to tumor growth[2]. There are multiple check-points in cell production have been identified like T cell immunoglobulin and mucin-domain containing-3, T cell immunoglobulin and ITIM domain, lymphocyte activation gene-3, indoleamine 2, 3-dioxygenase 1, and V-domain immunoglobulin suppressor of T cell activation, but to date only United States Food and Drug Administration (FDA) approved check-point inhibitors are those which targets cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death protein-ligand 1 (PD-L1)[3]. The mechanism behind is the inhibition of check point inhibitors namely CTLA-4, PD-1, or PD-L1 which results in the increased anti-tumor immune response. These check point inhibitors are expressed on T-cells and their activation leads to the decreased T-cell proliferation from inhibition of T-cell receptor mediated signaling, reduced cytokines secretion limiting inflammatory response and autoimmunity[4]. The immune check point inhibitors are the monoclonal antibodies directed against the above mentioned ligands which results in the immune activation against the tumor cells[5]. Pembrolizumab is a monoclonal antibody designed against check point inhibitor PD-1 receptor on surface of T-cells resulting in the proliferation of T-cells and enhanced intrinsic immune mediated anticancer activity[6]. PD-1 receptor is a cell surface protein expressed on activated T cells which on binding with the ligands PD-L1 and PD-L2 leads to the inhibition of kinase signaling pathways causing suppression of T-cell[7]. Pembrolizumab was originally approved by FDA for metastatic melanoma in 2014 and for non-small cell lung cancer in 2014[1]. Since then it has been widely used in the treatment of different cancers especially those with resistance to first line therapies. Excessive immune activation has been a frequent and serious side effect of the immune therapies. Most common adverse effects reported from the clinical trials are pneumonitis, colitis, thyroid abnormalities, liver and kidney issues[8]. Type 1 diabetes was only reported in 0.1% of the patients in the clinical trials making this rare but significant side effect of the treatment[1]. Here we present a case of a young female who presented with hyperglycemia after getting treatment with the pembrolizumab for the breast cancer.

**CASE PRESENTATION**

***Chief complaints***

Nausea, Vomiting and Hyperglycemia at outpatient chemotherapy infusion center.

***History of present illness***

The patient presented to the emergency department for the evaluation of hyperglycemia, which was found at the infusion center during 4th cycle. The patient complained of nausea, vomiting which was non-bilious and non-bloody associated with dizziness. The patient denied any fever, shortness of breath, chest pain, abdominal pain or loss of consciousness, recent weight loss, travel history, constipation or diarrhea.

***History of past illness***

Hypothyroidism and triple negative left invasive mammary breast carcinoma with Ki 67%-90% diagnosed an year ago which was at anatomical stage 2A/Clinical prognostic stage 2B status post chemotherapy with carboplatin and Paclitaxel along with 3 cycles of Pembrolizumab.

***Personal and family history***

The patient social history was significant for 2-3 cigarettes a day before getting diagnosed with breast cancer and occasional alcohol consumption and marijuana consumption. The family history was significant for breast cancer in mother and sister.

***Physical examination***

Physical examination was unremarkable.

***Laboratory examinations***

The initial blood work up revealed Hemoglobin level of 12.8 g/dL, white cell count of 4.7 K/CMM, Hematocrits of 37.2% and platelet count of 332 K/CMM. Complete metabolic panel was significant for sodium level of 133 mEq/L, Bicarbonate level of < 10 mEq/L with anion gap of > 19 mEq/L, blood glucose level of 343 mg/dL. Liver and Kidney functions were benign. Beta hydroxy butyrate level was found to be elevated > 46.8 mg/dL. Urinalysis was positive for glucose and ketones. Amylase and lipase level were within normal limits. Arterial blood gas analysis showed pH of 7.13 with pCO2 of 23 mmHg, pO2 of 65 mmHg, and bicarbonate level of 8 mmol/L. HbA1c level was found to be 6.8. During hospitalization, work up for the new onset type 1 diabetes mellitus (T1DM) was done. IA-2 antibody, Insulin antibody, glutamic acid decarboxylase antibody was negative. C-peptide level was found to be low at 0.24. Cortisol and Thyroid stimulating hormone level was within normal limits. So, involvements of other endocrine abnormalities were ruled out.

***Imaging examinations***

No imaging studies were done.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

Endocrinologist was consulted because of labile glucose level and to optimize insulin regimen on discharge.

**FINAL DIAGNOSIS**

Diabetic ketoacidosis.

**TREATMENT**

Intensive care unit was consulted and the patient was managed as per protocol for diabetic ketoacidosis.

**OUTCOME AND FOLLOW-UP**

Patient was discharged for the close follow up with endocrinologist. Pembrolizumab was stopped and the chemotherapy was continued.

Our literature review mentions the prior studies highlighting the effects of pembrolizumab leading to autoimmune diabetes. The mean number of cycles was 4 and the mean number of weeks leading to presentation after the start of treatment was 15.4. The mean HbA1c of the patients was 7.97. Below mentioned are the baseline characteristics of the patients along with the disease presentation (Tables 1 and 2)[9-56].

**DISCUSSION**

This study presents a comprehensive literature review of similar cases that were reported on various databases. These patients were started on various chemotherapy regimens for different cancer, but after no or little improvement from those modalities, were eventually started on immunotherapy particularly pembrolizumab. These patients presented to the emergency department with various chief complaints including from asymptomatic hyperglycemia to diabetic ketoacidosis (DKA) and were eventually diagnosed with insulin dependent diabetes mellitus. The time of presentation for all these patients varied a lot in terms of range from after just one cycle to as long as 19 cycles with average beingcycles. This average number of cycles is skewed most probably, because the most number of patients developed this diabetic complication earlier rather than later in the course of starting immunotherapy. This observation is also supported by a relatively lower value of glycated hemoglobin value as compared to classic type 1 diabetic patients who develop diabetic ketoacidosis[57]. At the same time, a diagnosis of T1DM was established by presence of one or the other classic antibodies in most of the patients. Among patients who were tested for these antibodies, many of them were positive for anti-glutamic acid decarboxylase antibodiesand some of them were positive for others like islet cell antibodies or insulin antigen 2 antibodies. This conclusion is based on the data from the patients who were tested for these antibodies. To some extent this data suggest that presence of these antibodies is lower in these patients as compared to patients with classic T1DM, where a presence of at least one antibody in 97.8%[58]. On reviewing the literature it was found that incidence of newly diagnosed diabetic ketoacidosis is more in patients receiving pembrolizumab dose of 400 mg every 6 wk as compared to conventional 200 mg every 3 wk[18]. These patients are more prone to develop other endocrinopathies as well particularly thyroid related issues along with diabetes[59]. The pathophysiology of these immune checkpoint inhibitors induced diabetes mellitus is still not clear. Human leukocyte antigen is the key structure involved in the presentation of different peptides, one of which might be containing “diabetogenic peptide” in genetically susceptible individuals[60]. Recognition of this complex by T cell receptor stimulates cytotoxic T-cells that lead to destruction of B-cells in pancreas. Alternatively, these auto-antigenic peptides gets presented to the regulatory T cells, stimulation of which leads to secretion of different kind of cytokines like Interleukin 1, Interleukin 2, Interferon gamma, Tumor necrosis factor alpha and beta. These cytokines in turn stimulate cytotoxic T cells and eventual destruction of B cells ensues. To avoid this phenomenon, interaction between PD-1 and its PD-L1 is really important to maintain self tolerance against pancreatic islets[9]. Different Immune checkpoint inhibitors affect different pathways. Pembrolizumab in particular inhibits the PD-1/PD-L1 pathway, which leads to destruction of pancreatic islet cells and development of T1DM.

The predisposing factors in an individual for development of immune checkpoint inhibitors induced diabetes is not well defined as opposed to individuals with classic T1DM. Individuals with certain genotypes like DR3-DQ2 and DR4-DQ8 have shown to have higher risk of developing classic T1DM as compared to the general population[61]. In our study, we have not included genotypes of patients as there was not much data available regarding that in most cases, but studies particularly focusing on these aspects have shown that individuals with high risk genotypes have developed diabetes more while being on immune checkpoint inhibitors as compared individuals with other genotypes[9]. So, these individuals were at a high risk, but rapid onset of diabetes with presentation of ketoacidosis and relatively a low glycated hemoglobin value as compared to classic T1DM makes it different. In our study, some of the patients also had history of autoimmune disease, which makes them more susceptible to develop other autoimmune disease. Patients with already diagnosed and well controlled type 2 diabetes are also shown to be at high risk of worsening diabetes and presenting with diabetic ketoacidosis along with blood work showing presence of autoantibodies.

Although this is one of the rare side effects of the immunotherapies but with development of new immunotherapy agents, these cases should be kept in mind particularly while giving therapies to patients with high risk factors. Initial check for glycated haemoglobin before starting therapy for both diagnosed and undiagnosed diabetic patients can be useful for the risk stratification. A regular and timely checkup for glucose along with education for signs and symptoms of hyperglycemia should be introduced in patients receiving these agents. This could lead to detection of early development or worsening diabetes. Another significant finding in most of the patients was continuation of immunotherapy after initial management of diabetic ketoacidosis was possible with introduction of as needed long and short acting insulin regimen. This is not the best option, but stopping immunotherapy in advanced malignancies, where very few treatment options are available is not desirable. The prognosis particularly because of the development of these endocrinopathies did not seem to change in most of the patients.

**CONCLUSION**

In the end, there is a need for a lot of research in this particular aspect regarding recognition of high risk individuals for developing these rare side effects, which might eventually help patients to avoid these side effects. Identifying different biomarkers apart from classic autoantibodies can also help in early detection of diabetes. More studies are needed to find out exact pathophysiology behind this side effect which is also the need of the hour.

**REFERENCES**

1 **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; **11**: e0160221 [PMID: 27472273 DOI: 10.1371/journal.pone.0160221]

2 **Wang Y**, Zhang H, Liu C, Wang Z, Wu W, Zhang N, Zhang L, Hu J, Luo P, Zhang J, Liu Z, Peng Y, Liu Z, Tang L, Cheng Q. Immune checkpoint modulators in cancer immunotherapy: recent advances and emerging concepts. *J Hematol Oncol* 2022; **15**: 111 [PMID: 35978433 DOI: 10.1186/s13045-022-01325-0]

3 **Zhang H**, Dai Z, Wu W, Wang Z, Zhang N, Zhang L, Zeng WJ, Liu Z, Cheng Q. Regulatory mechanisms of immune checkpoints PD-L1 and CTLA-4 in cancer. *J Exp Clin Cancer Res* 2021; **40**: 184 [PMID: 34088360 DOI: 10.1186/s13046-021-01987-7]

4 **Pardoll DM**. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; **12**: 252-264 [PMID: 22437870 DOI: 10.1038/nrc3239]

5 **Guleria I**, Gubbels Bupp M, Dada S, Fife B, Tang Q, Ansari MJ, Trikudanathan S, Vadivel N, Fiorina P, Yagita H, Azuma M, Atkinson M, Bluestone JA, Sayegh MH. Mechanisms of PDL1-mediated regulation of autoimmune diabetes. *Clin Immunol* 2007; **125**: 16-25 [PMID: 17627890 DOI: 10.1016/j.clim.2007.05.013]

6 **Faghfuri E**, Faramarzi MA, Nikfar S, Abdollahi M. Nivolumab and pembrolizumab as immune-modulating monoclonal antibodies targeting the PD-1 receptor to treat melanoma. *Expert Rev Anticancer Ther* 2015; **15**: 981-993 [PMID: 26313415 DOI: 10.1586/14737140.2015.1074862]

7 **Godwin JL**, Jaggi S, Sirisena I, Sharda P, Rao AD, Mehra R, Veloski C. Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer. *J Immunother Cancer* 2017; **5**: 40 [PMID: 28515940 DOI: 10.1186/s40425-017-0245-2]

8 **Chan MM**, Kefford RF, Carlino M, Clements A, Manolios N. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. *J Immunother* 2015; **38**: 37-39 [PMID: 25415286 DOI: 10.1097/CJI.0000000000000060]

9 **de Filette JMK**, Pen JJ, Decoster L, Vissers T, Bravenboer B, Van der Auwera BJ, Gorus FK, Roep BO, Aspeslagh S, Neyns B, Velkeniers B, Kharagjitsingh AV. Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. *Eur J Endocrinol* 2019; **181**: 363-374 [PMID: 31330498 DOI: 10.1530/EJE-19-0291]

10 **Clotman K**, Janssens K, Specenier P, Weets I, De Block CEM. Programmed Cell Death-1 Inhibitor-Induced Type 1 Diabetes Mellitus. *J Clin Endocrinol Metab* 2018; **103**: 3144-3154 [PMID: 29955867 DOI: 10.1210/jc.2018-00728]

11 **Farina KA**, Kane MP. Programmed Cell Death-1 Monoclonal Antibody Therapy and Type 1 Diabetes Mellitus: A Review of the Literature. *J Pharm Pract* 2021; **34**: 133-140 [PMID: 31269868 DOI: 10.1177/0897190019850929]

12 **Kyriacou A**, Melson E, Chen W, Kempegowda P. Is immune checkpoint inhibitor-associated diabetes the same as fulminant type 1 diabetes mellitus? *Clin Med (Lond)* 2020; **20**: 417-423 [PMID: 32675150 DOI: 10.7861/clinmed.2020-0054]

13 **Banatwalla R**, Kirresh OZ, Ahmed FW. Pembrolizumab-induced diabetes. *Endokrynol Pol* 2021; **72**: 414-415 [PMID: 34057191 DOI: 10.5603/EP.a2021.0053]

14 **Hernandez A**, Zeidan B, Desai P, Frunzi J. Diabetic Ketoacidosis Secondary to New Onset Type 1 Diabetes Mellitus Related to Pembrolizumab Therapy. *Cureus* 2021; **13:** e13302 [DOI: 10.7759/cureus.13302]

15 **Bansal S**, Saca D, Getz D, Rab A, Singhania N. New-Onset Type 1 Diabetes in an Elderly Female on Pembrolizumab. *Am J Med Sci* 2022; **363**: 371-372 [PMID: 34995577 DOI: 10.1016/j.amjms.2021.10.024]

16 **Kedzior SK**, Jacknin G, Hudler A, Mueller SW, Kiser TH. A Severe Case of Diabetic Ketoacidosis and New-Onset Type 1 Diabetes Mellitus Associated with Anti-Glutamic Acid Decarboxylase Antibodies Following Immunotherapy with Pembrolizumab. *Am J Case Rep* 2021; **22**: e931702 [PMID: 34185763 DOI: 10.12659/AJCR.931702]

17 **Cunha C**, Silva E, Vieira AC, Saraiva C, Duarte S. New onset autoimmune diabetes mellitus and hypothyroidism secondary to pembrolizumab in a patient with metastatic lung cancer. *Endocrinol Diabetes Metab Case Rep* 2022; **2022** [PMID: 35140188 DOI: 10.1530/EDM-21-0123]

18 **Kähler KC**, Kosova K, Bohne AS, Schreiber S, Hauschild A. Increased risk of immune checkpoint inhibitor-induced type 1 diabetes mellitus with the new approved 6-week scheme of pembrolizumab in patients with melanoma? *Eur J Cancer* 2020; **138**: 169-171 [PMID: 32890812 DOI: 10.1016/j.ejca.2020.07.028]

19 **Tohi Y**, Fujimoto K, Suzuki R, Suzuki I, Kubota M, Kawakita M. Fulminant type 1 diabetes mellitus induced by pembrolizumab in a patient with urothelial carcinoma: A case report. *Urol Case Rep* 2019; **24**: 100849 [PMID: 31211060 DOI: 10.1016/j.eucr.2019.100849]

20 **Edahiro R**, Ishijima M, Kurebe H, Nishida K, Uenami T, Kanazu M, Akazawa Y, Yano Y, Mori M. Continued administration of pembrolizumab for adenocarcinoma of the lung after the onset of fulminant type 1 diabetes mellitus as an immune-related adverse effect: A case report. *Thorac Cancer* 2019; **10**: 1276-1279 [PMID: 30964601 DOI: 10.1111/1759-7714.13065]

21 **Magis Q**, Gaudy-Marqueste C, Basire A, Loundou A, Malissen N, Troin L, Monestier S, Mallet S, Hesse S, Richard MA, Valéro R, Beliard S, Grob JJ. Diabetes and Blood Glucose Disorders Under Anti-PD1. *J Immunother* 2018; **41**: 232-240 [PMID: 29481423 DOI: 10.1097/CJI.0000000000000218]

22 **Samoa RA**, Lee HS, Kil SH, Roep BO. Anti-PD-1 Therapy-Associated Type 1 Diabetes in a Pediatric Patient With Relapsed Classical Hodgkin Lymphoma. *Diabetes Care* 2020; **43**: 2293-2295 [PMID: 32616607 DOI: 10.2337/dc20-0740]

23 **Li S**, Zhang Y, Sun Z, Hu J, Fang C. Anti-PD-1 pembrolizumab induced autoimmune diabetes in Chinese patient: A case report. *Medicine (Baltimore)* 2018; **97**: e12907 [PMID: 30407284 DOI: 10.1097/MD.0000000000012907]

24 **Boyle V**, Cundy T, Cutfield R. Rapid onset type 1 diabetes associated with the programmed cell death-1 inhibitor pembrolizumab. *Intern Med J* 2019; **49**: 930-931 [PMID: 31295781 DOI: 10.1111/imj.14340]

25 **Sankar K,** Macfarlane M, Cooper O, Falk J. Pembrolizumab-Induced Diabetic Ketoacidosis: A Review of Critical Care Case. *Cureus* 2021; **13:** e18983 [DOI: 10.7759/cureus.18983]

26 **Hakami OA**, Ioana J, Ahmad S, Tun TK, Sreenan S, McDermott JH. A case of pembrolizumab-induced severe DKA and hypothyroidism in a patient with metastatic melanoma. *Endocrinol Diabetes Metab Case Rep* 2019; **2019** [PMID: 30836329 DOI: 10.1530/EDM-18-0153]

27 **Chaudry A,** Chaudry M, Aslam J. Pembrolizumab: An Immunotherapeutic Agent Causing Endocrinopathies. *Cureus* 2020; **12:** e8836 [DOI: 10.7759/cureus.8836]

28 **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 [PMID: 30899528 DOI: 10.1136/bmjdrc-2018-000591]

29 **Zand Irani A**, Almuwais A, Gibbons H. Immune checkpoint inhibitor-induced diabetes mellitus with pembrolizumab. *BMJ Case Rep* 2022; **15** [PMID: 35039353 DOI: 10.1136/bcr-2021-245846]

30 **Maamari J**, Yeung SJ, Chaftari PS. Diabetic ketoacidosis induced by a single dose of pembrolizumab. *Am J Emerg Med* 2019; **37**: 376.e1-376.e2 [PMID: 30361152 DOI: 10.1016/j.ajem.2018.10.040]

31 **Alrifai T**, Ali FS, Saleem S, Ruiz DCM, Rifai D, Younas S, Qureshi F. Immune Checkpoint Inhibitor Induced Diabetes Mellitus Treated with Insulin and Metformin: Evolution of Diabetes Management in the Era of Immunotherapy. *Case Rep Oncol Med* 2019; **2019**: 8781347 [PMID: 31781446 DOI: 10.1155/2019/8781347]

32 **Hong AR**, Yoon JH, Kim HK, Kang HC. Immune Checkpoint Inhibitor-Induced Diabetic Ketoacidosis: A Report of Four Cases and Literature Review. *Front Endocrinol (Lausanne)* 2020; **11**: 14 [PMID: 32047478 DOI: 10.3389/fendo.2020.00014]

33 **Skorpen PK**, Margull J. Diabetic ketoacidosis following immunotherapy for lung cancer. *Tidsskr Nor Laegeforen* 2019; **139** [PMID: 30808100 DOI: 10.4045/tidsskr.18.0597]

34 **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**: 765-767 [PMID: 25828465 DOI: 10.1007/s00262-015-1689-1]

35 **Gaudy C**, Clévy C, Monestier S, Dubois N, Préau Y, Mallet S, Richard MA, Grob JJ, Valéro R, Béliard S. Anti-PD1 Pembrolizumab Can Induce Exceptional Fulminant Type 1 Diabetes. *Diabetes Care* 2015; **38**: e182-e183 [PMID: 26310693 DOI: 10.2337/dc15-1331]

36 Abstracts of the Endocrine Society of Australia Annual Scientific Meeting 2015, 23-26 August 2015. *Clin Endocrinol (Oxf)* 2016; **84 Suppl 1**: 1-49 [PMID: 26935124 DOI: 10.1111/cen.13010]

37 **Humayun MA**, Poole R. A case of multiple immune toxicities from Ipilimumab and pembrolizumab treatment. *Hormones (Athens)* 2016; **15**: 303-306 [PMID: 27376434 DOI: 10.14310/horm.2002.1656]

38 **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**: 765-767 [PMID: 27067877 DOI: 10.1007/s00262-016-1835-4]

39 **Alhusseini M**, Samantray J. Autoimmune diabetes superimposed on type 2 diabetes in a patient initiated on immunotherapy for lung cancer. *Diabetes Metab* 2017; **43**: 86-88 [PMID: 27291328 DOI: 10.1016/j.diabet.2016.05.007]

40 **Abdul Aziz MHariz F,** Fernando IP, Lenkanpally A, Fernando DJS. Diabetic ketoacidosis after treatment with pembrolizumab. *J Clin Transl Endocrinol Case Rep* 2017; **5**: 4-5 [DOI: 10.1016/j.jecr.2017.05.002]

41 **Tay WL,** Loh WJ, Kek PC. A case of pembrolizumab-induced type 1 diabetes mellitus presenting with severe diabetic ketoacidosis. *J Clin Transl Endocrinol Case Rep* 2017; **6**: 9-10 [DOI: 10.1016/j.jecr.2017.07.002]

42 **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 [PMID: 27761609 DOI: 10.1007/s00262-016-1913-7]

43 **Smith-Cohn MA**, Gill D, Voorhies BN, Agarwal N, Garrido-Laguna I. Case report: pembrolizumab-induced Type 1 diabetes in a patient with metastatic cholangiocarcinoma. *Immunotherapy* 2017; **9**: 797-804 [PMID: 28877632 DOI: 10.2217/imt-2017-0042]

44 **Mizab Mellah C**, Sánchez Pérez M, Santos Rey MD, Hernández García M. Fulminant type 1 diabetes mellitus associated with pembrolizumab. *Endocrinol Diabetes Nutr* 2017; **64**: 272-273 [PMID: 29056250 DOI: 10.1016/j.endinu.2017.01.005]

45 **Abayev J,** Dhawan N, Jetty V, Khan A, Goldenberg N. Abstract #100 Atypical Presentation of Congenitial Adrenal Hyperplasia. *Endocr Pract* 2018; **24:** 1 [[DOI: 10.4158/1530-891X-24.s1.1](https://doi.org/10.4158/1530-891X-24.s1.1)]

46 Irish Endocrine Society 42nd Annual Meeting, 19th and 20th October 2018. *Ir J Med Sci* 2018; **187**: 173-226 [PMID: 30120710 DOI: 10.1007/s11845-018-1877-z]

47 **Ryder M**, Randolph G. 88(th) Annual Meeting of the American Thyroid Association October 3-7, 2018 Marriott Marquis, Washington, DC. *Thyroid* 2018; **28**: 1227-1228 [PMID: 30141375 DOI: 10.1089/thy.2018.0524]

48 **Reslan Z,** Bennett M, Wong E, Jacques S, Lee A. Pembrolizumab‐induced auto‐immune type‐1 diabetes in a patient with metastatic melanoma. *J Pharm Pract Res* 2018; **48:** 262-264 [DOI: 10.1002/jppr.1329]

49 2019 ASPHO ABSTRACTS. Pediatr Blood Cancer. 2019; **66:** e27713 [DOI: 10.1002/pbc.27713]

50 Paper Abstract. *J Am GeriatrSoc* 2019; **67:** S1-384 [DOI: 10.1111/jgs.15898]

51 **Talib U,** ALpert A, Mena J, Matos A, Nagus I, Sycheva T, Blaski C. Pembrolizumab-induced type 1 diabetes presenting as diabetic ketoacidosis. *Chest* 2019; **156:** A2146-A2147

52 **Gunjur A**, Klein O, Kee D, Cebon J. Anti-programmed cell death protein 1 (anti-PD1) immunotherapy induced autoimmune polyendocrine syndrome type II (APS-2): a case report and review of the literature. *J Immunother Cancer* 2019; **7**: 241 [PMID: 31488221 DOI: 10.1186/s40425-019-0713-y]

53 **Singh NR.** Pembrolizumab: a case of drug-induced autoimmune diabetes mellitus and colitis. *J Pharm Pract Res* 2019; **49:** 50-54 [DOI: 10.1002/jppr.1436]

54 **Akopyan K,** Siddiqui A, Otekeiwebia A, Kroker-Bode C. Finding the culprit: a case of new onset type i diabetes mellitus (DM) and severe diabetic ketoacidosis (DKA) after the initiation of pembrolizumab. *Chest* 2020; **158:** A869 [DOI: 10.1016/j.chest.2020.08.807]

55 **Zagouras A**, Patil PD, Yogi-Morren D, Pennell NA. Cases from the Immune-Related Adverse Event Tumor Board: Diagnosis and Management of Immune Checkpoint Blockade-Induced Diabetes. *Oncologist* 2020; **25**: 921-924 [PMID: 32564463 DOI: 10.1634/theoncologist.2019-0806]

56 **Kethireddy N**, Thomas S, Bindal P, Shukla P, Hegde U. Multiple autoimmune side effects of immune checkpoint inhibitors in a patient with metastatic melanoma receiving pembrolizumab. *J Oncol Pharm Pract* 2021; **27**: 207-211 [PMID: 32390537 DOI: 10.1177/1078155220921543]

57 **Lamsal R**, Klyachman L, Adeyinka A, Kondamudi N, Pierre L. Is HbA1c an Indicator of Diabetic Ketoacidosis Severity in the Pediatric Population? *Pediatr Emerg Care* 2023; **39**: 216-218 [PMID: 36727771 DOI: 10.1097/PEC.0000000000002859]

58 **Basu M**, Pandit K, Banerjee M, Mondal SA, Mukhopadhyay P, Ghosh S. Profile of Auto-antibodies (Disease Related and Other) in Children with Type 1 Diabetes. *Indian J Endocrinol Metab* 2020; **24**: 256-259 [PMID: 33083265 DOI: 10.4103/ijem.IJEM\_63\_20]

59 **Paepegaey AC**, Lheure C, Ratour C, Lethielleux G, Clerc J, Bertherat J, Kramkimel N, Groussin L. Polyendocrinopathy Resulting From Pembrolizumab in a Patient With a Malignant Melanoma. *J Endocr Soc* 2017; **1**: 646-649 [PMID: 29264517 DOI: 10.1210/js.2017-00170]

60 **Abel M**, Krokowski M. Pathophysiology of immune-mediated (type 1) diabetes mellitus: potential for immunotherapy. *BioDrugs* 2001; **15**: 291-301 [PMID: 11437693 DOI: 10.2165/00063030-200115050-00002]

61 **Steck AK**, Rewers MJ. Genetics of type 1 diabetes. *Clin Chem* 2011; **57**: 176-185 [PMID: 21205883 DOI: 10.1373/clinchem.2010.148221]

**Footnotes**

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** Authors does not have any conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** July 13, 2023

**First decision:** September 26, 2023

**Article in press:** October 30, 2023

**Specialty type:** Oncology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Wu QN, China; Zhang H, China **S-Editor:** Liu JH **L-Editor:** A **P-Editor:** Chen YX

**Table 1 Baseline characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **No. of patients** | **Age/Sex** | **Type of cancer** | **Time from first administration (wk)** | **No. of cycle** |
| de Filette *et al*[9],2019 |  | 61/M | NSCLC | 8 | 2 |
| de Filette *et al*[9], 2019 | 91 | 65 | Melanoma/NSCLC |  | 4.5 |
| Clotman *et al*[10], 2018 |  | 73/F | Melanoma | 8 | 2 |
| Clotman *et al*[10], 2018 | 14 | 63 |  | 6 | 3 |
| Farina *et al*[11], 2019 | 10 | 62 | Melanoma/Lung cancer |  | 5 |
| Kyriacou *et al*[12], 2020 |  | 68/F | Lung cancer | 7 | 2 |
| Banatwalla *et al*[13], 2021 |  | 83/F | Melanoma | 23 | 7 |
| Hernandez *et al*[14], 2021 |  | 67/M | SCC tongue | 3 | 1 |
| Bansal *et al*[15], 2022 |  | 85/F | Lung adeno | 9 | 3 |
| Kedzior *et al*[16], 2021 |  | 51/F | Lung adeno | 8 | 2 |
| Cunha *et al*[17], 2022 |  | 59/F | Lung adeno | 3 | 1 |
| Kähler *et al*[18], 2020 | 5 | 74-85, 3F and 2M | Melanoma |  | 4 |
| Tohi *et al*[19], 2019 |  | 75/M | Urothelial CA | 10 | 3 |
| Edahiro *et al*[20], 2019 |  | 61/F | Lung adeno | 25 | 8 |
| Magis *et al*[21], 2018 |  | 41/F | Melanoma | 57 | 19 |
| Samoa *et al*[22], 2020 |  | 12/M | Hodgkin's lymphoma | 15 | 5 |
| Li *et al*[23], 2018 |  | 67/M | NSCLC | 10 | 3 |
| Boyle *et al* [24], 2019 |  | 56/M | Melanoma | 22 months |  |
| Boyle *et al* [24], 2019 |  | 74/F | Merkel cell cancer | 23 | 7 |
| Sankar *et al* [25], 2021 |  | 85/F | Bladder CA | 9 months |  |
| Hakami *et al* [26], 2019 |  | 52/M | Melanoma | 21 | 7 |
| Chaudry *et al*[27], 2020 |  | 75/M | NSCLC | 12 | 4 |
| Kotwal *et al*[28], 2019 | 11 | 61 |  |  | 4 |
| Zand *et al*[29], 2022 |  | 81/F | Melanoma | 26 | 8 |
| Maamari *et al*[30], 2019 |  | 47/F | Cardiac angiosarcoma | 6 | 1 |
| Alrifai *et al*[31], 2019 |  | 69/M | NSCLC | 15 | 4 |
| Hong *et al*[32], 2020 |  | 76/M | Lung | 11 | 3 |
| Hong *et al*[32], 2020 |  | 78/F | Melanoma | 4 | 1 |
| Hong *et al*[32], 2020 |  | 65/F | Biliary CA | 21 | 7 |
| Skorpen *et al*[33], 2019 |  | 60s/M | Lung adeno | 8 | 2 |
| Martin-Liberal *et al*[34], 2015 |  | 54/F | Melanoma | 9 | 3 |
| Gaudy *et al*[35], 2015 |  | 44/F | Melanoma | 8 | 2 |
| Aleksova *et al*[36], 2016 |  | 61/M | Melanoma | 6 | 1 |
| M A *et al*[37], 2016 |  | 55/M | Melanoma | 27 | 9 |
| Hansen *et al*[38], 2016 |  | 58/M | Melanoma |  | 17 |
| Alhusseini *et al*[39], 2017 |  | 65/M | Lung adenocarcinoma | 3 | 1 |
| F A *et al*[40], 2017 |  | 48/F | Melanoma | 2 | 1 |
| Tay *et al*[41], 2017 |  | 74/F | Melanoma | 3 | 1 |
| Chae *et al*[42], 2017 |  | 76/M | Lung adenocarcinoma | 1 | 1 |
| Smith-Cohn *et al*[43], 2017 |  | 61/F | Cholangiocarcinoma | 18 | 6 |
| C M *et al*[44], 2017 |  | 58/M | Melanoma |  | 4 |
| Abayev *et al*[45], 2018 |  | 71/M | Melanoma | 26 |  |
| Ioana *et al*[46], 2018 |  | 52/M | Melanoma | 13 |  |
| Kalkan *et al*[47], 2018 |  | 73/F | NSCLC | 9 | 3 |
| Reslan *et al*[48], 2018 |  | 79/M | Melanoma | 24 | 5 |
| Fernandez *et al*[49], 2019 |  | 15/M | Soft tissue sarcoma | 2 | 1 |
| Sfeir *et al*[50], 2019 |  | 90/M | Melanoma |  |  |
| Talib *et al*[51], 2019 |  | 67/F | Esophageal squamous cell CA | 8 | 2 |
| Gunjur *et al*[52], 2019 |  | 77/F | Melanoma | 3 Days | 1 |
| Singh *et al*[53], 2019 |  | 70/M | Melanoma | 10 | 3 |
| Akopyan *et al*[54], 2020 |  | 66/F | Urothelial CA | 6 months |  |
| Zagouras *et al*[55], 2020 |  | 52/M | Lung adenocarcinoma | 9 | 3 |
| Kethireddy *et al*[56], 2021 |  | 85/M |  | 9 | 3 |

NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma.

**Table 2 Diabetes characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Presentation** | **HbA1C** | **C-peptide** | **Auto Ab** | **Outcome** |
| de Filette *et al*[9] | DKA |  | 0.02 nmol/L | GADA | Not known |
| de Filette *et al*[9] | 71% DKA | 7.6 | Low in 84% | 51% GADA 18% IA2 13% ICA 26% Anti-Insulin | Not known |
| Clotman *et al*[10] | DKA | 7.1 | Low | GADA, ICA | Stayed on insulin |
| Clotman *et al*[10] | 70% DKA | 7.5 | Low in 93% | 56% GADA |  |
| Farina *et al*[11] | 69% DKA | 7.76 | 0.1 | 50% GADA+ | 97% remained on Insulin therapy |
| Kyriacou *et al*[12] | DKA | 7 | Low | GADA+ | Stayed on insulin |
| Banatwalla *et al*[13] | DKA | 8.2 | 0.09 | All neg | Stayed on insulin |
| Hernandez *et al*[14] | DKA | 6.9 |  |  | Stayed on insulin |
| Bansal *et al*[15] | HHS | 8.3 | Normal | GADA + | Stayed on insulin |
| Kedzior *et al*[16] | DKA | 8.3 | Undetected | GADA+ |  |
| Cunha *et al*[17] | DKA | 5.6 | Undetected | GADA+ | Stayed on insulin |
| Kähler *et al*[18] | DKA | 9.7, 6.5, 7.5, No data for other 2 | Low in 1 | GADA+ in 2 |  |
| Tohi *et al*[19] | DKA | 6.7 | Undetected | GADA negative | Stayed on insulin |
| Edahiro *et al*[20] | DKA | 8.4 | Low | GADA negative | Stayed on insuline |
| Magis *et al*[21] | DKA | 6.8 | < 0.003 | GADA negative, IA-2 Positive | Stayed on insulin |
| Samoa *et al*[22] | DKA | 8.9, Intial was 6.0 | Low | GADA negative, IA-2 Positive IA Positive | Stayed on insulin |
| Li *et al*[23] | DKA | 8 | Low | All ab negative | Stayed on insuline |
| Boyle *et al*[24] | DKA | 7.4 | Low | All ab negative | Stayed on insulin |
| Boyle *et al*[24] | DKA |  | Low | All ab negative |  |
| Sankar *et al*[25] | DKA | 6.8 |  | All ab negative | Stayed on insulin |
| Hakami *et al*[26] | DKA | 8.3 | < 0.001 | All ab negative | Stayed on insulin |
| Chaudry *et al*[27] | DKA |  |  | GADA + | Stayed on insulin |
| Kotwal *et al*[28] | 8 DKA, 1 HHS, 1 Ketosis, 1 Hyperglycemia | 9.7 | 5/6 Low | 4/7 GADA+, 1/7 IAA+, 1/7 IA2A+ | Stayed on insulin |
| Zand *et al*[29] | DKA | 8.9 |  | All ab negative | Stayed on insulin |
| Maamari *et al*[30] | DKA | 6.4 | Low | GADA+ | Stayed on insulin |
| Alrifai *et al*[31] | DKA | 9.2 | Low | GADA+ | Stayed on insulin |
| Hong *et al*[32] | DKA | 10.4 | Low | All ab negative | Stayed on insulin |
| Hong *et al*[32] | DKA | 11.4 | Low | All ab negative | Stayed on insulin |
| Hong *et al*[32] | DKA | 5.8 | Low | All ab negative | Stayed on insulin |
| Skorpen *et al*[33] | DKA | 8.4 | Undetected | All ab negative | Stayed on insulin |
| Martin-Liberal *et al*[34] | DKA |  |  | GADA+ | Stayed on insulin |
| Gaudy *et al*[35] | DKA | 6.85 | Undetected | All ab negative | Stayed on insulin |
| Aleksova *et al*[36] | DKA |  | Low | All ab negative | Stayed on insulin |
| M A *et al*[37] | DKA | 10.7 |  | All ab negative | Stayed on insulin |
| Hansen *et al*[38] | Simple T1DM | 7.1 | Low | GADA+ | Dced insulin |
| Alhusseini *et al*[39] | DKA | 8.5 | Undectable | GADA+, ICA+ | Stayed on insulin |
| F A *et al*[40] | DKA | 8 | Undectable | GADA+, IA+ | Stayed on insulin |
| Tay *et al*[41] | DKA | 9.3 | Undectable | All ab Negative | Stayed on insulin |
| Chae *et al*[42] | DKA | 5.8 | Low | GADA+, ICA+ | Stayed on insulin |
| Smith-Cohn *et al*[43] | DKA | 8.7 |  | GADA+ | Stayed on insulin |
| C M *et al*[44] | DKA | 7.4 | Undetectable | All ab Negative |  |
| Abayev *et al*[45] | DKA | 11.8 | Normal | All ab Negative | Stayed on insulin |
| Ioana *et al*[46] | DKA | 8.3 | Undetectable | All ab Negative |  |
| Kalkan *et al*[47] | DKA |  | Low | All ab Negative |  |
| Reslan *et al*[48] | DKA | 7.5 |  |  | Stayed on insulin |
| Fernandez *et al*[49] | DKA | 5.5 | Low | GADA+ |  |
| Sfeir *et al*[50] | DKA | 10.2 | Low | All ab negative | Stayed on insulin |
| Talib *et al*[51] | DKA | 7.9 | Low | GADA+ |  |
| Gunjur *et al*[52] | DKA | 6.9 | Low | GADA+, ICA+ | Stayed on insulin |
| Singh *et al*[53] | DKA |  |  | GADA+ | Stayed on insulin |
| Akopyan *et al*[54] | DKA |  |  | All ab negative | Stayed on insulin |
| Zagouras *et al*[55] | Hyperglycemia | 5.7 | Low | GADA+ | Stayed on insulin |
| Kethireddy *et al*[56] | T1DM | 9 |  | GADA+ | Stayed on insulin |

NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma; DKA: Diabetic ketoacidosis; GADA: Glutamic acid decarboxylase antibody; IA-2: Islet antibody; ICA: Islet cell antibodies; IAA: Insulin autoantibodies; ab: Antibodies.



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