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CASE REPORT

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

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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

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.

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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 4^{th} 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

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.

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.

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% IA213% ICA26% 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 PositiveIA 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.

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.

FOOTNOTES

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