Case report

Rapid onset type-1 diabetes and diabetic ketoacidosis secondary to nivolumab immunotherapy: a review of existing literature

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SUMMARY

Nivolumab is a programmed cell death receptor (PD-1) inhibitor that is increasingly used for various malignancies, both as a first line agent and as salvage therapy. Being a PD-1/PD-1 ligand checkpoint inhibitor, it is known to cause autoimmune inflammation of various organs and has been associated with thyroiditis, insulitis, colitis, hepatitis and encephalitis to name a few. There are increasing reports of nivolumab leading to acute onset fulminant type 1 diabetes and diabetic ketoacidosis (DKA). We present a case of a 68-year-old man who developed DKA after 2 doses of nivolumab for metastatic melanoma. He was found to have type 1 diabetes, but no diabetes related antibodies were positive. He recovered from diabetes and continues to use insulin 1 year after his diagnosis. This case and associated review illustrates the importance of educating and monitoring patients who start nivolumab therapy regarding this potentially life threatening complication.

BACKGROUND

Immune checkpoint inhibitors (ICI) are anticancer immunotherapeutic agents that work mainly by disrupting inhibitory signals to T cells. Nivolumab is one of these newer agents and works against the programmed cell death receptors (PD-1) found on T lymphocytes by inhibiting them.[1] PD-1 normally induces T cell tolerance, so that they don't attack our own cells. However, some cancer cells express the PD-1 ligand which can bind PD-1 and cause an impaired T cell response against cancer cells. Nivolumab prevents this PD-1 and PD-1L interactions, which allows the T cells to mount a response against cancer cells.[1] It was the subject of many trials and has shown efficacy in various cancers. Currently it is Food and Drug Administration (FDA) approved for the treatment of melanoma, non-small cell lung cancer (NSCLC), Renal cell carcinoma (RCC), squamous cell cancer (SCC) of the head and neck, Hodgkin's lymphoma, urothelial carcinoma and colorectal cancer.[1] Being an immunotherapeutic agent, it has been known to cause immune related adverse events (irae), including endocrinopathies like thyroiditis, diabetes mellitus, hypophysitis and adrenal insufficiency. Other adverse effects include colitis, hepatitis, nephritis, pneumonitis and encephalitis.[1 2] Autoimmune diabetes mellitus has been reported in many case series and retrospective reviews, but there are increasing reports of life threating DKA due to acute onset of fulminant diabetes in patients receiving nivolumab.[3] This case and associated review illustrates the importance of educating and monitoring patients who start nivolumab therapy regarding this potentially life threatening complication.

CASE PRESENTATION

A 68-year-old man with a medical history of severe Chronic Obstructive Pulmonary Disease (COPD), hypertension and diastolic heart failure, who also had a history of metastatic melanoma diagnosed 3 months ago and recently started on immunotherapy regimen with nivolumab. He was found confused and short of breath by his family, and taken to a local emergency department (ED). On evaluation he was found to be hypoxic with saturation in the 70s, hypotension, and tachycardia with HR 200–210 beats/min, an electrocardiogram (EKG) revealing supraventricular tachycardia. He did not respond to oxygen therapy and was subsequently intubated and brought to our hospital. At presentation in our ED, he was sedated and intubated and could not provide any history, but continued to be hypotensive and tachycardiac. A quick physical exam revealed a heart rate of 206, blood pressure 80/60 mm Hg and temperature of 98 F, and O_2 saturation of 96% on 100% FiO_2. Chest examination revealed mild left sided basal crepitations in the lungs, but was otherwise unremarked. Neurologic exam was not possible.

INVESTIGATIONS

Initial lab work in the ED showed an arterial PH of 7.15, PCO_2 of 61 mm Hg, PO_2 of 87 mm Hg, trop I of 0.3 ng/mL, white cell count of 26.6×10^9/L, Hgb of 16.4 g/L, Glucose of 643 mg/dL, Sodium of 131 mmol/L, potassium of 5.8 mmol/L, chloride of 84 mmol/L, bicarb of 18 mmol/L, Anion GAP of 34, lactic acid of 11.1 mmol/L, and mildly elevated transaminases. He underwent electric cardioversion in our ED, and was started on vasopressors and intravenous fluids. Pan CT of the body was performed to identify any source of infection. It showed evidence of left lower lobe pneumonia, but CT head, abdomen, pelvis were negative for any pathology.

DIFFERENTIAL DIAGNOSIS

The patient's mental status deterioration was thought to be due to hypoxic respiratory failure, due to a pneumonia. However, on initial evaluation he was found to have DKA too. This was surprising as he did not have a history of diabetes, and type 1 diabetes rarely presents at this age. He was further evaluated to confirm the type of diabetes. A C peptide level was performed that was very low at 0.1 ng/mL (normal >0.8), but autoantibodies including glutamic acid decarboxylase antibodies (GADA), Indole Acetic Acid Antibodies (IAA) and islet tyrosine phosphatase antibodies (IA-2) were negative. He was diagnosed with type 1 diabetes based on this, that was likely autoimmune diabetes secondary to nivolumab. This acute presentation of sudden onset diabetes with DKA and severe hyperglycemia has also been labelled fulminant diabetes.

TREATMENT

The patient was admitted in to the medical ICU, for the management of Hypoxic respiratory failure secondary to pneumonia, sepsis, DKA, acute kidney injury, hyperkalemia and supraventricular tachycardia (SVT). The patient remained intubated in the ICU for 4 days, during which his respiratory failure resolved with the help of intravenous antibiotics, aggressive pulmonary toilet and steroids for underlying COPD. His sepsis resolved and he was weaned off antibiotics. He was treated for his DKA with intravenous insulin, and his blood sugars normalised and Anion GAP closed by the next day of his admission. His acute kidney injury (AKI), electrolyte disturbances and elevated liver function tests (LFTs) also resolved. The patient was extubated on day 5 and moved out of the ICU.

OUTCOME AND FOLLOW-UP

The patient remained in hospital for another 7 days and was discharged to a swing bed facility where he stayed for another 14 days. He had been discharged on insulin, and continues to be seen regularly in the endocrine clinic for close follow-up 1 year after his DKA episode.

DISCUSSION

Programmed cell death inhibitors PD-1 and its ligand which has been termed programmed cell death inhibitors ligand PD-1L was first described in the 1990s. They play an important role in the regulation of T cells in the peripheral tissues by inducing immunologic tolerance.[4] However, it was discovered that many cancerous cells also express PD-1L and are able to evade the PD-1/PD-1L checkpoint. Therefore, it was thought that by inhibiting this interaction, the growth of tumour cells can be checked. After successful studies in animals, many trials were conducted on humans too.[4] One of the first trials involving ICI was nivolumab which is a fully humanised IgG4 anti-PD-1 antibody. It was initially tested on solid tumours, and then expanded to other cancers too. After many trials, it was finally approved by FDA in 2014, and is currently approved for the treatment of melanoma, NSCLC, RCC, SCC of the head and neck, Hodgkin's lymphoma, urothelial carcinoma and colorectal cancer, both as a first line agent in some cases, and second or third line in other cases.[4]

With the widespread use, there was increasing studies and case series describing the potential side effects. It can cause the various immune related side effects, and immune mediated diabetes is an important one reported.[5] The exact incidence of this is not known, though FDA data mentions an incidence of 0.09% with 0.11% of the diabetes presenting as DKA.[5 6] In a meta-analysis of 38 clinical trials (including eight phase III studies) that evaluated the use of immune-checkpoint inhibitors, the total number of patients who developed insulin dependent diabetes of any grade was 13, out of 7689 patients included in the meta-analysis.[7] Interestingly, they were all noted in patient's treated with PD-1 inhibitors except for one case. However, there are increasing reports of patients presenting with acute onset fulminant autoimmune diabetes, that results in potentially life threatening DKA in many cases. Some of the reported case series on auto immune diabetes type 1 from nivolumab, report rates of as high as 53% of DKA in such patients. This is particularly concerning as patients who develop DKA are at higher risk of morbidity and mortality.[8]

The exact mechanism by which PD-1 inhibitors damage the endocrine cells of the pancreas and cause autoimmune diabetes is not known. However it is known that PD-L1 is also expressed on the pancreatic islet cells and its interaction with PD-1 receptor is thought to prevent the activation of autoreactive T cells.[9] Studies on animals have shown that PD-1 inhibitors can cause destructive insulitis and precipitate diabetes in mice in days to weeks.[10–13]

Thus, The PD-1-PDLA1 system is thought to play role in body tolerance to pancreatic beta cell antigens. PDL1 has also been reported to be present in insulin positive cells in patients with type type I diabetes, and this can explain in part the potential for development of fulminant type I diabetes with use of PD-1 inhibitors via disruption of this system.[14] Some patients are considered to be more predisposed to developing diabetes after receiving PD-1 inhibitors. These include certain human leukocyte antigen (HLA) haplotypes. Initial studies reported in japan regarding patients developing fulminant diabetes were found to have certain high risk haplotypes for type 1 diabetes, however this has not been consistently found in patients who develop DKA from nivolumab therapy.[15] Further clouding the picture is the fact that many patients are reported to have antibodies against islet cells, while many others don't have any antibodies, and as such no clear association has been found. This may also signify that the mechanism may be different in different populations.[8]

We performed a comprehensive review on DKA as a complication of nivolumab therapy, to better characterise this patient population, and find any trends or associations that may be clinically significant. A literature search was performed on pubmed using MESH terms including 'nivolumab' and 'diabetic ketoacidosis', 'ketoacidosis', 'DKA' and 'fulminant diabetes'. Other major databases including Embase and Chochrane was also performed. Only cases that involved nivolumab and had developed DKA were included in this study. A total of 20 patients were included in this study, and their patient data is presented in table 1.[1 16–31]

A review of our case series shows that the mean age of the patients was n=59 years (34–83). There is not enough data available to calculate the incidence of DKA in each age group. Since older patients are more likely to develop cancer, they are more likely to receive nivolumab, and hence it is expected that they will be more likely to present with DKA. Females made up n=12 of our patients while n=10 of our patients were males. The most common malignancy reported was malignant melanoma in n=10 patients. It is expected as it was one of the first conditions nivolumab was approved for and is also used as a first line agent against this.[6] The doses received before the development of DKA was documented in n=16 out of the 22 cases. The median and mode was three doses before the development of DKA, with doses ranging from 1 to up to 27 reported in one

Table 1 Patient characteristics of our case series

S. No.	Case	Age/sex	Dx	Prior DM2 dx	Other chemo	Doses/days	A1c	C peptide	Ab	HLA testing	Pancreatic enzyme elevation Lipase/Amylase	Imaging	Outcome	Other complications
1	Hughes *et al*	55/F	Melanoma	No	Iplimumab	NA/5 months	6.9	Undetectable	No	A 2.1, DR 4	NA	NA	NA	Thyroiditis
2	Hughes *et al*	83/F	NSCLC	No	NA	NA/30	7.7	Undetectable	GADA	A 2.1, DR 4	NA	NA	NA	No
3	Hughes *et al*.	58/M	SCLC	Yes	Carboplatin/etoposide/paclitaxel	NA/7	9.7	Undetectable	GADA	A 2.1,	NA	NA	NA	No
4	Miyoshi *et al*	66/F	Melanoma	No	NA	3/NA	7.3	<0.01	No	DRB1 11:01 13:02:01 DQB1 03:01:01 06:04:01	71/43	NA	Survived/NA	No
5	Lowe *et al*	54/F	Melanoma	No	Iplimumab	3/NA	NA	<0.1	GADA	NA	NA	NA	Survived/DC	Colitis/hepatitis/thyroiditis
6	Ishikawa *et al*	54/M	Melanoma	No	NA	27/NA	7	0.1	No	B*15:01, *40:06, DRB1*04:05, *04:06, DQB1 *03:02, and *04:01	NA	NA	Survived/C	No
7	Li *et al*	63/F	NSCLC	No	Carboplatin/paclitaxel	2/27	6.4	NA	GADA	NA	NA	NA	Survived/C	Thyroiditis
8	Araujo *et al*	73/F	NSCLC	No	NA	NA/NA	7.2	Undetectable	GADA	DR3-DQ2 DR4-DQ8	NA	NA	NA	No
9	Alzenaidi *et al*	47/M	Melanoma	Yes	Iplimumab	2/NA	8	0.2	GADA	NA	553/NA	-ve	Survived/NA	No
10	Godwin *et al*	34/F	NSCLC	No	Carboplatin/premexted	2/28	7.1	<0.1	GADA, IAA, IA-2 ZnT8 (new)	A30 and DR9	NA	NA	Survived, C	thyroiditis
11	Chokr *et al*	61/M	Melanoma	No	Ipilimumab	3/NA	6.9	<0.1	No	NA	411/NA	NA	Survived, C	Rash
12	Capitao *et al*	74/F	Adenocarcinoma Lung	No	NA	NA/25	8.7	0.2	GADA	DRB1*04	236/141	NA	Survived/C	No
13	Chan *et al*	78/F	NSCLC	No	Carboplatin/gemcitabine	3/NA	NA	0.1	GADA	NA	NA	NA	Survived/DC	No
14	Lee *et al*	67/M	NSCLC	Yes	Carboplatin/paclitaxel/rad	1/14	7.6	<0.1	GADA	NA	NA	NA	Survived/C	Thyroiditis, encephalitis
15	Usui *et al*	31/M	NSCLC	No	NA	1/13	6.4	<0.3	GADA	DRB1*04:05-DQB1*04:01.	NA	NA	Survived/C	No
16	Meyers *et al*	51/M	Melanoma	NA	Iplimumab	2/35	NA	NA	NA	NA	NA	NA	Survived/C	Aplastic anaemia
17	Zaeid *et al*	70s/M	RCC	No	NA	3/NA	8.4	0.4	No	NA	118/27	-ve	Survived/DC	No
18	Tzoulis *et al*	56/F	Lung adenocarcinoma	No	Cisplatin/pemetrexed	3/NA	8.2	Low	GADA	NA	NA	-ve	Survived/C	Thyroiditis
19	Takahashi *et al*	74/F	Melanoma	No	NA	6/NA	8.6	<0.6	No	NA	NA/155	-ve	Survived/DC	No
20	Changizzadeh *et al*	42/M	Melanoma	No	Ipilimumab	3/NA	6.5	NA	No	NA	NA	NA	Survived/C	Colitis
21	Tassone *et al*	42/M	Melanoma	No	NA	4/60	6	0.2	No	DRB1*03:15-DQB1*02:06	NA	NA	Survived, follow-up 2 years	No
22	Harsch *et al*	65/F	HCC	No	Sorefinib	NA/8 months	NA	NA	No	NA	NA	NA	NA	No

DM 2, diabetes mellitus type 2; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

patient. This is significant, as most patients developed DKA with very few doses of nivolumab. There was one patient with 27 doses, which seems to be an outlier and would skew any mean calculated. The duration from the first dose till the development of DKA was very variable, ranging from a low of 7 days to 8 months in one patient.

The mean Haemoglobin A1c that was reported was 7.45% in the n=19 patients that A1c was reported (range 6.0–9.7). Interestingly, many patients had low A1c<7.0%, which signifies the acute onset of their diabetes. Regarding comorbidities, n=3 of the patients did have pre-existing diagnosed type 2 diabetes, that was complicated by the development of fulminant type 1 diabetes and DKA. The mean A1c in these patients was 8.43% as compared with 7.45% in the general patient population. All of the reported patients had undetectable to low C peptide levels, signifying that they had developed type 2 diabetes. n=4 of the patients also had lipase levels reported, n=3 of which were elevated, ranging from (236 to 553 U/L). Abdominal/pancreatic imaging was unremarkable in all patients that it was performed.

Antibodies were checked in most of the patients, and the most common antibody that was positive was GADA in n=12 patients of the total patients, a rate that is consistent with previous studies.[3] IAA and I2A were positive in n=1 patient each, and so was Zn8t. Interestingly some patients had these antibodies prior to starting nivolumab, after their prior stored blood samples were tested.[1] Though GADA antibody is present in many patients with type 1 diabetes, almost half of our patients had antibodies and half did not. We do not know if this signifies that there are different mechanisms of the development of diabetes in both these population groups. Also those patients that were GADA positive, had earlier onset of DKA, with a mean and mode of just two doses. This was consistent with previous studies.[3]

A total of n=13 patients were reported to be receiving other chemo or immunotherapies during or prior to nivolumab therapy. n=6 patients were receiving concomitant Iplimumab, and all of these patients had melanoma. n=5 patients also received carboplatin prior to nivolumab, and these were all patients with NSCLC. HLA subtype was checked in n=11 patients, however these were widely variable, and no conclusion can be drawn from this data alone.

All the patients survived the DKA episodes. In n=4 patients nivolumab therapy was discontinued, though it was continued in most of the patients. In n=8 patients, there was other irae also reported, the most common being thyroiditis in n=6 patients. Besides this, colitis was reported in n=2 patients, and hepatitis, encephalitis, rash and aplastic anaemia was reported in n=1 patient each. All patients continued to be on insulin therapy on follow-up.

Learning points

- Nivolumab is a programmed cell death receptors (PD-1) inhibitor that was recently introduced and is being increasing used both as a first line immunotherapy or for resistant patients with some malignancies
- Being an immunotherapeutic agent, it has been known to cause autoimmune inflammation of various organs and has been associated with thyroiditis, insulitis, colitis, hepatitis and encephalitis
- Autoimmune diabetes is one the known complications of nivolumab therapy, and interestingly, a high proportion of them present with rapid onset diabetes and diabetic ketoacidosis (DKA).
- All patients receiving therapy with nivolumab must be closely monitored for the development of diabetes and DKA.
- Patients should also be informed of this complication at initiation of therapy, as most patients would require lifelong insulin if they develop this complication

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