New-onset insulin-dependent diabetes due to nivolumab

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Summary

Nivolumab, a monoclonal antibody against programmed cell death-1 receptor, is increasingly used in advanced cancers. While nivolumab use enhances cancer therapy, it is associated with increased immune-related adverse events. We describe an elderly man who presented in ketoacidosis after receiving nivolumab for metastatic renal cell carcinoma. On presentation, he was hyperpneic and laboratory analyses showed hyperglycemia and anion-gapped metabolic acidosis consistent with diabetic ketoacidosis. No other precipitating factors, besides nivolumab, were identified. Pre-nivolumab blood glucose levels were normal. The patient responded to treatment with intravenous fluids, insulin and electrolyte replacement. He was diagnosed with insulin-dependent autoimmune diabetes mellitus secondary to nivolumab. Although nivolumab was stopped, he continued to require multiple insulin injection therapy till his last follow-up 7 months after presentation. Clinicians need to be alerted to the development of diabetes mellitus and diabetic ketoacidosis in patients receiving nivolumab.

Learning points:

- Diabetic ketoacidosis should be considered in the differential of patients presenting with metabolic acidosis following treatment with antibodies to programmed cell death-1 receptor (anti-PD-1).
- Autoimmune islet cell damage is the presumed mechanism for how insulin requiring diabetes mellitus can develop *de novo* following administration of anti-PD-1.
- Because anti-PD-1 works by the activation of T-cells and reduction of 'self-tolerance', other autoimmune disorders are likely to be increasingly recognized with increased use of these agents.

Background

Understanding how cancer escapes host immune regulation has led to the development of cancer 'immunotherapy'. In particular, antibodies such as nivolumab, targeting and inhibiting programmed cell death 1 receptor (PD-1(PDCD1)), can result in the preferential activation of T-cells with specificity for cancer (1). Multiple trials have already demonstrated significant response rates and improved survival with nivolumab in multiple neoplasms including melanoma (2, 3, 4, 5, 6, 7, 8, 9, 10, 11), non-small-cell lung cancer (NSCLC) (2, 3,

4, 12, 13, 14, 15) and renal cell carcinoma (RCC) (2, 3, 4, 16, 17).

However, inhibition of the PD-1 pathway results in a reduction of 'self-tolerance', with an apparent increase in immune-mediated adverse events (AE). Clinical trials investigating the efficacy of nivolumab in cancers have reported increased rates of autoimmune endocrinopathies, including: hypophysitis (5, 7, 8, 10, 11), adrenal insufficiency (4, 5, 7, 10, 12), thyroid disorders (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 18)

and hyperglycemia (2, 3, 4, 6, 8, 15, 17). We report a patient presenting critically ill with diabetic ketoacidosis (DKA) after receiving nivolumab. In addition, we provide a review of the literature reporting nivolumab-induced diabetes mellitus (DM). Acute care physicians' awareness of the acute complications of these novel therapies is essential for the timely management of these critically ill patients.

Case presentation

A Caucasian man, in his early seventies, reported to our emergency department with 3 days of dyspnea, abdominal pain, fatigue and polyuria. Symptoms were progressive despite drinking a significant amount of fluids to keep up with his subjective sense of dehydration. He denied fever, chest pain, edema and visual disturbances.

One year earlier, he had undergone radical right nephrectomy and retroperitoneal lymph node dissection for stage IVB metastatic RCC (metastases to mesenteric lymph nodes and peritoneum). He had received 3 cycles of nivolumab, 3 mg/kg (300 mg, weight: 90 kg with BMI of 28.4) intravenously every 2 weeks, with his last infusion 10 days prior to his acute presentation. Notably, the patient was not enrolled in a clinical trial.

Other comorbidities were hypertension and chronic kidney disease that did not require renal replacement therapy. He was on lisinopril and aspirin. He had not been on any systemic glucocorticoids. There was no personal or family history of pancreatitis, DM or other autoimmune disorders.

Patient was afebrile and normotensive with a pulse of 88 beats per minute, respiratory rate of 28 breaths per minute and oxygen saturation of 97% while breathing ambient air. On examination, he was in moderate respiratory distress due to hyperpnea. There was absent breath sounds on the left lung base with dullness to percussion and decreased tactile vocal fremitus. The rest of his examination was unremarkable. Chest radiographs showed small bilateral pleural effusions (left greater than right) but otherwise clear lung fields.

Investigation

Laboratory analyses (Table 1) showed severe hyperglycemia (878 mg/dL) and an anion gap metabolic acidosis (anion gap: 21) associated with 'large' serum acetones and urine ketones. Arterial blood gas confirmed a primary metabolic acidosis (pH: 7.23, HCO₃: 12) with partial respiratory compensation (PaCO₂: 18). Multiple pre-admission

outpatient fasting blood glucose levels, as recently as two weeks prior to admission, were normal (86–100 mg/dL), although the HbA1c at admission was increased at 8.4%. Other metabolic derangements (hyponatremia and hyperkalemia) were related to ketoacidosis. Additional workup for possible acute pancreatitis, acute coronary syndrome or infectious process was unrevealing. A random C-peptide level was low (0.4 ng/mL) with concomitant blood glucose of 194 mg/dL. Serum for glutamic acid decarboxylase (GAD65) antibody was drawn at the time of the acute presentation, and when it proved negative on follow-up, testing for other less common autoantibodies (IA-2 and IAA) and human leukocyte antigen typing was considered but deferred by the patient and clinical team given unclear management implications (19).

Treatment

The patient was diagnosed with DKA due to new-onset insulin-dependent autoimmune diabetes secondary to nivolumab. He was treated accordingly with intravenous hydration, insulin drip and electrolyte replacement. Thereafter, all the metabolic disturbances improved with resolution of hyperglycemia and acidemia. However, he continued to require insulin therapy and was subsequently discharged on subcutaneous insulin.

Outcome and follow-up

On follow-up, restaging computed tomography showed significant disease progression without pancreatic involvement. Nivolumab was stopped and changed to pazopanib (tyrosine kinase inhibitor). Despite remaining off PD-1 antagonists, the patient continued to require multiple daily insulin injections with insulin glargine (15 units twice daily) and aspartate (5 units with meals, weight 76 kg) at his last follow-up 7 months after hospital discharge. The patient subsequently died 8 months after his initial presentation due to complications of his metastatic RCC.

Discussion

Even though GAD65 antibodies were negative, the inappropriately low C-peptide and sudden onset and persistent hyperglycemia with presentation of DKA confirmed insulin-dependent DM. The repeatedly normal pre-nivolumab fasting blood glucose levels suggest the absence of diabetes prior to nivolumab, while the increased HbA1c at the time of admission suggests more

Table 1 Laboratory data.

Variable	Reference range, adult	Result
Erythrocyte count ($\times 10^{12}/L$)	4.32–5.72	3.3
Hematocrit (%)	38.8–50.0	29.5
Hemoglobin (g/dL)	13.5–17.5	9.0
Mean corpuscular volume (fL)	81.2–95.1	89.4
White cell count ($\times 10^9/L$)	3.5–10.5	20.4
Differential count (%)		
Neutrophils	44.4–70.9	95.1
Lymphocytes	17.8–41.5	0.8
Monocytes	4.7–14.8	3.7
Eosinophils	1.0–7.0	0
Platelet count ($\times 10^9/L$)	150–450	522
Sodium (mmol/L)	135–145	125
Potassium (mmol/L)	3.6–5.2	6.6
Chloride (mmol/L)	98–107	92
Bicarbonate (mmol/L)	22–29	12
Glucose (mg/dL)	70–100	878
Blood urea nitrogen (mg/dL)	8–24	41
Creatinine (mg/dL)	0.8–1.23	2.6 [†]
Total protein (g/dL)	6.3–7.9	6.7
Albumin (g/dL)	3.5–5.0	3.3
Bilirubin, total (mg/dL)	≤ 1.2	0.3
Magnesium (mg/dL)	1.8–2.5	2.7
Calcium	8.9–10.1	8.7
Alkaline phosphatase (U/L)	45–115	108
Alanine aminotransferase (U/L)	7–55	14
Aspartate aminotransferase (U/L)	8–48	84
Lipase (U/L)	7–60	118
Amylase (U/L)	26–102	27
Prothrombin time (s)	11.6–14.7	13.1
International normalized ration	0.8–1.1	1.0
Activated partial thromboplastin time (s)	22.7–36.1	35.4
B-type natriuretic peptide	≤ 67	206
Troponin T (ng/mL)	0.00–0.10	<0.01
Thyroid-stimulating hormone (IU/L)	0.3–4.2	1.5
Hemoglobin A1C (%)	<6.5	8.4
C-peptide (ng/mL)	1.1–4.4	0.4
Arterial blood gas		
pH	7.35–7.45	7.23
PaCO ₂ (mmHg)	35–45	17.6
PaO ₂ (mmHg)	80–100	99
Urine analysis		
Specific gravity	1.002–1.030	1.016
Leukocyte esterase	Negative	Negative
Nitrite	Negative	Negative
pH	5.0–8.0	5.0
Protein (mg/dL)	Negative	10
Glucose (g/dL)	Negative	>1
Bilirubin	Negative	Negative
Urobilinogen		Normal
Erythrocyte (cell/hpf)	0–2	<1
White cell (cell/hpf)		
Acetone blood	Negative	Large
Lactate (mmol/L)	0.9–1.7	1.4
Ammonia ($\mu\text{mol/L}$)	0–30	18
Glutamic acid decarboxylase (GAD65) antibody (nmol/L)	≤ 0.02	0.00

[†]Estimated glomerular filtration rate (eGFR) was 25 mL/min/1.73 m²; baseline Cr is 1.8–2.2 mg/dL.

Table 2 Characteristics of observational studies.

Study	Phase	Cancer	Study period	Sample size	Male n (%)	Nivolumab dose (mg/kg every 2 weeks)	Safety outcome CTACE* n (%)	Endocrinopathy* n (%)
(2)	1	Melanoma, CRC, prostate, NSCLC, RCC	1/2010	39	22 (56)	0.3, 1, 3, 10	Any grade 59 AE in 39 patients	Thyroid 1 (2.6)
(3) ^s	1	Melanoma, CRC, prostate, NSCLC, RCC	2/2012	296	195 (66)	0.1, 0.3, 1, 3, 10	Grade 3–4 15 AE grade 3 in 39 patients	Hyperglycemia 1 (3) [†]
(4) ^s	1	Melanoma, CRC, prostate, NSCLC, RCC	2/2012	207	121 (58)	0.1, 0.3, 1, 3, 10	207 (70)	10 (3)
(5)	1	Melanoma	2/2013	86	50 (58)	0.3, 1, 3, 10 [¶]	126 (61)	6 (3)
(6)	1	Melanoma	2008–2012	107	72 (67)	1, 3, 10	73 (85) 90 (84)	6 (7) 8 (7)
(18)	1	Hodgkin's lymphoma	6/2014	23	12 (52)	3	18 (78)	2 (9)
(7)	1	Melanoma	NR	33	18 (55)	1, 3, 10	286 (60)	7 (21)
(12)	2	NSCLC (squamous)	11/2012–7/2013	117	85 (73)	3	87 (74)	6 (5)
(16)	1	RCC	2008–2012	34	26 (76)	1, 10	29 (85)	3 (9)
(13)	1	NSCLC	11/2008–1/2012	129	79 (61)	1, 3, 10	91 (71)	18 (14)

*Number of total patients assessed for adverse events may be different from patients included in the study; patients may have had more than one adverse event; related adverse events if it was reported; †any grade; related adverse events if it was reported; ‡does not specify if diabetes or not; §same patient population; ¶escalating doses of nivolumab and ipilimumab administered concurrently or sequentially; ¶8 (6%) endocrinopathy (no further details).

CTCAE, common terminology criteria for adverse events; NR, not reported.

proximal post-nivolumab development of hyperglycemia, diabetes and glycation of hemoglobin. In all, this affirms the causal relationship between nivolumab and the new-onset DM presenting as DKA in our patient.

We performed an extensive literature search of Medline database through February 2018 to identify all published case reports of anti-PD-1-induced DM. Search term used was nivolumab, pembrolizumab and ipilimumab. For each report, we extracted age, gender, cancer type, nature and time frame of presentation, HbA1c, presence of autoantibodies, prior or concurrent chemotherapeutics, systemic steroids use and whether anti-PD-1 therapy was resumed. Reports' references were screened and all pertinent case reports were added. Additionally, we had previously performed a comprehensive literature search to identify all published articles that have investigated the impact of nivolumab on patients with cancer. Search term used was nivolumab and limits applied were: human and English. We reviewed the title and abstract of each article for possible inclusion. Articles that explored the effect of nivolumab on patients with cancer were included. For each included study, the information extracted included cancer type, study period, study design, sample size, gender, nivolumab dose, AE including common terminology criteria for adverse events (CTCAE) grade 3 or 4, and specifically, rates of endocrinopathy. Published manuscripts and supplemental materials were reviewed thoroughly for rates of treatment-related AE. Data about AE of any grade and of grade 3 or higher were gathered. Rates of thyroid disease, hypothyroidism and/or hyperthyroidism, were registered. Rates of hyperglycemia and rates of DM diagnosis, if reported, were also assembled and presented in tabular format. Our literature search produced 155 potential literature citations. After reviewing studies' title and/or abstract, a total of 17 studies were included (details are outlined in [Tables 2](#) and [3](#)).

Multiple trials have reported hyperglycemia as a potential AE with estimated risks of 0.5–11% (details are outlined in [Tables 2](#) and [3](#)). However, only three studies have reported on the outcome of formally diagnosed DM. An observational study by Topalian *et al.* (6) reported a rate of 2 cases of DM per 100 person-years of exposure with all cases being diagnosed after the first year of therapy. A randomized controlled trial (RCT) by Robert *et al.* (8) reported 1 case of DM in 206 melanoma patients. Another RCT by Borghaei *et al.* (15) reported 13 cases of hyperglycemia in 287 patients with non-squamous NSCLC but none were diagnosed with DM. None of the studies reported if hyperglycemia cases presented with DKA. There has been a growing number of case reports of

Table 3 Characteristics of randomized controlled trials.

Authors	Phase	Cancer	Study period	Design (control group)	Male n (%)	Nivolumab dose (mg/kg every 2 weeks)	Safety outcome (CTCAE)* n (%)		Endocrinopathy† n (%)	
							Any grade	Grade 3–4	Thyroid	Hyperglycemia
(8)	3	Melanoma	1/2013–2/2014	Dacarbazine	246 (59)	3	192 (93)	70 (34)	16 (8)	1 (0.5)‡
(9)	3	Melanoma	12/2012–1/2014	Standard chemotherapy	261 (64)	3	181 (68)	24 (9)	20 (7)	NR
(10)	1	Melanoma	NR	Combined with ipilimumab vs ipilimumab monotherapy	95 (67)	1, 3	86 (91)	51 (54)	22 (23)	NR
(11)	3	Melanoma	7/2013–3/2014	Nivolumab monotherapy vs combined with ipilimumab vs ipilimumab monotherapy	610 (65)	1, 3	311 (99)	136 (45)	40 (13)	NR
(14)	3	NSCLC (squamous)	10/2012–12/2013	Docetaxel	208 (76)	3	76 (58)	9 (7)	5 (4)	NR
(17)	3	RCC	10/2012–3/2013	Everolimus	619 (75)	3	319 (79)	76 (19)	NR	9 (2)§
(15)	3	NSCLC (non-squamous)	11/2012–12/2013	Docetaxel	319 (55)	3	199 (69)	30 (10)	23 (8)	13¶

*Number of total patients assessed for adverse events may be different from patients included in the study; patients may have had more than one adverse event; related adverse events if it was reported; †any grade; related adverse events if it was reported; ‡with diabetes; §does not specify if diabetes or not; ¶no cases of diabetes. CTCAE, common terminology criteria for adverse events; NR, not reported.

patients diagnosed with autoimmune diabetes following anti-PD-1 therapy. A comprehensive characteristic of these cases is summarized in Table 4. We have identified 42 cases of anti-PD-1-induced DM. The mean age is 61 years. There is no apparent gender or cancer preference though most cases were reported in patients with melanoma and NSCLC. Almost two-thirds of cases presented with DKA and within a time frame ranging from 1 week up to 1 year. About half of the cases had negative autoantibody serologies. Only two cases (20, 21) received systemic steroids specifically for pembrolizumab-induced DM. However, neither showed improvement nor resolution of DM. Half of the cases, resumed anti-PD-1 therapy after resolution of DKA or control of hyperglycaemia without further deterioration in DM control. Interestingly, we found two cases (22, 23) of autoimmune DM in patients with melanoma who received ipilimumab monotherapy (a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody).

Immunotherapy in general, and nivolumab in specific, has revolutionized cancer therapy, and their use is rapidly growing. Consequently, the number of patients exposed to nivolumab will increase and the total number of patients experiencing AE will expectedly increase (24).

AEs during nivolumab treatment are frequent and range from 40% to 98%. Most commonly, they include fatigue, rash, itching, diarrhea and infusion site reactions. They are largely managed by symptomatic and supportive care (25). The severe AEs (CTCAE grade 3 or 4) are estimated to occur between 5% and 72%. They include pneumonitis, hepatitis and cytopenias. They are typically managed by discontinuing nivolumab and administering systemic corticosteroids (2, 25). Limited data noted suggest treating nivolumab-induced autoimmune DM are unlikely to be effective once DM has developed, and better understanding of why some individuals develop this complication is required before potential therapeutic and even preventative interventions might be identified.

The PD-1 pathway plays a central role in the regulation of autoimmune diabetes (26). Blockade of PD-1 can precipitate type 1 diabetes in mice models across all ages (27) and mechanisms may involve both humoral and cellular autoimmunity (19). However, there remain significant gaps in understanding the interaction between PD-1 pathway and autoimmune diabetes. Sparse data are available regarding the time course, dose relationship, effect of concurrent immunotherapeutic or chemotherapeutic agents and management (e.g. immunomodulatory agents). Despite being an uncommon AE, developing irreversible insulin-dependent DM is life

Table 4 Characteristics of case reports of patients diagnosed with diabetes after receiving anti-PD-1 therapy.

Study	Age	Sex	Cancer	Presentation	Time Frame	HbA1c (%)	Autoantibodies	Prior or concurrent chemotherapeutics	Management	
									Systemic steroid	Resumed anti-PD-1
Nivolumab (19)	55	F	Melanoma	DKA	5 months	6.9	None	Ipilimumab	NR	NR
	83	F	NSCLC	DKA	<1 month	7.7	GAD65	None	NR	NR
	63	M	RCC	Hyperglycemia	4 months	8.2	GAD65, IA-2, IAA	Aldesleukin, bevacizumab, interferon	NR	NR
	58	M	SCLC	DKA ⁺	1 week	9.7	GAD65	Carboplatin, etoposide, paclitaxel	NR	NR
(29)	70	M	NSCLC	Hyperglycemia	15 weeks	9.8	None	NR	NR	NR
(30)	66	F	SCC Jaw	DKA	7 weeks	9.4	GAD65	NR	NR	NR
(31)	72	M	Hodgkin lymphoma	Hyperglycemia	57 days	7.3	None	ABVD, brentuximab	NR	Yes
(32)	66	F	Melanoma	DKA	4 months	7.3	None	None	NR	Yes
	70	F	Melanoma	Hyperglycemia	6 weeks	NR	None	None	NR	Yes
	40	M	Melanoma	NR	6 weeks	NR	NR	Dacarbazine, polychemotherapy, ipilimumab	NR	Yes
(33)	78	F	Melanoma	DKA ⁺	3 weeks	NR	GAD65	Dacarbazine; ipilimumab	NR	NR
	55	F	Melanoma	Hyperglycemia	1 year	7	None	Ipilimumab, dacarbazine, nimustine, cisplatin, tamoxifen	NR	Yes
(34)	73	M	Melanoma	DKA	6 weeks	8.8	GAD65, ZnT8A, IA-2	Interferon, vemurafenib, cobimetinib	NR	Yes
(35)	63	F	Melanoma	DKA	30 weeks	8.9	None	Dacarbazine	NR	No
(36)	54	F	Melanoma	Hyperglycemia	10 months	7	None	Cisplatin, dacarbazine, nimustine and tamoxifen	NR	Yes
(37)	34	F	NSCLC	DKA	4 weeks	7.1	GAD65, IA-2, IAA	Carboplatin, pemetrexed	NR	No
(38)	68	F	RCC	Hyperglycemia	98 days	6.9	None	Interferon, sunitinib, axitinib	NR	Yes
(39)	NR	NR	NSCLC	NR	NR	NR	NR	NR	NR	NR
(40)	63	M	NSCLC	DKA	27 days	7.2	GAD65	Carboplatin, paclitaxel, cisplatin	NR	No
(41)	83	M	SCC maxillary sinus	DKA	3 months	7.4	GAD65	None	Yes*	No
(42)	31	M	NSCLC	DKA	13 days	6.4	GAD65	NR	NR	Yes
(43)	62	F	NSCLC	Hyperglycemia	10 weeks	6.5	None	NR	NR	Yes
(44)	54	M	Melanoma	DKA	4 months	NR	GAD65	Ipilimumab	Yes*	No
	55	M	Pleomorphic carcinoma	DKA	10 days after cycle 9	8.2	None	Cisplatin, docetaxel, pemetrexed	NR	No
(45)	42	M	Melanoma	DKA	3 months	6.5	None	Ipilimumab	Yes*	NR
(46)	74	F	NSCLC	DKA	25 days	8.7	GAD65	Pemetrexed	NR	NR
(47)	66	M	Melanoma	Hyperglycemia	19 days	NR	GAD65, IA-2	Ipilimumab	Yes*	No
(48)	73	M	NSCLC	Hyperglycemia	25 weeks	9.4	None	NR	NR	No
(49)	40	M	Hodgkin lymphoma	NR	NR	NR	GAD65	COPP, brentuximab, gemcitabine, ICE	NR	NR
This case	70	M	RCC	DKA	6 weeks	8.4	None	None	No	No

Pembrolizumab	(19)	64	F	Melanoma	Hyperglycemia	<1 month	7.4	None	None	NR	NR	NR
	(50)	54	F	Melanoma	DKA	After cycle 3	NR	GAD65	Ipilimumab	NR	NR	Yes
	(51)	44	F	Melanoma	DKA	2 weeks after cycle 2	6.85	None	NR	NR	NR	Yes
	(52)	55	M	Melanoma	DKA	Cycle 9	10.7	None	Dacarbazine, ipilimumab	NR	NR	No
	(53)	58	M	Melanoma	Hyperglycemia	1 year	9.7	GAD65	Interferon, vemurafenib, IL-2, ipilimumab	No	No	No
	(32)	58	F	Melanoma	Hyperglycemia	3 weeks	NR	GAD65	Ipilimumab	NR	NR	Yes
	(21)	76	M	NSCLC	Hyperglycemia	4 weeks	5.8	GAD65, IA-2	Carboplatin, paclitaxel	Yes [†]	Yes	Yes
	(20)	60	M	Melanoma	DKA	5 weeks	7.1	None	Ipilimumab	No	NR	No
	(54)	58	M	Melanoma	DKA	3 months	7.4	None	BRAF/MEK inhibitor	NR	NR	NR
	(55)	66	M	NSCLC	DKA	6 weeks	7.6	GAD65	NR	NR	NR	Yes
	56)	67	F	Cholangiocarcinoma	NR	NR	NR	GAD65	Leucovorin, fluorouracil, oxaliplatin	NR	NR	NR
	(57)	58	M	Melanoma	DKA	62 days	6.8	None	Ipilimumab	NR	NR	NR

*Systemic steroids were used for reasons other than autoimmune diabetes (colitis and adrenal insufficiency); †systemic steroids were specifically used for autoimmune diabetes. However, there was no significant improvement or resolution of diabetes; ‡had diagnosis of DM prior of starting nivolumab.

threatening for the patient who presents unexpectedly with DKA. In addition, it has significant socioeconomic impact (28). As the use of anti-PD1 therapy expands, intensivists and hospitalists need to be alerted to the possibility of DKA presenting *de novo* in patients who are otherwise unlikely to develop type 1 DM.

Declaration of interest

A A Z, H K A, R W J and A S L declare that there is no conflict of interest, proprietary or financial, regarding the publication of this report.

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Patient consent

Patient is now deceased and next of kin could not be traced.

Author contribution statement

A A Z was responsible for the literature review and in the primary writing of the manuscript. H K A was the endocrinologist who was involved in the care of the patient's new diabetes and contributed expertise on the field of drug-induced autoimmune diabetes. R W J was the patient's primary oncologist and provided expertise on the mechanism of nivolumab and its contribution to autoimmune disorders. A S L was the intensivist in the care of the patient presenting with new-onset diabetic ketoacidosis and provided oversight on the writing and preparation of the manuscript.

References

- 1 Ribas A. Tumor immunotherapy directed at PD-1. *New England Journal of Medicine* 2012 **366** 2517–2519. (<https://doi.org/10.1056/NEJMe1205943>)
- 2 Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, Stankevich E, Pons A, Salay TM, McMiller TL, *et al.* Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *Journal of Clinical Oncology* 2010 **28** 3167–3175. (<https://doi.org/10.1200/JCO.2009.26.7609>)
- 3 Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DE, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *New England Journal of Medicine* 2012 **366** 2443–2454. (<https://doi.org/10.1056/NEJMoa1200690>)
- 4 Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *New England Journal of Medicine* 2012 **366** 2455–2465. (<https://doi.org/10.1056/NEJMoa1200694>)
- 5 Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K, *et al.* Nivolumab plus ipilimumab in advanced melanoma. *New England Journal of Medicine* 2013 **369** 122–133. (<https://doi.org/10.1056/NEJMoa1302369>)

- 6 Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, *et al.* Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *Journal of Clinical Oncology* 2014 **32** 1020–1030. (<https://doi.org/10.1200/JCO.2013.53.0105>)
- 7 Gibney GT, Kuchadkar RR, DeConti RC, Thebeau MS, Czupryn MP, Tetteh L, Eysmans C, Richards A, Schell MJ, Fisher KJ, *et al.* Safety, correlative markers, and clinical results of adjuvant nivolumab in combination with vaccine in resected high-risk metastatic melanoma. *Clinical Cancer Research* 2015 **21** 712–720. (<https://doi.org/10.1158/1078-0432.CCR-14-2468>)
- 8 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *New England Journal of Medicine* 2015 **372** 320–330. (<https://doi.org/10.1056/NEJMoa1412082>)
- 9 Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, Hoeller C, Khushalani NI, Miller WH, Lao CD, *et al.* Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncology* 2015 **16** 375–384. ([https://doi.org/10.1016/S1470-2045\(15\)70076-8](https://doi.org/10.1016/S1470-2045(15)70076-8))
- 10 Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, Giguere JK, Agarwala SS, *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *New England Journal of Medicine* 2015 **372** 2006–2017. (<https://doi.org/10.1056/NEJMoa1414428>)
- 11 Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New England Journal of Medicine* 2015 **373** 23–34. (<https://doi.org/10.1056/NEJMoa1504030>)
- 12 Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, Horn L, Lena H, Minenza E, Mennecier B, *et al.* Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncology* 2015 **16** 257–265. ([https://doi.org/10.1016/S1470-2045\(15\)70054-9](https://doi.org/10.1016/S1470-2045(15)70054-9))
- 13 Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, Powderly JD, Heist RS, Carvajal RD, Jackman DM, *et al.* Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *Journal of Clinical Oncology* 2015 **33** 2004–2012. (<https://doi.org/10.1200/JCO.2014.58.3708>)
- 14 Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *New England Journal of Medicine* 2015 **373** 123–135. (<https://doi.org/10.1056/NEJMoa1504627>)
- 15 Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *New England Journal of Medicine* 2015 **373** 1627–1639. (<https://doi.org/10.1056/NEJMoa1507643>)
- 16 McDermott DF, Drake CG, Sznol M, Choueiri TK, Powderly JD, Smith DC, Brahmer JR, Carvajal RD, Hammers HJ, Puzanov I, *et al.* Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *Journal of Clinical Oncology* 2015 **33** 2013–2020. (<https://doi.org/10.1200/JCO.2014.58.1041>)
- 17 Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *New England Journal of Medicine* 2015 **373** 1803–1813. (<https://doi.org/10.1056/NEJMoa1510665>)
- 18 Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattray D, Freeman GJ, *et al.* PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *New England Journal of Medicine* 2015 **372** 311–319. (<https://doi.org/10.1056/NEJMoa1411087>)
- 19 Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B & Herold KC. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. *Diabetes Care* 2015 **38** e55–e57. (<https://doi.org/10.2337/dc14-2349>)
- 20 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 Reports* 2016 **2016**. (<https://doi.org/10.1136/bcr-2016-217454>)
- 21 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 Immunology, Immunotherapy* 2017 **66** 25–32. (<https://doi.org/10.1007/s00262-016-1913-7>)
- 22 Jørgensen LB & Yderstræde K. Acutely induced diabetes mellitus in a 63-year-old female after treatment with ipilimumab for metastatic melanoma. *Ugeskrift for Læger* 2017 **179** V03170188.
- 23 Tsiogka A, Jansky GL, Bauer JW & Koelblinger P. Fulminant type 1 diabetes after adjuvant ipilimumab therapy in cutaneous melanoma. *Melanoma Research* 2017 **27** 524–525. (<https://doi.org/10.1097/CMR.0000000000000384>)
- 24 Haanen JBAG, van Thienen H & Blank CU. Toxicity patterns with immunomodulating antibodies and their combinations. *Seminars in Oncology* 2015 **42** 423–428. (<https://doi.org/10.1053/j.seminoncol.2015.02.011>)
- 25 Barbee MS, Ogunniyi A, Horvat TZ & Dang TO. Current status and future directions of the immune checkpoint inhibitors ipilimumab, pembrolizumab, and nivolumab in oncology. *Annals of Pharmacotherapy* 2015 **49** 907–937. (<https://doi.org/10.1177/1060028015586218>)
- 26 Ansari MJ, Salama AD, Chitnis T, Smith RN, Yagita H, Akiba H, Yamazaki T, Azuma M, Iwai H, Khoury SJ, *et al.* The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. *Journal of Experimental Medicine* 2003 **198** 63–69. (<https://doi.org/10.1084/jem.20022125>)
- 27 Guleria I, Gubbels Bupp M, Dada S, Fife B, Tang Q, Ansari MJ, Trikuladhanathan S, Vadivel N, Fiorina P, Yagita H, *et al.* Mechanisms of PDL1-mediated regulation of autoimmune diabetes. *Clinical Immunology* 2007 **125** 16–25. (<https://doi.org/10.1016/j.clim.2007.05.013>)
- 28 Gosmanov AR, Gosmanova EO & Dillard-Cannon E. Management of adult diabetic ketoacidosis. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 2014 **7** 255–264. (<https://doi.org/10.2147/DMSO.S50516>)
- 29 Mellati M, Eaton KD, Brooks-Worrell BM, Hagopian WA, Martins R, Palmer JP & Hirsch IB. Anti-PD-1 and anti-PDL-1 monoclonal antibodies causing type 1 diabetes. *Diabetes Care* 2015 **38** e137–e138. (<https://doi.org/10.2337/dc15-0889>)
- 30 Munakata W, Ohashi K, Yamauchi N & Tobinai K. Fulminant type I diabetes mellitus associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma. *International Journal of Hematology* 2017 **105** 383–386. (<https://doi.org/10.1007/s12185-016-2101-4>)
- 31 Miyoshi Y, Ogawa O & Oyama Y. Nivolumab, an anti-programmed cell death-1 antibody, induces fulminant type 1 diabetes. *Tohoku Journal of Experimental Medicine* 2016 **239** 155–158. (<https://doi.org/10.1620/tjem.239.155>)
- 32 Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, Schmidgen MI, Gutzmer R, Utikal JS, Göppner D, *et al.* Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-

- effects of anti-PD-1 therapy. *European Journal of Cancer* 2016 **60** 190–209. (<https://doi.org/10.1016/j.ejca.2016.02.025>)
- 33 Okamoto M, Okamoto M, Gotoh K, Masaki T, Ozeki Y, Ando H, Anai M, Sato A, Yoshida Y, Ueda S, *et al.* Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. *Journal of Diabetes Investigation* 2016 **7** 915–918. (<https://doi.org/10.1111/jdi.12531>)
 - 34 Gauci ML, Laly P, Vidal-Trecan T, Baroudjian B, Gottlieb J, Madjlissi-Ezra N, Da Meda L, Madelaine-Chambrin I, Bagot M, Basset-Seguín N, *et al.* Autoimmune diabetes induced by PD-1 inhibitor-retrospective analysis and pathogenesis: a case report and literature review. *Cancer Immunology, Immunotherapy* 2017 **66** 1399–1410. (<https://doi.org/10.1007/s00262-017-2033-8>)
 - 35 Teramoto Y, Nakamura Y, Asami Y, Imamura T, Takahira S, Nemoto M, Sakai G, Shimada A, Noda M & Yamamoto A. Case of type 1 diabetes associated with less-dose nivolumab therapy in a melanoma patient. *Journal of Dermatology* 2017 **44** 605–606. (<https://doi.org/10.1111/1346-8138.13486>)
 - 36 Ishikawa K, Shono-Saito T, Yamate T, Kai Y, Sakai T, Shimizu F, Yamada Y, Mori H, Noso S, Ikegami H, *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. *European Journal of Dermatology* 2017 **27** 184–185. (<https://doi.org/10.1684/ejd.2016.2923>)
 - 37 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. *Journal for Immunotherapy of Cancer* 2017 **5** 40. (<https://doi.org/10.1186/s40425-017-0245-2>)
 - 38 Sakurai K, Niitsuma S, Sato R, Takahashi K & Arihara Z. Painless thyroiditis and fulminant type 1 diabetes mellitus in a patient treated with an immune checkpoint inhibitor, nivolumab. *Tohoku Journal of Experimental Medicine* 2018 **244** 33–40. (<https://doi.org/10.1620/tjem.244.33>)
 - 39 Araújo M, Ligeiro D, Costa L, Marques F, Trindade H, Correia JM & Fonseca C. A case of fulminant Type 1 diabetes following anti-PD1 immunotherapy in a genetically susceptible patient. *Immunotherapy* 2017 **9** 531–535. (<https://doi.org/10.2217/imt-2017-0020>)
 - 40 Li L, Masood A, Bari S, Yavuz S & Grosbach AB. Autoimmune diabetes and thyroiditis complicating treatment with nivolumab. *Case Reports in Oncology* 2017 **10** 230–234. (<https://doi.org/10.1159/000456540>)
 - 41 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 Reports in Oncology* 2017 **10** 897–909. (<https://doi.org/10.1159/000480634>)
 - 42 Usui Y, Udagawa H, Matsumoto S, Imai K, Ohashi K, Ishibashi M, Kirita K, Umemura S, Yoh K, Niho S, *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. *Journal of Thoracic Oncology* 2017 **12** e41–e43. (<https://doi.org/10.1016/j.jtho.2016.12.015>)
 - 43 Lowe JR, Perry DJ, Salama AKS, 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. *Journal for Immunotherapy of Cancer* 2016 **4** 89. (<https://doi.org/10.1186/s40425-016-0196-z>)
 - 44 Marchand L, Paulus V, Fabien N, Pérol M, Thivolet C, Vouillarmet J & Saintigny P. Nivolumab-induced acute diabetes mellitus and hypophysitis in a patient with advanced pulmonary pleomorphic carcinoma with a prolonged tumor response. *Journal of Thoracic Oncology* 2017 **12** e182–e184. (<https://doi.org/10.1016/j.jtho.2017.07.021>)
 - 45 Changizzadeh PN, Mukkamalla SKR & Armenio VA. Combined checkpoint inhibitor therapy causing diabetic ketoacidosis in metastatic melanoma. *Journal for Immunotherapy of Cancer* 2017 **5** 97. (<https://doi.org/10.1186/s40425-017-0303-9>)
 - 46 Capitaó R, Bello C, Fonseca R & Saraiva C. New onset diabetes after nivolumab treatment. *BMJ Case Reports* 2018 **2018**. (<https://doi.org/10.1136/bcr-2017-220999>)
 - 47 Villarreal J, Townes D, Vrablik M & Ro K. A case of drug-induced severe endocrinopathies: what providers in the emergency department need to know. *Advanced Emergency Nursing Journal* 2018 **40** 16–20. (<https://doi.org/10.1097/TME.000000000000173>)
 - 48 Kumagai R, Muramatsu A, Nakajima R, Fujii M, Kaino K, Katakura Y, Okumura N, Ohara G, Kagohashi K, Satoh H, *et al.* Acute-onset type 1 diabetes mellitus caused by nivolumab in a patient with advanced pulmonary adenocarcinoma. *Journal of Diabetes Investigation* 2017 **8** 798–799. (<https://doi.org/10.1111/jdi.12627>)
 - 49 Chang E, Rivero G, Patel NR, Chiao EY, Lai S, Bajaj K, Mbue JE & Yellapragada SV. HIV-related refractory Hodgkin lymphoma: a case report of complete response to nivolumab. *Clinical Lymphoma, Myeloma and Leukemia* 2018 **18** e143–e146. (<https://doi.org/10.1016/j.clml.2017.12.008>)
 - 50 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 Immunology, Immunotherapy* 2015 **64** 765–767. (<https://doi.org/10.1007/s00262-015-1689-1>)
 - 51 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. (<https://doi.org/10.2337/dc15-1331>)
 - 52 Humayun MA & Poole R. A case of multiple immune toxicities from Ipilimumab and pembrolizumab treatment. *Hormones* 2016 **15** 303–306. (<https://doi.org/10.14310/horm.2002.1656>)
 - 53 Hansen E, Sahasrabudhe D & Sievert L. A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome. *Cancer Immunology, Immunotherapy* 2016 **65** 765–767. (<https://doi.org/10.1007/s00262-016-1835-4>)
 - 54 Mizab Mellah C, Sánchez Pérez M, Santos Rey MD & Hernández García M. Fulminant type 1 diabetes mellitus associated with pembrolizumab. *Endocrinología, Diabetes y Nutrición* 2017 **64** 272–273. (<https://doi.org/10.1016/j.endinu.2017.01.005>)
 - 55 Leonardi GC, Oxnard GR, Haas A, Lang JP, Williams JS & Awad MM. Diabetic ketoacidosis as an immune-related adverse event from pembrolizumab in non-small cell lung cancer. *Journal of Immunotherapy* 2017 **40** 249–251. (<https://doi.org/10.1097/CJI.000000000000173>)
 - 56 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. (<https://doi.org/10.2217/imt-2017-0042>)
 - 57 Scott ES, Long GV, Guminski A, Clifton-Bligh RJ, Menzies AM & Tsang VH. The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. *European Journal of Endocrinology* 2018 **178** 175–182. (<https://doi.org/10.1530/EJE-17-0810>)

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