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Immune checkpoint inhibitor-induced diabetes mellitus with nivolumab

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SUMMARY

Immune checkpoint inhibitors (ICIs) have been increasingly used in the treatment of various advanced cancers; however, therapy can be complicated by immune-related adverse events (irAEs). We present the case of a man in his 40s, with metastatic melanoma treated with nivolumab immunotherapy who developed ICI-induced diabetes mellitus (ICI-DM). Hyperglycaemia in the absence of ketoacidosis was incidentally noted when he presented to the emergency department for review of an urticarial rash. Further testing, including haemoglobin A1c and C-peptide level, confirmed his presentation was most consistent with ICI-DM and he was commenced on appropriate diabetes treatment. This report aims to detail an atypical presentation of ICI-DM and to highlight the importance of clinician awareness in identifying this irAE in patients receiving ICIs.

BACKGROUND

Developments in targeted immunotherapy have resulted in marked improvements in outcomes and survival in patients with various advanced cancers. The two main subclasses of immune checkpoint inhibitors (ICIs) are programmed death-1 receptor (PD-1) inhibitors including programmed death-ligand 1 (PD-L1) inhibitors and second subclass cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors. ICIs reverse negative immune regulation and promote the immune response towards targeting cancer cells. However, they can also lead to immune-related adverse events (irAEs) in any organ system, with endocrinopathies being among those more commonly reported.[1] ICI-induced diabetes mellitus (ICI-DM) is one such endocrinopathy and has particular clinical significance as the majority of patients present in diabetic ketoacidosis (DKA) and require lifelong treatment with insulin therapy.[2] ICI-DM has been reported with PD-1 and PD-L1 inhibitors and rarely with CTLA-4 inhibitors.[2 3]

Nivolumab, a PD-1 inhibitor, is approved for the treatment of metastatic melanoma, non-small cell lung cancer, mesothelioma, renal cell carcinoma and head, neck and oesophageal squamous cell carcinoma. This report details a case of ICI-DM identified due to hyperglycaemia without ketoacidosis in a patient receiving nivolumab immunotherapy for metastatic melanoma.

CASE PRESENTATION

A man in his 40s presented to the emergency department of a regional hospital with a 2-day history of generalised urticarial rash.

He was diagnosed with a melanoma on his upper back a year prior and had metastases in the left axillary, subpectoral and bilateral cervical lymph nodes identified on PET scan at the time of diagnosis. The melanoma was BRAF positive and the primary was unresectable. He was referred to medical oncology and commenced on nivolumab/ipilimumab, a combination of PD-1 and CTLA-4 inhibitors. His baseline endocrine workup prior to initiation of treatment, which included morning cortisol, thyroid function tests (TFTs) and random blood glucose, was unremarkable.

His initial combination therapy involved four doses of ipilimumab (3 mg/kg) with nivolumab (1 mg/kg), and he was subsequently continued on monthly nivolumab, receiving 13 doses prior to presentation. He experienced a localised erythematous rash 2 weeks after his first dose of immunotherapy, however had no rashes with subsequent doses. Throughout his immunotherapy, his routine monitoring blood results remained stable (including TFTs, cortisol, monthly random blood glucose) and within normal limits.

His other medical history included rectal adenocarcinoma for which he had undergone local resection, hypertension, obesity class 3 with BMI of 39 kg/m^2 and sinusitis. Aside from the monthly nivolumab, his only other medication was amlodipine, which had been commenced a week prior to presentation. He had a documented adverse drug reaction to valsartan, which was an acute kidney injury.

On examination, he appeared generally well with a Glassgow Coma Scale of 15. He was afebrile, heart rate was 100 bpm, blood pressure was 150/90 mm Hg, respiratory rate was 16/min, oxygen saturation was 98% on room air. He was obese with weight of 125.5 kg, height of 180 cm and BMI of 39 kg/m^2. He had a widespread, blanching, erythematous maculopapular rash across his axillae, chest, back, face and arms. His examination was otherwise unremarkable.

INVESTIGATIONS AND DIAGNOSIS

Bedside investigations showed a blood glucose level of 18.1 mmol/L and ketones 0.4 mmol/L. His urinalysis showed large glycosuria (>1000 mg/dL) but was otherwise unremarkable. Formal laboratory investigation results are included in table 1.

His presentation was discussed with his medical oncology team and the rash was considered unlikely to be related to nivolumab due to

Table 1 Laboratory results on day of admission

Parameters	Results	Laboratory range
Haemoglobin, g/L	149	135–180
White cell count, 10^9/L	7.1	4.0–11.0
Platelets, 10^9/L	246	140–400
Sodium, mmol/L	127	135–145
Potassium, mmol/L	4.7	3.5–5.2
Chloride, mmol/L	92	95–110
Bicarbonate mmol/L	27	22–32
Anion gap, mmol/L	8	4–13
Urea, micromole/L	7.7	2.1–7.1
Creatinine, micromole/L	124	60–110
eGFR, mL/min/1.73 m^2	59	> 60
C-reactive protein, mg/L	4.5	<5
Erythrocyte sedimentation rate, mmL/hr	<5	<10

eGFR, estimated glomerular filtration rate.

the timeline. He was admitted for further investigation and commenced on antihistamines and topical steroid cream. Oral steroids were withheld due to concerns of dampening the effects of immunotherapy, as requested by medical oncology.

Due to the abrupt onset of hyperglycaemia, ICI-DM was considered, and this was supported by an haemoglobin A1c (HbA1c) that was disproportionate to the level of hyperglycaemia (results in table 2). C-peptide level, islet autoantibodies and an endocrinopathy screen were also performed.

TREATMENT

Dermatology was consulted and the rash was thought to be a drug reaction to amlodipine. Biopsies were taken and a dermatology clinic referral was made. The biopsies were later found to be consistent with the clinical suspicion of a lichenoid drug eruption. Candesartan replaced amlodipine for the management of the patient's hypertension.

For his new diagnosis of diabetes, metformin and insulin glargine were commenced, and the patient was referred to the outpatient endocrinology clinic and diabetes educator.

Table 2 Additional laboratory results

Parameters	Results	Laboratory range
Glucose, mmol/L	27.6	
Haemoglobin A1c, %	7.1	4.3–6.0
Thyroid stimulating function, mU/L	1.0	0.3–4.5
Free T4, pmol/L	13	7.0–17
Zinc transporter 8 (ZnT8) antibodies, RU/mL	<10	<10
Glutamic acid decarboxylase antibody, units/mL	<5.0	<5.0
Insulin antibody-2 antibody, units/mL	<15.0	<15.0
C- peptide, nmol/L	0.6	0.3–1.4
Anti-tissue transglutaminase, CU	3	<20
Morning cortisol, nmol/L	310	
Insulin-like growth factor–1, nmol/L	21	9.2–29
Adrenocorticotrophic hormone, ng/L	10	10–50
2 Methoxy tyramine 47 pmol/L	47	<120
Plasma normetadrenaline, pmol/L	553	120–1300
Metadrenaline 250 pmol/L (20–540)	250	20–540
Supine aldosterone/renin ratio	23	<55

The patient continued nivolumab therapy as scheduled the following week.

OUTCOME AND FOLLOW-UP

On further endocrine follow-up, the patient's HbA1c has remained persistently elevated (11.6% at 3 months and 8.4% at 12 months). His insulin regimen was escalated accordingly and he continues on a basal-prandial regime with insulin glargine and insulin aspart. Metformin was also continued and semaglutide was commenced for his central adiposity and inadequate glycaemic control.

DISCUSSION

PD-1 is expressed on T lymphocytes and when activated by its ligands, PD-L1 or PD-L2, inhibits cell proliferation as part of 'self-tolerance'.[4] Cancer cells can express PD-L1 to exploit this self-tolerance, hence the role of PD-1 and PD-L1 inhibitors in reactivating the antitumour immune response.[2]

The pathogenesis of ICI-DM has not been fully elucidated; however, the role of the PD-1/PD-L1 pathway in the development of T1DM in non-obese diabetic (NOD) mouse models is well established.[5] NOD mice with a knockout of PD-1 or PD-L1, or those exposed to PD-1 or PD-L1 monoclonal antibodies, are predisposed to developing T1DM with lymphocytic infiltration of pancreatic islets.[6] PD-L1 upregulation in islet cells has been found in NOD mice during the progression of diabetes, and in human islets from T1DM organ donors.[7] This is thought to represent a self-tolerance mechanism to reduce autoimmune destruction of islet cells and may explain why PD-1 and PD-L1 inhibitor therapy can induce diabetes mellitus.[2]

The incidence of immune-related endocrinopathies with ICI has been reported to be approximately 10% in systematic reviews. Among these, thyroid toxicities are the most common, and while new onset diabetes mellitus was initially thought to be rare, cases have increasingly reported resulting in variable prevalence up to 2%.[3 4 8] Primary thyroid dysfunction is common with both PD-1 and CTLA-4 inhibitors, whereas ICI-DM and hypophysitis are more commonly associated with PD1 immunotherapy.[9 10] In our case, the patient had completed initial PD-1/CTLA-4 dual therapy and continued on PD1-monotherapy.[9 10]

There have been wide discrepancies in the time from ICI initiation to diabetes onset, with a systematic review by Liu *et al* reporting a median onset time of 12 weeks (range 0–122).[4 11] Another systematic review by Akturk *et al* reported a median of 10.5 weeks (range 0.71–64) for nivolumab.[8] Lo Preiato *et al* noted that approximately half of the reported ICI-DM cases occurred within the third cycle or 8th week, and 16.5% after the 12th cycle.[4] In our case, ICI-DM was detected approximately 1 year (51 weeks) after initiation of treatment.

Significant hyperglycaemia is suggested to occur rapidly and the majority of reported cases of ICI-DM have been in patients presenting in DKA.[4 11 12] HbA1c is generally lower than 10% at time of diagnosis and C-peptide levels are either undetectable or inappropriately low for the degree of hyperglycaemia.[2 4 13] There are increasing articles evaluating the role of C-peptide in aiding diagnosis and monitoring of ICI-DM given the proposed mechanism of autoimmune destruction of pancreatic islet cells. Some authors have suggested interval testing of C-peptide level to confirm which patients will require lifelong insulin therapy and one

longitudinal study reported no difference in C-peptide level from baseline to diagnosis of ICI-DM between patients with and without ICI-DM.[4 14 15] Insulin therapy was eventually ceased in a few cases where C-peptide levels were normal, B-cell function was preserved and ICI therapy was discontinued indefinitely.[16 17]

ICI-DM has been reported with both positive and negative T1DM-associated autoantibodies, with at least one autoantibody being present in 40%–50% of cases.[4 12 13] Of these, GAD antibody positivity is the most common and has additionally been correlated with a shorter time to onset of ICI-DM.[8 11 18] Similarly, the relevance of T1DM-associated human leucocyte antigen (HLA) loci to ICI-DM requires further clarification.[4 13] HLA DR4 was only detected in 49.3% of cases, and in some cases, protective phenotypes for T1DM were present.[4] There is insufficient data to determine whether a family history of diabetes or an elevated BMI is associated with an increased risk of ICI-DM.[4]

There is variability in the recommended endocrinopathy monitoring investigations for patients receiving immunotherapy, however blood glucose level monitoring, thyroid function testing and assessment for adrenal insufficiency are generally advised.[19 20] Additionally, it has been recommended that patients are informed about symptoms of hyperglycaemia to promote early recognition of ICI-DM.[2 4] Clinician awareness of this potential irAE is also important, given our patient did not present with such symptoms and hyperglycaemia was an incidental finding.

Once identified, management of ICI-DM should follow standard local guidelines for DKA and insulin-dependent diabetes mellitus. PD-1 immunotherapy can often be restarted once an insulin regimen is instituted and stabilised.[19–21]

CONCLUSION

In conclusion, with the increasing use of ICIs in cancer management, it is anticipated that the incidence and prevalence of ICI-DM will continue to rise. Further research is required to identify the most appropriate screening tests for early identification of ICI-DM, with an aim to prevent acute complications such as DKA, and to guide optimal long-term management of this condition. Current guidelines recommend discussion with patients around the potential for ICI-DM prior to initiation of therapy, and regular blood glucose monitoring while patients are receiving ICIs.

Learning points

- Immune checkpoint inhibitor-induced diabetes mellitus (ICI-DM) has increasingly been reported with prevalence up to 2%, and the majority of patients present in diabetic ketoacidosis and require lifelong insulin therapy.
- Clinicians should be aware of this immune-related endocrinopathy to prompt early identification with appropriate testing (eg, blood glucose level, haemoglobin A1c, C-peptide), to reduce the risk of patients presenting in diabetic ketoacidosis and facilitate appropriate initiation of insulin treatment and subsequent monitoring.
- ICI-DM may present atypically without overt signs or symptoms of hyperglycaemia or ketoacidosis.

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