Presentation of new onset type 1 diabetes with diabetic ketoacidosis and hyperosmolar hyperglycaemia after a single dose of nivolumab and ipilimumab

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Summary
A Caucasian man in his 60s with recent diagnosis of metastatic renal cell carcinoma presented to the emergency department with a 5-day history of severe polyuria, polydipsia and fatigue and 1-day history of confusion, abdominal pain, nausea and vomiting. Investigations revealed an overlap of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). He had received the first dose of immunotherapy with nivolumab and ipilimumab 3 weeks prior to this attendance. New-onset type 1 diabetes (T1DM) was confirmed based on the clinical features at presentation, seropositivity for glutamic acid decarboxylase antibodies and significant insulin deficiency. He is currently on a multiple daily injections of insulin and uses intermittent-scanned glucose monitoring. Given the irreversible impact on beta-cell function and clinical response with insulin resulting in improved diabetes control, immunotherapy was resumed for his metastatic cancer with good radiological response. Although rare, new-onset T1DM can present with DKA and HSS overlap after a single dose of nivolumab/ipilimumab in individuals without pre-existing history of diabetes.

Learning points
- Although rare, new onset of T1DM after immunotherapy can present with DKA and HSS overlap after a single dose of nivolumab/ipilimumab in individuals without pre-existing history of diabetes and normal glycaemic parameters.
- Due to the irreversible destruction of beta-cells, treatment with steroids is not indicated in contrast to other settings such as immunotherapy-induced hypophysitis.
- Presence of low c-peptide levels post-acute presentation is indicative of an irreversible impact on beta-cell function and supports resuming immunotherapy given the significant benefits on cancer prognosis.
- Clinicians must maintain a high index of suspicion in regards to diagnosis and management of new-onset type 1 diabetes and advice patients on reporting symptoms suggestive of diabetes and/or diabetes-related hyperglycaemic emergencies.

Background
Immune checkpoint inhibitors (ICI) have been a breakthrough innovation in the management of metastatic malignancies, leading to improved prognosis of advanced cancers. They are currently approved for the treatment of several solid tumours and haematological malignancies, including melanoma and Hodgkin’s lymphoma. These
novel therapies block checkpoint proteins involved in T-cell function, such as the programmed cell death receptor 1 (PD-1) and the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), leading to T-cell activation and direct tumour cell attack (1).

Ipilimumab, a CTLA-2 inhibitor, and nivolumab, a PD-1 inhibitor, have been successfully used as a combination therapy in metastatic renal cell carcinoma, melanoma, oesophageal squamous cell carcinoma, colorectal cancer and metastatic non-small cell lung carcinoma while ongoing trials are investigating their efficacy in other malignancies such as breast cancer (1). Recent evidence supports the use of nivolumab/ipilimumab combination as first line for the management of advanced renal cell carcinoma with improved outcomes on overall and progression-free survival (1). With the wider clinical use of these agents and the potential for off-target effects requiring urgent clinical attention and intervention, it is important that immune-mediated adverse events are recognised and reported by clinicians.

It is well established that the use of ICI can result in endocrinopathies, which most commonly include primary hypothyroidism following destructive thyroiditis, hyperthyroidism associated with Grave's disease and pituitary hypophysitis. Type 1 diabetes (T1DM), as a result of auto-immune destruction of pancreatic beta cells, is a rarer side effect that has been reported in less than 1% of the cases where people usually present with acute onset of severe hyperglycaemia or diabetic ketoacidosis (DKA). It can occur with monotherapy (nivolumab, pembrolizumab) but more frequently with combination therapy (nivolumab and ipilimumab) within the first month and up to several months after treatment (2). Hyperosmolar hyperglycaemic state (HHS) typically presents in elderly patients with type 2 diabetes and less frequently in T1DM and is characterised by persistent and gradually increasing hyperglycaemia with serious metabolic sequelae if left untreated (3). The interval between initiation of treatment and the onset of symptoms varies (between 1 and 228 weeks) and symptoms can develop months after the last infusion (4). This is due to nivolumab’s ability to bind to T cells for prolonged periods with the therapeutic effect persisting for at least 20 weeks after discontinuation of treatment.

We present a case of new-onset T1DM presenting with DKA concomitant with HHS following a single cycle of ipilimumab and nivolumab for the treatment of metastatic renal cell carcinoma.

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Case presentation

A Caucasian man in his 60s with no significant past medical history presented with 6-week history of shortness of breath and weight loss (15 kg). His body mass index at presentation was 26 kg/m². Initial investigation with a chest x-ray showed a right pleural effusion and lung metastases that were confirmed by a chest-abdomen-pelvis CT scan that also revealed a right renal mass. Subsequent work-up included lung biopsy confirming renal cell carcinoma with an International Metastatic renal cell carcinoma Database Consortium (IMDC) risk score of 3, indicative of poor prognosis. He was started on immunotherapy with nivolumab and ipilimumab with the plan to assess response after four cycles. One day prior to the initiation of immunotherapy, his HbA1c was suggestive of prediabetes as per American Diabetes Association guidelines (5.7%; American Diabetes Association Standards of medical care in diabetes, 2022) (5) but normal as per British criteria (prediabetes defined as HbA1c 6–6.4%; NICE Guideline 38, Sept. 2017) (6) and his estimated glomerular filtration rate (eGFR) was 67 mL/min.

Three weeks after the first dose, he presented to the emergency department with a 5-day history of severe polyuria, polydipsia and fatigue and 1-day history of confusion, abdominal pain, nausea and vomiting. Clinically he had no stigmata of insulin resistance.

Investigation

Initial laboratory investigations identified an overlap of DKA (pH: 7.1 and HCO₃⁻: 10 mmol/L from venous blood gas, blood ketones >7 mmol/L, lactate 1.27 mmol/L) and HHS (severe hyperglycaemia and hyperosmolality: blood glucose of 51 mmol/L, serum osmolality: 355 mOsm/kg H₂O) along with severe dehydration and acute pre-renal kidney failure with eGFR that had dropped from 67 to 30 mL/min (Table 1). Blood ketones (β hydroxybutyrate) were measured with a hand-held ketone meter (4SURE smart duo meter, Nipro Diagnostics, Southampton, UK). His clinical features were likely to predominantly relate to DKA pathology.

New-onset T1DM was confirmed based on the seropositivity for glutamic acid decarboxylase antibodies (GADA) titre >2000 U/mL (reference range (RR): 0–4.9 U/mL) and significant insulin deficiency (c-peptide: 66 pmol/L with paired glucose: >15 mmol/L). Anti-tyrosine phosphatase antibodies and zinc transporter...
8 antibody titre levels were not raised (IA2: < 0.8 U/mL (RR: 0–7.4), anti-ZnT8: 7.6 U/mL (RR: 0–149) respectively). Endocrine tests showed normal pituitary, adrenal and thyroid function (9:00 am cortisol: 368 nmol/L, thyroid-stimulating hormone (TSH): 2.79 mIU/L, free T4: 15.5 pmol/L, free T3: 3.8 pmol/L, thyroid auto-antibody titres were not raised and prolactin: 217 mIU/L) (Table 1). There were no symptoms or signs of adrenal disease. There are variations at cortisol assays and thus normal ranges at different centres; the Elecsys Cortisol II assay (Roche, Basel, Switzerland) is used in our centre with the reference range of 133–537 nmol/L.

### Treatment

He was transferred to intensive care unit for further management that included fluid resuscitation, intravenous insulin infusion and frequent laboratory monitoring. He remained in the intensive care unit for 4 days and after stabilisation, intravenous insulin was replaced by multiple daily injections (MDI) of insulin on the fourth day as per our hospital clinical guidelines for new-onset T1DM (insulin detemir twice daily and insulin aspart before each meal).

### Outcome and follow-up

Self-management and dose adjustment of insulin were aided by the use of intermittent-scanned glucose monitoring. He remains on MDI of insulin with most recent results showing HbA1c: 8.5% (69 mmol/L) 8 months following diagnosis. Latest time in range (glucose between 3.9 and 10 mmol/L) is 31%, high (10.1–13.9 mmol/L) 38% and very high (13.9 mmol/L) 31%. Immunotherapy with ipilimumab and nivolumab was resumed with good radiological response in his metastatic disease on his most recent oncology review.

### Discussion

New-onset T1DM after administration of immunotherapy results from the destruction of pancreatic beta cells by autoreactive T cells, and evidence from animal studies shows the progression of prediabetes to diabetes in non-obese mice with PD-1/PD-L1 axis blockade (7). It occurs in slightly less than 1% of patients, with the majority being treated with anti-PD-1/PD-L1 or combination therapy (4). Nivolumab is associated with the development of T1DM at about 0.1–0.2% of patients, while in the case of ipilimumab, pre-treatment with anti-PD-1 or interferon...
The combination of nivolumab and ipilimumab typically leads to earlier disease onset compared to monotherapy with the anti-PD-1 or PD-L1 (on average after 2.7 cycles vs 4.5 cycles) as shown by a recent systemic review, but onset after a single dose is rarely reported (8). New-onset T1DM most commonly presents with DKA and moderately elevated HbA1c due to rapid destruction of beta cells and severe insulinopenia. However, overlap with HHS is less frequent with only two cases reported in the literature after seven and two doses of nivolumab, respectively (9, 10). Insulin deficiency consists of the hallmark of both conditions with marked hyperglycaemia and severe dehydration in HHS and ketone body production in DKA. This is to our knowledge the first case reported in the literature with DKA and HHS overlap after a single dose of nivolumab/ipilimumab.

Individuals with positive islet antibodies, or genetic predisposition, such as the presence of certain human leukocyte antigen haplotypes (in particular HLA-DR4) are more susceptible and tend to develop hyperglycaemia earlier, potentially indicating that pre-existing autoimmunity further enhances the risk of hyperglycaemia with ICI treatment (8). There are however no large studies that have evaluated the prevalence and clinical consequences of auto-immune markers/phenotypes pre-ICI treatment. In most case reports including ours, it is unclear whether GADA preceded or followed the initiation of immunotherapy; however, it is worth noting that both seroconversion and the presence of autoantibodies before the start of immunotherapy have been reported (11). Overall, islet autoantibodies are present in up to 53% of the reported cases of ICI associated T1DM, with a predominance of GADA followed by ICA (6). Although current guidance doesn’t suggest pre-screening for islet autoantibodies, detecting people at high risk for T1DM could be proven useful in the future, considering promising upcoming therapies to slow down beta cell destruction such as teplizumab (12).

In contrast to the management of several other immune-mediated side effects of immunotherapy, treatment with steroids is not indicated in immunotherapy-induced T1DM due to the extensive irreversible destruction of beta-cells and potential exacerbation of hyperglycaemia. Often resuming immunotherapy is crucial for cancer prognosis and long-term survival rates and as the diabetes can be managed with insulin, the risk benefit ratio for the individual is often in favour of restarting immunotherapy. This is further supported by the irreversible impact on beta-cell function as indicated by low c-peptide levels.

**Conclusion**

Although rare, new-onset T1DM after immunotherapy can present with a DKA and HHS overlap after a single dose of nivolumab/ipilimumab in individuals without pre-existing history of diabetes and normal glycaemic parameters. Clinicians must maintain a high index of suspicion in regards to diagnosis and management of new onset T1DM, which can present acutely after immunotherapy. Patient education and awareness of these rarer side effects of immunotherapy is also essential to enable prompt diagnosis and initiation of treatment.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Patient consent**

Written informed consent for publication of their clinical details was obtained from the patient.

**Author contribution statement**

Patient was under the care of DC, SH, JK and DS. Report was written by DS and JK with contributions and comments from SH and DC.

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