CASE REPORT

New onset diabetes after nivolumab treatment

Ricardo Capitao, Carlos Bello, Ricardo Fonseca, Catarina Saraiva

Department of Endocrinology, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

Correspondence to
Dr Ricardo Capitao, ricardomiguelcapitao@gmail.com

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SUMMARY

The authors describe a case of a life-threatening diabetic emergency 25 days after initiation of nivolumab (3 mg/kg) for stage 4 lung adenocarcinoma. She was admitted to the emergency department, with hyperglycaemia-related signs and symptoms, such as polyuria, polydipsia, weight loss, confusion, asthenia, dehydration, hypotension and Kussmaul respiratory pattern. Her body mass index was 21.9 kg/m^2 and she did not show acanthosis nigricans. Arterial blood gas determination revealed high anion gap metabolic acidaemia and blood tests showed hyperglycaemia (1060 mg/dL), hyperketonaemia (beta-hydroxybutyrate: 6.6 mmol/dL), elevated total serum osmolality (389 mOsm/kg), low serum and urinary C-peptide and positive antiglutamic acid decarboxylase antibodies. Since nivolumab was initiated a few days before, and due to its known immune-mediated endocrine adverse events, we assumed the diagnosis of new onset immune-mediated type 1 diabetes mellitus. After prompt and adequate treatment of diabetic ketoacidosis/hyperosmolar hyperglycaemic state, she was discharged improved on multiple daily injections of insulin.

BACKGROUND

In some cancers, the production of programmed Cell death protein 1 (PD-1) ligands is increased. These molecules bind to the PD-1 receptor in T cells and inhibit the immune response against the tumour.[1]

Immune checkpoint inhibitors (ICI) are a class of recently Food and Drug Administration (FDA)-approved highly effective anticancer agents. Their mechanism of action relies on the (re)activation of the patients own immune system against cancerous cells. These agents act by either blocking cytotoxic T-lymphocyte antigen 4 (anti-CTLA4) or PD-1 (or its ligand).[2 3]

Nivolumab is a human immunoglobulin (Ig)G4 antiprogrammed cell death-1 (anti-PD-1) monoclonal antibody that works as an ICI by blocking the PD-1 receptor. It is currently approved for the treatment of cancer such as metastatic melanoma, non-small cell lung cancer and advanced renal cell carcinoma.[4]

By activating the immune system, ICI-related adverse events are distinct from the ones caused by conventional chemotherapy, being usually of autoimmune nature. For unknown reasons, the endocrine system is particularly susceptible to immune-mediated damage by these agents. The most commonly described immune-mediated endocrine adverse events (irAE) hypophysitis, hypothyroidism, thyroiditis and primary adrenal insufficiency. New onset type 1 diabetes mellitus (T1DM) is an exceedingly rare irAE.[1 2]

In this case, the prompt recognition of symptoms and glucose measurement could have avoided the development of serious complications of acute and newly onset DM. In the future, it would be important to identify possible risk factors for the development of T1DM, for instance, the total dose exposure to the drug, human leucocyte antigen (HLA) genotype, the presence of autoantibodies associated with T1DM before treatment, the combination with other therapies and medical history of other autoimmune diseases prior to initiation of treatment. Patients should also be warned about T1DM-related symptoms in order to be promptly evaluated and treated and thus preventing the worsening of newly diagnosed DM.

A proper differential diagnosis is also crucial since these patients should be treated with insulin instead of other antidiabetic drugs. It is also important to start treatment as soon as possible due to the rapid onset of acute complications of DM

CASE PRESENTATION

The authors report on a 74-year-old woman with a medical history of arterial hypertension and hypercholesterolaemia, medicated with clonidine, diltiazem, aspirin, simvastatin, nebivolol and furosemide. There was no reference to prior DM or infections. Her estimated glomerular filtration rate was 50 mL/min/1.73 m^2 and her fasting plasma glucose levels were at the normal ranges before the admission (last fasting glucose 82, 90 days prior to the event). There was no relevant family history, namely, DM or autoimmune diseases.

A stage 4 lung adenocarcinoma (pleural involvement), localised to the left inferior lobe, was diagnosed 8 months prior to the event and, for this reason, she started treatment with pemetrexed for 4 months (three cycles) which, due to pharmacological intolerance and disease progression, was stopped. Consequently, she had switched the chemotherapy to nivolumab, 3 mg/kg, which had been administrated two times: 25 and 10 days before the admission to the emergency department (ED).

She was then admitted to the ED with symptoms of polyuria, polydipsia, weight loss (5 kg), vomiting, confusion and asthenia that lasted for 3 days. She denied any other previous or concomitant symptoms, fasting for >8 hours, alcohol consumption or taking any new drugs.

The physical examination revealed prostration, dehydration, hypotension (80/42 mm Hg, mean arterial pressure of 55 mm Hg) and Kussmaul

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respiratory pattern with 34 cpm. Her body mass index was 21.9 kg/m^2 and she did not show any signs of insulin resistance such as acanthosis nigricans.

Arterial blood gas determination revealed high anion gap metabolic acidaemia: pH 7.07, pCO_2 27 mm Hg, HCO_3 7.8 mmol/L, anion gap 41 mmol/L and lactate 1.0 mmol/L.

Blood tests showed haemoglobin (Hb) 11.5 g/dL, leucocytes 15.8×10^9/L, platelets 320×10^9/L, C reactive protein 5.4 mg/dL, glucose 1060 mg/dL, ketonaemia (beta-hydroxybutirate) 6.6 mmol/dL (reference range <0.5 mmol/L), creatinine 2.40 mg/dL, blood urea nitrogen 130 mg/dL, corrected sodium 142 mmol/dL, total serum osmolality 389 mOsm/kg, potassium 6.90 mmol/dL, phosphorus 9.7 mg/dL, lipase 236 U/L (reference range 13–60 U/L) and amylase 141 U/L (reference range <110 U/L).

The diagnosis of new onset DM was established and she was treated accordingly.

INVESTIGATIONS

Additional tests were performed and demonstrated serum C-peptide of 0.2 ng/mL, with a concomitant blood glucose of 1060 mg/dL (normal range at our laboratory for serum C-peptide: 1.1–4.4 ng/dL), urinary C-peptide 0.2 µg/24 hours (normal range at our laboratory: 17.2–181 µg/24 hours) and HbA1c 8.7%. The antibodies associated withT1DM were positive for antiglutamic acid decarboxylase (GAD) (66 U/L, positive if >1.0 U/L).

Additional hormonal parameters were also tested to exclude other immune-mediated endocrinopathies associated with ICI, such as hypophysitis, hypothyroidism and adrenal insufficiency. Adrenocorticotropic hormone, follicle-stimulating hormone, luteinising hormone, morning serum cortisol, free T4 and thyroid-stimulating hormone were all within the normal reference values for the age and sex of the patient.

Abdominal CT did not reveal metastatic disease of the pancreas.

HLA genotype was also tested and the allele DRB1*04 was detected.

DIFFERENTIAL DIAGNOSIS

The patient presented with a new onset DM complicated by diabetic ketoacidosis (DKA). However, some features cannot exclude an overlap between DKA and hyperosmolar hyperglycaemic state (HHS) which has been reported in more than one-third of patients presenting with a hyperglycaemic crisis.[5]

It is important to note that mild ketonaemia may be present in HHS as well as the symptoms reported by the patient were longer than those described in typical DKA presentations (usually <24 hour).[5] She also had unusually high levels of glucose and osmolality for typical DKA.

The absence of insulin resistance signs, such as overweight or acanthosis nigricans, as well as the presentation with ketoacidosis, low serum/urinary C-peptide and the presence of anti-GAD antibodies made the diagnosis of T1DM more likely. As such, the authors assumed the diagnosis of immune-mediated T1DM. Since the HbA1c reflects the average glycaemic control in the previous 3 months, its current elevation makes the exact moment of DM onset difficult to ascertain.

TREATMENT

The patient was treated with insulin infusion, sodium chloride infusion and then she started on subcutaneous insulin with long and rapid-acting insulin analogues. At discharge, her total daily insulin dose was 37 Units which correspond to a total of 0.62 Units/kg of body weight.

OUTCOME AND FOLLOW-UP

After initial treatment, the patient recovered from DKA, dehydration and acute kidney injury (currently estimated glomerular filtration rate of 54–73 mL/min/1.73 m^2). She was well adapted and compliant with insulin regimen with the support of her family and continued the treatment with nivolumab. After discharge, she was followed in endocrinology and lung oncology outpatient clinics, and 3 months later her HbA1c was 7.2% and showed a good response to chemotherapy with no recurrence of the oncological disease until now.

DISCUSSION

Other authors also reported the onset of DM after anti-PD-1 therapy,[6] some of them in patients under treatment with nivolumab.[3–5 7–17] The time of onset varied between 1 and 48 weeks.[5–15 15–23] DKA was not invariably present in all patients.

Specific variations in HLA molecules are associated with an increased risk of or protection against the development of T1DM.[6] There is a lack of information regarding the haplotype testing in the cases published, but a few patients were found to have haplotype DRB1*04 as reported in this case.[2 12 20] This haplotype has been suggested to contribute to the development of T1DM after anti-PD-1 therapy.[7] Therefore, in the future, the search for specific haplotype can possibly help to identify patients at risk of DKA.

The mechanism underlying insulin deficiency is probably related to inappropriate activation of T cells and consequently the destruction of pancreatic cells responsible for insulin production. This can be useful to further understand the pathophysiology of the T1DM since the inhibition of PD-1 could be one of the contributing factors for T1DM in patients not treated with nivolumab. In this case, the presence of anti-GAD antibodies favours an immune-mediated subtype of T1DM. It would be interesting to demonstrate that these antibodies were absent before the initiation of therapy with nivolumab. In addition to this, one study demonstrated that patients with T1DM had reduced expression of PD-1 in T cells compared with other types of DM.[24]

Other factors that may influence predisposition to hyperglycaemia and autoimmunity, according to other authors, included combined use with other immune modulators, pancreatic metastases and pre-existing type 2 DM.[3] Our patient was previously treated with pemetrexed (a folate analogue metabolic inhibitor that impairs metabolic processes essential for cell replication), but its real contribution to the development of T1DM remains to be proven.

Nevertheless, our patient was treated with furosemide that could have aggravated the dehydration and the severity of the symptoms.

Contributors RC, RCF and CTB: conception and design of study; acquisition of data. All authors: analysis and/or interpretation of data; drafting the manuscript; revising the manuscript critically for important intellectual content and approved the submitted version of the manuscript to be published.

Patient's perspective

'Despite of diabetes I am very grateful for everything that medical team did for me and I do not regret the decision of initiating Nivolumab. My family was also very supportive and important for my recovery. My biggest concern is to control cancer once I am able to control my diabetes'.

Learning points

- Nivolumab is a medication that interacts with the immune system, thus it is important to be aware of possible immune-mediated side effects such as type 1 diabetes mellitus (T1DM).
- In patients presenting with suggestive clinical/laboratory features of T1DM and diabetic ketoacidosis (DKA), such as weight loss, polyuria, polydipsia, dehydration, Kussmaul breathing, hypotension and high glycaemia with anion gap metabolic acidosis, autoimmune T1DM should be suspected regardless of the patient's age, particularly, if patients are under treatment with immune checkpoint inhibitors (ICI). In spite of, typically diagnosed at younger ages, these drugs can precipitate autoimmune T1DM in older patients as described in this 74-year-old patient and others case reports.[3]
- The evaluation of glycaemia is a simple and affordable test and should be performed regularly in patients treated with ICI. In this case, fasting plasma glucose levels were only evaluated 90 days prior to the event. It would be reasonable to evaluate glycaemia a few days after the initiation of nivolumab (eg, 5–7 days) and before the administration of the second dose, to assess if DM has developed. Haemoglobin A1c was also elevated (8.7%), which means that the diabetes was probably already present for, at least, a few weeks prior to the onset of the DKA. Therefore, a more regular monitoring of glycaemia would probably lead to an earlier diagnosis and treatment of DM.
- Patients with T1DM should be immediately treated in order to avoid DKA which can begin shortly after the initial treatment (25 days in this case) and shortly after the initial symptoms (3 days in this case).
- Patients treated with nivolumab and newly diagnosed DM should be evaluated by physicians with experience in DM in order to be treated correctly.

Competing interests None declared.

Patient consent Obtained.

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