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Pembrolizumab-induced diabetes

Pembrolizumab, a checkpoint inhibitor, has improved the prognosis of advanced malignancies such as malignant melanoma [1]. Programmed cell death protein 1 (PD-1) is a negative regulator of T-cell activation, generally expressed on chronically activated T cells, especially CD8+ T cells [2] . PD-1 inhibitors like pembrolizumab prevent programmed death-ligand 1 (PD-L1) expressed by tumour cells from binding to PD-1 on the T cells. This restores the T-cell antitumor response resulting in tumour apoptosis. However, it is a double-edged sword resulting in endocrinopathies such as hypophysitis, thyroiditis, and rarely new-onset diabetes. The pancreas also expresses PD-L1, and PD-1 inhibitors can result in the T cells mediating an immune response against the beta cells, resulting in cell destruction and acute onset insulin deficiency [2, 3].

We report a case of 83-year-old Caucasian female who presented with rapid onset of lethargy, polyuria, and polydipsia over the preceding three days. She was treated with Pembrolizumab (seven cycles given: first cycle given 23 weeks ago) following a diagnosis of metastatic melanoma. She had no pre-existing history of diabetes mellitus and had normal capillary blood glucose levels three weeks prior to admission.

On examination, she had dry mucous membranes with a heart rate of 104 beats per minute, blood pressure was 164/100 mm Hg, oxygen saturations were 99% on room air, respiratory rate 14 breaths per minute, and temperature 37°C. Chest, abdominal, and cardiovascular examinations were unremarkable.

The venous blood gas demonstrated pH 7.37 (7.35–7.45), bicarbonate 23.7 mmol/L (22-28), lactate 2.5mmol/L (0-2), blood glucose 35.1mmol/L, and blood ketones 2.2 mmol/L. Laboratory investigations are shown in Table 1. Serum C-peptide (244 pmol/L) was low for glucose value. CT pancreas was unremarkable.

She was initially treated with a variable-rate insulin infusion. Subsequently, she was started on a basal-bolus insulin regimen. She was diagnosed with pembrolizumab-induced diabetes.

Pembrolizumab was restarted once her blood glucose was stable. After 10 months her urine C-peptide was 0.09 nmol/L and the urine C-peptide/creatinine ratio was 0.02 nmol/mmol, in keeping with severe insulin deficiency. The patient remains stable on basal-bolus insulin therapy with HbA1c of 66 mmol/mol (8.2%).

Pembrolizumab-induced diabetes is a serious, albeit rare, adverse effect of pembrolizumab. The reported incidence is 0.2% [4], with 43 cases reported in the literature, the majority of patients having malignant melanoma.

Patients may present with osmotic symptoms including polydipsia or polyuria, non-specific symptoms such as headaches and vomiting, or they may be asymptomatic. The onset of diabetes was variable in the literature, with the majority of patients presenting between 3 and 20 weeks of starting pembrolizumab. Our case presented at 23 weeks of starting pembrolizumab.

The most common findings are elevated blood glucose levels, elevated ketones, mildly elevated HbA_{1c} (< 75 mmol/mol, 9%), and reduced C-peptide levels [4]. C-peptide has a better discriminative value if the test is done sometime after the diagnosis. Therefore, a normal/elevated level at presentation does not exclude the presence of insulin deficiency. In our case, serum C-

peptide at presentation was low for glucose levels. In addition, it took a few months before urine C-peptide levels demonstrated severe insulin deficiency.

Whilst most cases in the literature present with diabetic ketoacidosis, diabetes autoantibodies are often absent at diagnosis, in keeping with acute beta-cell destruction[4]. In our case, antibodies were absent. Several studies have reported mild elevations of serum amylase and serum lipase, without features of pancreatitis on imaging, although pancreatic atrophy may be seen [5, 6].

With the increasing use of check-point inhibitors like pembrolizumab, it is important to consider this diagnosis in all patients on pembrolizumab presenting with new-onset diabetes, and not discharge these patients from the emergency department with oral hypoglycaemic agents without specialist input. Patients invariably need long-term insulin treatment due to pancreatic failure.

Consent to publish

Written consent was obtained from the patient to publish the clinical details in this article.

Conflicts of interest

None declared.

Author contributions

F.W.A. conceived and presented the idea. R.B. and O.Z.K. equally contributed to the writing of the manuscript. F.W.A edited and revised the manuscript. R.B., O.Z.K., and F.W.A. reviewed and authorised the final version of the manuscript. F.W.A, R.B, and O.Z.K are the guarantors of this work, and thus take responsibility for the integrity of the information and the accuracy of the information.

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Tables 1. Laboratory values at the time admission

Blood test	**Value (normal range)**
Haemoglobin [g/L]	133 (115–165)
White cells [x 10^9/L]	10.2 (4–10)

Platelets [x 10^9/L]	393 (150–410)
Urea [mmol/L]	5.0 (2.7–5)
Sodium [mmol/L]	126 (136–145)
Potassium [mmol/L]	4.9 (3.5–5.1)
Creatinine [µmol/L]	72 (62–106)
Alanine aminotransferase [IU/L]	8 (0–33)
Alkaline phosphatase [IU/L]	87 (35–104)
Bilirubin [µmol/L]	6 (0–21)
Amylase [U/L]	47 (28–100)
C-reactive protein [mg/L]	24 (0–5)
Thyroid stimulating hormone [mU/L]	1.07 (0.27–4.2)
Free thyroxine [pmol/L]	19.2 (12–22)
Follicle-stimulating hormone [IU/L]	64.3 (3.5–12.5)
Luteinizing hormone [IU/L]	14.8 (2.4–12.6)
9 am cortisol [nmol/L]	594 (>285)
Prolactin [mIU/L]	202 (102–496)
Glycated haemoglobin [mmol/mol]	76 (0–42)
Glucose [mmol/L]	35.1 (3.2–11.1)
Measured serum osmolality [mOsm/kg]	292 (285–295)
Urine C-peptide [nmol/L]*	1.81
Urine C-peptide/creatinine ratio [nmol/mmol]*	0.65 (> 0.6)
Serum GAD-65 antibodies	Negative
Serum IA2 antibodies	Negative
Serum zine transporter 8 antibodies	Negative

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