

# Acute presentation of immunotherapy-related diabetes mellitus without ketoacidosis, low C-peptide or elevated HbA1c

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## Summary

The rapid rise in the use of immune checkpoint inhibitors as systemic cancer therapy has seen the emergence of immunotherapy-induced diabetes, a severe irreversible immunotherapy-related adverse event. Affected patients typically present with diabetic ketoacidosis (DKA) and low C-peptide consistent with insulin deficiency secondary to autoimmune  $\beta$ -cell destruction. We present the unusual case of a 61-year-old female with metastatic ampullary duodenal adenocarcinoma with primary tumour adjacent to the pancreatic head. She was commenced on immunotherapy after conventional systemic chemotherapy. Acute-onset hyperglycaemia was detected after 7 weeks on weekly blood glucose monitoring, with no glucocorticoid use or prior history of diabetes. On presentation, there was no evidence of DKA, and her glycated haemoglobin level was within the normal non-diabetic range at 5.3%, reflecting the acuity of her presentation. Initial serum C-peptide was preserved; however, it became undetectable a few weeks later, confirming insulin deficiency. We describe a case of atypical presentation of immunotherapy-induced diabetes, review the existing literature on this emerging clinical entity and discuss the differential diagnosis for new-onset diabetes mellitus in patients with metastatic cancer.

## Learning points

- Regular proactive glycaemic monitoring in patients receiving immunotherapy, particularly antibodies against programmed death ligand 1 and PD1, can facilitate very early detection of immunotherapy-induced diabetes, prompting insulin commencement and avoiding life-threatening presentations of diabetic ketoacidosis.
- Glycated haemoglobin can be within the normal range in patients diagnosed acutely with immunotherapy-induced diabetes.
- Serum C-peptide can be preserved initially in patients diagnosed with immunotherapy-induced diabetes but is likely to become undetectable during their illness.
- New-onset diabetes in patients with metastatic cancer carries a broad differential diagnosis.

## Background

Immunotherapy-induced diabetes is a rare immunotherapy-related adverse event (iRAE) associated with the use of immune checkpoint inhibitors (ICIs) in systemic cancer treatment. The most common ICIs used are monoclonal antibodies targeting CTLA-4, PD1 and PDL1. CTLA-4 is expressed on T-cells and binds to ligands CD80 and CD86, dampening the initial T-cell response by downregulating CD4+ helper T-cell activity and upregulating CD4+ regulatory T-cell immunosuppression. PD1, however, is induced on effector T-cells in peripheral tissues and binds to PDL1 to dampen T-cell activity against self-antigens; however, tumour cells can upregulate PDL1 expression as a mechanism to evade the host immune system (1). The use of ICIs disrupts these inhibitory pathways, thereby activating cytotoxic CD8+ T-cells and enabling them to destroy malignant cells.

PD1 inhibition has the greatest association with new-onset diabetes, and this is characterised by acute pancreatic  $\beta$ -cell destruction, leading to absolute insulin deficiency. While the underlying pathogenesis remains unclear, reduced PD1 expression in CD4+ T-cells has been observed in type 1 diabetes mellitus (T1DM) and PD1 blockade has been shown to precipitate diabetes in pre-diabetic non-obese mice. Since pancreatic islet cells express PDL1, it is theorised that pharmacological inhibition of PD1/PDL1 interaction from ICIs leads to the activation and proliferation of autoreactive CD8+ T-cells, causing a T-cell-mediated  $\beta$ -cell destruction (2, 3).

Patients with immunotherapy-induced diabetes typically experience new-onset hyperglycaemia or an unexplained worsening of pre-existing diabetes, with majority presenting in potentially life-threatening DKA. These presentations are often accompanied by raised glycated haemoglobin (HbA1c) levels and low or undetectable fasting C-peptide levels, indicating absolute deficiency of endogenous insulin production, reflective of  $\beta$ -cell destruction. The time of onset of diabetes has been reported to vary widely, with a median onset of 6–25 weeks after induction of ICI (2, 4, 5, 6, 7).

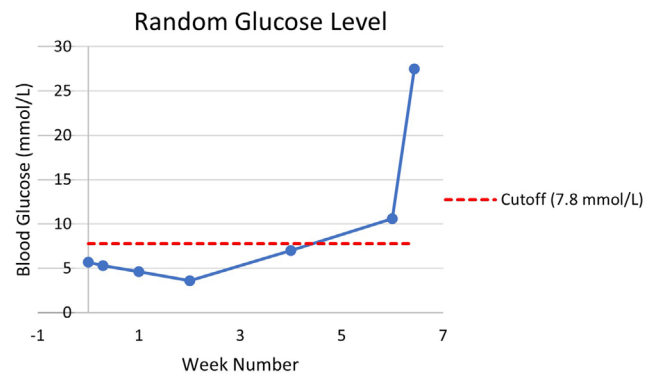
## Case presentation

A 61-year-old female was diagnosed with metastatic ampullary adenocarcinoma when she presented with obstructive jaundice and underwent common bile duct stent. She received external beam radiotherapy and 15 months of palliative chemotherapy with gemcitabine and nab-paclitaxel followed by single-agent gemcitabine

and then 7-months of FOLFOX chemotherapy (fluorouracil, leucovorin and oxaliplatin) complicated by grade 1 peripheral neuropathy. She then switched to immunotherapy with 3-weekly cycles of combination PD1 and CTLA-4 blockade. Routine weekly serum biochemistry detected gradual increment in serum lipids, and she was commenced on pancrelipase for presumed exocrine pancreatic insufficiency, although she did not develop classical symptoms of this and diagnosis was not confirmed with faecal elastase. As part of monitoring for iRAEs, she had weekly blood glucose levels (BGLs), which were initially normal. BGL monitoring then detected acute hyperglycaemia of 27.5 mmol/L (reference range 3.0–7.8 mmol/L) 7 weeks after commencing immunotherapy (Fig. 1), prompting hospital admission. She had no personal or family history of diabetes, and the immunotherapy was otherwise well tolerated. She was not receiving glucocorticoid medications. She had Eastern Cooperative Oncology Group status 0.

## Investigation

Further investigations during her admission showed normal serum ketones <1 mmol/L, pH 7.4, and bicarbonate 24 mmol/L, excluding diabetic ketoacidosis (DKA). HbA1c of 5.3% was within the non-diabetic range and C-peptide concentration was 'inappropriately normal' but somewhat preserved at 0.74 nmol/L (reference range:



**Figure 1**

Random glucose levels. Week 0 represents the start of immunotherapy. The figure demonstrates the trend in blood glucose levels (BGLs) represented by the blue line with the y-axis showing the BGL value in mmol/L and the x-axis showing the number of weeks since commencing immunotherapy. A cut-off of 7.8 mmol/L is used as this is the upper limit of normal in the local laboratory. Initial approximately weekly BGL monitoring demonstrated normoglycaemia. At 6 weeks, the BGL rose to 10.2 mmol/L (above reference range but not within range for diabetes diagnosis) followed by a rapid increase to 27.5 mmol/L at the seventh week highlighting the acute presentation and early detection of the patient's diabetes.

0.37–1.47 nmol/L). T1DM-associated autoantibody screening was negative, including anti-zinc transporter 8 (ZnT8) antibodies of <10 U/mL, anti-glutamic acid decarboxylase antibodies of <5 U/mL, anti-insulinoma antigen-2 antibodies of <8 U/mL and insulin autoantibodies of <0.4 U/mL. Thyroid function tests indicated biochemical euthyroidism: thyroid-stimulating hormone 0.66 mIU/L (reference range 0.40–4.80 mIU/L), free thyroxine (fT4) 15.5 pmol/L (reference range 8.0–16.0 pmol/L) and fT3 5.2 pmol/L (reference range 4.0–6.0 pmol/L). A CT abdomen and pelvis scan performed at the time of diabetes diagnosis (Fig. 2) showed dilatation of the pancreatic duct measuring up to 12 mm and a primary tumour adjacent to the pancreatic head (59 × 36 mm) which had increased from 6 weeks prior (36 × 42 mm).

### Treatment

Her hyperglycaemia was managed with s.c. insulin injections in hospital, and she was discharged 5 days later with basal bolus insulin regimen consisting of insulin glargine (Optisulin) 26 units nocte and insulin aspart (NovoRapid) 12 units three times a day with meals. Immunotherapy was continued.

### Outcome and follow-up

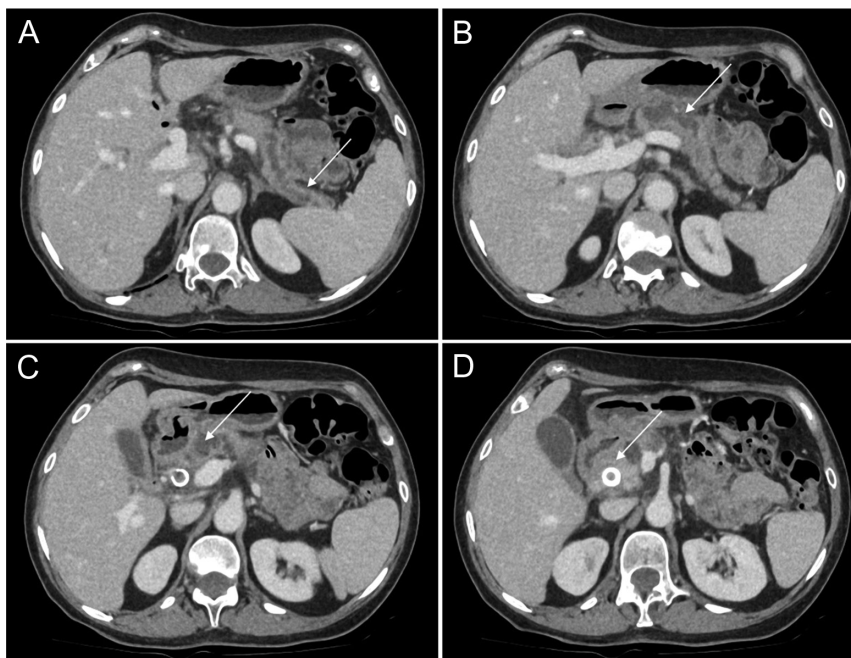
She has been followed up for 3 months since diagnosis of diabetes and has regular follow-up with oncology

and endocrinology services. Her insulin regimen was rationalised to NovoMix 30 mixed insulin at a total daily dose of 48 units (0.8 units/kg/day). Repeat fasting serum C-peptide concentration 2 months after diagnosis of diabetes was undetectable at <33 pmol/L (reference range: 200–1200 pmol/L), confirming absolute insulin deficiency. Progress CT abdomen and pelvis scan 1-month post-diabetes diagnosis showed interval reduction in the size of the primary tumour adjacent to the pancreatic head (40 × 42.5 mm), similar to the scan 6 weeks pre-admission, indicating that the initial increase in tumour size at time of diabetes diagnosis likely represented immunotherapy-related ‘pseudo-progression’.

### Discussion

The differential diagnosis of new-onset diabetes in a patient with metastatic malignancy is broad and can be divided into non-malignancy-related (e.g. T1DM and T2DM) or malignancy-related causes, which can be disease related (type 3c diabetes secondary to pancreatic cancer or metastases resulting in exocrine and endocrine pancreatic insufficiency) or treatment related (glucocorticoid- or immunotherapy-induced diabetes).

Given the patient’s well-documented rapid onset of profound hyperglycaemia (<1 week), T2DM was considered very unlikely as this is characterised by insidious, progressive insulin resistance and hyperglycaemia. She also did not receive glucocorticoids as part of her



**Figure 2**

CT abdomen/pelvis scan demonstrating ampullary tumour adjacent to pancreatic head. Different axial-view slices of venous-phase CT abdomen/pelvis with contrast are demonstrated at the time of diabetes diagnosis (A–D). Panels A and B, respectively, demonstrate the pancreatic tail (indicated by the white arrow) and body (indicated by the white arrow) which are preserved. Panel C demonstrates evidence of pancreatic duct dilatation (indicated by the white arrow) at the head of the pancreas adjacent to the primary ampullary duodenal adenocarcinoma which is shown in panel D (indicated by the white arrow). The common bile duct stent (seen as a white ring-like structure) can also be visualised in panel D adjacent to the duodenal adenocarcinoma.



systemic cancer treatment. The decline in her C-peptide concentrations to undetectable within 2 months of diabetes onset later confirmed absolute insulin deficiency rather than insulin resistance as the driving pathogenesis of her diabetes. Hence, the three main differentials were T1DM, T3cDM and immunotherapy-induced diabetes.

The approximate 50% increase in the size of her primary duodenal tumour located adjacent to the pancreatic head raised the possibility of T3cDM, particularly given concerns regarding pancreatic exocrine insufficiency developing prior to diagnosis of her diabetes. This has been extensively linked to the development of diabetes, where inflammation and subsequent oxidative stress and fibrosis of the pancreas are believed to result in  $\beta$ -cell loss mediated by pro-inflammatory cytokines such as interleukin 1 $\beta$ , tumour necrosis factor  $\alpha$  and interferon  $\gamma$  (8). Insulin secretion from  $\beta$ -cells, however, is typically preserved until majority of pancreatic exocrine function is lost. This differential was deemed less likely given the rapid onset of hyperglycaemia, given the lack of confirmed exocrine pancreatic insufficiency and given the tumour was not widely infiltrating the pancreas but rather adjacent to the pancreatic head with the pancreatic body and tail structurally preserved (Fig. 2).

While our patient's acute and severe new-onset hyperglycaemia is suggestive of an immune-related cause, the negative autoantibody screen and time course of onset of diabetes shortly after commencement of immunotherapy support the diagnosis of immunotherapy-induced diabetes rather than T1DM or late-onset autoimmune diabetes of the adult. It is unclear whether traditional T1DM autoantibodies are involved in the disease process of immunotherapy-induced diabetes. Among reported cases of immunotherapy-induced diabetes, approximately half of patients have  $\geq 1$  positive autoantibodies, though in a majority of cases it is uncertain whether autoantibodies were present prior to immunotherapy or were produced as a result of post-immunotherapy seroconversion (2, 4, 5). However, an association has been observed between positive autoantibodies and a quicker onset of diabetes after commencement of immunotherapy (4). The prognostic value of autoantibodies in immunotherapy-induced diabetes is currently still uncertain, as is the use of HLA genomic profiling, where HLA-DR4 genotype has been observed to be associated with immunotherapy-induced diabetes (3, 4, 5).

Our patient had an unusual presentation of the rare condition of immunotherapy-induced diabetes mellitus without DKA, elevated HbA1c or low C-peptide, likely

due to very early detection of hyperglycaemia facilitated by weekly BGL monitoring. This contrasts with the classic presentation of acute DKA with elevated HbA1c and low C-peptide levels (2, 4, 5, 6, 7, 9). The median time from ICI commencement to associated diabetes diagnosis is variable, ranging from 6 weeks to 25 weeks (2, 4, 5, 6, 9). Across multiple reviews and case series, 59–86% of immunotherapy-induced diabetes cases first presented with DKA (2, 4, 5, 6, 7, 9), with asymptomatic hyperglycaemia being especially uncommon (5, 6). Moreover, HbA1c was elevated in almost all patients, with high median HbA1c levels ranging from 7.5% to 10.1% (2, 4, 5, 6, 7, 9). C-peptide levels have also been reported as low or undetectable during the first presentation in a large majority of cases of immunotherapy-induced diabetes (2, 4, 5, 6, 7, 9). In a review of 42 cases of PD1-blockade-associated diabetes, 30/32 (94%) had low/undetectable C-peptide and 33/35 (94%) had elevated HbA1c (2). A more recent extensive literature review of 200 cases found the median age of diabetes onset 64 years and time of onset 9 weeks post ICI commencement, 75.5% associated with anti-PD1/programmed death ligand 1 (PDL1) monotherapy, 67.5% DKA rate at presentation, median HbA1c 7.8% and undetectable C-peptide <1 month from diagnosis in 63.4% of cases (10). It is unclear how rapidly C-peptide becomes undetectable after onset of diabetes due to lack of cases with initially normal C-peptide and infrequent serial follow-up of C-peptide levels.

Given no reliable biomarker is available in predicting the development of immunotherapy-induced diabetes, routine monitoring of BGLs should be considered (similar to monitoring of serum thyroid function tests and cortisol levels as part of screening for other iRAEs) in patients receiving immunotherapy (particularly anti-PD1 or PDL1 agents) to facilitate early detection and treatment of this potentially life-threatening condition. In this case, the success of routine glycaemic monitoring has been demonstrated, whereby our patient's immunotherapy-induced diabetes was detected and treated promptly, preventing the development of potentially life-threatening DKA. The inability to de-escalate insulin therapy after commencement, as seen in our patient and other case reports of immunotherapy-induced diabetes, also indicates that the immune-mediated  $\beta$ -cell destruction is likely irreversible, and hence immunotherapy was continued in our patient after diagnosis of diabetes. With the increasing use of ICIs in systemic treatment of malignancies, more research is warranted on iRAEs regarding presentation, early diagnosis and underlying pathogenesis.





### Declaration of interest

The authors declare that there is no conflict of interest to disclose.

### Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

### Patient consent

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

### Author contribution statement

Shejil Kumar diagnosed and managed the patient under supervision by Peter Rohl and conceived the case report. Cun An Phang and Shejil Kumar drafted the manuscript. Shejil Kumar and Peter Rohl critically reviewed the manuscript.

### Acknowledgements

All authors approved of the final version of the manuscript for publication.

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Received in final form 6 October 2022

Accepted 11 November 2022