CASE REPORT

# Anti-PD-L1 therapy and the onset of diabetes mellitus with positive pancreatic autoantibodies

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## SUMMARY

An 84-year-old woman with metastatic squamous cell carcinoma of the nasopharynx and no history of diabetes was started on the antiprogrammed cell death ligand-1 (anti-PD-L1) antibody durvalumab. Four months later, she presented in diabetic ketoacidosis with glucose 488 mg/dL, anion gap 16, positive serum ketones and $A_{1C}$ 9.1%. Antiglutamic acid decarboxylase 65 (GAD) antibody was 13 U/mL (normal, <0.5 U/mL), c-peptide 0.4 ng/dL (normal, 1.1–4.3 ng/mL) and glucose 142 mg/dL. A man with metastatic papillary urothelial carcinoma was treated with the PD-L1 inhibitor atezolizumab. He had no history of diabetes. Nine weeks after initiation, he developed fatigue and polyuria with blood glucose 336 mg/dL, c-peptide 0.6 ng/mL, $A_{1C}$ 8.2% and GAD antibodies 28.4 U/mL (normal, <1 U/mL). Due to the diagnosis of autoimmune diabetes, both patients were treated with insulin. Autoimmune diabetes is a rare immune-related adverse effect of PD-L1 inhibitors. We present the first two cases with documented positive pancreatic autoantibodies.

## BACKGROUND

Immune checkpoint inhibitors are effective anti-cancer agents that stimulate the immune system to destroy tumour cells. They consist of monoclonal IgG antibodies directed against T-cell inhibitory molecules, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1). PD-L1 inhibitors approved for use include atezolizumab, avelumab and durvalumab; they are used to treat non-small cell lung, bladder and Merkel cell skin cancers.[1] They demonstrate response rates of approximately 25%–40% and are also being evaluated for use in other cancers. Common side effects of these medications include fatigue, cough, nausea, skin rash, musculoskeletal pain, peripheral oedema and urinary tract infections. PD-1 and PD-L1 inhibitors have also been associated with immune-related events including dermatitis, colitis, hypophysitis, thyroid disease, adrenal insufficiency and autoimmune diabetes.[2] CTLA-4 has been associated with dermatitis, enterocolitis, hepatitis and hypophysitis.[3] Although PD-1 inhibitors have been associated with pancreatic autoantibodies, there have been no documented autoantibody positive diabetes cases reported with anti-PD-L1 therapy.[4 5]

## CASE PRESENTATION

Case 1: An 84-year-old woman with metastatic squamous cell carcinoma of the nasopharynx was started on the anti-PD-L1 antibody durvalumab in a phase I trial after disease progression with carboplatin and paclitaxel. She had a history of hypertension but no prior history of hyperglycaemia. Her random blood glucose was 107 mg/dL 2 weeks prior to starting durvalumab. She had no prior history of autoimmune disease and no evidence of other immune-related adverse events. Thyroid-stimulating hormone (TSH), FT4, FT3 were normal. Diabetes-related antibodies, human leukocyte antigen (HLA) typing, TPO antibody, cortisol, adrenocorticotropic hormone (ACTH) were not checked prior to durvalumab dosing. Her body mass index (BMI) was 19 kg/m$^2$ and a family history was notable for a grandmother with adult-onset diabetes mellitus.

The following events were noted after receiving durvalumab:

- Three months after initiation, the patient had an episode of vaginal candidiasis and then recurrent bacterial cystitis.
- After 4 months and 11 doses, the patient developed hyperglycaemia with blood glucose 326 mg/dL, polyuria, polydipsia and fatigue. Her haemoglobin $A_{1C}$ was 9.1% (76 mmol/mol), and she was started on sitagliptin.
- Shortly thereafter, she was admitted to the hospital for diabetic ketoacidosis with glucose 488 mg/dL, anion gap 16 and positive urine and serum ketones. She was started on insulin and metformin and continued on sitagliptin.
- Investigations included antiglutamic acid decarboxylase 65 (GAD) antibody 13 U/mL (normal, <0.5 U/mL) and c-peptide 0.4 ng/dL (normal, 1.1–4.3 ng/dL) with glucose 142 mg/dL (table 1). Islet cell antibody was not available. Her oral medications were stopped and insulin therapy was titrated.
- Due to her autoimmune status, metformin and sitagliptin were discontinued and basal-bolus insulin therapy was initiated.
- She remained on durvalumab, and despite residual tumour, she was clinically stable requiring long-term insulin.

Case 2: A male with metastatic papillary urothelial carcinoma was enrolled in a phase II clinical trial of the anti-PD-L1 antibody atezolizumab but had disease progression after three 21-day cycles. He had a history of hypertension, hyperlipidaemia and prostate cancer but no diabetes. Previous random

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**Table 1** Patients' diabetes-related characteristics after receiving anti-PD-L1 therapy

| | Case 1 | Case 2 |
|---|---|---|
| Anti-PD-L1 Therapy | Durvalumab | Atezolizumab |
| Time from initiation of therapy to onset of diabetes (weeks) | 18 | 9 |
| Clinical presentation | Vaginal candidiasis, recurrent bacterial cystitis, fatigue, polyuria, DKA | Fatigue, polyuria |
| Blood glucose at diagnosis | 326 mg/dL | 379 mg/dL |
| HbA1C at diagnosis | 9.1% (76 mmol/mol) | 8.2% (66 mmol/mol) |
| C-peptide (blood glucose) | 0.4 ng/mL (142 mg/dL)* | 1.1 ng/mL (386 mg/dL)*<br>0.6 ng/mL (336 mg/dL)† |
| GAD antibody | 13 U/mL§ | 28.4 U/mL‡ |
| Islet cell antibodies | Not available | Negative |

*At diagnosis.
†2 months after diagnosis.
‡Normal <1 U/mL.
§Normal <0.5 U/mL.
DKA, diabetic ketoacidosis; GAD, glutamic acid decarboxylase; HbA1C, glycated haemoglobin.; PD-L1, programmed cell death ligand-1.

blood glucose levels were normal, ranging from 93 to 127 mg/dL, measured as recently as 3 weeks prior. No diabetes-related antibodies were checked prior to diagnosis. The patient did not have a prior history of autoimmune disease, and no other immune-related adverse events were identified. TSH, free T4, free T3 and testosterone were normal. Thyroid peroxidase antibody, cortisol and ACTH were not checked. Prior testing for celiac disease, including serologies and HLA-DQ8 was negative. His BMI was 32.4 kg/m$^2$ and he had a family history of adult-onset type 2 diabetes mellitus in his mother and cousin.

The following events were noted after receiving atezolizumab:

- Nine weeks after initiation of atezolizumab (3 weeks after his last dose), he developed hyperglycaemia (glucose 379 mg/dL), fatigue and polyuria. His haemoglobin $A_{1C}$ was 8.2% (66 mmol/mol). He was started on metformin and basal-bolus insulin.
- Investigations included c-peptide 1.1 ng/mL (normal, 0.8–3.1 ng/mL) with blood glucose 386 mg/dL. GAD antibodies were elevated at 28.4 U/mL (normal, <1 U/mL). Islet cell antibodies were negative. Metformin was stopped.
- Two months later, c-peptide was 0.6 ng/mL with blood glucose 336 mg/dL. He had no history of pancreatic tumour invasion or glucocorticoid use.
- Due to his cancer progression, he was switched to gemcitabine and cisplatin. He continued to require insulin therapy for his diabetes despite stopping anti-PD-L1 therapy. Unfortunately, he succumbed to his cancer a year later.

## DISCUSSION

These cases add to the emerging literature that cancer treatment with PD-L1 inhibitors may precipitate the onset of autoimmune diabetes. They are the first cases reported with positive pancreatic autoantibodies. The low c-peptide levels and positive GAD antibodies suggest a mechanism of autoimmune islet cell destruction. The patients' atypical age and acuity of onset following anti-PD-L1 antibody therapy suggest a causative role. Furthermore, there are preclinical data that point to specific mechanisms.

Anti-PD-L1 antibodies are effective anticancer agents that stimulate the immune system to induce tumour cell death.[6] Normally, the binding of PD-1 and B7 on the surface of T-cells to PD-L1 on tumour cells and macrophages causes T-cell deactivation. Blockade of the PD-1/PD-L1 pathway prevents this deactivation, which leads to tumour destruction. However, non-specific immunological activation whereby T-cells react to self-antigens can lead to immune-related adverse events. Common side effects of PD-1/PD-L1 inhibitors include immune-related dermatitis, colitis, hepatitis, pneumonitis and endocrinopathies such as hypophysitis, thyroid disorders and adrenal insufficiency.[7] However, hyperglycaemia is a rare adverse event occurring in up to 1% of patients.[5] Autoimmune diabetes has been reported as a rare side of effect PD-1 inhibitors, with several pancreatic autoantibody positive cases.[4 8] However, there are only two reported cases of presumed autoimmune diabetes occurring after PD-L1 inhibitors and both lack evidence supporting an autoimmune mechanism. In the first case, c-peptide was low but GAD and anti-insulin antibodies were negative.[4] Pancreatic autoantibodies and c-peptide were not available in the second case.[5] In those who develop autoimmune diabetes after receiving PD-1 and PD-L1 inhibitors, reports suggest insulin is required lifelong.[2 4 5]

The mechanism of diabetes onset has been shown in preclinical studies. PD-1 pathway blockade rapidly precipitates the onset of autoimmune diabetes in the non-obese diabetic (NOD) mouse model.[9] More specifically, PD-L1 blockade increases proliferation of CD4 +T helper type 1 cells, which promotes CD8 +cytotoxic T-cell infiltration of the pancreas leading to rapid destruction of islet cells in genetically predisposed mice.[10]

Although anti-PD-1 and anti-PD-L1 antibodies act on the same pathway, they have mechanistic differences, which may be clinically relevant. For instance, unlike PD-1 inhibitors, PD-L1 inhibitors block the binding of PD-L1 to B7-1 on T-cells, which also results in T-cell downregulation.[11] In NOD mice, blockade of PD-L1 resulted in greater rates of diabetes and GAD-reactive T-cells than PD-1 blockade.[9]

These cases are examples of autoimmune diabetes developing in patients without a history of autoimmune disease or evidence of other immune-related adverse effects. Based on these observations, we recommend checking pancreatic autoantibodies in patients without a history of diabetes who develop even mildly elevated blood glucose, so that appropriate treatment can be initiated before complications arise. Clinicians should be aware that onset of diabetes may be immediate or delayed by many months.[8] Unfortunately, HLA typing was not available in these patients, so we do not know if they would have been predisposed to type 1 diabetes regardless of immune check point inhibitor therapy. Conversely, we do not know if patients without a predisposing HLA type develop type 1 diabetes with these agents. Further research is needed to determine if HLA typing in patients prior to starting these agents would be helpful in predicting predisposition to type 1 diabetes.

## Learning points

- Autoimmune diabetes mellitus should be recognised as a rare side effect of anti-PD-L1 antibodies, a category of immune checkpoint inhibitors.
- The onset of diabetes may range from weeks to months and may occur in patients without evidence of other immune-related adverse effects or prior history of autoimmune disease.
- We recommend checking pancreatic autoantibodies and c-peptide in patients who develop even mildly elevated blood glucose so that patients can be treated promptly and avoid complications such as diabetic ketoacidosis.

**Contributors** The following authors made the following contributions to this manuscript. 1. JW was instrumental in the acquisition of data of each of the patients reviewed in this case report. She was also involved in review of outside literature as well as reporting of the cases. 2. AD was involved in the care of both patients and provided contributions in reporting as well as analysis and interpretation of the data. 3. AD was involved in the care of the first patient and provided contributions in reporting as well as analysis and interpretation of the data. 4. MF was involved in the care of the second patient, planning, reporting as well as analysis and interpretation of the data. All authors are in agreement with submitting these cases as reported, including background, case presentations and discussion.

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