CASE REPORT

Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma

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SUMMARY

Immune checkpoint inhibitors offer patients with advanced melanoma substantial improvements in survival. Unlike chemotherapy, immune checkpoint inhibitors such as ipilimumab and pembrolizumab cause unique immune-related adverse events (irAEs), including the development of endocrinopathies. We report a case of a man aged 60 years who developed diabetic ketoacidosis (DKA) following the use of pembrolizumab for the treatment of metastatic melanoma. He received four cycles of ipilimumab, before proceeding to pembrolizumab. Five weeks after initiating pembrolizumab, he presented in DKA with a pH of 7.0, bicarbonate of 7 mmol/L, blood glucose of 27 mmol/L and serum ketones of 5.9 mmol/L. Antibodies to glutamic acid decarboxylase (anti-GAD) and Islet antigen 2 (IA-2) were negative and C-peptide was low at 57 pmol/L (300–2350 pmol/L). There was no personal or family history of autoimmune conditions. Standard immunosuppression for irAEs was started using prednisolone in an attempt to salvage β cell function but was unsuccessful. To the best of our knowledge, this is the first reported attempt at reversing pembrolizumab-induced type 1 diabetes using glucocorticoids.

BACKGROUND

Programmed-death-1 (PD-1) inhibitors are widely used for the treatment of metastatic melanoma and are increasingly indicated for a range of other tumour types, including lung and renal cell carcinoma. Clinicians should be aware of important immune-related adverse events (irAEs) and of responses to immunosuppression used to ameliorate irAEs. The latter has not been previously described in the setting of PD-1 inhibitor-induced type 1 diabetes.

CASE PRESENTATION

A Caucasian man aged 60 years presented with a 6-month history of persistent dry cough. Chest X-ray and CT scan demonstrated a 4 cm hilar lesion obstructing the anterior segment of his right upper lobe. Bronchoscopy and endobronchial laser was performed to relieve the obstruction and establish the histopathological diagnosis. Histopathology was consistent with melanoma, given the strong and diffuse S100 staining as well as expression of SOX10 in subsequent biopsies. The origin of the primary was unknown. A brain MRI demonstrated a 21×16 mm homogeneously T2 hyperintense lesion abutting the right internal carotid within the

parapharyngeal space. FDG PET demonstrated oligometastatic disease with a highly avid right hilar mass, a 4 cm soft tissue mass involving the ascending colon and a 3 cm lesion in the left buttock (figure 1A).

Following repeat biopsy, BRAF, NRAS and KIT genotyping did not show mutations in these oncogenes. He was treated as per 'wild type' metastatic melanoma with ipilimumab 3 mg/kg intravenously. Shortly after his first treatment of ipilimumab, he presented with a partial bowel obstruction secondary to malignant intussusception from the previously visualised ascending colon melanoma mass (figure 1A). The causative melanoma deposit was excised via an open right hemicolectomy.

Postoperatively, there were no significant complications and he completed four cycles of ipilimumab but progressed 2 days after the final infusion with worsening dry cough and dyspnoea at rest. Repeat CT and PET scans demonstrated progressive disease with a 56×31 mm right hilar mass again causing collapse of the anterior aspect of the right upper lobe (figure 1B). Multimodal therapy with bronchoscopic laser followed by radiotherapy to the right upper lobe (20 Gy over 5 fractions) was completed within 3 weeks of his final ipilimumab infusion and was successful in relieving the right upper lobe obstruction.

Five weeks after completion of ipilimumab, pembrolizumab, a PD-1 inhibitor, was initiated at 2 mg/kg intravenously. After two doses of pembrolizumab (week 5), he presented with a 2-day history of polyuria and polydipsia in the absence of an infective precipitant and was found to be in diabetic ketoacidosis (DKA). There was no personal or family history of type 1 diabetes, thyroid or other autoimmune disease and previous glucose tests had been normal.

At presentation, his blood glucose was 27 mmol/L, serum ketones were high at 5.9 mmol/L, bicarbonate low at 7 mmol/L with a corresponding serum pH of 7.0. A concomitant C-peptide level was low at 57 pmol/L, albeit 4 hours following insulin administration. His HbA1c was 7.1% (54 mmol/mol) (normal range: 4–6%, 20–42 mmol/mol), indicating insulin deficiency of a short duration. Antibodies to GAD and IA-2 were negative. He also had mild thyroid dysfunction with a thyroid-stimulating hormone of 0.01 mU/L (N 0.30–5.00 mU/L), T4 26.4 pmol/L (N 7.5–21.0 pmol/L) and T3 4.6 pmol/L (N 3.8–6.0 pmol/L). Thyroid antibodies were negative. A lipase level was

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Figure 1 Serial FDG PET: (A) baseline FDG PET showed oligometastatic disease involving a highly avid right hilar mass, 4 cm soft tissue mass involving the ascending colon and a 3 cm lesion in the left buttock. (B) Following completion of four cycles of ipilimumab, he developed right upper lobe obstruction secondary to the right hilar mass (now 5.1 cm) requiring endobronchial laser and palliative radiotherapy. Following two doses of pembrolizumab, he sustained DKA and systemic treatment was halted. (C) His PET scan 5 weeks postpembrolizumab showed a near-complete metabolic response with his buttock lesion regressing to from 4.2 to 0.9 cm. (D) Serial imaging at 13 months displayed a sustained complete metabolic response with resolution of his right hilar and left buttock metastases.

normal at 20 U/L (N 0–60 U/L). He was managed according to a standard DKA protocol and was subsequently transitioned to regular subcutaneous insulin and educated in diabetes self-management.

After multidisciplinary case discussion and literature review, six cases of type 1 diabetes with PD-1 inhibitors were noted at the time of presentation, but no cases described attempts to retrieve pancreatic islet cell function using corticosteroid immunosuppression for irAEs.^{1 2} In an effort to reverse his diabetes, immunosuppression was trialled using oral prednisolone at 2 mg/kg for 3 days, then 1 mg/kg for 10 days with a weaning schedule for a total of 6 weeks treatment, consistent with standard irAE therapy. *Pneumocystis jiroveci* prophylaxis was provided using trimethoprim+sulfamethoxazole (160+800 mg) orally daily. Expected insulin resistance occurred and insulin doses were escalated to control blood glucose levels.

Given the rapid and dramatic response to pembrolizumab, no further oncological treatment has been required to date.

INVESTIGATIONS

Insulin is produced as a preprohormone that is cleaved in equimolar amounts of C-peptide and insulin on release into serum. C-peptide levels reflect the body's endogenous pool of insulin. Type 1 diabetes is classically defined as a state of relative or absolute insulin deficiency relative to blood glucose levels, with low measured c peptide.

However, the administration of exogenous insulin can suppress endogenous insulin production and also result in low C-peptide levels.

Furthermore, prednisolone causes insulin resistance and hyperglycaemia, increasing insulin requirements. Thus, monitoring for a response to prednisolone therapy in this case was

complex. Blood glucose levels and changes in insulin requirements were difficult to interpret in the context of high-dose glucocorticoids and C-peptide levels may have been suppressed by exogenous administration of insulin. While the presence of anti-GAD and/or anti-IA2 antibodies can assist in the diagnosis of type 1 diabetes, they are only present in up to 85% of patients with type 1 diabetes.³

Many weeks following completion of prednisolone therapy, our patient remained hyperglycaemic and insulin-dependent, quickly becoming ketotic with insulin omission, suggesting that he had not normalised his islet cell function. Although a glucagon challenge test was not performed, repeat C-peptide levels were measured weekly for the first 8 weeks and at 3 and 6 months following his initial presentation and remained undetectable. IA-2 and anti-GAD auto-antibody testing were also repeated 6 months following his presentation and were again negative.

Given that other endocrinopathies such as hypophysitis and primary adrenal dysfunction are well-described irAEs, pituitary and adrenal function were tested and found to be normal.

DIFFERENTIAL DIAGNOSIS

Melanoma of unknown primary with spindle cell morphology can be confused with malignant peripheral nerve sheath tumours (MPNST).⁴ MPNST are rare entities and may arise from neurofibromas but can also have similar appearances to synovial sarcoma and fibromyxoid tumours. Immunohistochemistry of melanoma and MPNST can exhibit S100 and SOX-10 staining. However, melanoma can be distinguished by the presence of specific markers such as HMB-45, Melan-A and tyrosinase. In our case, immunohistochemistry of these melanoma specific markers was absent; however, the diagnosis was secured on the

basis of strong diffuse S100 staining as well as SOX-10 staining combined with morphological findings, including epithelioid cells and notable lymphocytic infiltration.

The diagnosis of type 1 diabetes is typically made following a clinical presentation with polydipsia, polyuria, often with preceding weight loss. This is accompanied by a high serum glucose level and an inappropriately low C peptide and glycated haemoglobin A1c >6.5% (48 mmol/mol). The presence of high blood ketones is also supportive of absolute insulin deficiency, the hallmark of type 1 diabetes and helps to differentiate it from type 2 diabetes.⁵ However, a subset of patients with type 2 diabetes are also prone to ketosis, known as 'ketosis prone type 2 diabetes'.⁶ These patients are typically middle aged, have a family history of type 2 diabetes and may have markers suggesting insulin resistance such as obesity or acanthosis nigricans.⁷ Autoantibodies are typically negative. They may present with DKA following an acute insult such as infection, and develop ketones as a result of insensitivity to insulin and/or a transient loss of ability to release adequate amounts of endogenous insulin to counter the insult. Following a DKA episode and improvements in β -cell function, these patients do not always require ongoing insulin therapy.^{6, 8} Excluding secondary causes of diabetes, such as pancreatic insufficiency (eg, due to cystic fibrosis, haemochromatosis, chronic pancreatitis pancreatic ischaemia), drugs (eg, corticosteroids, protease inhibitors, ciclosporine), endocrinopathies such as Cushing's syndrome and acromegaly that may cause or exacerbate underlying diabetes primarily through increased insulin resistance, is also essential prior to making the diagnosis.

Our case presented with all the clinical and biochemical features of type 1 diabetes, albeit with negative anti-GAD and anti-IA2 antibodies and required maintenance insulin therapy.

OUTCOME AND FOLLOW-UP

Our patient was subsequently discharged with ongoing ambulatory endocrine phone and clinic visits to support care, alongside primary oncology follow-up.

Pembrolizumab was ceased, given the severity of the immune-related toxicity. After a starting schedule of 150 mg for 3 days (2 mg/kg), oral prednisolone was given for 10 days at 75 mg/kg (1 mg/kg) with a weaning schedule of 25 mg/week. When the prednisolone dose reached 25 mg, it was further weaned to 10 mg and ceased after a total treatment period of 6 weeks. Unfortunately, there was no recovery of islet cell function. He remained insulin-dependent following prednisolone cessation with a total daily insulin dose of ~0.8 units/kg, consistent with doses frequently required in patients with type 1 diabetes. He now has presumed permanent type 1 diabetes, management of which has proved challenging for the patient and required ongoing diabetes unit support. His thyroid abnormalities resolved without further intervention.

Follow-up FDG PET 6 weeks after his second dose of pembrolizumab demonstrated a dramatic near-complete metabolic response (figure 1C). There was only faint FDG uptake in his right upper lobe mass and the left buttock mass had regressed from 4.2 to 0.9 cm. Serial FDG PET scans to 13 months post-pembrolizumab display a sustained response with resolution of the buttock and lung masses (figure 1D).

DISCUSSION

Immune checkpoint inhibitors such as ipilimumab and pembrolizumab form part of the armamentarium of systemic treatment against advanced melanoma. Ipilimumab is an anti cytotoxic-lymphocyte antigen-4 (CTLA-4) antibody which promotes

T-cell signalling during antigen presentation by dendritic cells and therefore facilitates adaptive immune responses to melanoma. Pembrolizumab and nivolumab are anti-PD-1 inhibitors. On binding of cytotoxic T cells (CD8+) bearing PD-1 with PD-L1 on melanoma cells, immune responses are halted. Pembrolizumab disrupts the PD-1 to PD-L1 axis and facilitates immune responses to melanoma.

Although long-term survival data are pending, pembrolizumab has surpassed ipilimumab as the first-line immune checkpoint inhibitor for advanced melanoma with superior efficacy and tolerability in a recent phase III trial.⁹ Objective response rates to pembrolizumab were 36% compared with 13% with ipilimumab, which translated to significantly improved 24-month survival rates of 55% versus 43%, respectively.¹⁰ Importantly, the rate of severe or life-threatening CTCAE (Common Terminology Criteria for Adverse Events) grade 3–4 immune-related adverse events such as rash, diarrhoea, colitis, endocrinopathies, pneumonitis and hepatitis are significantly lower with PD-1 inhibitors compared with ipilimumab (16–19% vs 4–8%).^{9, 11} PD-1 inhibitors are thought to exert fewer irAE due to its specific mode of action at the tumour micro-environment level as opposed to ipilimumab, which promotes T cell priming within lymph nodes.

The most common endocrinopathy associated with pembrolizumab and other PD-1 inhibitors is thyroid dysfunction, occurring in 10–15% of patients.^{9, 11} Hypothyroidism and hyperthyroidism, including transient thyroiditis, usually do not lead to serious sequelae with close management and replacement therapy as required. Hypophysitis is a well-described irAE to ipilimumab occurring in ~2–4% of treated patients, but is infrequent with PD-1 inhibitors (<1%).¹¹ Although patients with hypophysitis can present in extremis with hypotensive shock, appropriate pituitary axis testing and hormone replacement therapy usually leads to good outcomes.^{12, 13}

To the best of our knowledge, there have been no reported cases of type 1 diabetes secondary to ipilimumab monotherapy. However, sporadic cases of type 1 diabetes following administration of PD-1 inhibitors have been described in patients with advanced melanoma, renal cell carcinoma or non-small cell lung cancer of variable onset of within 1 week to 5 months of treatment.^{1, 2, 14–20} The presence of antibodies to GAD and IA-2 antibodies is variable. Of the published case reports (n=10), three patients had high titres positive to GAD or IA2, two were only weakly positive and five cases had negative antibodies.^{2, 17–20} A further five cases have been reported; however, the antibody status of the patients was not documented.⁹ The antibody status of these patients has not been associated with duration or type of PD-1 inhibitor therapy. There have been sporadic cases of type 1 diabetes in trials of PD-1 inhibitors, but antibody data are sparse from these studies. HbA1c levels have also been variable, some as low as 6.85% (52 mmol/mol),²⁰ perhaps indicating more rapid β -cell destruction and a shorter duration of dysglycaemia. This may be comparable to the presentation of fulminant type 1 diabetes, prevalent in East Asia, characterised by an abrupt onset of DKA, low HbA1c, negative autoantibodies and an abnormal glucagon stimulation test.^{21, 22} However, these patients typically also have elevated pancreatic enzymes, a feature not present in our patient. The exact mechanisms underlying the predisposition to and pathophysiology of diabetes irAE remain unknown and could be related to underlying genetic predisposition or HLA genotype.^{1, 2} Patients invariably sustain permanent insulin deficiency with PD-1 inhibitor-induced type 1 diabetes, but one patient did regain islet cell function following cessation of the drug.¹⁶ Additionally, most patients who

developed type 1 diabetes secondary to a PD-1 inhibitor also displayed an antitumour response.^{1 16 17 20}

Management algorithms of irAE have been developed based on early experience with ipilimumab.²³ First-line management of grade 3 irAE are immunosuppressive corticosteroids at 1–2 mg/kg/day methylprednisolone intravenously for 2–3 days before conversion to oral prednisolone with a weaning period over 4–6 weeks in an attempt to reverse the affected organ from immune-mediated damage. Colitis that does not respond to corticosteroids may require additional immunosuppression with tumour necrosis factor- α (TNF- α) inhibitors. Notably, the use of immunosuppression to ameliorate irAEs from ipilimumab or combination ipilimumab–nivolumab does not appear to alter efficacy.^{24–26} Generally, endocrinopathies are irreversible, but appropriate replacement and close monitoring are sufficient to manage these irAEs safely. Primary hypothyroidism, the most common observed thyroid perturbation however, is often permanent necessitating lifelong thyroxine therapy.²⁷ Likewise, hypophysitis is invariably permanent but can be life-threatening without early recognition and appropriate hormone replacement using standard regimens. However, one case of hypophysitis has reported return of the pituitary–adrenal axis.^{23 28} The incidence of irAEs appears to be independent of response to ipilimumab treatment.^{25 26}

Glucocorticoids are effective in reversing many of the irAEs; however, they are generally considered toxic to β cells. Thus, it may be possible that other immunomodulating agents may be more appropriate in reversing immunotherapy-induced type 1 diabetes. Rituximab, a monoclonal antibody that targets the CD20 receptor unique to B-cells, antithymocyte globulin, TNF- α and IL-1 receptor antagonists are under investigation for the treatment and/or prevention of type 1 diabetes in the general population, without proven efficacy.²⁹ It is unclear whether they would have efficacy in reversing the development of type 1 diabetes following immunotherapy.

In addition to our attempt at reversing his type 1 diabetes with corticosteroids, our case is notable for the usage of multimodality treatment that led to a deep and prolonged response after life-threatening progression of the melanoma. Complete radiological responses to pembrolizumab for melanoma occur in ~12% of patients.¹⁰ The combination of ipilimumab, with sequential radiotherapy and pembrolizumab, may have resulted in the observed rapid, deep response, which would have been expected infrequently with PD-1 inhibitor monotherapy. The major precipitant of the onset of type 1 diabetes is mostly likely due to pembrolizumab; however, preclinical models of PD-1 or CTLA-4 inhibition implicate these agents in the development of type 1 diabetes.^{30–32} Additionally, the elimination half-life of ipilimumab is ~15 days and in our case, pembrolizumab was started 5 weeks after the final ipilimumab dose. Hence, the CTLA-4 antibody would not have undergone complete systemic elimination and concurrent administration of the two immune checkpoint inhibitors synergistically increase response rate and irAEs.¹¹ Interestingly, one report of fulminant diabetes secondary to pembrolizumab given soon after ipilimumab, also lead to a deep response.²⁰ Furthermore, radiation may synergise with immune checkpoint inhibitors by expanding the diversity of the T-cell receptor repertoire.³³ Hence, ipilimumab and radiation may have contributed to our patient's response and development of type 1 diabetes.

Endocrinopathies and hormonal deficiencies are generally an accepted sacrifice for the benefit of survival in patients treated with immunotherapy for metastatic melanoma. However, as many patients will have longlasting benefits from their

immunotherapy, the burden of irAEs, especially hypophysitis and type 1 diabetes, can significantly impact quality of life and should not be disregarded. Clinicians should be aware of the development of endocrinopathies with PD-1 inhibitors as indications for these therapies increase. Additionally, the use of other novel immune checkpoint inhibitors and/or radiation in conjunction with PD-1 inhibitors may further increase the incidence of irAEs. Further research is necessary to determine whether other immunosuppressive therapies may be more effective in reversing PD-1-induced type 1 diabetes.

Learning points

- ▶ The development of type 1 diabetes as an immune-related adverse event (irAE) is uncommon, but clinically important to recognise.
- ▶ Our case is the first reported to attempt reversal of β cell dysfunction using immunosuppressive glucocorticoids; however, glucose control deteriorated and benefit was not observed. Other immunosuppressive agents such as monoclonal antibodies, which are not toxic to the pancreatic islet cell, may be more effective.
- ▶ The burden of irAEs will likely increase with increased patient survival and expanding indications for immune checkpoint inhibitors for other tumour types, including non-small cell lung cancer and renal cell carcinoma, among others.
- ▶ Immune check point inhibitors have resulted in improved long-term survival rates in patients with metastatic melanoma.

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