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Case Report

Diabetes associated with immune checkpoint inhibition: presentation and management challenges

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What's new?

- Immune checkpoint inhibitor-related Type 1 diabetes is rare in clinical trials, but case reports published between 2015 and 2017 suggest that real-world incidence may be higher than previously anticipated.
- We describe nine cases of this life-threatening immune-mediated Type 1 diabetes. To our knowledge this is the largest series reported in the literature to date.
- Patients presented with fulminant, symptomatic hyperglycaemia within weeks of commencing immune checkpoint inhibitors.
- The unprecedented survival benefit seen with immune checkpoint inhibitors across many cancers is anticipated to result in their widespread use as a single agent and in combination with other cancer therapies in the near future.

Abstract

Background In recent years, immune checkpoint blockade has become a standard therapy for a wide range of cancers. Adverse events, including endocrinopathies, result from the induction of autoimmunity.

Case report We report a case series of nine individuals who presented with immunotherapy-induced Type 1 diabetes between 2015 and 2017. Onset of diabetes occurred within 12 weeks of commencing therapy. Anti-glutamic acid decarboxylase antibodies were present in six people. Retrospective testing of islet antibodies in pre-treatment samples was possible in two people and this revealed anti-glutamic acid decarboxylase seroconversion in the first and high anti-glutamic acid decarboxylase titres pre- and post-treatment in the second person. Six people had high risk human leukocyte antigen haplotypes. Clinical and genetic factors are described and compared with previously published cases.

Conclusion

Introduction

Immunotherapy is based on the premise that an enhanced immune system can recognize and eradicate cancers. Checkpoint blockade with cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 pathway (PD1/PD-L1) is rapidly becoming the standard of care in a range of cancers, including melanoma, non-small-cell lung cancer, renal cell carcinoma and head and neck cancer, with unprecedented impact on overall survival [1–5].

CTLA-4 and PD1 are inhibitory cell-surface receptors expressed on activated T cells that limit immune activation. In contrast to anti-CTLA-4, which amplifies T-cell activation in lymphoid organs and tumours, anti-PD1 predominantly overcomes exhaustion of anti-tumour T effector cells within the tumour bed. T-cell exhaustion represents a state of cellular dysfunction induced during chronic antigen/tumour exposure, leading to failure to control tumour progression [6]. A common analogy is that checkpoint inhibitors act by 'releasing the brakes' on the immune system to combat the tumour [7]. Conversely, T-cell exhaustion phenotypes are thought to confer better prognosis in autoimmune diseases. With restoration of exhausted T-cell function mediated by PD1 pathway blockade, induction of collateral immune-related adverse events (AEs) such as rash, hepatitis, nephritis, pneumonitis, colitis and endocrinopathies are common. While most immune-related AEs are responsive to immunosuppression, endocrinopathies tend to be irreversible and require ongoing hormone replacement [8].

The incidence of immunotherapy-induced Type 1 diabetes is reported to be ~0.4% [1]; however, reports suggest that the real-world incidence may be significantly higher [8–32]. Cohort studies of islet antibody-positive people (mainly first-degree relatives of people with Type 1 diabetes) have found that ~10% with a single positive antibody will progress to Type 1 diabetes [33]. Factors that lead to progression to diabetes may include differences in gene expression of diabetogenic T cells, viral antigen reactivity and metabolic pathways used by autoreactive T cells [34]. The relationship between PD1 and its ligands in the development of diabetes has been established in mice. PD1–PD-L1 interaction inhibits the activation, expansion, and effector function of islet-reactive T cells through the lifespan of the animal [35].

In keeping with the mechanism of PD1 pathway blockade, one hypothesis is that progression to fulminant islet autoimmunity may be increased or accelerated in a proportion of healthy individuals with positive islet antibodies.

Research design and methods

We describe our experience of nine people presenting with anti-PD1-mediated Type 1 diabetes between 2015 and 2017. Treatment was undertaken at two tertiary centres in Melbourne, Australia: the Peter MacCallum Cancer Centre and Eastern Health. The authors were responsible for management and follow-up. Demographics, treatment history, diabetes

presentation, the presence of islet antibodies and human leukocyte antigen (HLA) type were characterized. Where feasible, serum obtained before treatment commenced was tested for evidence of pre-existing islet autoimmunity.

A literature review of PubMed and Medline for case reports of anti-PD1-related diabetes identified 28 cases. Clinical information from our series was compared with published cases, with a focus on timing and kinetics of diabetes in relation to commencing anti-PD1-based therapy, the presence of high-risk HLA genotype and pre-treatment evidence of islet autoimmunity that could account for the accelerated development of diabetes.

Results

Demographics and clinical characteristics are detailed in Table 1. Biochemistry, HLA genotype and islet antibodies are summarized in Table 2. Individuals were aged 23–82 years and presented within 1–12 weeks (mean 6.4 weeks, median 6 weeks) of the first dose of anti-PD1 treatment with diabetic ketoacidosis (DKA) or symptomatic hyperglycaemia requiring hospital admission. Person 1 had an existing history of autoimmunity (rheumatoid arthritis). Person 9 had a history of Type 2 diabetes treated with metformin, a sulfonylurea and empagliflozin. In four people who developed other immune-related AEs, diabetes was the first immune-related AE to manifest. Person 1 presented 6 weeks after anti-PD1 treatment with DKA and concomitant pancolitis. Person 5 presented 8 weeks after anti-PD1 treatment with DKA and thyroiditis. Six months later he developed a widespread rash and inflammatory polymyositis. Person 6 presented with DKA 6 weeks after anti-PD1 treatment, while thyroiditis and rash occurred 6 months later. Person 8 was diagnosed with DKA 12 weeks after treatment and hypophysitis 6 weeks later. Three people received prior anti-CTLA4 therapy. There was no significant difference in diabetes presentation compared with those treated with PD1 inhibitor monotherapy. Person 7 was treated with glucocorticoids in an attempt to salvage β -cell function, with no improvement in glycaemia. A full report of this case has been published by Aleksova *et al.* [19].

Antibodies to glutamic acid decarboxylase (GAD), tyrosine phosphatase-related islet antigen 2, insulin and zinc co-transporter 8 were measured. GAD antibody was positive in six out of nine people. Pre-treatment testing in person 4 identified GAD antibodies >1000 U/mL (reference range <5 U/mL). Conversely, person 8 had undetectable pre-treatment GAD

antibodies and demonstrated seroconversion 12 weeks after treatment to 7.6 U/ml. HLA typing was performed in six of the nine people in our series. All had at least one high-risk class II HLA allele (DR3, DR4, DQ2 or DQ8). Person 6 had both susceptibility and resistance haplotypes. The 28 previously published cases between 2015 and 2017 are summarized in Table 3.

Discussion

Consistent with other reports, the majority of people in our series presented with DKA within weeks of starting anti-PD1-based therapy. HbA_{1c} tended to be lower at onset, in keeping with rapid islet destruction and hyperglycaemia, allowing less time for glycosylation of haemoglobin. Individuals exhibited marked glycaemic variability, with frequent episodes of hypoglycaemia despite regular insulin adjustment. This rapid onset and fulminant course implies an accelerated islet autoimmunity in contrast to the more protracted kinetics of spontaneous Type 1 diabetes in children and young adults [33,34]. It is noteworthy that immunosuppressive doses of corticosteroids are not helpful in reversing islet cell destruction. The result is phenotypic Type 1 diabetes, with features of fulminant diabetes described in Japan, Korea and in a case published in Australia [36]. Nine of the published cases highlight this distinct phenotype (Table 3). Understanding how PD1 blockade impacts immune response in individuals with varying autoimmune susceptibility is critically important.

C-peptide level was low in most cases despite presenting in <12 weeks. Similar rapid progression to diabetes was seen in people with diabetes given islet transplantation from their co-twin or HLA-matched sibling who, given HLA identity, received little or no immunosuppression [37]. This observation provided critical evidence that Type 1 diabetes is an autoimmune disease. The effect is attributable to endogenously accumulated islet reactive activated memory T cells in the diabetic sibling which caused rapid graft failure. In PD1 inhibitor treatment, T cells are activated by exogenous intervention. In both situations, β cells are exposed to a high number of activated T cells over a short period of time.

The prevalence of GAD antibody positivity in most published cases is in keeping with GAD being the most common antigen specificity in adult-onset Type 1 diabetes [38]. Person 4 in our series had elevated levels of GAD antibodies pre-treatment and these remained high throughout therapy. This finding was also reported by Gauci *et al.* [30]. By contrast, the GAD

antibody titre in person 8 was <0.6 U/ml pre-treatment, but elevated at 7.6 U/ml at diabetes presentation. Lowe *et al.* [18] described a similar outcome of GAD antibody seroconversion and development of DKA 2 weeks after the third infusion of combination ipilimumab/nivolumab.

Collectively, in our series and other published cases, there were 18 people with elevated GAD antibodies at diabetes presentation and 17 without.

Person 9 had pre-existing Type 2 diabetes which was well controlled on triple oral antihyperglycaemic agents. Matsumura *et al.* [24] also described a person with pre-existing diet-controlled diabetes, who developed severe hyperglycaemia with very low C-peptide level and persistently negative GAD antibody on nivolumab. Person 9 had been on a stable dose of a sodium-glucose co-transporter-2 (SGLT2) inhibitor for over 6 months and was well on the day of anti-PD1 treatment. This individual presented with DKA 2 days after pembrolizumab therapy, but remained antibody-negative. In this case, C-peptide level was higher at diabetes presentation than in other cases. SGLT2 inhibitors have been associated with euglycaemic DKA when used to treat both Type 1 and Type 2 diabetes. The exact contribution of the SGLT2 inhibitor to the rapid manifestation of DKA remains uncertain. It is plausible that ketosis was accelerated during early autoimmune pancreatic destruction, resulting in a relatively preserved C-peptide concentration in this person. There have been no published cases of DKA in the setting of combined SGLT2 and PD1 inhibitor use; however, caution should be exercised in this cohort, particularly as development of DKA 2 days after immune checkpoint inhibitor administration is the earliest pancreatic immune-related AE reported to date. Unfortunately, HLA-typing was not possible in this case but may have been useful in delineating aetiology.

Notably, the six that were HLA-typed in the present series demonstrated high risk alleles. Preclinical studies support the premise that PD1 loss may induce specific autoimmune disease depending on pre-existing genetic background [39]. In published cases, 14 people had at least one high risk HLA allele, two had high risk and protective alleles, three had no high risk alleles and 11 reports did not record HLA (Table 3). The clinical utility of HLA-typing and baseline islet antibody testing to stratify risk and manage potential immune-related AEs remains to be prospectively evaluated.

Understanding the underlying mechanisms of immune-related AEs may provide insights and facilitate the development of targeted approaches to deal with the autoimmune side effects of immune checkpoint inhibitors. Recent studies have shown that blocking interleukin-7 receptor- α with monoclonal antibodies in non-obese diabetic mice has been shown to prevent and reverse autoimmune diabetes by inducing exhaustion of auto-reactive T cells [40]. In humans, abatacept (CTLA-4 Ig) was found to increase endogenous C-peptide production in newly diagnosed Type 1 diabetes and is now being trialled in antibody-positive relatives with normal glucose tolerance [41].

In conclusion, PD1 inhibitor-induced diabetes is a rare and irreversible complication. As checkpoint inhibitors become standard of care in many tumour types and with the introduction of combination approaches, we anticipate an increased incidence of iatrogenic Type 1 diabetes. The clinical phenotype is a steroid-unresponsive, accelerated and fulminant islet autoimmunity that usually presents with DKA. People receiving anti-PD1 therapy should receive education on recognizing symptoms of hyperglycaemia to aid early presentation. This series has prompted a prospective study to investigate predictive risk factors, including pre-treatment islet antibodies and HLA status. This will clarify whether checkpoint inhibitors are an accelerator or initiator of Type 1 diabetes and guide future management and potentially prevention of this complication. Endocrinologists and oncologists need to be increasingly vigilant to ensure early recognition and prompt treatment for this life-threatening form of diabetes.

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None.

Competing interests

None declared.

References

1. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy – immune checkpoint blockade and associated endocrinopathies. *Nat Rev Endocrinol* 2017; **13**:195–207.
2. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A *et al*. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer.

N Engl J Med 2016;**375**:1823–1833

3. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;**373**:1803–1813
4. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L *et al.* Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015;**372**:2521–2532.
5. Ferris RL, Blumenschein GJ, Fayette J, Guigay J, Colevas AD, Licitra L *et al.* Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;**375**:1856–1867
6. McKinney EF, Lee JC, Jayne DR, Lyons PA, Smith KG. T cell exhaustion, costimulation and clinical outcome in autoimmunity and infection. *Nature* 2015; **523**:612–616.
7. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;**12**: 252–264.
8. Hoffman L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S *et al.* Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;**60**:190–209.
9. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P *et al.* Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;**366**:2455–2465
10. Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, Herold K. Precipitation of autoimmune diabetes with anti-PD1 immunotherapy. *Diabetes Care* 2015;**38**:e55–e57.
11. Mellati M, Eaton K, Brooks-Worrell B, Hagopian W, Martins R, Palmer J *et al.* Anti-PD-1 and Anti-PDL-1 monoclonal antibodies causing type 1 diabetes. *Diabetes Care* 2015;**38**:e137–e138.
12. Martin-Liberal J, Furness AJ, Joshi K, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. *Cancer Immunol Immunother* 2015; **6**: 765–767.
13. Gaudy C, Clévy C, Monestier S, Dubois N, Préau Y, Mallet S *et al.* Anti-PD1 pembrolizumab can induce exceptional fulminant type 1 diabetes. *Diabetes Care* 2015; **11**: e182–183.
14. Chae YK, Chiec L, Mohindra N, Gentzler R, Patel J, Giles F. A case of Pembrolizumab-induced type-1 diabetes mellitus and a discussion of immune check

- point inhibitor-induced type 1 diabetes. *Cancer Immunol Immunother* 2017; **66**: 25.
15. Godwin JL, Jaggi S, Sirisena I, Sharda P, Rao AD, Mehra R *et al*. Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer. *J Immunother Cancer* 2017; **5**:40.
16. Thoreau B, Gouaillier-Vulcain F, Machet L, Mateus C, Robert C, Ferreira-Maldent N *et al*. Acute lower limb ischaemia and diabetes in a patient treated with anti-PD1 monoclonal antibody for metastatic melanoma. *Acta Derm Venereol* 2017; **97**: 408–409.
17. Miyoshi Y, Ogawa O, Oyama Y. Nivolumab, an Anti-Programmed Cell Death-1 Antibody, Induces Fulminant Type 1 Diabetes. *Tohoku J Exp Med* 2016; **239**:155–158.
18. Lowe JR, Perry DJ, Salama AK, Mathews CE, Moss LG, Hanks BA. Genetic risk analysis of a patient with fulminant autoimmune type 1 diabetes mellitus secondary to combination ipilimumab and nivolumab immunotherapy. *J Immunother Cancer* 2016; **4**:89.
19. Aleksova J, Lau PK, Soldatos G, McArthur G. Glucocorticoids did not reverse type 1 diabetes mellitus secondary to Pembrolizumab in a patient with metastatic melanoma. *BMJ Case Rep* 2016; doi:10.1136/bcr-2016-217454.
20. Okomoto, M, Okamoto M, Gotoh K, Masaki T, Ozeki Y, Ando H *et al*. Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. *J Diabetes Investig* 2016; **7**:915–918.
21. Hansen E, Sahasrabudhe D, Sievert L. A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome. *Cancer Immunol Immunother* 2016; **65**:765–767
22. Teramoto Y, Nakamura Y, Asami Y, Imamura T, Takahira S, Nemoto M *et al*. Case of type 1 diabetes associated with less-dose nivolumab therapy in a melanoma patient. *J Dermatol* 2016; **44**:605–606.
23. Fukui A, Sugiyama K, Yamada T, Tajitsu M, Cao X, Nagai J *et al*. A Case of Nivolumab-Induced Fulminant Type 1 Diabetes with Steroids and Glucagon-Like Peptide 1 Administration during the Early Onset. *J Clin Case Rep* 2016; **6**:883.
24. Matsumura K, Nagasawa K, Oshima Y, Kikuno S, Hayashi K, Nishimura A *et al*. Aggravation of diabetes, and incompletely deficient insulin secretion in a case with type 1 diabetes-resistant HLA DRB1*15:02 treated with nivolumab. *J Diabetes Investig* 2018;**9**:438–441.

25. Shah M, Maxfield L, Feroz R, Donohue K. Rapid Development of Type 1 Diabetes Mellitus after Initiation of Anti-PD-1 Therapy. *Int J Cancer Clin Res* 2016; **3**:66.
26. Munakata W, Ohashi K, Yamauchi N, Tobinai K. Fluminant type 1 diabetes mellitus associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma. *Int J Hematol* 2017; **105**:383–386.
27. Asai S, [HYPERLINK "https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Takuyuki+Katabami"](https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Takuyuki+Katabami) Katabami T, [HYPERLINK "https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Shin+Kawanabe"](https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Shin+Kawanabe) Shin Kawanabe, Division of Metabolism and Endocrinology, Department of Internal Medicine, St. Marianna University School of Medicine Yokohama City Seibu Hospital" Kawanabe S, [HYPERLINK "https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Kana+Igarashi"](https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Kana+Igarashi) Kana Igarashi, Division of Metabolism and Endocrinology, Department of Internal Medicine, St. Marianna University School of Medicine Yokohama City Seibu Hospital" Igarashi K, [HYPERLINK "https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Hisashi+Fukuda"](https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Hisashi+Fukuda) Hisashi Fukuda, Division of Metabolism and Endocrinology, Department of Internal Medicine, St. Marianna University School of Medicine Yokohama City Seibu Hospital" Fukuda H, [HYPERLINK "https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Yasushi+Tanaka"](https://www.jstage.jst.go.jp/search/global/_search/-char/en?item=8&word=Yasushi+Tanaka) Yasushi Tanaka, Division of Metabolism and Endocrinology, Department of Internal Medicine, St. Marianna University School of Medicine" Tanaka Y. A Case of Fulminant Type 1 Diabetes Mellitus Developed After the Administration of Nibormab, a Immune Checkpoint Inhibitor. *J Japan Diabetes Soc* 2017; **60**: 237–243.
28. Li L, Masood A, Bari S, Yavuz S, Grosbach AB. Autoimmune Diabetes and Thyroiditis Complicating Treatment with Nivolumab. *Case Rep Oncol* 2017; **10**:230–234.
29. Hickmott L, De La Peña H, Turner H *et al.* *Targ Oncol* 2017; **12**: 235.
30. Gauci ML, Laly P, Vidal-Trecan T, Baroudjian B, Gottlieb J, Madjlessi-Ezra N *et al.* Autoimmune diabetes induced by PD-1 inhibitor —retrospective analysis and pathogenesis: a case report and literature review. *Cancer Immunol Immunother* 2017; **66**:1399–1410.

31. Usui Y, Udagawa H, Matsumoto S, Imai K, Ohashi K, Ishibashi M *et al.* Association of serum anti-GAD antibody and HLA haplotypes with type 1 diabetes mellitus triggered by nivolumab in patients with non-small cell lung cancer. *J Thorac Oncol* 2017; **12**:e41–e43.
32. Ishikawa K, Shono-Saito T, Yamate T, Kai Y, Sakai T, Shimizu F *et al.* A case of fulminant type 1 diabetes mellitus, with a precipitous decrease in pancreatic volume, induced by nivolumab for malignant melanoma: analysis of HLA and CTLA-4 polymorphisms. *Eur J Dermatol* 2017;**27**:184–185.
33. Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A *et al.* Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA* 2013;**309**:2473–2479.
34. Garyu JW, Uduman M, Stewart A, Rui J, Deng S, Shenson J *et al.* Characterization of Diabetogenic CD8+ T Cells: immune therapy with metabolic blockade. *J Biol Chem* 2016;**291**:11230–11240.
35. Ansari MJ, Salama AD, Chitnis T, Smith RN, Yagita H, Akiba H *et al.* The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. *J Exp Med* 2003;**198**:63–69.
36. Lee I, Harrison LC, Colman PG. Fulminant type 1 diabetes in Australia in the absence of humoral and cellular immune responses to pancreatic islet autoantigens. *Diabetes Res Clin Pract* 2012;**95**:e4–e6.
37. Sutherland DE, Sibley R, Xu XZ, Michael A, Srikanta AM, Taub F *et al.* Twin-to-twin pancreas transplantation: reversal and reenactment of the pathogenesis of type 1 diabetes. *Trans Assoc Am Physicians* 1984;**97**:80–87.
38. Wasserfall E, Montgomery L, Yu L, Michels A, Gianani R, Pugliese A *et al.* Validation of a rapid type 1 diabetes autoantibody screening assay for community-based screening of organ donors to identify subjects at increased risk for the disease. *Clin Exp Immunol* 2016;**185**:33–41.
39. Okazi T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. *Int Immunol* 2007;**19**:813–824.
40. Penaranda C, Kuswanto W, Hofmann J, Kenefeck R, Narendran P, Walker LS *et al.* IL-7 receptor blockade reverses autoimmune diabetes by promoting inhibition of effector/memory T cells. *Proc Natl Acad Sci U S A* 2012;**109**:12668–12673.

41. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R *et al.* Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;**378**:412–419.

Table 1 Demographics and clinical characteristics

Patient	Age/sex	Tumour type	Tumour stage	Immune check point inhibitor	Onset of diabetes since first Anti-PD1 exposure	RECIST Response /duration of response
1	70/M	Melanoma	IV M1b	Pembrolizumab	6 weeks	PR/20 months (Treatment discontinued at 6 weeks)*
2	82/M	SCC (oropharynx)	IV (T2N2C)	Pembrolizumab + carboplatin/5FU	9 weeks	SD/21 months (Treatment ongoing)
3	61/M	Melanoma	Resected IIIC	Pembrolizumab	8 weeks	SD/14 months (Treatment discontinued 8 weeks)*
4	53/F	Melanoma	IV M1b	Pembrolizumab +/- epacadostat	3 weeks	PR/8 months (Treatment ongoing)
5	23/M	Melanoma	IV M1b	Pembrolizumab	8 weeks	PR/21 months (Treatment discontinued at 7 months)*
6	61/M	Melanoma	IV M1b	Sequential ipilimumab, then pembrolizumab	6 weeks	PR/24 months (Treatment ongoing)
7	60/M	Melanoma	IV M1c	Sequential ipilimumab, then pembrolizumab	5 weeks	CR/29 months (Treatment discontinued at 1.5 months)*
8	50/M	Melanoma	IV M1c	Ipilimumab and nivolumab	3 months	SD/5 months (Treatment ongoing)
9	65/M	Melanoma	IV M1c	Pembrolizumab	2 days	Not restaged/1.5 months

(Treatment
withdrawn)*

CR, complete response; F female; M, male; PD, progressive disease; PD1, programmed cell death protein-1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; SCC, squamous cell carcinoma; SD, stable disease.

*Persons 1, 3, 5, 7 and 9 discontinued treatments at the time of diagnosis of Type 1 diabetes mellitus. They maintained the responses they had achieved despite no additional doses of anti-PD1 therapy. Person 3 received treatment in the adjuvant setting. He discontinued pembrolizumab after 8 weeks and remained disease free for a further 7 months before developing disease progression in the brain. Patient 5 discontinued pembrolizumab at 7 months because of several immune-related toxicities including myositis and Type 1 diabetes. He maintained the partial response for 21 months and has now progressed with intracranial metastases.

Table 2 Diabetes presentation

Patient	Relevant background	Diabetes presentation	Other immune toxicities	Biochemistry†	HbA1c	Antibodies	HLA§
1	CVID Rheumatoid arthritis	DKA	Colitis	Glucose 50 mmol/l Serum ketones 6 mmol/l pH 6.99	73.8 mmol/mol (8.9%)	GAD >2000 U/mL (<5) IA2 <0.3 U/mL (<15) Insulin Ab 0.3 U (<0.7)	-
2	-	Symptomatic hyperglycaemia with ketosis	Hypothyroidism, rash, arthritis	Glucose 36mmol/l Urinary ketones ++ C peptide <0.03 nmol/l	69.4 mmol/mol (8.5%)	GAD <0.6 U/mL (<5) IA2 <0.3 U/mL (<15) Insulin Ab 0.3 U (<0.7) ZnT8 Ab 0.2 U (<3.1)	DRB1*04 (DR4) DQB1*03:02 (DQ8)
3	-	DKA	-	Glucose 15 mmol/l Serum ketones 5.8 mmol/l pH 7.30 C peptide <0.03 nmol/l	60.7 mmol/mol (7.7%)	GAD >2000 U/mL (<5) IA2 <0.3 U/mL (<15) Insulin Ab 0.3 U (<0.7) ZnT8 Ab 0.3 U (<3.1)	DRB1*04 (DR4)
4	-	DKA	-	Glucose 34 mmol/l Serum ketones 5.8 mmol/l pH 7.09 C peptide 0.04 nmol/l	55.2 mmol/mol (7.2%)	GAD >2000 U/mL (<5) IA2 <0.3 U/mL (<15) Insulin Ab 0.4 U (<0.7)	DRB1*03 (DR3) DRB1*04 (DR4) DQB1*03:02 (DQ8)
5	-	DKA	Thyroiditis (thyrotoxic phase followed by hypothyroidism), rash, inflammatory polymyositis	Glucose 41.4 mmol/l Urinary ketones ++ pH 7.20 C peptide 0.11 nmol/l	58 mmol/mol (7.5%)	GAD 12.0 U/mL (<1.45) IA2 <1.1 U/mL (<1.1) Insulin Ab 1.2 U (0-0.7)	DRB1*03 (DR3) DRB1*04 (DR4) DQB1*03:02 (DQ8)
6	Large pancreatic metastasis	DKA	Immune rash and thyroiditis	Glucose 15.1 mmol/l Serum ketones present pH 7.14 C peptide 0.12 nmol/l	70 mmol/mol (8.6%)	GAD >2000 U/mL (<5) IA2 <1.1 U/mL (<10) ZnT8 <15 (<15)	DRB1*03 (DR3) DRB1*15 (DR15) DQB1*06 (DQ6)
7	Prostate cancer	DKA	-	Glucose 27 mmol/l Blood ketones 5.9 mmol/l	62 mmol/mol (7.8%)	GAD <0.6 U/mL (<5) IA2 <0.3 U/mL (<15)	-

				C peptide 0.057nmol/l			
8	-	DKA	Hypophysitis (adrenal and thyroid axis)	Glucose >41.5 mmol/l Serum ketones 6.1 pH 7.04 C peptide 0.01nmol/l	43 mmol/mol (6.3%)	GAD 7.7 U/mL (<5) IA2 <0.3 U/mL (<15)	DRB1*04 (DR4) DQB1*03:02 (DQ8)
9	Type 2 diabetes on an SGLT2 inhibitor ‡	DKA	-	Glucose 24 mmol/l Serum ketones 6 mmol/l pH 7.24 C Peptide 0.38 nmol/l	57 mmol/mol (7.4%)	GAD <0.6 U/mL (<5) IA2 <0.3 U/mL (<15)	-

CVID, Common variable immune deficiency; DKA, diabetic ketoacidosis; GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen; IA2, islet antigen 2; SGLT2, sodium glucose co-transporter- 2; ZnT8, zinc co-transporter 8.

‡Biochemistry reference ranges: Glucose 4–6 mmol/l, serum ketones <0.6 mmol/l, C peptide 0.30-2.40 nmol/l.

§ HLA: DR3 and DR4: strongly associated with diabetes, DQ8: linked to juvenile diabetes, coeliac disease and rheumatoid arthritis, DR15 and DQ6: resistance to diabetes

Table 3 Review of cases published to date

Author/ year published	Age/ gender	Tumour Type	Onset of diabetes	Diabetes presentation	Antibody and HLA status† (As reported)
Hughes <i>et al</i>, 2015 [10]	55/F	Melanoma	5 months	DKA	Antibody negative HLA A2.1+, DR4+
	83/F	Non-small-cell lung cancer	< 1 month	DKA	Antibody positive (GAD only) HLA A2.1+, DR4+
	63/M	Renal cell carcinoma	4 months	Elevated random glucose	Antibody positive (GAD, ICA512, Insulin Ab) HLA A2.1+, DR4+
	58/M	Small cell lung cancer	1 week	DKA	Antibody positive (GAD only) HLA A2.1+
	64/F	Melanoma	< 1 month	Elevated glucose with ketonuria	Antibody negative HLA DR4+
Mellati <i>et al</i>, 2015 [11]	70/M	Adenocarcinoma (lung)	15 weeks	Hyperglycaemia followed by DKA	Antibody negative HLA not known
	66/F	Sarcomatoid squamous cell carcinoma (jaw)	7 weeks	DKA	Antibody positive (GAD only) HLA DR3-DQ2/DR4-DQ8
Martin-Liberal <i>et al</i>, 2015 [12]	54/F	Melanoma	After 3 rd infusion	Hyperglycaemia	Antibody positive (GAD only) HLA A2 DR4 DQ8
Gaudy <i>et al</i>, 2015 [13]	44/F	Melanoma	2 weeks after second dose	DKA 'Fulminant Type 1 diabetes'	Antibody negative No high risk HLA haplotype
Chae <i>et al</i>, 2016 [14]	76/M	Adenocarcinoma (lung)	1 month	Asymptomatic hyperglycaemia	Antibody positive HLA not known
Godwin <i>et al</i>, 2016 [15]	34/F	Non-small-cell lung cancer	4 weeks	DKA	Antibody positive (GAD, IA2, Insulin Ab) No high risk HLA
Thoreau <i>et al</i>, 2016 [16]	73/M	Melanoma	26 weeks	DKA and acute leg ischaemia	Antibody negative HLA not known
Miyoshi <i>et al</i>, 2016 [17]	66/F	Melanoma	4 months	DKA 'Fulminant Type 1 diabetes'	Antibody negative (GAD, IA2, ZnT8) HLA DRB1 HLA DQB1
Lowe <i>et al</i>, 2016 [18]	54/M	Melanoma	4 months	DKA 'Fulminant Type 1 diabetes'	Antibody positive (GAD only)

				diabetes'	HLA-I A2 and HLA-II DQB1*0602
Okamoto <i>et al</i>, 2016 [20]	55/F	Melanoma	12 months	Elevated glucose with ketonuria 'Fulminant Type 1 diabetes'	Antibody negative HLA DRB1*04:05-DQB1*04:01
Hansen <i>et al</i>, 2016 [21]	58/M	Melanoma	51 weeks	Symptomatic hyperglycaemia	Antibody positive (GAD) HLA not known
Teramoto <i>et al</i>, 2016 [22]	63/F	Melanoma	30 weeks	DKA	Antibody negative (GAD, IA2 and Insulin) HLA not known
Fukui <i>et al</i>, 2016 [23]	62/F	Melanoma	130 days	Symptomatic hyperglycaemia 'Fulminant Type 1 diabetes'	Antibody negative (GAD and IA2) HLA DRB1*13:02 and DQB1*06:04
Matsumura <i>et al</i>, 2016* [24]	68/M	Adenocarcinoma (lung)	40 days	Severe hyperglycaemia with low c peptide	Antibody negative (GAD) HLA A*24:02 and DRB1*09:01 and DRB1*15:02
Shah <i>et al</i>, 2016 [25]	77/F	Squamous cell carcinoma (lung)	10 days	Hyperglycaemia and ketosis	Antibody negative HLA-A2, HLA-DR4 both negative
Munakata, <i>et al</i>, 2016 [26]	72/M	Hodgkin lymphoma	57 Days	Hyperglycaemia 'Fulminant Type 1 diabetes'	Antibody negative HLA-B*40:02
Asai, <i>et al</i>, 2017 [27]	50/M	Adenocarcinoma (lung)	After 5 th cycle	Hyperglycaemia 'Fulminant Type 1 diabetes'	Antibody negative HLA not known
Li <i>et al</i> 2017 [28]	63/M	Squamous cell carcinoma (lung)	27 days	DKA	Antibody positive (GAD) HLA not known
Hickmott <i>et al</i> 2017 [29]	57/M	Urothelial cancer	After 5 th cycle	Hyperglycaemia and ketosis	Not available
Gauci <i>et al</i> 2017 [30]	73/M	Melanoma	6 weeks	DKA	Antibody positive (GAD and ZnT8) HLA not known
Usui <i>et al</i> 2017 [31]	31/M	Non-small-cell lung cancer	2 weeks	Hyperglycaemia 'Fulminant Type 1 diabetes'	Antibody positive (GAD) HLA DRB1*04:05-DQB1*04:01
	62/F	Non-small-cell lung cancer	10 weeks	Symptomatic hyperglycaemia	Antibody negative HLA DRB1*09:01-

					DQB1*03:03
Ishikawa <i>et al</i> 2017 [32]	54/F	Melanoma	Unavailable	Hyperglycaemia 'Fulminant Type 1 diabetes'	Antibody status and HLA not known

F, female; GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen; IA2, islet antigen 2; M, male; ZnT8, zinc co-transporter 8.

*Person with pre-existing Type 2 diabetes.

†HLA A2 DR4 DQ8, HLA DR3-DQ2, HLA A*24:02 and DRB1*09:01, DRB1*04:05-DQB1*04:01: high risk haplotypes for Type 1 diabetes, HLA DRB1*04:05-DQB1*04:01, HLA-B*40:02, HLA DRB1*09:01-DQB1*03:03: associated with Type 1 diabetes in Japan and fulminant diabetes, HLA DRB1*13:02 and DQB1*06:04: weakly associated with Type 1 diabetes, HLA-II DQB1*0602, HLA DRB1*15:02: protective for Type 1 diabetes, HLA DRB1 11:01 13:02:01, HLA DQB1 03:01:01 06:04:01: not associated with Type 1 diabetes.

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