Type 1 diabetes induced by immune checkpoint inhibitors

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Abstract

With the increasing use of immune checkpoint inhibitors (ICI) including anti-cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and anti-programmed cell death-1 (PD-1) in cancers, ICI-induced type 1 diabetes has been reported throughout the world. In this review, we aim to summarize the characteristics of this disease and discuss the mechanism of it. As an immune-related adverse event, type 1 diabetes developed after the administration of anti-PD-1 or anti-PD-ligand 1 (PD-L1) in the combination with or without anti-CTLA-4. It usually presented with acute onset, and 62.1% of the reported cases had diabetic ketoacidosis. Only a third of them had positive autoantibodies associated with type 1 diabetes. Susceptible HLA genotypes might be associated. T-cell-stimulation by blocking of the interaction of PD-1 and PD-L1 in pancreatic β cells was the main mechanism involved in the pathology. Insulin was the only effective treatment of ICI-induced type 1 diabetes. In conclusions, ICI-induced type 1 diabetes is a potentially life-threating adverse event after the immunotherapy of cancers. Screening and early recognition is important. Further investigation of the mechanism may help to better understand the pathology of type 1 diabetes.

Keywords: Programmed cell death-1; Type 1 diabetes; Immune checkpoint inhibitors

Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies directed against regulatory immune checkpoint molecules that inhibit T cell activation. These molecules include cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1), which are located on the surface of T cells, and programmed cell death ligand-1 (PD-L1) which is expressed on tumor cells and other antigen presenting cells. The CTLA-4 and PD-1 immune checkpoints maintain immune tolerance to self.[1,2]

CTLA-4 is presented on T cells within the lymph tissue, and acts as a competitive inhibitor of the costimulatory molecule CD28 through binding to CD80/86 of antigen presenting cells. PD-1 is expressed on chronically activated T cells in peripheral tissues and transmits negative signaling to the immune response by binding to its ligands PD-L1 and PD-L2. ICIs trigger an immune mediated anti-tumor response by blocking the interactions between CTLA-4 and CD80/86 or PD-1 and PD-L1.[1]

ICIs now have been increasingly used to treat variable cancers including melanoma and other tumors.[3] The names and types of ICIs are listed in Supplementary Table 1 (http://links.lww.com/CM9/A261). Nivolumab and pembrolizumab are commonly used anti-PD-1. Anti-PD-L1 includes atezolizumab and durvalumab. Anti-CTLA-4 includes ipilimumab. Immune-related adverse events (irAEs) are toxicities caused by non-specific activation of the immune system, and can affect almost any organ system. The irAEs include pneumonitis, colitis, hepatitis, dermatitis, nephritis, pancreatitis, vitiligo, pruritus, and endocrinopathies, including thyroiditis, hypophysitis, primary adrenal insufficiency, and type 1 diabetes.[4] Among these irAEs, type 1 diabetes was not common but often life threatening due to its rapid onset and irreversibility. Better understanding of ICI-induced type 1 diabetes is necessary for all health care providers.

In this review, we overviewed the published articles about type 1 diabetes induced by ICIs, most of which were case reports and some were cohort studies. Then we discussed the mechanism and possible indication to the pathogenesis of type 1 diabetes.

Type 1 Diabetes Induced by ICIs

Occurrence

ICIs-induced diabetes mellitus was estimated to be rare in clinical trials. It was first reported to happen in only one

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patient of a clinical trial of 207 patients treated with PD-L1 in 2012.[5] A meta-analysis comprising 7551 patients of 38 randomized clinical trials indicated 0.2% (13 cases) of ICI induced diabetes. Among these 13 cases with diabetes reported, 12 cases were associated with the use of anti-PD-1 therapy and one case was with CTLA-4 inhibitor ipilimumab treatment.[6] However, in the real world observations, the occurrence of ICI-induced type 1 diabetes was much higher than that reported in the clinical trials. A retrospective cohort study of 538 patients with metastatic melanoma treated with anti-PD-1 based immunotherapy, which was documented in a single center from 2015 to 2018, showed 10 (1.9%) patients developed insulin deficient diabetes.[7] Another retrospective study of 1444 ICI treated patients with variable cancers, found that 12 (0.8%) patients had new-onset insulin-dependent diabetes. However, among these patients, no case was induced by CTLA-4 inhibitor ipilimumab treatment alone. Another study with 1163 patients treated with PD-1 inhibitor, 12 (1%) patients developed type 1 diabetes.[8] Another case series reviewed over a 6-year period at two academic institutions, identified 27 patients developing type 1 diabetes, accounting for 0.9% in all these patients received either anti-PD-1 or anti-PD-L1 antibodies treatment.[9]

Clinical characteristics

A total of 103 cases were reported about the ICI-induced insulin deficient diabetes (Supplementary Table 2, http://links.lww.com/CM9/A261). Among them, there were 13 cases in Asians,[10-21] including one case in China.[10] The age ranged from 28 to 87 years. Fifty-eight patients were male, and 31 were female, with the other 14 patients without gender information. Forty-eight (46.6%) of the patients had melanoma, probably because metastatic melanoma was the first indication for approved ICIs. The other types of cancer include non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, and other cancers. Nighty-three (90.3%) patients used anti-PD-1 alone or in combination with anti-CTLA-4 ipilimumab, including 52 patients treated with nivolumab and 41 with pembrolizumab. Six patients used anti-PD-L1 as a single agent or a component of combination therapy. Type 1 diabetes induced by anti-CTLA-4 alone was not reported.

Based on the reviewed literature, the duration from ICIs administration to hyperglycemia ranged from 5 days to 23 months (1–27 cycles of ICIs). Hemoglobin A1c (HbA1c) ranged from 5.8% to 13.7%. Sixty-four (62.1%) patients presented with diabetic ketoacidosis (DKA) at the time of diagnosis. Forty-five (43.7%) patients had a HbA1c lower than 8.7%, indicating the possibility of fulminant type 1 diabetes.[22] The C-peptide levels were significantly lower than the normal range or decreased quickly after diagnosis of diabetes.

In total, 25 (32.9%) of 76 patients had one or more positive autoantibodies associated with type 1 diabetes. Among 65 patients tested for anti-glutamic acid decarboxylase antibody, 22 (33.8%) were positive. Among 37 patients tested for islet antigen type 2 antibody, 5 (13.5%) were positive. Four (6.2%) of 65 tested cases were anti-insulin antibody positive, 1 of 17 tested cases was islet cell antibody positive, while 1 of 24 tested cases was zinc transporter 8 antibody positive.

Insulin injection was the main treatment for all the ICI-induced type 1 diabetes. Only one case reported a reversion of pancreatic β cell function and stopped insulin use.[23]

Difference Between ICI-induced and Spontaneous Type 1 Diabetes

ICI-induced type 1 diabetes is different in many aspects with conventional spontaneous type 1 diabetes. First, the onset age in ICI-induced type 1 diabetes is much older than naturally spontaneous type 1 diabetes. This can be ascribed to the higher incidence of cancer and higher frequency of using ICIs in elderly people. Second, compared with conventional type 1 diabetes, the higher incidence of DKA and fulminant type 1 diabetes in ICI-induced type 1 diabetes suggests the rapid deterioration of β cell function. Third, the positive rate of diabetes associated antibodies in ICI-induced type 1 diabetes is lower than spontaneous type 1 diabetes or latent autoimmune diabetes of the adult. Lastly, some case series and cohort studies indicated the association between certain HLA haplotypes and ICI-induced type 1 diabetes.[24] The frequency of HLA-DR4 was reported to be proximally 60% in ICI-induced type 1 diabetes and was much higher than that in conventional type 1 diabetes.[9] These differences reflect the special mechanism of ICI-induced type 1 diabetes which will be discussed in the following part of the article. However, the specific hereditary susceptibility and the other environmental risk factors associated to ICI-induced type 1 diabetes are not clear.

Mechanism of ICI-induced Type 1 Diabetes

Autoimmune type 1 diabetes is characterized by insulin-secreting pancreatic β cells destructions. And in this autoimmune process, auto-activated T cells play critical roles. The promotion of this destruction process involves both genetic and environmental factors, most of which are not clear so far. The immune response stimulated by ICI therapy could be one of the environmental factors leading to the destruction process. As described above, PD-1 is presented on T cells. The engagement of PD-1 with its ligands PD-L1 or PD-L2 transmits inhibitory signals to maintain immune tolerance. PD-L1 is widely expressed not only in lymphoid tissues, but also in target organs including pancreatic β cells. Blocking the interaction of PD-1 and PD-L1 might stimulate T cell proliferation and activation then leading to the destruction of β cells, providing a possible mechanism for anti-PD-1 induced type 1 diabetes.[25]

This speculation was supported by studies both in mouse and in human. A study indicated PD-1 and PD-L1 blockade precipitated diabetes in prediabetic non-obese diabetic mice.[26] Forced expression of PD-1 through PD-1 transgenic mouse decreased the incidence of type 1 diabetes.[27] Transgenically overexpressing PD-L1 in β cells also delayed the onset of diabetes.[28] In humans, PD-L1 has been found expressed in the islets of people with type 1 diabetes. Lower expression of PD-1 in T cells was found in people with type 1

diabetes compared with healthy controls or those with type 2 diabetes.[29,30] PD-L1 serum levels were also lower in patients with type 1 diabetes than in healthy people.[31] Some PD-1 gene haplotypes were found to be associated with susceptibility of type 1 diabetes in Japanese children.[32] A single nucleotide polymorphism of PD-L1 was found to be associated with type 1 diabetes susceptibility in Chinese.[33]

It was found that during the progression of autoimmune diabetes, only the expression of PD-L1 increased on β cells in animal models, but not the expression of CD80 or CD86 (ligands of CTLA-4).[34] This was confirmed by the absence of anti-CTLA-4 monotherapy induced type 1 diabetes in published case reports. Thus, we speculate the interaction of CTLA-4 and its ligands play a trivial role in the mechanism of ICI-induced type 1 diabetes.

Recommendations of Clinical Practice With ICI-induced Type 1 Diabetes

Treatment of ICI-induced type 1 diabetes

Unlike other irAEs, insulin-deficient diabetes could not be successfully treated with high-dose corticosteroids or other immunosuppressive agents.[24] The reason behind this phenomenon is not clear. Some researchers attempted to use prednisolone in patients with ICI-induced type 1 diabetes, but the blood glucose control deteriorated and no benefit was observed.[35] Insulin remains the only effective therapy for all cases in ICI-induced type 1 diabetes. Because of the rapid loss of β cell function, intensified insulin treatment including multiple daily injections are often needed.[36]

Recommendations for ICI-induced type 1 diabetes in current guidelines

Since the acute onset and the high percentage of DKA in ICI-induced type 1 diabetes, early diagnosis and treatment are of importance to decrease the mortality and to improve the prognosis. Until now, authorities in both endocrinology and oncology have called the health care providers to pay attentions to ICI-induced type 1 diabetes and have given recommendations on screening.[36,37] Fasting or random plasma glucose testing and HbA1c testing are recommended before and at each administration of anti-PD-1 therapy. Patients accepting ICIs should be educated with the symptoms of hyperglycemia and ketoacidosis to raise awareness. If type 1 diabetes is suspected, HLA type, C-peptide, and type 1 diabetes associated antibodies should be tested to confirm the diagnosis, and insulin therapy should be initiated on time. Insulin treatment should be continued at home with self-glucose-monitoring under the guidance of diabetologists.

Future Assuming

With the increasing use of ICIs in multiple cancers, ICI-induced type 1 diabetes is becoming a prominent problem threating people's health and their qualities of life. There are still many unresolved issues in the pathogenic process of ICI-induced type 1 diabetes. Future investigations may focus on the specific mechanism of T cells activation, the function of different subtypes of T cells expressing PD-1, such as CD4+ T cells, CD8+ T cells and regulatory T cells, the interaction of T cells and immunoglobin-producing B cells, susceptible HLA types or other genotypes, and new biomarkers representing susceptibility, to better understand the pathology of ICI-induced type 1 diabetes, as well as all type 1 diabetes as a whole.

Conclusions

Type 1 diabetes induced by ICIs especially anti-PD-1 therapy is a severe adverse effect of immunotherapy to cancer. The actual incidence of this disease might be underestimated previously. Because of the rapid declination of pancreatic β cell function and high possibility of DKA, it is necessary to raise attention of this disease and to give well management. Moreover, further studies are needed to investigate the specific mechanism of ICI-induced type 1 diabetes.

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Conflicts of interest

None.

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