Introduction

Pembrolizumab is a novel monoclonal antibody against programmed cell death protein-1 (PD-1), which is used in the treatment of cancers like advanced melanoma and non-small cell lung cancer. Several endocrine-related autoimmune adverse events have been reported with the use of Pembrolizumab such as thyroiditis, and hypophysitis (1). Autoimmune T1 DM (T1DM) is relatively less commonly reported but can present more dramatically with more permanent effect. We report a case of T1 DM which developed after initiation of Pembrolizumab in a patient with metastatic uveal melanoma.

Case Description

- 48 year old man with a history of stage IV uveal melanoma metastatic to the stomach, lung and left adrenal gland
- He was treated with immune-modulators ipilimumab and temetinib, 6 months and 4 months prior, respectively, before developing symptoms of hyperglycemia. Due to cancer progression, he was initiated on pembrolizumab
- His hemoglobin A1c while on ipilimumab and temetinib was 5.4% and 5.7% respectively
- During the sixth cycle of treatment with pembrolizumab, he developed polyuria and polydipsia
- His blood sugars were in the 500s and hemoglobin A1c was elevated to 8.9%
- He was treated on Glipizide and Metformin and referred to Endocrinology
- On endocrine evaluation, he was found to have insulin level of 2.0 μU/mL, c-peptide 0.6 ng/mL with a random plasma glucose of 318 mg/dL
- He had an elevated anti-GAD65 antibody level at 0.07 nmol/L and was diagnosed with new onset autoimmune Type 1 Diabetes
- Insulin therapy was initiated. His symptoms resolved completely. On follow up, 6 months later, he continues to maintain good glycemic control on multiple dose regimen of insulin.

Role of Anti-PD-1/PD-L1 blocking antibody in Cancer Therapy

a) Tumor cells express both cancer-driving mutations and “passenger” mutations that cause the expression of neoantigens. Neoantigens are recognized by T cells of the immune system as being foreign, and initiate an immune response against the tumor. This response is subdued, however, due to interactions between the receptor PD-1 and its ligand PD-L1, which is expressed on tumor cells leading to activation of signaling pathways that inhibit T-cell activity and thus inhibit the anti-tumor immune response.

b) Antibodies that block the PD-1 pathway work by either binding PD-1 or PD-L1, thus inhibiting the binding of ligand and receptor, resulting in reactivation of T-cell activity, proliferation, and enhancing anti-tumor immunity.

Role of PD-L1 in the pathogenesis of Type 1 DM

- The initiation phase of type 1 diabetes (T1D) takes place in the pancreas, where conventional dendritic cells (cDCs) capture and process β-cell antigens.
- Activated cDCs prime pathogenic islet antigen-specific T cells after migration to the draining lymph node, and macrophages promote this activation through interleukin-12 (II-12) secretion.
- B cells present β-cell antigen to diabetogenic T cells and secrete autoantibodies (not shown).
- The activation of islet antigen-specific T cells can be inhibited by cDCs through various mechanisms, such as engagement of programmed cell death ligand 1 (PD1).
- In the pancreas, β-cells can be killed by diabetogenic T cells and NK cells through the release of interferon-γ (IFNγ), granzymes and perforin, as well as by macrophages through the production of tumour necrosis factor (TNF), IL-1β and nitric oxide.
- β-cells can inhibit diabetogenic T cells by expressing PD1. This complex crosstalk between innate and adaptive immune cells results in the development or the prevention of T1D.

APC, antigen-presenting cell; TCR, T cell receptor.

Discussion

- Pembrolizumab is an IgG4 monoclonal antibody targeting the co-inhibitory immune checkpoint molecule programmed cell death-1 (PD-1).
- It was approved by the FDA for the treatment of advanced melanoma in September 2014.
- PD-1 is a key immune regulator with a protective role against the development of autoimmune diabetes.
- Forced PD-1 expression in transgenic mice significantly reduces the incidence of autoimmune diabetes (3).
- Blockade of PD-1 or its ligand, PD-L1, rapidly precipitates diabetes in pre-diabetic Non obese diabetic mice (NOD).
- We believe that the institution of immune therapy unmasked the underlying autoimmunity.
- A decreased expression of PD-1 gene has been observed in CD4+ T cells of patients with autoimmune T1DM in recent studies (3).

Conclusions

- In the context of the increasing indications of anti-PD1 therapy in different cancers, blood glucose screening may have a role in preventing life-threatening complications like diabetic ketoacidosis.
- More studies are needed in human models to study the role of PD1 blockade and deficiency in the pathogenesis of T1DM.

References


http://www.nature.com/naturejournal/v515/n7528/images/515496a-f1.jpg