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Case Report

Checkpoint Inhibitor Associated Autoimmune Diabetes and Hashimoto's Thyroiditis

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2. Key words

Checkpoint inhibitors; Hashimoto's thyroiditis; Autoimmune DM; IRAEs

1. Abstract

1.1. Background: Anti-PD-1 antibodies have activity across many cancers. Changes in the balance of the immune system may lead to some autoimmune manifestations, also referred to as immune-related adverse events (IRAEs). These adverse events were described affecting different systems of the body, including the endocrine system.

1.2. Case Presentation: A 61-year-old patient was treated with Pembrolizumab and developed autoimmune DM and Hashimoto's thyroiditis.

1.3. Conclusion: To our knowledge, this is the first reported case of a patient who developed autoimmune diabetes and Hashimoto's thyroiditis, likely as a consequence of PD-1 inhibition with pembrolizumab.

3. Introduction

The field of tumor immunology significantly developed and changed therapeutic options for many malignancies, especially using immune checkpoint inhibitors [1]. The latter enhance the activation of the immune system to control tumor growth. Antibodies targeting programmed death 1 (PD-1) receptor or programmed death ligand 1 (PDL-1) have shown clinical responses in multiple tumor types [2]. Immune checkpoints are crucial for maintaining self–tolerance and regulating the immune system, preventing it from attacking cells in a random manner [3]. By unbalancing the immune system, immune check-point blockade favors the development of autoimmune manifestations, also referred to as immune-related adverse events (IRAEs) [4].

Pembrolizumab and Nivolumab are humanized monoclonal antibody against PD-1 receptor. These agents are associated with adverse effects that can affect multiple organs of the body and are most commonly seen in the skin, GI tract, lungs, endocrine system etc [5]. As for endocrinopathies, hypothyroidism is the most common adverse event (~7%). Other auto-immune endocrine disorders described in patients treated with PD-1 inhibitors include: hyperthyroidism (3.2%), hypophysitis (1.1%), but also primary adrenal insufficiency and insulin-deficient diabetes mellitus (DM) in smaller number of events [6]. Recently, immune-related hypoparathyroidism was also described in this context and seems even rarer [7]. Here, we describe a case of new onset autoimmune polyendocrinopathy which appeared shortly after starting PD-1 inhibitors therapy and synchronously associated hashimoto's thyroiditis with hypothyroidism and positive Glutamic Acid Decarboxylase (GAD) antibody-related insulin deficient diabetes in a post-menopausal woman with no autoimmune background.

4. Case Presentation

A 61-year-old female was addressed to the Emergency Room (ER) at our institution due to weight loss, polydipsia, polyuria and fatigue in the last few days. Her past medical history was significant for an endometrial adenocarcinoma of uterus and ovary diagnosed four years before her admission. Initially, there was no evidence of systemic involvement. She was treated surgically with no adjuvant therapy. Seven months before her admission, a hormonal therapy with Tamoxifen and Megestrol was initiated due to lymph nodes metastases. A month later, the therapy was switched to anti- PD1 immunotherapy with Nivolumab. Three months before admission, the treatment was switched again to Pembrolizumab. There was a significant response to the treatment with elimination of the lymphadenopathy. The patient was on regular follow-up at the oncology outpatient clinic.

A week prior to her admission, a high glucose level of 450 mg/dL

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was measured at the general practitioner clinic whereas her fasting blood glucose was always strictly normal in the previous blood tests. Metformin was initiated. However, because of high glucose levels and continuation of symptoms, she was addressed to the ER. At presentation, physical examination revealed a thin woman, with stable hemodynamic status (blood pressure 108/60 mmHg, pulse 56 bpm, room air saturation 100%, body temperature 36.5℃), BMI 24 kg/m2, and no abnormal finding was detected. Laboratory data showed hyperglycemia and high anion-gap metabolic acidosis with respiratory compensation, with elevated urinary ketones, compatible with Diabetic Keto-Acidosis (DKA) (Table 1).

Table 1: Blood laboratory data

Test	Range	Units	Result
Glucose	72 - 99	mg/dL	**547**
PH	7.38 - 7.42		**7.32**
HCO3	22 - 28	mmol/L	**10.8**
PCO2	38 - 42	mmHg	**21**
Anion gap	3 – 11	mmol/L	28.2
Complete blood count (CBC)			Normal
Glutamic acid decarboxylase antibodies (GAD-II AB)	< 30	IU/mL	**228.5**
Insulin antibodies	< 5.5	%	**8.9**
Thyroid stimulating hormone (TSH)	0.35 – 5.5	mcU/mL	**57.5**
Free tetraiodothyronine (FT4)	10 - 20	pmol/L	**7.63**
Free triiodothyronine (FT3)	3.5 – 6.5	pmol/L	**1.86**
Anti-thyroid peroxidase antibodies (anti-TPO AB)	0 - 35	IU/mL	**906**

The patient was treated with a classic DKA therapeutic protocol including intravenous insulin and fluids and showed quick clinical and laboratory improvement.

Laboratory tests were expanded during hospitalization and showed positive Glutamic Acid Decarboxylase (GAD) and anti-insulin antibodies suggesting auto-immune pathophysiology in the development of the diabetes mellitus; further explorations showed hashimoto's thyroiditis with high titer of anti-thyroid peroxidase antibodies (TPO) and new hypothyroidism (Table 1) whereas the patient had normal TSH levels prior to Pembrolizumab treatment. There was no sign of other endocrinopathies: her pituitary hormone profile was normal and there was neither clinical nor laboratory signs suggesting primary cortisol deficiency (adrenalitis with Addison syndrome). She was started on a basal-bolus insulin regimen, instructed to check 6 times a day and as needed her blood sugars with a glucose reading machine, to inject insulin and to adapt her boluses doses according to carbohydrate count and pre-meal hyperglycemic correction factor as usually performed for any patient with new onset type 1 DM. She was also started with PO thyroxine. After a couple of weeks, both DM and hypothyroidism significantly improved. At the light of these side effects and the excellent previous tumor response, her oncologist decided to postpone the treatment. On follow-up after 6 months, the malignant disease was stable without flaring and titers of GAD as well as anti-TPO antibodies remained elevated despite anti PD-1 agents were stopped.

5. Discussion

In this case report, we describe a patient several months after initiation of immunological treatment with PD-1 inhibitor for endometrial carcinoma. At first, the patient presented to her GP with severe hyperglycemia and was treated with Metformin. Her advanced age probably suggested that the patient had new onset type 2 DM. A week later, the patient presented with a DKA event. Retrospectively, high levels of GAD antibodies are suggestive of autoimmune DM. A differential diagnosis for the etiology of autoimmune DM in this patient includes late-onset auto-immune diabetes of the adult (LADA)/type 1 DM, and adverse event of PD-1 inhibitor treatment. The acute presentation and the need for insulin treatment one week after presentation of hyperglycemia are not compatible with the indolent presentation of LADA [8]. It would be reasonable to assume that the development of DM was secondary to the immunological treatment.

There is limited amount of data regarding the incidence of autoimmune DM in patient received PD-1 inhibitors. Among patients treated with all kinds of checkpoint inhibitors, 0.2% developed autoimmune DM [6]. As for treatment with PD-1 inhibitors, a review reported 5 cases of patients who developed severe hyperglycemia or DKA 1 week to 5 months after initiation of PD-1 inhibitor therapy [9]. 3 additional cases were published with a similar clinical presentation [10, 11]. However, some cases of checkpoint inhibitors-related DM were reported to be unrelated to the occurrence of typical T1DM antibodies, raising the possibility of a more complex pathophysiology [12].

Interestingly, in our case, synchronously to the diabetes, a new onset Hashimoto's thyroiditis developed. A similar case was previously described with the use of Nivolumab in a 63 year-old male , but the fulminant T1DM occurred after 27 days of treatment, whereas Hashimoto's thyroiditis appeared only later (after 3 months) [13]. Appearance of Hashimoto thyroiditis secondary to PD-1 inhibitors therapy is the most common among endocrinopathies (7% of patients) [6].

Polyendocrinopathy resulting of checkpoint inhibitors treatment

is rare. A case of a patient with a thyroiditis followed by a primary adrenal insufficiency was described [14]. In this case we describe for the first time a patient who developed an autoimmune DM and Hashimoto's thyroiditis.

The reasons for differential autoimmune involvement of the endocrine glands between patients and different treatment regimens are not entirely clear [15]. Further investigation should be made in order to understand the specific pathophysiology of the different adverse effects

This case highlights the diversity of potential endocrine toxicity of checkpoint inhibitors. Physicians must be aware of these adverse events in order to avoid morbidity and mortality of patients. New onset of DM during checkpoint inhitor therapy should be actively screened, and if diagnosed, should prompt initiation of insulin therapy rather than oral anti-diabetic medications to avoid potentially lethal complications as DKA.

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