BJCR
Brazilian Journal of Case Reports

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Publicações Científicas de Acesso Aberto

Case Report

Multiple endocrinopathies acquired using a checkpoint inhibitor - Pembrolizumab: A Case Report

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Abstract: Immunotherapy with checkpoint inhibitors (ICIs) has been increasingly employed for the treatment of many malignancies, and endocrinopathies are one of their most frequent side effects. This case report describes a 70-year-old man who faced many endocrinopathies (primary hypothyroidism, secondary adrenal insufficiency, and diabetes mellitus) after initiation of immunotherapy with an ICI (pembrolizumab) for treatment of urothelial bladder cancer. We discuss the prevalence, physiopathology, screening, and diagnosis of each of these abnormalities. Clinicians need to be aware of these endocrine complications of ICI therapy and be ready for early diagnosis and appropriate management.

Keywords: Pembrolizumab; Case reports; Autoimmune Diseases; Drug-Related Side Effects and Adverse Reaction; Antineoplastic Agents.

Citation: Barreto Marcelino GCS, Mota de Miranda EL, Sebastianes F M. Multiple endocrinopathies acquired using a checkpoint inhibitor - Pembrolizumab: A Case Report. Brazilian Journal of Case Reports. 2025 Jan-Dec; 05(1):bjcr15.

https://doi.org/10.52600/2763-583X.bjcr.2025.5.1.bjcr15

Received: 20 April 2024
Accepted: 20 June 2024
Published: 12 August 2024

1. Introduction

Food and Drug Administration (FDA) approved for the first time immunotherapy for advanced melanoma treatment in 2011, with ipilimumab. In recent years, immunotherapy with checkpoint inhibitors (ICI) has been shown to be effective in the treatment of several malignancies and prescription of these drugs has markedly increased [1,2]. ICIs are monoclonal antibodies against proteins known as immune regulators that maintain homeostasis and tolerance by modulating the duration and amplitude of physiological immune function.

ICIs increase progression-free survival and global survival in these oncologic patients. Pembrolizumab is an ICI that blocks PD-1 (programmed cell death 1), a negative regulator expressed in immune and tumor cells [2]. Autoimmune diseases induced by immunotherapy with checkpoint inhibitors have been described, but the association of multiple autoimmune diseases is found less often [1]. Endocrine glands are the most often afflicted tissues by autoimmunity in these patients [3]. In this case report, we describe the clinical condition of a patient who developed hypothyroidism, secondary adrenal insufficiency and type 1 diabetes mellitus after using pembrolizumab.

In this case report, we aim to expand medical knowledge about the association between autoimmune aggressions and the use of ICIs such as pembrolizumab, providing clinical information that may help in the diagnosis and management of these conditions in patients undergoing immunotherapy.

2. Case Report

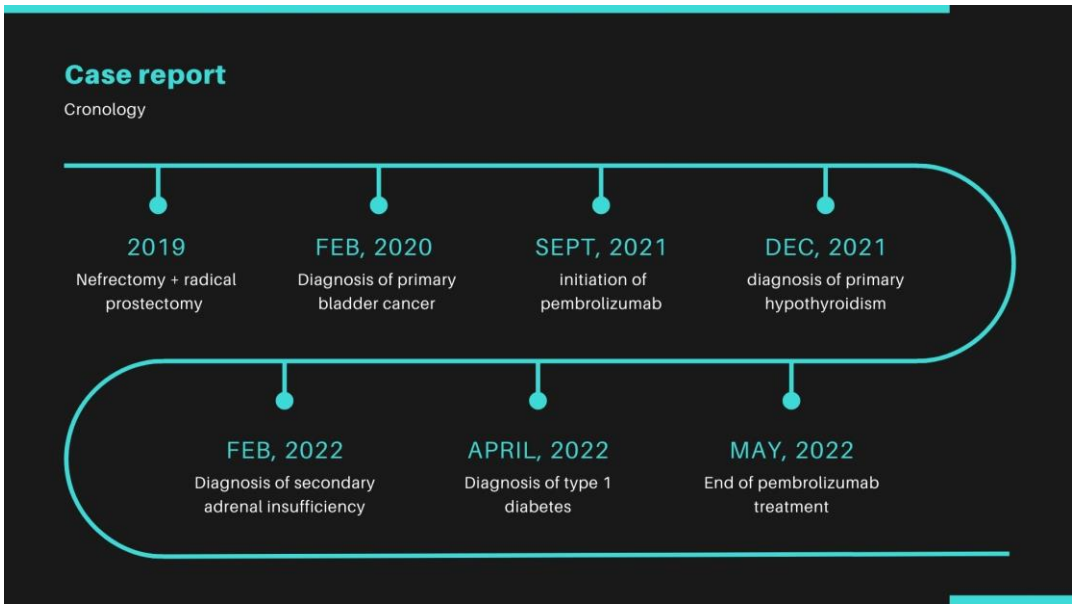
A 70-year-old man was diagnosed with primary bladder cancer (urothelial carcinoma) in February 2020 (Figure 1). He underwent neoplasm endoluminal resection

followed by treatment with BCG. He had a history of metabolic syndrome (grade 1 obesity, systemic arterial hypertension, hypertriglyceridemia, and inappropriate fasting glycemia) and prostate cancer and renal cancer treated with prostatectomy and nephrectomy in January 2019. Treatment with pembrolizumab was started in September 2021 due to advanced urothelial carcinoma of the bladder. In December 2021, periodical exams were performed, and an increased level of TSH (29 mU/L -reference range < 5.0) was found. A diagnosis of primary hypothyroidism was made and levothyroxine replacement was started.

In February 2022, he was hospitalized with complaints of inappetence, weight loss of 7 kg, asthenia, dizziness, and nausea. Laboratory tests revealed hypopotassemia and low levels of serum cortisol and ACTH. A diagnosis of secondary adrenal insufficiency was made, indicating pituitary involvement. No abnormalities were found on magnetic resonance imaging of the sella turcica. During hospitalization, he received initially intravenous hydrocortisone. Glucocorticoid therapy was progressively reduced, and he was discharged from the hospital with prednisone at a dose of 5 mg/day.

In April 2022, the patient complained of fatigue, weight reduction, xerostomia, polyuria, polydipsia, and nocturia. His blood glucose level was above 600 mg/dL, so insulin therapy was started in a "*basal-bolus*" scheme, with insulin glargine and fiasp. In May 2022, eight months after pembrolizumab had been started, the risks exceeded the benefits of continuing the ICI therapy, and the decision was made to discontinue this treatment. In July 2023, the last time the patient was evaluated, he was using glargine insulin (26 units/day), fiasp insulin (around 25 units/day, divided between the 3 main meals), metformin XR 2 g/day, prednisone 5 mg/day, levothyroxine 125 mcg/day, rosuvastatin 10 mg/day, esomeprazole 30 mg/day and paroxetine 40 mg/day. The patient as of now is in good conditions, following regular medical checkups with an endocrinologist.

Figure 1. Cronology of events.



3. Discussion

Immunotherapy has now become one of the most important advances in cancer treatment, especially in cases of advanced malignancy. Immune checkpoint inhibitors (ICIs) increase the immune response against malignant cells more effectively through a unique mechanism that blocks negative regulators expressed on immune or tumor cells [1, 2]. These regulators include CTLA-4 (cytotoxic T-lymphocyte-associated protein-4), PD-1 (programmed cell death protein-1) and PD-L1 (programmed cell death ligand 1) [2]. CTL-

4 and PD-1 are expressed by lymphocytes and PD-L1 are expressed by immune and epithelial cells and some neoplastic cells.

The targets of ICI (CTLA-4, PD-1, and PD-L1) are key regulators of immune tolerance and prevent autoimmunity in the physiologic state. Immune checkpoints are hijacked by the cancer cell to achieve immune evasion and avoid T-cell killing. Pharmacologic blockade, therefore, can result in not only anti-tumor immunity but also autoinflammation at other sites, which clinically manifest as immune-related adverse events [3].

PD-1 and PD-L1 monoclonal antibodies have shown to be effective against many solid tumors but may be associated with many adverse events such as hypothyroidism, hypophysitis, primary and secondary adrenal insufficiency, and gastrointestinal, dermatological, hepatic alterations [4, 5, 6, 7, 8] and others, such as myasthenia gravis [9, 10]. Endocrine adverse effects of ICI therapy occur in about 10% of patients – these dysfunctions are generally permanent and do not contraindicate the maintenance of ICI therapy [5]. Thyroid disease and hypophysitis are the most common, but adrenal glands, pancreas, and parathyroid glands may also be affected [4, 5, 11]. Type 1 diabetes mellitus may be rarer [6, 11]. In the present case report, our patient, after using immunotherapy with Pembrolizumab (anti-PD-1), developed primary hypothyroidism, secondary adrenal insufficiency, and type 1 diabetes mellitus.

The study that supported pembrolizumab use by our patient was performed by Bellmunt et al. [12]. In this randomized trial, patients with advanced urothelial carcinoma of the bladder were treated with chemotherapy or pembrolizumab. Pembrolizumab treatment for a mean of 3.5 months led to the development of these endocrinopathies: hypothyroidism (6,4%), hyperthyroidism (3.8%), thyroiditis (0.8%) and adrenal insufficiency (0.4%). Diabetes mellitus new cases were not reported. Therefore, thyroid diseases are by far the most common endocrinopathies developed by these patients. In a systematic review [12], pembrolizumab-induced diabetes has been reported to occur in 0.4% of patients.

The exact mechanisms that elicit these adverse effects are very complex and not fully understood. In thyroid disease, an increase in the levels of pre-existing thyroid antibodies was observed [13]. Expression of therapeutic targets (CTLA-4 and PD-1) by pituitary endocrine cells may play a role in hypophysitis [14,15], but pathogenesis is still uncertain [16]. PD-L1 is also expressed in pancreatic islet cells [5]. Primary thyroid disease is the most common endocrine immune-related adverse effect of ICI and typically occurs 4 to 10 weeks after initiation of treatment. The disease process usually begins with a painless destructive thyroiditis, which includes a brief, self-limiting thyrotoxic phase that lasts 3 to 6 weeks, followed by a prolonged hypothyroid phase [5]. More rarely, isolated hyperthyroidism such as Graves´s disease may be seen. The presence of antithyroid antibodies increases the risk of thyroid disease in patients initiating ICI treatment [5].

Secondary adrenal insufficiency due to ICI therapy manifests mainly with symptoms of fatigue, anorexia, nausea, vomiting, diarrhea, and hyponatremia [17,18] and most of these symptoms were found in our patient. Hypophysitis develops respectively in about 3% of patients under treatment with CTLA-4 inhibitors and in 1% in other ICI therapies [5]. It typically occurs 8 to 10 weeks after therapy initiation. Secondary adrenal insufficiency occurs in 83% of these patients, while secondary hypothyroidism and hypogonadism occur in 77% and 53% of patients, respectively. Screening is not usually performed, and most patients are diagnosed after the development of adrenal insufficiency symptoms. Although our patient developed only secondary adrenal deficiency, multiple pituitary hormone deficiencies may be found in many of these patients. Imaging of the pituitary is recommended to exclude metastasis. Mild to moderate enlargement of the pituitary and stalk thickening may be seen in the acute phase, but the resolution of these changes is often seen on repeat imaging within days to weeks [5]. The pituitary morphology on our patient's MRI scan was normal, and such a pattern was found after a few days and weeks in 90% of patients with ICI-induced hypophysitis and secondary adrenal insufficiency [19,20].

Regarding the development of Diabetes Mellitus in our patient, he has been diagnosed with inappropriate fasting glucose since 2016. He had therefore been taking 1 g of metformin/day. In February 2022, his fasting glycemia was 101 mg/dL and his glycated hemoglobin was 6.2%. In April 2022, seven months after starting the use of ICI with pembrolizumab, he began to manifest the classic symptoms of hyperglycemia, confirmed by laboratory tests. Apart from prior diabetes mellitus risk factors in our patient (metabolic syndrome and prediabetes), no other risk factor for an acute and intense glycemia elevation was found in our patient. His glucocorticoid therapy was in a physiological range and there was no infection or use of other hyperglycemic drugs. Follow-up showed a lack of response to other antidiabetic drugs apart from insulin and plasma C peptide levels were found to be low. These findings were consistent with an acute development of a severe beta cell dysfunction, probably induced by pembrolizumab. Fast, aggressive destruction of beta islet cells, likely mediated by T-cells, requiring rapid insulin replacement, is characteristic of ICI-related diabetes mellitus [5]. For this reason, acute diabetic ketoacidosis is an initial presentation in a significant subset of these patients [21].

The time from initiation of ICI to development of diabetes varies from as little as 4 weeks to more than 12 months. Studies have shown that diabetes mellitus is a very rare manifestation, found in less than 1% of cases followed up with ICI immunotherapy, but it is also worth noting that this alteration was more often found in patients who underwent therapy with anti-PD1 medications [11]. Risk is increased for both the precipitous development of type 1 diabetes as well as insidious worsening of preexisting diabetes mellitus. The mechanism for diabetes development in patients on ICI is hypothesized to be due to activation of autoreactive T-cells due to inhibition of PD-1, leading to T-cell destruction of pancreatic beta cells. Mice studies show that non-obese diabetic mice develop rapid-onset diabetes after PD-1 blockade. Predisposing factors such as HLA DRB1*03/04 genotype may explain why some individuals are at greater risk of developing diabetes mellitus induced by immune checkpoint blockade [11]. Interestingly, autoantibodies have been found in about half of the documented cases of ICI-induced diabetes (ICI-DM) [22]. On the other hand, more than 90% of patients with type 1 diabetes mellitus unrelated to PD-1 inhibitor use develop at least one autoantibody [21]. ICI-DM is characterized by more severe and rapid destruction of pancreatic beta cells than type 1 DM. Exocrine pancreatic inflammation may also be involved in ICI-DM pathogenesis since elevated amylase and lipase were found in about one-third of these patients [23].

Although there is no universally accepted standard for screening and monitoring for endocrine diseases in ICI-treated patients, the French Endocrine Society [23] suggested monitoring at each course of treatment for the first 6 months: natremia, fasting glycemia (for anti-PD1/ PD-L1 therapy) and plasma TSH, T4L, 8 a.m. cortisol level and testosterone level (in males). In addition, HLA genotyping before treatment may be useful for surveillance in patients with the HLA DRB1*03/04 alleles. It is important to sensitize professionals to the risk of sudden and severe ketoacidotic decompensation in patients treated with anti-PD1 therapy [24].

4. Conclusion

In the present report, we see an unusual but relevant association between the use of pembrolizumab, an immune checkpoint inhibitor (ICI), and the emergence of multiple endocrine autoimmune conditions: primary hypothyroidism, secondary adrenal insufficiency, and diabetes mellitus. Endocrinopathies are frequent side effects of ICI, but simultaneous manifestation of several autoimmune conditions, including diabetes mellitus, is uncommon [6, 11].

Vague symptoms due to malignant disease and anti-cancer treatment are common, and this poses a diagnostic challenge to most endocrinopathies, which may lead to non-specific symptoms. For example, the most frequent side effect of ICI is fatigue, mostly without endocrine cause. Diagnosis of endocrine disorders may also be complicated by

polypharmacy and episodes of severe illness secondary to immunosuppression, which may complicate diagnostic testing of hormonal axes.

Therefore, clinicians may carefully monitor patients undergoing immunotherapy with ICI, since the impact of chronic side effects on people's quality of life is also not well known. Some may be easily managed, while others may have a major impact on a person's day-to-day life. Healthcare professionals need to be aware of the possibility of these endocrine complications and be ready for early diagnosis and appropriate management.

Funding: None.

Research Ethics Committee Approval: We declare that the patient approved, by signing an informed consent form, the use of its informations for the present study.

Acknowledgments: None.

Conflicts of Interest: None.

Supplementary Materials: None.

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