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REVIEW ARTICLE

When Hormones are Being Difficult: A Rare Case and the Literature Review of Pembrolizumab-Induced Polyendocrinopathy

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Abstract

Immune Checkpoint inhibitors (ICIs) such as nivolumab, pembrolizumab, and ipilimumab are monoclonal antibodies against cytotoxic T lymphocyte antigen 4 (CTLA4) or program death (PD)1 and its ligand PDL1. Agents targeting PD1, such as pembrolizumab, have shown widespread efficacy in the past and are also associated with a wide range of immune-related adverse events (irAEs), including endocrine toxicities. A 31-year-old female with a medical history significant for Stage IIb Breast cancer on chemo and immunotherapy (pembrolizumab) presented with nausea, vomiting, and generalized abdominal pain. Laboratory studies showed a blood glucose level of 356 mg/dl, elevated Anion gap 18 meq/L, beta-hydroxybutyrate 46 mg/d, and low C-peptide levels <0.10 ng/ml. The patient was treated for Diabetic Ketoacidosis (DKA). Further testing revealed high Thyroid Stimulating Hormone (TSH) levels along with elevated thyroid peroxidase levels of 38 IU/L. After discharge from the hospital on insulin and levothyroxine therapy, the patient reported increasing fatigue and further testing revealed low cortisol levels <0.5 mcg/dl with elevated ACTH consistent with primary adrenal insufficiency. The patient was started on hydrocortisone therapy with improvement in symptoms. Endocrine toxicities are not uncommon in patients receiving pembrolizumab, but polyendocrinopathy in a relatively rare side effect of pembrolizumab. Only a few cases of pembrolizumab-induced polyendocrinopathy have been reported so far which we have mentioned in this article. While patients are on immunotherapy, close monitoring for clinical signs & symptoms can lead to an early diagnosis, substantially improving morbidity and mortality.

Keywords: Breast cancer, Immunotherapy, Pembrolizumab, Hypothyroidism, Type 1 diabetes mellitus, Adrenal insufficiency

1. Introduction

Immune Checkpoint inhibitors (ICIs) such as nivolumab, pembrolizumab, and ipilimumab are monoclonal antibodies against cytotoxic T lymphocyte antigen 4 (CTLA4) or program death (PD)1 and its ligand PDL1. In September 2014, it was initially granted accelerated approval by the FDA for refractory, advanced melanoma. Since then, it has obtained approvals for various other cancer-related indications, and numerous additional indications are currently undergoing clinical development. Agents targeting PD1, such as pembrolizumab, have shown widespread efficacy in the recent past and their response rates range from 15 to 90% depending upon the cancer type.[1] The increased immune responses induced by these agents can result in immune-related adverse events (irAEs) that vary from mild to fatal endocrine toxicities, including hypothyroidism, hypophysitis, adrenal Insufficiency, and pancreatic insufficiency resulting in Type 1 Diabetes Mellitus (DM).[2] There have been rare circumstances when multiple endocrinopathies have been reported simultaneously in patients

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receiving ICIs (e.g., pembrolizumab). The term used to define these polyendocrinopathies is polyglandular autoimmune syndrome type II (PGA) which is a triad of type 1 diabetes mellitus (T1DM), autoimmune thyroiditis, and primary adrenal insufficiency.[3,4] Although current literature reports various endocrinopathies due to the use of ICIs for various cancer treatments, the autoimmune polyendocrine syndrome is a constellation reported rarely in literature so far. In this review, we focus primarily on PGA type II as a result of PD-1 agent (pembrolizumab) use in a breast cancer patient (see Table 1).

2. Case presentation

Our patient is a 31-year-old female with a medical history only significant for Stage IIb Breast cancer (Triple-negative) on chemotherapy (carboplatin/taxol) along with Immunotherapy (pembrolizumab) who presents to the Emergency Department for the evaluation of nausea, vomiting, and generalized abdominal pain for one day. On arrival, the vital signs were within normal limits. Physical examination was consistent with generalized abdominal tenderness with no evidence of rebound tenderness. The rest of the physical examination was unremarkable. Laboratory studies showed a blood glucose level of 356 mg/dl (reference range of 70–110 mg/dl), serum bicarbonate level of 8 meq/L (reference range of 24–35 meq/L), elevated Anion gap 18 meq/L (reference range 8–16 meq/L), and beta-hydroxybutyrate 46 mg/d (reference range 1–4.16 mg/dl). The patient's clinical findings and laboratory data were suggestive of Diabetic Ketoacidosis. So, the patient was admitted to the Intensive Care Unit (ICU) and was started on Insulin Infusion. Further testing revealed low C-peptide levels <0.10 ng/ml (reference range 0.8–3.85 ng/ml) along with elevated thyroid peroxidase levels 38 IU/L (reference range <9), Hemoglobin A1c (HgbA1c) 7.1% (reference range 4.5–6.4%), and TSH levels 36 mcIU/ml (reference range 1–4.16 mcIU/ml) eventually leading to a diagnosis of Type-I diabetes mellitus and hypothyroidism. There was no notable past medical history of hypothyroidism, diabetes mellitus, or adrenal abnormalities. The patient's thyroid function testing before the initiation of treatment revealed TSH levels of 2.02 mcIU/ml (reference range 1–4.16 mcIU/ml), a free T4 level of 1.13 ng/dl (reference range 0.70–1.60 ng/dl), and a HgbA1c of 5.3 (reference range <5.7) which rule out underlying endocrine abnormalities in this patient. During the hospital stay, an Ultrasound (US) of the neck was done, consistent with diffuse heterogeneity of the thyroid parenchyma (Image 1 and 2). Pembrolizumab was held four weeks after the start of therapy due to its severe side effects, and no significant treatment response was noted during the short period of time when she received the treatment. Eventually, she was discharged home on subcutaneous insulin therapy and levothyroxine with close outpatient follow-up. Despite being off of the pembrolizumab, she endorsed increased fatigue on regular outpatient follow-ups for the past few weeks. The early morning cortisol level was sent, which came out to be very low (<0.5 mcg/dl; reference range 1–75.0 mcg/dl), and the diagnosis of primary adrenal insufficiency was made. The patient was eventually started on oral hydrocortisone with significant improvement in symptoms.

3. Discussion

Pembrolizumab, a monoclonal IgG4 antibody, binds PD1 receptors on cytotoxic T lymphocytes, restoring its activity against tumor cells. It, thereby, prevents interaction with its ligand PD-L. But sometimes, an exaggerated T cell activation can result in immune-related adverse events. It is implicated in previous studies that the development of Type 1 diabetes was associated with low C-peptide levels, with some patients even having negative anti-GAD antibodies.[5,6] It was more common in high-risk HLA haplotypes so a multifactorial phenomenon can be attributed. Meanwhile, in some studies, thyroid dysfunction was associated with enhanced uptake of 18F-fluorodeoxyglucose, indicating an inflammatory mechanism.[7,8] Nonetheless, PGA type 2 has a polygenetic basis with a higher

Table 1. Cases with pembrolizumab induced endocrinopathy.

Sr. no	Author/Year	Age/Gender	Cancer type	Endocrine toxicity	Drug	Reference number
1	Hakami et al./2019	52/M	Nodular Melanoma	DKA, hypothyroidism	Pembrolizumab	7
2	Gunjur et al./2019	78/F	Acral Melanoma	DM, hypothyroidism, hypoadrenalism	Pembrolizumab	6
3	Kong et al./2016	68/M	Squamous cell lung cancer	Type 1 DM, hyperthyroidism	Pembrolizumab	8
4	Paepegaey et al./2017	55/F	Choroidal Melanoma	Thyroiditis, primary adrenal failure	Pembrolizumab	12
5	Alhusseini et al./2017	65/M	Adenocarcinoma of lung	T1DM, hyperthyroidism	Pembrolizumab	13
6	Hanna et al./2018	70/M	Lung adenocarcinoma	Adrenal failure, interstitial nephritis	Pembrolizumab	14

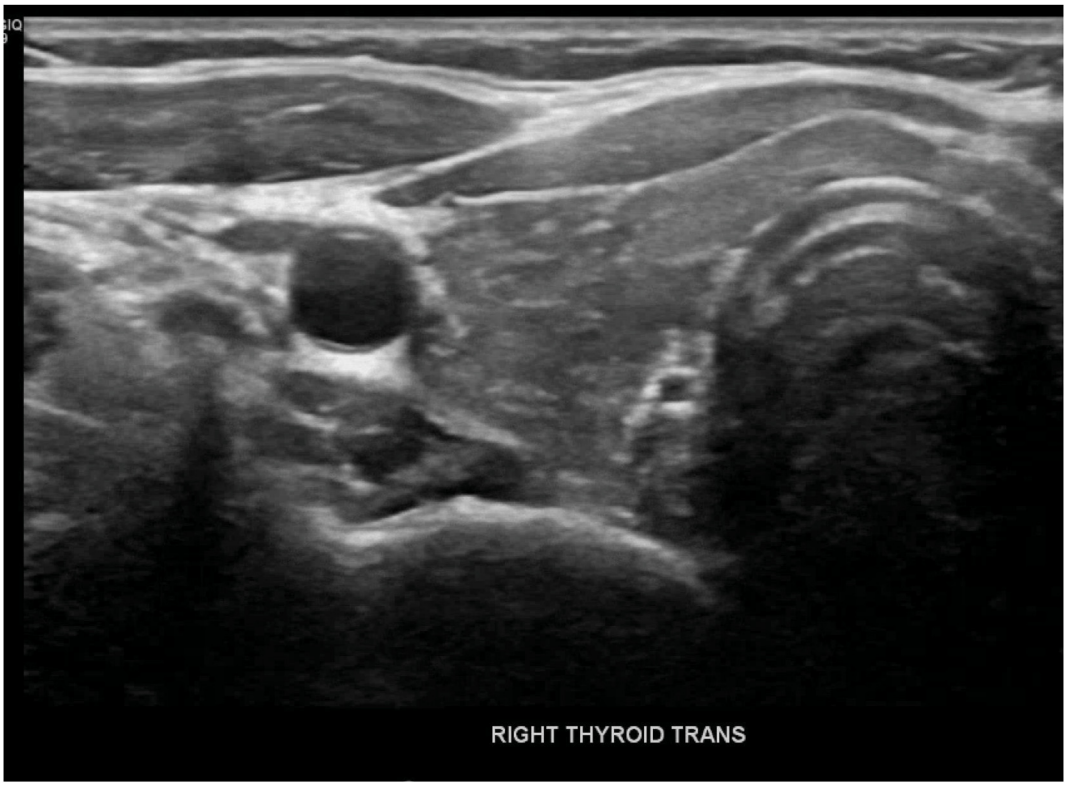

Image 1. US thyroid right.

propensity of developing in females, especially in patients who carry mutations in HLA DR3 and DR4 serotypes. The age of onset ranges from childhood to late adulthood, with most cases occurring between the age of 20−40 years.[9-11]

In recent years, immune checkpoint inhibitors have become a mainstay in cancer treatment targeting a wide spectrum of cancer types, including Melanoma, Breast, Lung, and Renal cell carcinoma. Endocrine adverse events are a fairly common type of immune-mediated adverse event of using these drugs. Data from clinical trials of immune checkpoint inhibitors confirm that thyroiditis and hypophysitis are the most frequently encountered endocrinopathies. On the other hand, Type 1 DM and Adrenal insufficiency are rare side effects of ICIs, especially with pembrolizumab[2,5,6]. However, our patient developed polyendocrinopathy, which can be categorized into one of three types of polyglandular autoimmune syndrome (PGA). Our patient fulfills the criteria for PGA-II as she reported type 1 diabetes mellitus, thyroiditis, and adrenal insufficiency, completing the triad, which is extremely uncommon.

Our patient exhibited a typical disease progression for PGA-II starting from Type I Diabetes Mellitus followed by a hypothyroidism diagnosis confirmed by the laboratory results. Subsequently, she developed symptoms of incessant fatigue leading to the diagnosis of adrenal insufficiency in the following weeks. Even though there have been a few occurrences of PGA-II cases in patients treated with ICI, no PGA-II has been identified yet in a Breast cancer patient being treated with pembrolizumab so far, to the best of our knowledge, which makes this a unique case.

PGA-II is typically more prevalent in females when compared to males, with a mean age for onset of Adrenal insufficiency being 36 years which was also consistent with our patient.[3] Furthermore, adrenal insufficiency is seen in all patients suffering from PGA-II, with some reporting concurrent hypothyroidism and/or type 1 Diabetes Mellitus. Since adrenal insufficiency is a rare kind of IrAE, we can predict polyendocrinopathy if we can detect it early in its course, thus helping us avoid catastrophic complications in the future.[2] Adrenal cortex antibodies and 21 hydroxylase antibodies are positive in autoimmune-mediated adrenal insufficiency, so monitoring their levels and adrenal hormones regularly will prompt us to its early diagnosis.

It is fascinating that our patient developed adrenal insufficiency a few weeks after we stopped

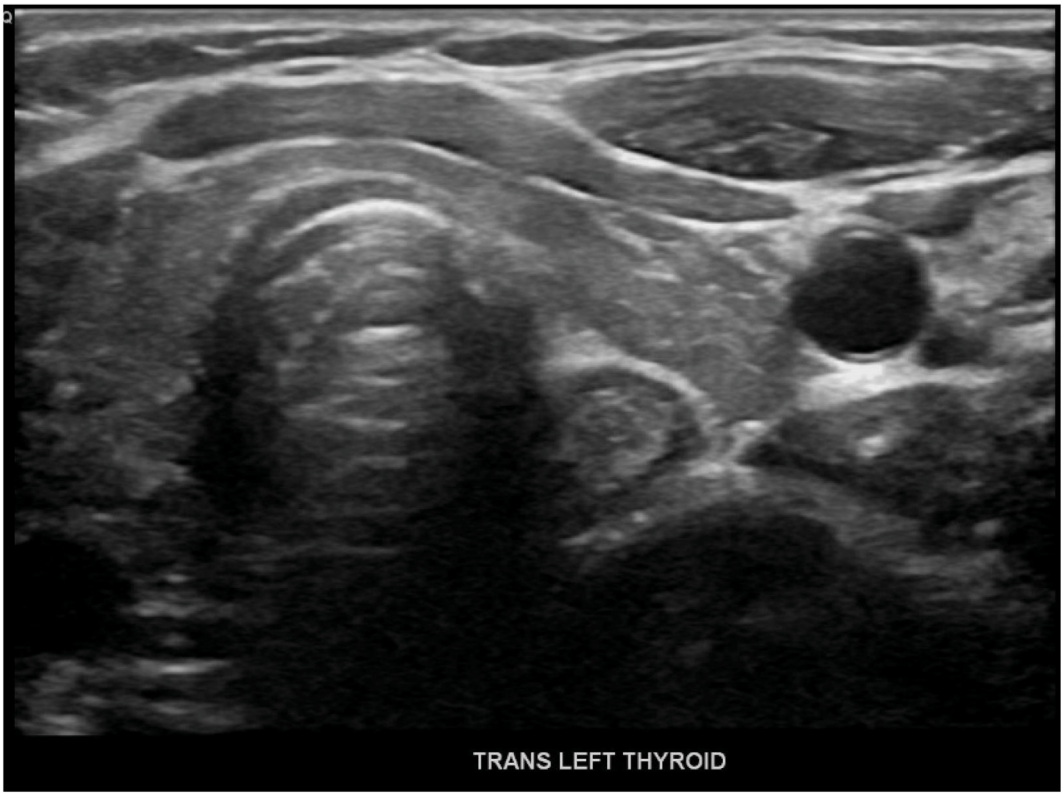

Image 2. US thyroid left.

pembrolizumab, which suggests these effects are attributable to autoimmune pathophysiology.[5] Also, this persistent effect was testified in one of the published series of anti-PD-1 therapy-induced Diabetes mellitus, which highlighted that it could take up to 228 weeks for the onset of disease after initiating treatment. This stochastic nature of the pathology certainly makes it a challenge to monitor. Moreover, our patient had surprisingly negligible C-peptide levels, whereas her HbA1C was only slightly elevated, signifying the rapid destruction of pancreatic Beta islet cells pointing towards an autoimmune phenomenon. Even though ICI-mediated endocrinopathies are postulated to be autoimmune in nature, only 40% of the patients with type 1 Diabetes Mellitus showed evidence of positive serology with one autoantibody.[3] Therefore, this sheds light on the underlying multifactorial pathway contributing to the pathogenesis of the disease.[2]

Predicting which patients are more susceptible to these side effects is difficult. But genetic testing for certain HLA types, specifically DR3 and DR4 in the context of PGA-II may be helpful. Beterele et al. reported convincing evidence regarding HLA-DR3 correlation with Adrenal Insufficiency and HLA-DR3 and DR4 in Type I DM & AD. The association between HLA and autoimmunity is well established but has not been explored in the context of irAEs, especially endocrinopathy.

Notably, the development of certain IrAEs is associated with enhanced anti-PD-1/PD-L1 treatment response. One retrospective case series of Non-Small Cell Lung Carcinoma (NSCLC) patients treated with such therapy is associated with improved progression-free survival and Overall Survival associated with thyroiditis, the most common IrAE.[3] Therefore, if a patient shows better than expected treatment response there might be a possibility of endocrine IrAEs. The significance of monitoring for endocrine AEs increases manifold in such situations. As discussed previously, various labs, autoimmunity, and clinical, genetic markers could be utilized to monitor for IrAEs.

The importance of educating patients regarding worrisome symptoms cannot be emphasized enough. Patients should be informed of clinically alerting signs like persistent headaches, elevated heart rate, profound tiredness or fatigue, cold intolerance, constipation, change in weight, labile mood, polyuria, polydipsia, abdominal pain, and loss of consciousness. These can expedite the detection process, which would facilitate optimal treatment. There are various case reports depicting

different side effects related to the usage of pembrolizumab, as summarized in the table below.

Appropriate tests for thyroid dysfunction can be obtained, like Thyroglobulin, thyroid hormones, and thyroid peroxidase antibodies. Meanwhile, blood electrolytes, cortisol levels, ACTH stimulation test, and adrenal gland imaging can direct us to the diagnosis of adrenal insufficiency. C-peptide and beta cell antibodies will aid in the diagnosis of type 1 Diabetes.

Insulin therapy is the primary treatment in immunotherapy-provoked Diabetes Mellitus or Diabetic ketoacidosis. For Addison's disease, corticosteroids and fludrocortisone would require initiation. Thyroid dysfunction is treated according to the manifestations; methimazole is the appropriate drug for hyperthyroidism, whereas levothyroxine is commenced for hypothyroidism.

Since endocrine dysfunction can pose life-threatening complications, patients on ICI drugs should be frequently assessed. Physicians should adopt a high index of suspicion for potential signs and symptoms of PGA-II as early detection and optimizing management can have a substantive effect on the morbidity of patients.

Conflict of interest

There is no conflict of interest.

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