Case Report

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Immunotherapy-Induced Thyroiditis in Cancer Patients

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Abstract

Hyperthyroid patients may have increased or decreased radioiodine uptake on I-123 uptake and scan, which helps to differentiate the etiology of the hyperthyroid state. Thyroiditis is an uncommon complication of cancer immunotherapy and, in this situation, is likely secondary to an autoimmune response. The typical presentation of thyroiditis, regardless of the etiology, is elevated T4 and/or T3, low TSH and low radioactive iodine uptake. Herein we report a case of cancer immunotherapy-induced thyroiditis in a 34-year-old female diagnosed with right breast grade 2 invasive ductal carcinoma with ER and PR positive, Her2neu negative tumor markers. Due to her ER-positive tumor, 8-cycles of chemo-immunotherapy with Paclitaxel + Pembrolizumab were prescribed. The patient began to complain of intermittent palpitations halfway through her treatment, and her TSH after 6 cycles of treatment was <0.01 U/ml. She had negative TSI or anti-TPO (Pre-treatment TSH- 1.54 U/ml) antibodies. I-123 thyroid uptake and scan demonstrated faint thyroid activity with very low I-123 uptake, consistent with thyroiditis. Her treatment was ultimately continued and continued close monitoring of thyroid function tests was recommended.

Introduction

Immunotherapy treatments have become an integral part of cancer therapy. Though they are effective therapeutic agents, they can cause several side effects, including endocrine, gastrointestinal, and dermatologic toxicity [1]. An uncommon side effect of these treatments is autoimmune thyroiditis, which can present in an atypical manner. Proper evaluation of this condition includes biochemical testing (initial hyperthyroid state followed by a hypothyroid state) and radioiodine uptake and scan to determine the etiology of the initial hyperthyroid state. Herein we describe the clinical presentation, imaging findings and clinical management of a 34-year-old female who presented in a hyperthyroid state after undergoing chemotherapy with pembrolizumab therapy.

Case Presentation

A 34-year-old female was diagnosed in October 2018 with right breast invasive ductal carcinoma, grade 2 with tumor markers positive for estrogen and progesterone receptors and negative for Her2neu. She also had metastatic right axillary lymph nodes. MRI of her breasts demonstrated multicentric disease, which required a mastectomy. In view of her ER-positive tumor marker, adjuvant immunotherapy with Pembrolizumab and an 8-cycle arm of neoadjuvant chemotherapy with Paclitaxel was initiated in November 2018. After the 6th cycle of adjuvant immunotherapy, she presented with intermittent palpitations. Her EKG, chest radiograph and CT Chest Pulmonary Embolism Protocol were all negative. Laboratory tests showed TSH <0.01 U/ml (pre-treatment TSH was 1.54 U/ml), with elevated free T4 (2.2 ng/dL) and T3 (818 pg/dL). Her family history was negative for endocrine dysfunction, and she had no prior history of thyroid disease. Subsequently, she was subsequently started on propranolol and prednisone for presumed thyroiditis, and Pembrolizumab therapy was held pending further workup. Thyroid uptake scan was ordered for further evaluation, which demonstrated no significant uptake in the neck. The 24-hour iodine uptake was calculated at 0.1%, which is significantly below the normal range of 7-30% (Figure 1). From a prior CT scan, the patient's thyroid was confirmed to be in the correct anatomical location (Figure 2). Overall, these findings were consistent with thyroiditis, which was believed to be related to the administration of pembrolizumab. Ultimately, her endocrinologist advised her to resume Pembrolizumab therapy with close monitoring of her thyroid function.

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Figure 1: *I-123 thyroid uptake imaging demonstrates essentially non-visualization of the thyroid gland with no significant uptake in the neck in the normal location of the thyroid as seen on recent CT examination (figure 2). The 24-hour iodine uptake is estimated at 0.1%. This value is significantly below the normal range of 7-30%. The findings are most consistent with immunotherapy-induced thyroiditis.*

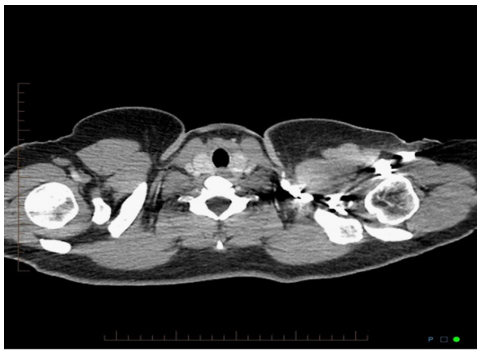

Figure 2: *Axial section of the CT chest without IV contrast demonstrated the normal thyroid gland in expected normal location in this patient.*

Discussion

Autoimmune abnormalities are a known complication of immunotherapy drugs, which can be used to treat a wide range of malignancies including lung and breast cancer and melanoma, to name a few [2]. Specifically, autoimmune endocrine adverse effects resulting from cancer immunotherapy drugs include hypophysitis, hyperthyroidism, hypothyroidism and adrenal insufficiency. There are several immune checkpoint inhibitor drugs already on the market for cancer immunotherapy, such as the anti-CTLA-4 (ipilimumab and tremelimumab) and anti-PD1 antibodies (pembrolizumab, nivolumab and pidilizumab), all of which have been shown to have autoimmune side effects. Ipilimumab, pembrolizumab and nivolumab, however, are the most commonly used and studied for their adverse effects. Anti-PD-L1 agents are being developed as well (atezolizumab, durvalumab and avelumab), which have similar side effect profiles to pembrolizumab [3-5]. Ipilimumab was the first immune checkpoint inhibitor targeting CTLA-4 and was FDA-approved in 2011. In 2014, pembrolizumab was introduced as an alternative to ipilimumab for the treatment of metastatic melanoma. Later, combined ipilimumab and pembrolizumab therapy was used with improved therapeutic efficacy, though this regimen showed an increased rate of immune-related thyroid dysfunction and toxicity. Currently, the indications of combined therapy have been expanded to treat unresectable and metastatic melanoma, metastatic small and non-small cell lung cancers, head and neck squamous cell carcinoma, Hodgkin lymphoma, and advanced clear cell renal cell carcinoma [3, 4].

Pembrolizumab is a monoclonal antibody which binds to and blocks target programmed death receptor-1 (PD-1) receptors, re-activating T cells and allowing them to generate an immune response against cancer cells. PD-1 receptors are minimally expressed on resting immune cells. Upon receiving inflammatory signals, PD-1 becomes overexpressed on T-cells, B-cells, NK cells, and macrophages, among others. Binding of PD-1 with its ligand (PD-L1) inhibits the inflammatory response. Unfortunately, many tumor cells express PD-L1, suppressing T-cell activation and allowing them to escape the immune response. Similar negative T-cell regulatory effects are produced by CTLA-4 receptors. Therefore, immune-related thyroid dysfunction is similar in both ipilimumab (targeting CTLA-4) and pembrolizumab (targeting PD-1), but with varying frequency of adverse events. Ipilimumab is reported to have a higher incidence of hypophysitis compared to thyroid dysfunction, whereas the reverse happens with pembrolizumab [4]. Autoimmune thyroiditis is one of the common side effects seen with the use of immunotherapy in cancer treatment. The pathogenesis of this immunotherapy-induced autoimmune thyroiditis is related to the immunological activation at the level of the thyroid by immunological mechanisms, inflammatory mechanisms or both. Elevated free T3 and T4 followed by hypothyroidism after immunotherapy treatment in these patients is compatible with autoimmune etiology causing inflammatory thyroid destruction. Immunotherapy-induced hyperthyroidism accompanied by low or absent I-123 uptake on thyroid scintigraphy and negative anti-TSH receptor antibodies is suggestive of inflammatory/destructive disease. This is different from the common presentation of hyperthyroidism in Graves' disease, where patients present with hyperthyroidism, increased uptake on I-123 thyroid scintigraphy, and positive anti-TSH receptor [3].

Recently, pembrolizumab use has been identified as a cause of immune-related thyroid dysfunction. Delivanis et al studied 93 patients who had at least one infusion of pembrolizumab. 13 of 93 patients developed thyroid dysfunction, of which 7 patients (54%) had thyroiditis, while 3 had hypothyroidism (23%). Data from phase 2 and 3 clinical trials reported that 3.2% - 10.1% of patients developed thyroid dysfunction. They also reported that anti-TPO antibodies were abnormal in several patients; however, few were patients with pre-existing hypothyroidism, and, interestingly, none of their patients with thyroiditis had abnormal anti-TPO antibodies prior to taking pembrolizumab. They also showed that 4 of the 7 patients who developed thyroiditis recovered [4]. Pembrolizumab-induced thyroiditis demonstrates diffuse increased FDG uptake on PET/CT with a median time of onset at 12 weeks from the start of immunotherapy [4, 6]. The differential diagnosis for this pattern of diffuse FDG uptake includes other inflammatory processes such as Hashimoto thyroiditis.

There is a significant risk of developing severe hypothyroidism in patients who have pre-existing thyroid disease [4]. The literature reports an increased risk of worsening hypothyroidism in patients with high anti-TPO antibodies at baseline or a history of hypothyroidism. It is debated whether this worsening

thyroid function is due to autoantibodies or is the result of the humoral immunologic response to thyroid antigens released during thyroiditis phase [3,4]. It is also reported by multiple studies that there is an acute but transient thyroiditis which is followed by resolution or progression to hypothyroidism [4-8]. The literature reports that patients on pembrolizumab may present as subclinical or overt hypo- or hyperthyroidism, though subclinical presentations and hypothyroidism are more common. It is also documented that patient may present initially with biochemical thyrotoxicosis with subsequent hypothyroidism or as recurrent severe hypothyroidism in patients with pre-existing hypothyroidism [3]. In conclusion, it is important to understand the incidence and presentation of thyroid dysfunction in patients on pembrolizumab in order to optimize therapy and allow close monitoring for functional balance during cancer immunotherapy.

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