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Case Report

Reduced Tumor Size of Untreated Papillary Thyroid Carcinoma After Immune Checkpoint Inhibitor–Induced Thyroiditis

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ABSTRACT

Background/Objective: Immune checkpoint inhibitors (CPIs) activate antitumoral immune responses and are used to treat multiple types of primary and metastatic malignancies. Thyroid dysfunction is a known immune-related adverse event of CPI therapy. There are few data on the effect of CPI and CPI-induced thyroiditis on primary papillary thyroid carcinoma (PTC). We present a patient who developed CPI-induced thyroiditis during treatment for a nonthyroid malignancy and subsequent regression of a coexisting untreated primary PTC.

Case Report: A 49-year-old man with metastatic colon adenocarcinoma was found to have a large right thyroid nodule with biopsy confirmation of PTC. He did not have compressive symptoms or evidence of metastatic PTC. Resection was not performed because of colon cancer therapy. Treatment with CPI (ezabenlimab, an anti–programmed cell death protein 1 antibody) was initiated for the treatment of colon cancer. Four months after the initiation of CPI therapy, testing showed thyroid–stimulating hormone and free thyroxine levels of 174.9 (0.3-4.0 mIU/L) and 0.67 (0.93-1.70 ng/dL), respectively, consistent with CPI-induced hypothyroidism. Levothyroxine therapy was initiated. Repeat imaging 3 months later demonstrated a decrease in the tumor size to 4.1 × 4.9 × 4.2 cm (calculated volume change, −8.3% from baseline). At the last imaging, 1 year after the onset of CPI-induced thyroiditis, the PTC continued to decrease in size and measured 2.9 × 3.9 × 3.2 cm (volume change, −60.7% from baseline).

Discussion: CPI-induced thyroiditis suggests the development of an immune response against thyroid tissue and may reflect a similar increased immune response against PTC cells leading to tumor regression in this case.

Conclusion: Further research to assess the immunologic mechanism underlying this association is warranted to potentially develop improved immunotherapy for PTC.

Introduction

Immune checkpoint inhibitors (CPIs) are cancer therapies that target regulatory mechanisms on T cells, including the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 system.[1] Several cancers exploit these endogenous regulatory systems to evade immune destruction, including some thyroid cancers.[2] Treatment with CPI activates antitumoral immune responses by blockade of these regulatory proteins or their ligands, leading to increased T cell activation.[1] CPIs induce tumor shrinkage and prolong survival in multiple types of primary and metastatic malignancies.[3] Although there is growing evidence that CPI may show benefit in anaplastic thyroid carcinoma,[4] few data exist for well-differentiated thyroid cancers.

Papillary thyroid carcinoma (PTC) is the most common form of differentiated thyroid cancer, most often presenting as a thyroid

Abbreviations: CPI, checkpoint inhibitor; FDG, fluorodeoxyglucose; IrAE, immune-related adverse event; PD-1, programmed cell death protein 1; PTC, papillary thyroid carcinoma; TSH, thyroid-stimulating hormone; VC, volume change.

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nodule and diagnosed by fine needle aspiration biopsy.[5,6] Surgical resection is the standard therapeutic approach for PTC > 1 cm in diameter, and most patients have an excellent prognosis.[5] In patients who are of very advanced age, have other life–limiting conditions, or are on necessary treatments that preclude surgery, immediate intervention may be deferred in favor of active surveillance given the indolent nature of most PTCs.

Immune–related adverse events (IrAEs) are common during CPI therapy and may affect numerous organ systems, including endocrine tissues. Thyroiditis is a known IrAE, affecting 10% to 40% of patients depending on the agent(s) and regimen used.[7,8] CPI-induced thyroiditis may have a recognized hyperthyroid phase but almost universally results in hypothyroidism requiring full replacement levothyroxine therapy.[9] In patients with nonthyroid cancers treated with CPI, the onset of thyroid dysfunction is associated with improved survival.[10] However, in patients with thyroid cancer, the incidence and prognostic significance of CPI-induced thyroiditis would be difficult to assess because such patients have almost universally undergone thyroid removal previously.

Herein, we report a notable case of a patient with incidental PTC managed by active surveillance who was treated with CPI for metastatic nonthyroid malignancy and subsequently developed a CPI-induced thyroid IrAE and objective reduction in his PTC size.

Highlights

- Immune checkpoint inhibitors (CPIs), such as programmed cell death protein 1 inhibitors, are effective therapies for several cancer types but frequently involve immune-related adverse events, which often involve the thyroid and/or other endocrine organs
- When CPI-induced thyroiditis occurs, patients may or may not have a recognized hyperthyroid phase but typically develop hypothyroidism requiring levothyroxine therapy
- To date, there remain few data regarding the effect of CPI on primary untreated papillary thyroid carcinoma (PTC)
- The current case of a patient with metastatic colon adenocarcinoma who experienced significant regression of a large right thyroid PTC after CPI therapy and thyroid immune-related adverse events demonstrates a likely direct efficacy of anti–programmed cell death protein 1 therapy on PTC in the setting of an immune response provoked by CPI-induced thyroiditis
- A small number of other cases have shown reduction in PTC disease burden after CPI but have not assessed the relation to CPI-induced thyroiditis

Clinical Relevance

Immune checkpoint inhibitors (CPIs) are effective therapies for several cancer types; however, few data exist regarding their effects on primary untreated papillary thyroid carcinoma (PTC). This case shows significant regression of a large PTC after CPI therapy and CPI-induced thyroiditis, demonstrating a likely direct efficacy of CPI on primary PTC.

Case Report

A 49-year-old man presented for endocrinology evaluation of a right thyroid nodule, which was found incidentally on a fluorodeoxyglucose (FDG) positron emission tomography scan and had moderate-grade FDG avidity. The FDG positron emission tomography scan was obtained for initial staging of metastatic colon adenocarcinoma (T4aN2M1b, stage IVB) that had been diagnosed at 1.5 months.

The patient reported mild fatigue on initial evaluation but otherwise did not have any other symptoms of hypothyroidism. He had not noticed any neck masses, dysphagia, dyspnea, hoarse voice, or neck pain. He reported a 50-lbs weight loss in the month preceding his cancer diagnosis. He had no childhood radiation exposures. His medical and study histories only included hypertension and right hemicolectomy 1.5 prior. His family history was negative for thyroid cancer but notable for a maternal diagnosis of Graves disease and a sister with hypothyroidism.

On the initial physical examination assessment, the patient was well appearing with a body mass index of 27.4 kg/m^2. He did not have warm or moist skin, tremor, tachycardia, or other signs of hyperthyroidism. On neck examination, no diffuse thyromegaly, thyroid tenderness, or discrete thyroid nodules were palpated, and there was no cervical lymphadenopathy.

The thyroid–stimulating hormone (TSH) level was normal at 3.5 mIU/L (reference range, 0.3-4.0 mIU/L), with free thyroxine and free triiodothyronine levels within their respective reference ranges. Thyroglobulin antibody and thyroperoxidase antibody were both negative.

Thyroid ultrasound revealed a 4.4 × 4.9 × 4.4-cm solid, hypoechoic mass with coarse internal macrocalcifications. The nodule was well circumscribed without evidence of extrathyroidal involvement. Fine needle aspiration biopsy cytology showed a high cellularity sample classified as PTC (Bethesda VI).[6] CT imaging measured the same thyroid mass at 4.1 × 5.1 × 4.4 cm. Given the priority of continuing therapy for metastatic adenocarcinoma, the patient began active surveillance for PTC rather than immediate thyroidectomy.

The patient received 18 cycles of FOLFOXIRI + bevacizumab for 9 months, before starting a clinical trial of a peptide-based vaccine and immune CPI, ezabenlimab (anti–PD-1 antibody). This treatment was administered for 5 weeks before discontinuation because of progression of colon adenocarcinoma. Two months after discontinuation of CPI therapy, the patient had worsening fatigue, and the thyroid function tests revealed TSH, free thyroxine, and free triiodothyronine levels of 174.9 mIU/L, 0.67 ng/dL (0.93-1.70 ng/dL), and 1.3 pg/dL (2.5-4.3 pg/dL), respectively. Levothyroxine was initiated at a full replacement dose. Levothyroxine was progressively increased by 50 μg per day every 1 to 3 months at times when the TSH level increased. No other adverse events of this therapy were identified.

During the 9 months from identification of PTC to CPI initiation, the PTC dimensions increased slightly on CT to 4.3 × 5.1 × 4.3 cm (Fig. *A* and *B*), with the calculated volume change (VC) remaining stable (+2.5%) from the size at the initial diagnosis.[11] At the time of identification of CPI-induced hypothyroidism 4 months later, the nodule had continued to grow to 4.1 × 5.8 × 4.7 cm (VC, +21.5% from baseline). Subsequent imaging another 2.5 months later showed a slight decrease in the PTC size (VC, −8.3% from baseline). On final imaging 12 months after the identification of CPI-induced hypothyroidism, the PTC size had decreased to 2.9 × 3.9 × 3.2 cm, which corresponded to a volume reduction of −60.7% compared with the initial size (Fig. *C* and *D*) as well as −67.6% compared with when the tumor was largest. The patient died from complications of progressive metastatic colon adenocarcinoma 3 months after the last imaging having never received surgical intervention, radioactive iodine, or systemic therapy for PTC.

Discussion

In this case, we present a patient with an unresected primary PTC that significantly reduced in volume after the patient

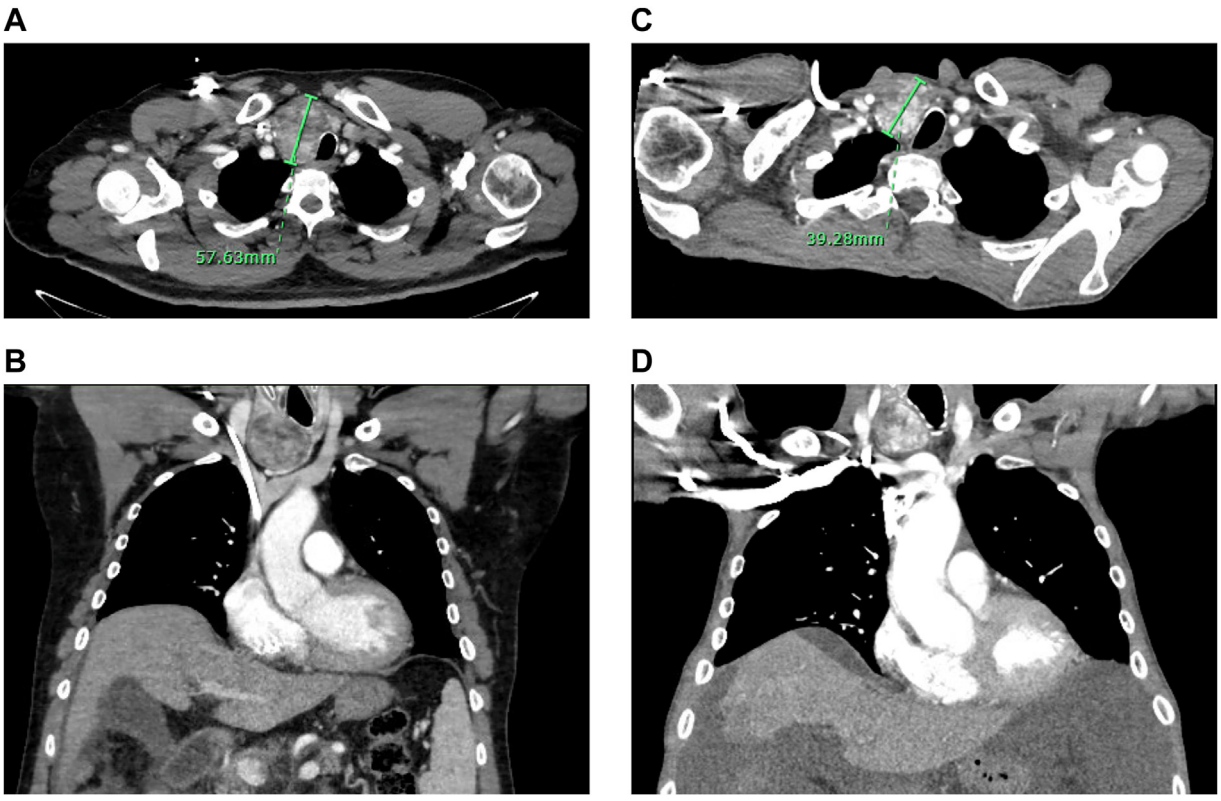

Fig. Regression of papillary thyroid carcinoma (PTC) after initiation of immune checkpoint inhibitor (CPI) therapy and occurrence of CPI-induced thyroiditis. Contrast-enhanced computed tomography imaging of the neck and chest in transverse (*A*) and coronal (*B*) planes revealed the pretreatment tumor size of a fine needle aspiration biopsy–proven PTC of 4.1 × 5.8 × 4.7 cm. The patient subsequently developed CPI-induced thyroiditis and resultant hypothyroidism. At the last follow-up, 12 months after CPI-induced thyroiditis, similar transverse (*C*) and coronal (*D*) computed tomography images showed a significant reduction in the tumor size to 2.9 × 3.9 × 3.2 cm, representing a 60.7% decrease in the tumor volume.

experienced thyroiditis from immune CPI therapy, which he had received for the treatment of another coexisting nonthyroid malignancy. PTC is the most common form of differentiated thyroid cancer, and surgical resection is the standard therapeutic approach for most tumors > 1 cm in diameter. CPIs are not used frequently in the treatment of PTCs. The use of CPIs in patients with iodine-refractory, progressive metastatic PTCs has been reported[5,12]; however, the effect of CPI on primary PTCs has only been described in case reports (Table). Similar to our current case, patients reported in previous literature were treated with CPI for other, nonthyroidal malignancy, and the effects upon the coexisting PTC were observed.

Ocampo et al[13] reported a reduction in the size of a lymph node positive for metastatic PTC after nivolumab treatment for hepatocellular carcinoma; however, information about the primary thyroid tumor was not provided. In another case, Palermo et al[14] described a patient with a 1.4-cm PTC that could no longer be identified by ultrasound 6 months after nivolumab treatment for renal cell carcinoma. Core biopsy of the thyroid parenchyma showed lymphocytes and histiocytes, consistent with a previous report of CPI-induced thyroiditis,[15] although no thyroid test results were provided.[14] Finally, Kotwal et al[16] reported a patient with CPI-induced thyroiditis enrolled in a study profiling of intrathyroidal lymphocytes who had a reduction in the size of a PTC. The patient was a 40-year-old woman treated with pembrolizumab for metastatic melanoma with a 1.4 × 0.9 × 0.9-cm PTC that decreased in size by ultrasound to 0.7 × 0.3 × 0.3 cm after 1 year of therapy, although the exact timing in relation to thyroid IrAE is unknown.[16] Compared with the study by Kotwal et al,[16] the present case was a significantly larger (>4 cm) tumor with preceding growth, suggesting CPI response in a potentially more aggressive lesion. In contrast to these reports, another case demonstrated the occurrence of a new PTC in a patient receiving pembrolizumab.[17]

The current case is unique in documenting the progressive regression of a large primary PTC after exposure to CPI therapy and new-onset hypothyroidism consistent with thyroid IrAE. We speculate that this observation suggests that the T cell–driven immune response against thyroid follicular cells observed in CPI-induced thyroiditis[15,18] also included an increase in immune response directed toward the patient's PTC, leading to a reduction in the PTC size. There are other possible explanations for the reduction in the PTC size. The patient also received prior chemotherapy; however, the PTC showed interval growth on this therapy. The patient also received a peptide-based vaccine concurrent with CPI; however, thyroiditis and/or thyroid tumor response has not been associated with this treatment, and therefore, it seems less likely to be a primary driver of the disease response observed in our patient.

Therefore, this case suggests a direct effect of anti–PD-1 therapy and associated thyroiditis on regression of primary untreated PTC. Despite the unknown efficacy of CPI for PTC, these limited data suggest a potential role for CPI therapy in the treatment of unresectable PTC. Further research to elucidate the immunologic effects on primary PTC of CPI-induced thyroiditis is warranted.

Disclosure

The authors have no multiplicity of interest to disclose.

Table
Case Reports Showing the Responses of Untreated Papillary Thyroid Carcinoma in Patients who Received Immune Checkpoint Inhibitors for Separate Nonthyroid Malignancies

Citation	Patient	Malignancy	Therapy	Response
Gorospe et al,[17] 2020	63-year-old man	Squamous cell lung cancer	Pembrolizumab	• A new right thyroid nodule found 12 mo after starting CPI • Underwent total thyroidectomy, which revealed a 0.8-mm PTC with 5/9 metastatic cervical lymph nodes
Palermo et al,[14] 2020	54-year-old man	Renal cell carcinoma	Nivolumab	• A thyroid nodule, with a size that increased from 4 × 4 × 5 mm to 14 × 10 × 18 mm over 16 mo. FNA cytology was suspicious for PTC (TIR4) • Six months after the initiation of CPI, ultrasound showed "slightly irregular echotexture" of the thyroid without evidence of the PTC lesion
Ocampo et al,[13] 2021	60-year-old man	Hepatocellular carcinoma	Nivolumab	• A supraclavicular lymph node (with FNA-confirmed PTC metastasis) regressed from 3.6 × 2.7 cm to 2.9 × 2.2 cm (34% decrease) after 3 mo on CPI • Reduction in the Tg level from 32 ng/dL to 14 ng/dL after 22 mo
Kotwal et al,[16] 2020	40-year-old woman	Melanoma	Pembrolizumab	• ^{18}FDG-avid thyroid nodule measuring 1.4 × 0.9 × 0.9 cm reduced to 0.7 × 0.3 × 0.3 cm (94% decrease) after 1 y of therapy
Chen et al, 2023	49-year-old man	Colon adenocarcinoma	Ezabenlimab	• An initially enlarging right thyroid PTC measuring 4.3 × 5.1 × 4.3 cm before CPI therapy began to decrease after thyroid IrAE • The tumor at the last assessment 1.5 y after the last CPI exposure measured 2.9 × 3.9 × 3.2 cm (61% decrease)

Abbreviations: CPI = checkpoint inhibitor; ^{18}FDG = 18-fluorodeoxyglucose; FNA = fine needle aspiration; PTC = papillary thyroid carcinoma; Tg = triglyceride.

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