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Case Report

Recurrent Poorly Differentiated Thyroid Cancer Successfully Treated With Radiation and Immunotherapy

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Abstract

A 65-year-old patient presented with recurrent, locally advanced poorly differentiated thyroid cancer despite 2 neck surgeries, and with newly diagnosed brain and skull base metastases. He was treated with palliative stereotactic radiosurgery to the brain and skull base lesions. Thereafter, as no targetable genetic alteration was identified and antiangiogenic multikinase inhibitors were deemed at high risk of hemorrhagic complications, off-label systemic therapies were considered. The mechanistic target of rapamycin (mTOR) inhibitor everolimus could not be obtained due to lack of insurance coverage, so the patient was treated with single-agent pembrolizumab. He showed an initial remarkable response, but unfortunately had disease progression in the neck and upper mediastinum after 1 year of therapy. At that time, he was treated with external beam radiotherapy, with concomitant pembrolizumab. He was then found to have an *CTSB::ALK* fusion, which has previously been described in 2 cases of thyroid cancer. However, as he showed a positive response to radiation with pembrolizumab, he continued single-agent immune checkpoint inhibition and had a persistent marked response almost a year after completing radiation. The patient was then followed at an outside institution and was transitioned to hospice at time of progression per his preference. He died 4 years after his initial diagnosis.

Key Words: poorly differentiated thyroid cancer, pembrolizumab, immunotherapy, radiation therapy, synergy, *ALK* fusion

Abbreviations: ^{18}F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography with computed tomography; ALK, anaplastic lymphoma kinase; ATC, anaplastic thyroid carcinoma; CNB, core-needle biopsy; CTSB, cathepsin B; DTC, differentiated thyroid cancer; EBRT, external beam radiation therapy; EML4, echinoderm microtubule-associated protein-like 4; FTC, follicular thyroid cancer; KI, kinase inhibitor; LN, lymph node; mTOR, mechanistic target of rapamycin; NGS, next-generation sequencing; NSCLC, non–small cell lung carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid cancer; RAI, radioactive iodine; RET, rearranged during transfection; RT, radiation therapy; SBRT, stereotactic body radiation therapy; STRN, striatin; TC, thyroid cancer; TME, tumor microenvironment; TSH, thyrotropin.

Introduction

Poorly differentiated thyroid carcinomas (PDTCs) represent a small subset of differentiated thyroid cancers (DTCs) characterized by high-grade pathologic features [1]. They are associated with a more aggressive clinical course than papillary (PTC) and follicular (FTC) thyroid cancers, including higher rates of locally invasive disease, distant metastases, recurrences, and mortality [2]. Similar to other DTCs, the most common oncogenic drivers in PDTC are mutually exclusive pathogenic variants in *BRAF* and *RAS*, although rearrangements in the *anaplastic lymphoma kinase* (*ALK*) or *rearranged during transfection* (*RET*) genes have been described in up to 14% of cases [2, 3]. PDTCs are also enriched in other alterations that contribute to the aggressiveness and dedifferentiation, including *TERT* promoter, *EIF1AX*, and PI3K/AKT/mTOR pathway pathogenic variants [3]. PDTCs are a heterogeneous group that holds an intermediate position on the spectrum of follicular-derived thyroid cancers (TCs), between the well-differentiated PTC/FTCs and the undifferentiated anaplastic thyroid carcinomas (ATCs). Therefore, some PDTCs can still concentrate I^{131} while others are refractory to radioactive iodine (RAI) and thyrotropin (TSH) suppression and require early initiation of systemic therapy with kinase inhibitors (KIs) [2].

Use of external beam radiation therapy (EBRT) to the neck in DTC is limited to selected cases, although its safety and efficacy have been demonstrated in patients with gross residual or unresectable disease, including 34 patients with PDTC [4]. Additionally, evidence demonstrating the efficacy of immunotherapy in PDTC is sparse [5, 6]. Yet, there are increasing data to support the use of immunotherapy in ATC, especially in combination with KIs [6-8]. Here, we report a case of metastatic PDTC demonstrating a marked sustained response to the combination of EBRT and the programmed cell death protein-1 (PD-1) inhibitor pembrolizumab.

Case Presentation

A 65-year-old man presented to an outside institution with a 13 cm heterogeneous left-sided cervical mass replacing the

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thyroid lobe, and a conglomerate of adjacent metastatic lymphadenopathy. The mass complex extended to the superior mediastinum and prevertebral space, and there was tumor invasion into the left internal jugular vein. The patient underwent a left lobectomy with modified radical left neck dissection. Pathology revealed an angioinvasive PDTC arising from a PTC. Following surgery, he received 151 mCi of adjuvant RAI, and a posttherapy scan showed uptake in the residual right thyroid lobe only. An ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography scan (^{18}F-FDG PET/CT) 5 months later showed hypermetabolic residual/recurrent left level II, left retropharyngeal and right paratracheal lymph nodes (LNs), as well as a 3 cm left thyroid bed mass extending to the anterior mediastinum with a maximal standardized uptake value of 49. Completion right lobectomy with right paratracheal LN dissection was performed. Pathology again showed an angioinvasive PDTC, with 3 metastatic LNs out of the 5 resected. The patient then presented to our institution for a second opinion.

Diagnostic Assessment

Restaging showed a residual mass in the left thyroid bed, measuring 5.5 cm and invading the left sternocleidomastoid muscle and right internal jugular vein (Fig. 1A and 1B), as well as a 2 cm retropharyngeal LN (Fig. 1C). Brain magnetic resonance imaging revealed a 2 cm left parietal lobe metastasis and a left skull base lytic lesion (Fig. 1D and 1E). Ultrasound-guided core-needle biopsy (CNB) of the left thyroid bed mass confirmed residual/recurrent PDTC, and programmed death ligand-1 (PD-L1) immunostaining showed a tumor proportion score of 70%. DNA- and RNA-based next-generation sequencing (NGS) performed on the CNB specimen revealed pathogenic variants in the *TERT* promoter, *TP53*, and *ATR*. No fusions were identified. This molecular testing was performed using an institutional NGS assay that screens for point mutations and copy number variations in 146 genes, and clinically relevant known intergenic and intragenic fusions in 51 genes.

Treatment

The patient was treated with single-session Gamma Knife stereotactic radiosurgery to the left parietal metastasis to 2000 cGy, and stereotactic body radiation therapy (SBRT) to the left skull base and retropharyngeal node metastases, receiving a total dose of 2700 cGy in 3 fractions. After multidisciplinary discussion, he was then started on single-agent pembrolizumab, which was considered to be the only treatment option given the absence of a targetable genetic alteration, the high estimated risk of hemorrhage with antiangiogenic agents, and insurance denial of the mechanistic target of rapamycin (mTOR) inhibitor everolimus. The patient demonstrated a remarkable response to pembrolizumab with significant tumor shrinkage achieved after 8 months (Fig. 2A and 2B). Thyroglobulin decreased from 619 ng/mL (619 µg/L) (normal reference range, 1.59-50.03 ng/mL, 1.59-50.03 µg/L) to 81 ng/mL (81 µg/L).

Unfortunately, after 1 year of pembrolizumab monotherapy, there was evidence of disease progression in the neck and upper mediastinum (Fig. 2C) with concordant increase in thyroglobulin levels to 245 ng/mL (245 µg/L). NGS testing on cell-free DNA (liquid biopsy) showed no detectable

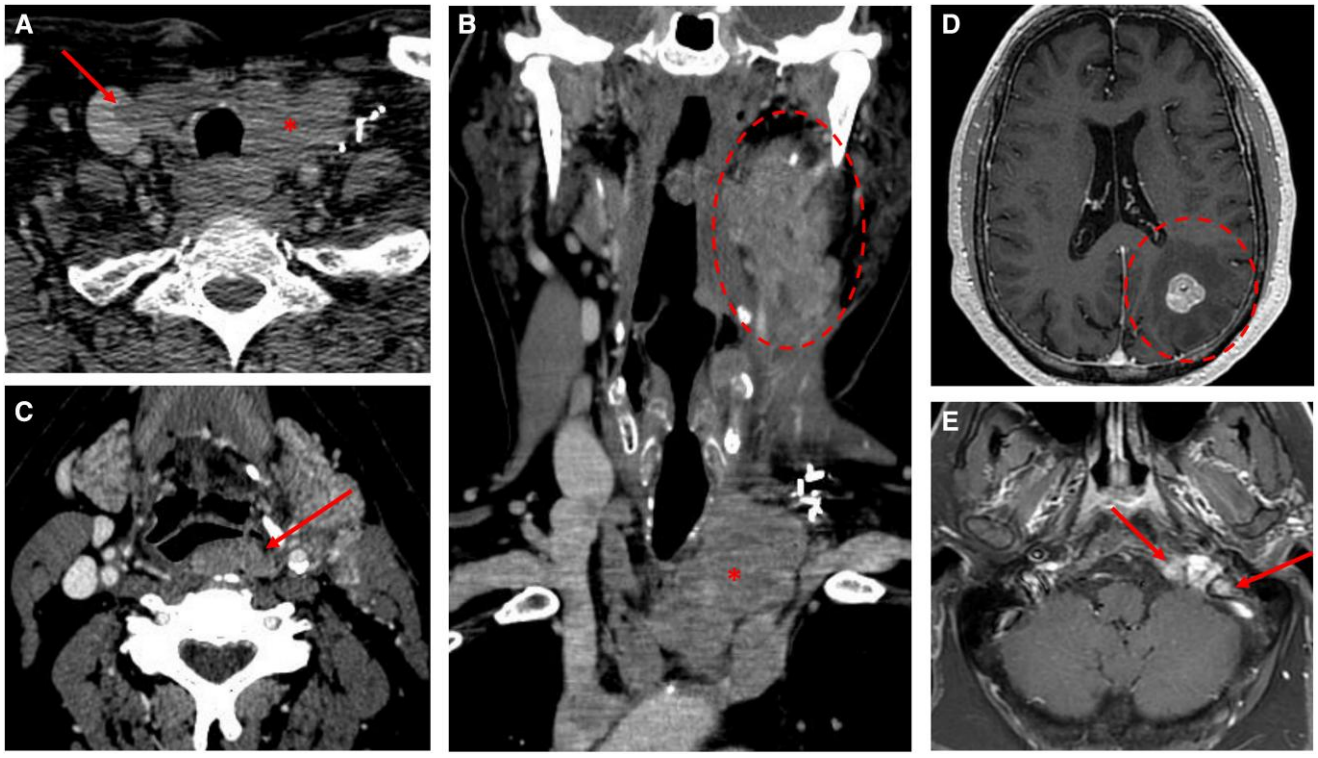

Figure 1. Contrast-enhanced A and C, axial and B, coronal computed tomography images of the neck at initial presentation to our institution (July 2021) demonstrating a lobular 3.4 × 6 cm mass in the left thyroid bed, extending inferiorly into the anterior mediastinum (A and B, *). There is focal invasion of the right internal jugular vein (A, arrow). Conglomerate left level 2 nodal metastases also seen measuring up to 5.5 cm in craniocaudal dimension (B, dotted circle), as well as a 2.3 cm left retropharyngeal lymphadenopathy causing mass effect on the left lateral aspect of the pharynx (C, arrow). Contrast-enhanced axial magnetic resonance images of D, the brain and E, skull base demonstrating a 1.8 × 1.6 cm enhancing cerebral metastasis of the left parietal lobe (D, dotted circle) with regional edema and mild mass effect. An enhancing osseus metastasis to the skull base centered on the left petrous temporal bone with involvement of the jugular tubercle and likely soft tissue extension to the jugular foramen (E, arrows) was also present.

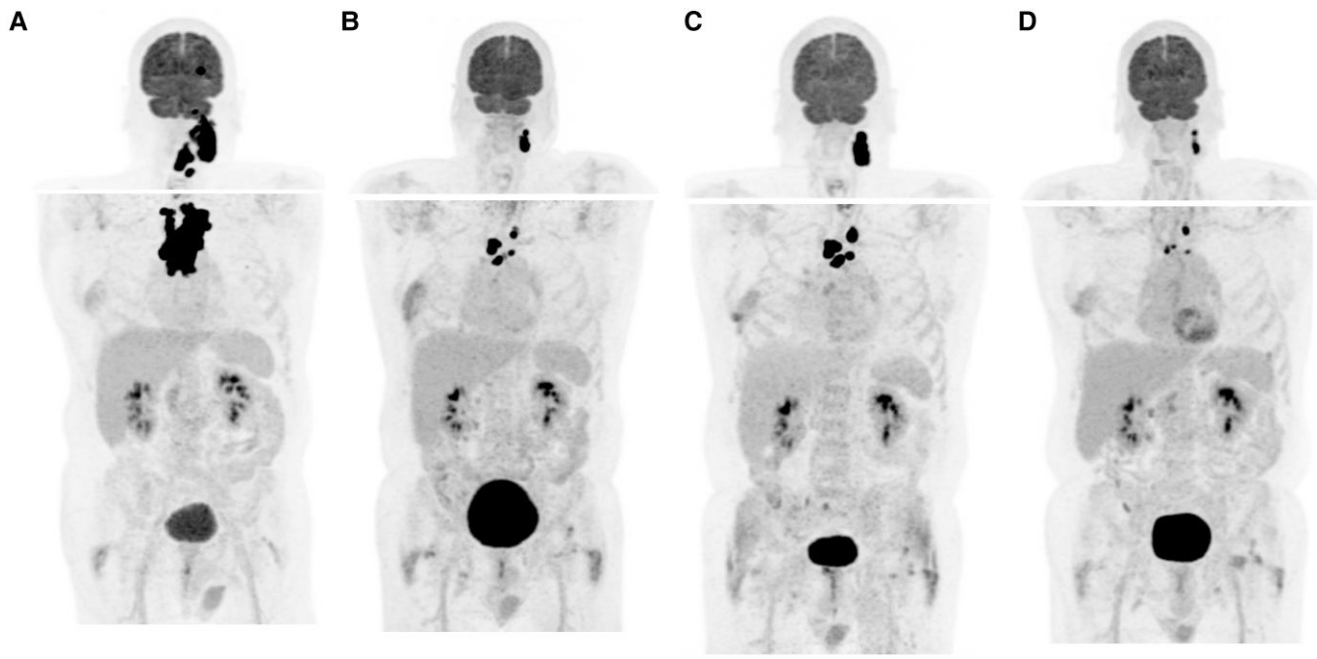

Figure 2. Maximum intensity projection (MIP) ^{18}FDG-PET/CT images A, at baseline (July 2021); B, after 10 cycles of pembrolizumab monotherapy demonstrating significant tumor reduction (April 2022); C, after 12 cycles of pembrolizumab showing disease progression in the left neck and upper mediastinum (July 2022); and D, 10 months after radiation therapy completion demonstrating a marked response to pembrolizumab + radiation (June 2023).

emergent resistance genetic alteration. However, as we had not yet identified an oncogenic driver for the patient's tumor, it was decided to repeat complete NGS testing on the CNB specimen from the previous year, using a different assay. Surprisingly, on repeat testing, a *CTSB::ALK* fusion was identified. Additionally, there was no microsatellite instability and tumor mutational burden was low at 2 mutations/Mb. Following a multidisciplinary discussion, consensus was to treat the progressive neck disease with EBRT while attempting to obtain an off-label ALK inhibitor. The patient was treated with SBRT (2700 cGy in 3 fractions) to the left neck, and volumetric modulated arc therapy to the upper mediastinum (5250 cGy in 14 fractions) (Fig. 3). He did not receive concurrent radiosensitizing cytotoxic chemotherapy but he continued pembrolizumab, receiving an infusion 2 days prior to the start of radiation therapy (RT). He tolerated RT very well with minimal toxicity including grade 0 dermatitis, mucositis, and nausea, and grade 1 pain, esophagitis, dysphagia, and fatigue (per NCI CTC v4.0).

Outcome and Follow-up

At the first restaging visit after completing RT, imaging showed a positive response to therapy, so it was decided to wait before initiating any additional KI. At his last visit at our institution, 9 months after completing RT, the patient had an ongoing response with considerable shrinkage of the cervical tumor (Fig. 2D) and no evidence of new distant sites of disease. Thyroglobulin level was 10.7 ng/mL (10.7 µg/L) with a TSH of 0.22 µIU/mL (0.22 mIU/L) (normal reference range, 0.27-4.20 µIU/mL, 0.27-4.20 mIU/L) and negative antithyroglobulin antibodies. Due to insurance issues, the patient was then unable to return to our institution for follow-up, and 3 months later, he had disease progression and was transitioned to hospice at an outside institution. We reached out to him and offered treatment within a clinical trial or with standard-of-care ALK inhibitor, but he declined. He died a few months later, 4 years from his initial diagnosis.

Discussion

Due to the rarity and heterogeneity of PDTCs, there is no established standard of care for these patients. While some respond to RAI and TSH suppression, others exhibit a more aggressive clinical course resembling ATC. Therefore, treatment of PDTC is challenging and choice of therapy relies on the clinical presentation, including extent of disease and rate of progression.

ATCs are characterized by a tumor microenvironment (TME) richly infiltrated by macrophages and T cells, and they highly express PD-L1 [9]. Consequently, immunotherapy has shown encouraging results in these tumors, especially when combined with KIs [6-8]. However, in a study looking at the immune expression profile in different subtypes of TC [10], PDTCs were shown to have a TME with scant immune cells, although this was heterogeneous. Therefore, clinical evidence for immunotherapy in PDTC is very limited. In the phase 2 KEYNOTE-158 study of pembrolizumab monotherapy in advanced TC, responses were observed in 7 of 103 patients including 1 patient with PDTC who had a complete response [11]. Additionally, in a recently published phase 2 trial looking at the combination of ipilimumab + nivolumab in patients with aggressive TC, 5 patients with PDTC were included, 1 of whom had a partial response [12]. Combination of the anti-PD-L1 atezolizumab with the mitogen-activated protein kinase kinase (MEK) inhibitor cobimetinib has also shown some efficacy in a small cohort of 8 patients with *RAS* and *NF1*/2-mutated PDTC, with a disease control rate of 88% [5].

To our knowledge, this is the second report of a marked response to pembrolizumab monotherapy in a patient with PDTC. In this case, on progression on single-agent pembrolizumab, additional disease control was achieved by combining RT with immunotherapy. While it remains unclear whether pembrolizumab added to the locoregional control obtained with radiotherapy, there are preclinical data suggesting that radiation may enhance the antitumor response to immunotherapy. Radiation

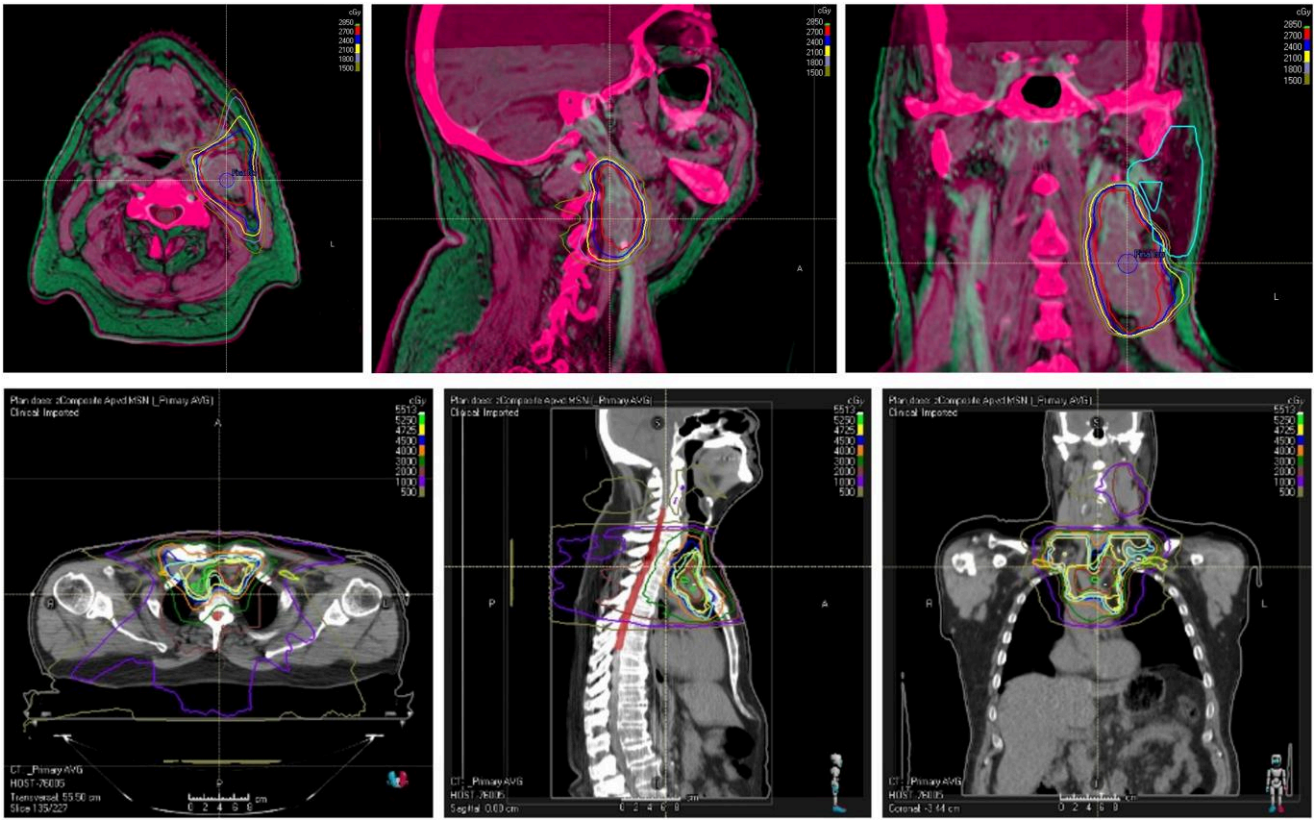

Figure 3. Radiation fields to the left neck (2700 cGy in 3 fractions, upper series) and upper mediastinum (5250 cGy in 14 fractions, lower series).

activates antigen-presenting cells through the DNA damage and reactive oxygen species it induces, upregulates the major histocompatibility complex and tumor-associated antigens, and increases the expression of certain cytokines and chemokines involved in the immune response [13]. Combination of RT with immunotherapy has shown synergistic effects in multiple preclinical studies [14]. However, clinical data are more limited, especially in TC. A case report of a 63-year-old woman with stage IVB recurrent ATC described successful treatment with concurrent RT and pembrolizumab. The patient received a total of 10 cycles of pembrolizumab and demonstrated a 26-month sustained response that was still ongoing at the time of publication of the case report [15]. Recently, another case series of 5 patients with ATC reported encouraging results with hypofractionated RT and pembrolizumab, with 2 patients achieving complete responses [16]. On the other hand, in a phase 1 pilot study of durvalumab + tremelimumab combined with SBRT in 12 patients with metastatic ATC, there were no confirmed responses and only 1 patient had stable disease [17]. Similarly, a phase 2 trial in 3 patients with ATC treated with concomitant chemoradiotherapy and pembrolizumab showed disappointing survival outcomes and raised concerns for increased toxicity with this combination, especially in the lungs [18]. One hypothesis to explain differences in toxicity between this trial and our patient could be the fact that he did not receive concurrent cytotoxic chemotherapy, which might have been responsible for the increased toxicity in the trial cohort. Given these limited data, an ongoing phase 2 trial is further investigating postoperative intensity-modulated RT with concurrent pembrolizumab ± radiosensitizing chemotherapy in patients with ATC (NCT04675710).

ALK rearrangements, leading to constitutional activation of the ALK receptor tyrosine kinase, can be detected in various solid tumors, most frequently non–small cell lung carcinoma (NSCLC), where they represent approximately 3% of oncogenic drivers [19]. Data from the Thyroid Cancer Genome Atlas reported a prevalence of 0.8% of *ALK* fusions in PTC [20], although others report a prevalence of up to 3% in all TC histologies [21]. The most common *ALK* fusion partners in TC are *striatin* (*STRN*) and *echinoderm microtubule-associated protein-like 4* (*EML4*) [19, 21]. In TC, *ALK* fusions are thought to be more prevalent in the PDTC subtype. In a case series of 44 patients with *ALK* fusion-positive TCs, 16% of tumors were PDTCs on pathology [21]. Additionally, *STRN::ALK* fusions have been shown to play a role in progression from PTC to PDTC in a mouse model [22]. Recently, novel *ALK* fusion partner genes have been reported in TC, including *cathepsin B* (*CTSB*), which has been identified in 2 other patients [21]. This gene is expressed in normal thyroid follicular cells, thus driving the expression of the fused part of the *ALK* gene coding for the tyrosine kinase domain. In *CTSB::ALK* rearrangements, *ALK* is fused with an untranslated exon 1 of *CTSB*, with predicted translation starting in *ALK* exon 16 or 17. Although *CTSB::ALK* is not a widely described oncogenic fusion, lack of another driver genetic alteration in our patient points toward the pathogenic nature of this rearrangement.

Beyond prognostic value, identification of an *ALK* fusion is key for therapeutic purposes. In fact, there are multiple KIs targeting ALK, such as crizotinib, lorlatinib, and alectinib, which are currently Food and Drug Administration approved for *ALK*-fusion–positive metastatic NSCLC and have been successfully used in advanced *ALK*-driven TCs in case reports [23, 24].

In conclusion, this is the first case report of a recurrent PDTC successfully treated with a combination of pembrolizumab and RT showing a significant, durable response. Additionally, we report the third case of TC harboring an *CTSB::ALK* fusion, adding to the evidence that this might be a novel pathogenic *ALK* rearrangement.

Learning Points

- Poorly differentiated thyroid carcinomas (PDTCs) are a heterogeneous subtype of thyroid cancer that can be challenging to treat.
- Although initially considered as "cold" tumors, the immune phenotype of PDTCs appears to be variable with some perhaps more aggressive tumors that may respond to immunotherapy.
- Radiation may enhance the antitumor response to immunotherapy in PDTCs and undifferentiated thyroid cancers.
- In the absence of an identified driver genetic alteration in thyroid cancer, additional molecular testing should be performed to look for oncogenic fusions as these can be targeted with specific kinase inhibitors.
- *Anaplastic lymphoma kinase* (*ALK*) rearrangements are present in up to 3% of thyroid cancers and may be more prevalent in the PDTC subtype.

Contributors

All authors made individual contributions to authorship. S.H.: conceptualization; literature review; data curation; writing—original draft. M.S.N., J.P., M.E.Z., M.K.G.M., and R.D.: supervision; validation; writing—review and editing; patient care. M.K.G.M.: preparation of radiology images. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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