A Case of Papillary Thyroid Carcinoma and Kostmann Syndrome: A Genomic Theranostic Approach for Comprehensive Treatment

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Conflict of interest: None declared

Patient: Female, 32
Final Diagnosis: Papillary thyroid carcinoma
Symptoms: Cervical node metastasis
Medication: —
Clinical Procedure: Radioactive iodine treatment
Specialty: Oncology

Objective: Rare co-existence of disease or pathology

Background: Theranostics is a combined diagnostic and treatment approach to individualized patient care. Kostmann syndrome, or severe congenital neutropenia, is an autosomal recessive disease that affects the production of neutrophils. Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy associated with gene alterations, including in the mitogen-activated protein kinase (MAPK) signaling pathway gene. Translocation of the ETS variant 6/neurotrophic receptor tyrosine kinase 3 (ETV6/NTRK3) gene has been implicated in radiation-induced and pediatric forms of thyroid carcinoma but has rarely been described in sporadic PTC. This report is of a case of PTC in a patient with Kostmann syndrome associated with ETV6/NTRK3 gene translocation.

Case Report:
A 32-year-old woman with a history of Kostmann syndrome, acute myeloid leukemia (AML), and chronic graft versus host disease (GVHD) was diagnosed with PTC and cervical node metastases and soft tissue invasion following total thyroidectomy and bilateral modified radical neck dissection. Her postoperative radioactive iodine (RAI) scan confirmed lymph node metastasis. Gene expression studies identified increased expression of iodine-handling genes and ETV6/NTRK3 gene fusion. Because of the bone marrow compromise due to Kostmann syndrome and AML, a careful genomic and molecular analysis was performed to guide therapy.

Conclusions:
This is the first reported case of the association between PTC, Kostmann syndrome, and ETV6/NTRK3 gene translocation in which multimodality treatment planning was optimized by genomic profiling.

MeSH Keywords: Gene Fusion • Genomics • Iodine Radioisotopes • Nanomedicine • Neutropenia • Thyroid Neoplasms

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Background

Papillary thyroid carcinoma (PTC) is the most common endocrine neoplasm and the most common thyroid cancer. Several risk factors have been implicated in the development of PTC, including prior exposure to radiation, and estrogen, obesity, and diabetes mellitus [1]. PTC can be categorized by etiology into familial, radiation-induced, and sporadic cases. There are also histological subtypes and grades and molecular markers that characterize PTC into subcategories [2].

Modern genomic techniques have identified several common mutations in PTC [3]. Sporadic cases of PTC are often caused by activating mutations in the BRAF and RET genes, two oncoproteins that dysregulate components of the MAPK gene signaling pathway. These findings help understand the molecular biology and predict the prognosis of a particular neoplasm. Genome sequencing data can be used to develop tailored approaches to surgical care, chemotherapy, and radiation therapy [4].

Recently, a rare gene translocation between the ET variant 6 (ETV6) gene on chromosome 12, and the neurotrophic receptor tyrosine kinase 3 (NTRK3) gene on chromosome 15 has gained attention in thyroid carcinoma, as this functional mutation codes for a constitutively active tyrosine kinase growth receptor with autonomous capabilities for activating the MAPK and PI3K gene mediated growth and proliferation cascades without the presence of growth ligands [5]. The ETV6/NTRK3 oncogene fusion was first clinically described in 1998 in congenital fibrosarcoma [6]. Since then, this novel oncogene has been implicated in carcinogenesis of secretory breast carcinoma, congenital mesoblastic nephroma, acute myeloid leukemia (AML), salivary gland tumors, and PTC [7–12].

Retrospective studies of the association between gene mutations and thyroid cancer have been important in identifying ETV6/NTRK3 gene fusion in radiation-induced PTC [12,13], but little is known about this association in patients without a previous history of radiation exposure. In 2018, a case report identified a sporadic pediatric case of ETV6/NTRK3-positive PTC in a young Japanese girl [14]. This case is the first to report the association between PTC, Kostmann syndrome, and ETV6/NTRK3 gene translocation in which multimodality treatment planning was optimized by genomic profiling.

Case Report

We present a 32-year-old woman with a history of Kostmann syndrome (severe congenital neutropenia), juvenile rheumatoid arthritis, Type 1 diabetes mellitus, acute myeloid leukemia (AML), hemochromatosis, and chronic graft-versus-host disease (GVHD). She underwent total thyroidectomy and bilateral modified radical neck dissection for PTC. Surgical pathology indicated classical papillary thyroid type with 13 out of 46 cervical lymph nodes to be positive for metastatic PTC with minimal soft tissue invasion. She received postoperative radioactive iodine (RAI) therapy.

Her medical history was rather extensive and was significant for AML with a difficult post-transplant course complicated by multi-organ failure, multiple blood transfusions, and graft versus host disease (GVHD). Medical management of her post-transplant complications included continued phlebotomy for hemochromatosis, chronic anticoagulation for paroxysmal atrial fibrillation, and immunosuppressive therapy for chronic GVHD.

Tissue samples from the surgical excision of the thyroid tumor underwent next-generation sequencing (NGS) using the ThyroSeq Genomic Classifier [15] which showed fusion of the ETS variant 6/neurotrophic receptor tyrosine kinase 3 (ETV6/NTRK3) oncogenes. Because of the patient’s prior history of myelosuppression in the setting of Kostmann syndrome, AML, and the associated complications, the safety of the use of RAI therapy was questioned. The tumor tissue specimen underwent further molecular analysis for iodine-handling and thyroid metabolism gene expression. NGS showed normal iodine uptake and thyroid metabolism genes (TG, TSHR, THRA, THRB, TPO, PAX8, SLC26A4, SLC5A5, SLC5A8, DIO1, DIO2, DUOX1, DUOX2, NIXX2-1, FOXE1, GLIS3), indicating the suitability for RAI imaging with 10 mCi of $^{131}I$. Imaging showed strong activity in the cervical lymph nodes, supporting the diagnosis of lymph node metastasis.

Given the molecular profile and imaging studies, the PTC in this patient was considered to be an aggressive tumor with residual cervical nodal disease but was a highly RAI avid tumor. She was appropriately counseled and was advised to have RAI therapy. We determined an activity of 150 mCi of $^{131}I$ to be appropriate for treatment, based on dosimetric evaluation (Figure 1). She tolerated RAI treatment with no adverse effects (Figure 2). Also, the patient’s bone marrow function remained stable on follow up.

Discussion

Studies in genomics have created a new foundation in the understanding of the oncogenesis of thyroid cancer. The landmark paper published in 2014 by The Cancer Genome Atlas (TCGA) project, identified several genomic alterations in PTC and their associations with tumor morphology and function [3]. Next-generation sequencing (NGS) technology allows interrogation of the entire genome of thyroid cancer, including point mutations and copy number alterations. ThyroSeq version 2 genomic and molecular profiling sequences has detected more
than 1000 hotspots of 14 thyroid cancer-related genes, and 42 types of gene fusions are now known to exist in thyroid cancer [15,16]. In this patient, ThyroSeq analysis of the thyroid tumor tissue showed a the ETS variant 6/neurotrophic receptor tyrosine kinase 3 (ETV6/NTRK3) gene mutation with chromosomal rearrangement of the NTRK3 gene. ETV6/NTRK3 gene fusions are more frequent in pediatric cases of PTC and in PTC associated with radiation exposure but are uncommon in sporadic cases of PTC.

In 2013, a study of pediatric thyroid tumors from the Chernobyl Tissue Bank and an age-matched control group of sporadic PTCs from the US found NTRK translocations in five cases of from a total study sample of 53 tumors, with no statistical significance between the groups [12]. In 2014, another study of post-Chernobyl pediatric thyroid tumors that were previously negative for BRAF and RET mutations found that 14.5% of the frozen tissue samples harbored the ETV6/NTRK3 fusion product. In comparison, only 2% of their sporadic adult PTC control group possessed the mutation, and seven ETV6/NTRK3
tumors were in the sporadic adult PTC control group, but no clinical information or medical history was provided for these patients [17]. This previous study also demonstrated that radiation exposure caused ETV6/NTRK3 translocations in a population of in vitro thyrocytes [17]. In 2014, The Cancer Genome Atlas (TCGA) Research Network published the findings from an analysis of 484 adult thyroid tumors that showed NTRK3 fusions in six tumors (1.2%) but made no specific correlations with radiation exposure or clinical history for these cases [3]. In 2015, a study of 84 pediatric thyroid tumors that had developed following the Fukushima nuclear incident in Japan showed four ETV6/NTRK3-positive cases [13]. A 2016 study of 27 pediatric PTC tumors found seven cases harboring the oncogene and noted that their growth rates and metastatic potential were particularly aggressive [18]. A 2017 case series of 12 patients described the morphologic features of ETV6/NTRK3 translocation in PTC in an adult population without radiation exposure, but the clinical data was limited and did not yield any definitive associations, specifically with regard to underlying thyroid disease or hereditary factors [19]. A 2018 case report of a sporadic ETV6/NTRK3-positive PTC in a seven-year-old Japanese girl matched exon translocations with cases associated with the Fukushima nuclear incident, but the young girl did not have a history of radiation exposure [11].

Figure 2. Coronal MRI neck studies with (A) spin echo, (B) inversion recovery, and (C) post-gadolinium T1 fat saturation demonstrating no residual tumor, lymphadenopathy, or pathologic infiltration.
Review of the literature has identified 46 ETV6/NTRK3-positive thyroid tumors (Table 1). The patient presented in this report was a case of sporadic ETV6/NTRK3-positive PTC that was not associated with radiation exposure or pediatric onset, unlike other previously reported tumors. Her medical history was significant for hematologic malignancy and chronic immunosuppression. Although acute myeloid leukemia (AML) has previously been linked to the ETV6/NTRK3 oncogene, different exon translocations than those in PTC have been documented in the literature [17]. ETV6/NTRK3 rearrangements in PTCs occur with fusion points that differ from those identified in other tumor types (between exon 5 or 4 of ETV6 to exon 13 of NTRK3) as they lack exon 13 of NTRK3 [17].

The aggressive presentation of PTC in the present case, with lymph node metastasis and extrathyroid invasion, prompted an immediate consideration for RAI therapy. However, given the patient’s history of bone marrow compromise due to Kostmann syndrome and AML, it was critical to assess whether her PTC would respond to radioactive iodine treatment as a radioactive resistant PTC would have subjected the patient to unnecessary further bone marrow deterioration. RAI has been known to adversely affect the bone marrow due to radiation damage, causing thrombocytopenia and leukopenia [20]. To determine the radioactive avidity of the PTC, in this patient, we expanded the genomic profile of the PTC to include the detection and sequencing of iodine-handling genes. This secondary level of the genomic analysis showed a high degree of expression of several genes, including TG, TSHR, THRA, THRB, TPO, PAX8, SLC26A4, SLC5A5, SLC5A8, DIO1, DIO2, DUOX1, DUOX2, NKK2-1, FOXE1, and GLIS3.

Mutations in the thyroglobulin (TG) gene, located on chromosome 8q24 encoding the prohormone thyroglobulin (TG), have been reported in thyroid carcinoma, and more frequently in differentiated thyroid carcinomas, including PTC. Reduced expression of TG appears to be associated with dedifferentiation of cancer cells, which does not necessarily initiate thyroid carcinogenesis, but the hormonal dysregulation may increase cancer progression. Serum TG is clinically used to monitor thyroid cancer recurrence after initial treatment. TG dysregulation is a known oncogene that correlates with tumor differentiation [15, 21].

The thyroid stimulating hormone receptor (TSHR) gene, located on chromosome 14q31, is responsible for encoding the thyroid stimulating hormone receptor. Once this receptor is activated by thyroid stimulating hormone (TSH), a chain of intracellular signaling sets off via second messengers like cAMP and orchestrates thyroid cell proliferation and maintenance of thyroid function [15]. Deregulation of TSHR appears to play an important role in thyroid carcinogenesis [22]. Specifically, hypermethylation of TSHR promoter has been frequently found in thyroid carcinoma, with a prevalence of 34–59% in PTC. Some forms of undifferentiated thyroid carcinoma also seem to exhibit epigenetic silencing via hypermethylation, with various studies supporting the theory that TSHR silencing is a secondary genetic event in thyroid carcinogenesis and not necessary for the initiation of thyroid carcinoma. Therefore, the methylation of TSHR may serve as a marker for thyroid malignancy [23].

Loss of normal function of thyroid hormone receptors (TRs), which are transcription factors that regulate cell proliferation, differentiation and apoptosis, via deletion or mutations have been implicated in cancer development, progression, and metastasis. The THRA and THRB genes encode thyroid hormone (T3)-binding TR isoforms. Genome-wide association studies (GWAS) have shown loss in the expression of THRB gene was reported in malignancies including lung, melanoma, breast, head and neck, renal cell, uterine cervical, ovarian, and

Table 1. ETV6/NTRK3-positive papillary thyroid carcinoma cases in the literature.

|                | Sporadic | Radiation-induced | Total cases |
|----------------|----------|-------------------|-------------|
|                | Adult    | Pediatric         | Adult       | Pediatric |         |
| Ricarte-Filho 2013 [12] | –        | 2                 | –           | 2         | 4       |
| Leeman-Neill 2014 [17]  | 3        | –                 | –           | 9         | 12      |
| Cancer Genome Atlas Research Network 2014 [3] | –        | –                 | –           | –         | 6       |
| Mitsutake 2015 [13]    | –        | –                 | –           | 4         | 4       |
| Prasad 2016 [18]       | –        | 7                 | –           | –         | 7       |
| Seetahala 2017 [19]    | 12       | –                 | –           | –         | 12      |
| Otsubo 2018 [14]       | –        | 1                 | –           | –         | 1       |
| Total              | 6*–15    | 10                | 0–6*        | 15        | 46      |

* The Cancer Genome Atlas Research Network study did not specify patient characteristics for tumors in their sample.
testicular tumors and rearrangement of the THRA gene has been reported in leukemia, breast, and stomach cancer [24]. TR mutations have been associated with PTC tumorigenesis, by loss of normal function, with a frequency of 62–93% [25]

The thyroid peroxidase (TPO) gene is an essential part of thyroid hormone synthesis and is a membrane-bound enzyme that is part of the iodide-handling machinery that forms thyroxine (T4) and triiodothyronine (T3). Variations in the heterogeneity of mRNA expressions of TPO have been detected in malignant thyroid cancer, with the noted difference that total TPO mRNA expression, specifically in follicular variant of PTC, was lower than in normal thyroid gland [26].

The SLC5A5 gene encodes the sodium/iodide symporter (NIS), the SLC26A4 gene encodes the anion exchange protein, pendrin, and the SLC5A8 gene encodes apical iodide transporter (AIt), which members of the sodium-solute transporter family and critical components in iodine metabolism. In thyroid cancer, the expression of molecules that metabolize iodine can be lost by hypermethylation of these genes, which results in the inability to concentrate iodine [27]. Hypermethylation of SCL5A5, a known tumor suppressor gene in PTC, has been associated with advanced tumors, multifocality, and extrathyroid invasion [28]. SLC5A5 gene contains NIS upstream enhancer (NUE) sequence that has both PAX-8 and cAMP response element (CRE) binding sites, which are required to regulate the transcription of SLC5A5.

The PAX-8 gene encodes a transcription factor that is critical for normal thyroid development. PAX8/PPARY chromosomal rearrangement is found in thyroid carcinoma [15]. However, our patient had high expression levels of PAX-8, without a chromosomal rearrangement. It is unclear whether simultaneous high expression of SLC5A5 and PAX-8 impair an aberrant process of regulation of transcription factors in thyroid carcinoma. PAX-8 involvement in SLC5A5 gene regulation is noteworthy.

The DIO1 and DIO2 iodothyronine deiodinase type 1 (D1) and type 2 (D2) genes encode for deiodinase enzymes which are involved in the activation and deactivation of thyroid hormones. D1 is involved in serum T3 production, and D2 controls the local conversion of T4 to T3 in the hypothalamus and pituitary and to negatively regulate TSH secretion. DIO1 expression is associated with increased risk of PTC, and under-expression of DIO1 and DIO2 are more frequently found in PTC, which may be due to dedifferentiation, but the specific roles of these genes in tumor initiation or progression remain to be determined [29].

The DUOX1 and DUOX2 genes encode nicotinamide adenine dinucleotide phosphate (NADPH) oxidases that provide H2O2 for thyroid peroxidase mediated iodide incorporation at the apical membrane of thyroid follicular cells necessary for thyroid hormone biosynthesis. Disorders in DUOX1 and DUOX2 have been known to play a role in congenital hypothyroidism and autoimmune thyroid disease. The upregulation of DUOX1 and DUOX2 in thyocytes seems to correlate with the induction of oxidative stress, which leads to direct DNA damage and tumorigenesis [30].

Common variants located on the FOXE-1 and NKX2-1 genes have been associated with differentiated thyroid carcinoma (DTC) in GWAS [31]. NKX2-1 thyroid-specific enhancer-binding protein gene encodes thyroid transcription factor-1 (TTF-1) and the forkhead box E1 (FOXE-1) gene encodes thyroid transcription factor-2 (TTF-2). The interplay between three transcription factors specific to thyroid tissue, TTF-1/NKX2-1, TTF-2/FOXE-1, and PAX-8 have been shown to determine thyroid morphogenesis and normal thyroid physiology [32]. In PTC, FOXE-1 variants were associated with the degree of tumor aggression, including stage, grade tumor size, and the presence of lymphatic invasion [32,33].

The GLIS3 gene encodes for Kruppel-like zinc finger transcription factor GLI-similar 3. GLIS3 appears to act downstream of TSH and TSHR to promote TSH/TSHR-mediated proliferation of thyroid cells and biosynthesis of thyroid hormone. Enhanced GLIS3 binding at promoters of the sodium iodide transporters NIS and PDS has been described, thereby controlling the regulation of thyroid hormone biosynthesis [34]. GLIS3 variants have been observed in congenital hypothyroidism of various phenotypes from aplasia/dysplasia to dyshormonogenesis in humans [35]. A murine study of hypothyroidism in GLIS3KO mice showed that the expression of this gene was related to dyshormonogenesis rather than thyroid gland dysgenesis, but the underlying mechanism of hypothyroidism associated with GLIS3 mutation remains to be determined [36].

In this case, the PTC metastasized to 13 cervical lymph nodes and showed extra-thyroid invasion, which is associated with reduced survival [37]. Although one study noted that ETV6/NTRK3-positive tumors behaved aggressively, these findings were from pediatric patients, a population known to show augmented growth and metastatic potential of thyroid neoplasms. The presence of extrathyroid invasion and nodal metastases in our patient’s disease merited adjuvant radioactive iodine-131 therapy [38]. The evidence of RAI avidity of the patient’s metastatic nodes on RAI scan as well as the molecular panel of the iodine-handling machinery and thyroid metabolism gene expressions that our patient’s PTC exhibited, provided a novel theranostic approach to treating this patient’s thyroid disease.

The future of specific targeted therapy in thyroid cancer depends on the development of chemotherapeutic agents that...
can potentially target the gene itself or the byproduct (protein expressions) of the various pathways of thyroid metabolism that can become aberrant in thyroid cancer. Currently, inhibitor therapy is directed at a broader level of oncogenesis, specifically at the protein products of the NTRK genes. Inhibitors such as lestaurtinib, midostaurin, and altiratinib that target NTRK3 protein products have been shown to generate a clinical response in solid tumors that harbor NTRK gene fusions, but these have not been studied in thyroid carcinomas. There are currently phase 2 clinical trials underway for other agents that target the NTRK3 tyrosine kinase receptor, such as entrectinib, in various solid tumors, including patients with ETV6-NTRK3 thyroid carcinoma [4].

Genomic and molecular profiling is currently being used for investigation of indeterminate category thyroid nodules to enhance the diagnostic accuracy of cytoology. ThyroSeq genomic profiling has clear benefits in defining malignant subtypes with different prognoses that may direct future therapy, such as the extent of surgical treatment and requirement for lymph node dissection. Furthermore, expanded molecular profiling, including expression of iodine-handling genes, may identify specific cancers that are suitable for adjuvant treatment with RAI.

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Conclusions

A case is presented of a 32-year-old woman who underwent total thyroidectomy with bilateral modified radical neck dissection for parathyroid carcinoma (PTC) with cervical lymph node metastasis and perithyroid soft tissue invasion. The PTC expressed the ETS variant 6/neurotrophic receptor tyrosine kinase 3 (ETV6/NTRK3) gene. Although previous recent studies have identified 46 previous cases of ETV6/NTRK3-positive thyroid tumors, this case of PTC was sporadic and not associated with radiation exposure and was not of pediatric onset. Little is known regarding the clinical behavior of this genetic subset of tumors in adults, but this patient underwent aggressive surgical care and nuclear medicine therapy, guided by a comprehensive approach using postoperative radioactive iodine (RAI) imaging and analysis of iodine uptake.

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Ethical approval

This report was conducted in compliance with ethical standards.

Conflict of interest

None.

None.
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