

Recurrent Papillary Thyroid Carcinoma with Unique Molecular Signatures and Literature Review

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1. Abstract

Papillary thyroid carcinoma (PTC) is a common endocrine tumor with a favorable survival rate. Although most PTC cases have a good prognosis, some PTCs exhibit more aggressiveness and invasiveness, often accompanied by lymph node metastasis, a high recurrence rate, and poor prognosis. Distinguishing the signature of highly invasive and metastatic PTC is important for further clinical treatment. In this study, we report two cases of recurrent PTC with tracheal invasion and review the gene mutation signature. Next-generation sequencing (NGS) revealed BRAF, TERT, and IDH1 mutations in recurrent papillary carcinoma in case 1, and TSC2 and EIFAX mutations in case 2.

2. Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for over 90% of all thyroid cancer cases, with a 5-year survival rate exceeding 98% [1]. However, more than 25% of patients experience recurrence during long-term follow-up [2]. Independent risk factors for recurrence include neck lymph node metastases, extrathyroidal growth, age at diagnosis, tumor size, pathological subtypes, and male gender [3]. Among extrathyroidal extensions, invasion of the upper aerodigestive tract (ADT) by PTC indicates more aggressive tumor behavior, identifying a subgroup of patients at greater risk of recurrence and death [4]. Although thyroid cancer rarely invades the trachea, when it does, it can result in airway bleeding and obstruction, potentially leading to fatal outcomes. To characterize the features of these rare

invasions, we conducted a retrospective review of clinical and genetic data from two patients who experienced PTC recurrence with tracheal involvement.

3. Case Presentation

3.1. Case 1

A 58-year-old female with a history of gastric adenocarcinoma and hypertension. Eleven years earlier, she underwent a left thyroidectomy and lymph node dissection. The pathology report indicated PTC with invasion into surrounding muscles. Six years before the tumor was recurrent on the left side of the neck, she underwent tumor resection. Now she presented with complaints of difficulty swallowing and occasional breathing difficulties. Enhanced computerized tomography of the neck (CECT) revealed a 47×21mm mass with heterogeneous enhancement, involving the left lobe area and upper esophagus (Figure 1A). To manage the condition, the patient underwent bilateral enlarged thyroidectomy and total laryngectomy. Subsequent histopathological examination of the excised tissue shows the tumor with a solid and irregular growth pattern. Some area shows classic papillary architecture (Figure 1B-C). The neoplastic cells were strongly positive for PAX8 and partially positive for TG. Calcitonin, PTH, CgA, Syn, P63, and P40 are negative (Figure 1D-F). According to the H&E and immunohistochemistry, we confirmed the recurrent papillary thyroid carcinoma diagnosis.

Next-Generation Sequencing (NGS) analysis was performed due to the tumor's recurrence, to identify possible genetic alterations responsible for its progression. The NGS results revealed the presence of mutations in BRAF, TERT, and IDH1 genes (Table 1). The patient died after 3 months without further therapy.

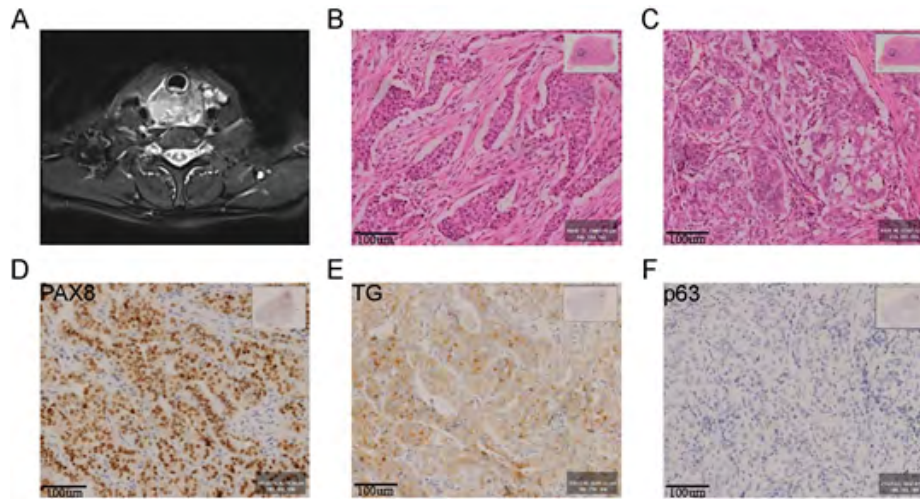


Figure 1: The CT examination showed the enhancing lesion invaded the trachea **A**. The histological examination showed the tumor cells grow in sheets and solid form, with some areas of papillary architecture **B, C**. Tumor cells showed diffuse PAX8 nuclear expression **D** and variable tg expression **E**. Solid areas were negative for p63.

3.2. Case 2

A 69-year-old male with a history of gout and a total thyroidectomy performed eleven years earlier for columnar cell type PTC. Five years ago, he experienced a recurrence on the left original thyroid area and received radioactive iodine (RAI) therapy after a lumpectomy. Three years before the current presentation, multiple nodules were found in the left lung, and histopathological examination confirmed PTC. NGS analysis indicated mutations in EGFR, KRAS, TSC2, and NOTCH2 genes (Table 1). Now he presented with a left-sided neck tumor that gradually increased in

size. The CECT revealed thickened soft tissue in the glottis and sub-glottic area, resulting in airway stenosis (Figure 2A). To manage the condition, total laryngectomy was performed and subsequent histological examination confirmed the diagnosis of PTC (Figure 2B). It was composed of well-developed papillae lined by cigar shaped nuclei with nuclear pseudostratification. The neoplastic cells were positive for TG (Figure 2C). The NGS result showed the mutation of TSC2 and EIFAX (Table 1). Following laryngectomy, he was treated briefly with Seed Brachytherapy in lung. Another round of RAI (200mCi) was given. Approximately one and a half years following laryngectomy, the patient is alive with disease.

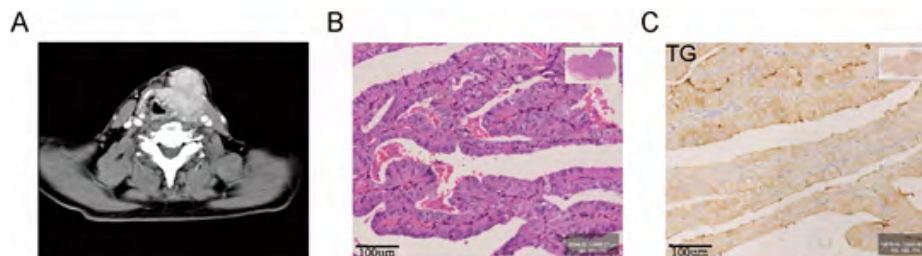


Figure 2: The CT examination showed the enhancing lesion invaded the trachea **A**. The histological examination showed the tumor cells grow papillae with fibrovascular cores **B** and TG expression **C**.

Table 1: Frequencies of mutations in carcinomas by location.

	Gene	Nucleotide change	Amino Acid Changes	Exon Position	Mutation type	Mutation Ratio
Case 1-larynx	BRAF	1799T>A	p.Val600Glu	exon15	missense mutation	35.89%
	TERT	-124C>T	/	/	promoter mutation	30.70%
	IDH1	623A>G	p.Tyr208Cys	exon6	missense mutation	50.61%
Case 2-Lung Metastasis	KRAS	c.35G>C	p.Gly12Ala	exon2	missense mutation	2.21%
	KRAS	c.50G>C	p.Ser17Thr	exon2	missense mutation	2.17%
	TSC2	c.3647_3648dup	Pro1218fs	exon31	frameshift mutation	25.79%
	TSC2	c.939del	Asn314fs	exon10	frameshift mutation	46.72%
	NOTCH1	c.1558T>C	p.Phe520Leu	exon10	Missense mutations & splice region mutations	3.22%
Case 2-larynx	TSC2	c.3647_3648dup	Pro1218fs	exon31	frameshift mutation	23.24%
	TSC2	c.939del	Asn314fs	exon10	frameshift mutation	44.69%
	EIF1AX	c.70A>G	p.Arg24Gly	exon2	missense mutation	2.06%

4. Discussion

Diagnosing and treating recurrence and metastasis in PTC are still clinical challenges. Like other malignancies, cancer heterogeneity appears in the primary and recurrence PTCs. The cancer heterogeneity is not only limited to histopathological diversity but also is manifested as variations in several genetic alterations [5]. Here we reported the pathology and gene signature of two recurrent PTC with upper ADT invasion. Although the upper ADT is close to the thyroid gland, the incidence of invasion by PTC is extremely low. Whereas mortality will rise when the upper ADT is invaded [6]. The WHO TNM classification classifies the upper ADT invasion as the T4a category. The invasion of PTC is correlated with histological subtyping and molecular alterations. Several aggressive variants of PTC have been described, namely tall cell, columnar cell, hobnail cell, and diffuse sclerosing variants. Elder age at diagnosis (≥ 55 years) is a poor prognostic factor [7].

In both cases, the first recurrence occurred more than five years after the thyroidectomy and appeared tracheal invasive on the second recurrence. The NGS panel used to sequence the above-mentioned specimens uses a panel designed to detect somatic mutations in 77 thyroid cancer-related genes. The panel covers the full-length coding sequence plus splice sites for tumor suppressors, and mutational hotspots for oncogenes. Base calling, mapping, and variant annotation were performed using Illumina's suite.

Molecular analyses of case 1 in recurrent tumor tissues revealed a telomerase reverse transcriptase (TERT) promoter mutation with BRAF and IDH1 mutation. TERT is a catalytic subunit of telomerase that maintains telomere repeats in DNA strands [8]. Mutations in the TERT gene promoter increase telomerase activity and play an important role in cellular immortality and tumorigenesis. TERT promoter mutations in thyroid cancers are often accompanied by BRAF or RAS mutations. Coexisting BRAF V600E and TERT promoter mutations have a robust synergistic impact on the aggressiveness of PTC, including a sharply increased tumor recurrence and patient mortality, while either mutation alone has a modest impact [9,10]. Isocitrate dehydrogenase 1 (IDH1) mutations are present in many different types of cancer, including PTC. IDH1 variants occurred at higher frequency follicular variant of PTC and undifferentiated thyroid carcinomas than the observed variants in classical PTC [11]. Our case showed aggressive clinical behavior and had TERT promoter mutations.

In case 2, both the lung specimen and the larynx surgical specimen with the PTC were found to harbor the same TSC2 c.3647_3648dup and c.939del, it was concluded that the TSC2 contributed to the pathogenesis. In healthy individuals, the protein product of the TSC2 gene is tuberlin, which generates a functional complex that inhibits the mTOR (mammalian target of the rapamycin) signaling pathway [12]. Mutations in the TSC2 genes result in overexpression of the mTOR pathway, resulting in the formation of

neoplasms. KRAS gene is an oncogene from the mammalian RAS gene family and plays an important role in the MAPK pathway. KRAS gene has an effective function on increased risk for PTC [13]. It is reported that NOTCH1 mutation was significantly associated with Event-free survival [14]. In case 2, the mutation in lung tissue was quite different from the later recurrence in the larynx. EIF1AX mutation occurs in the larynx tumor. EIF1AX encodes a protein that mediates the transfer of Met-tRNA to 40S ribosomal subunits to form the 40S preinitiation complex for protein translation. EIF1AX was identified as a cancer gene in PTC [15].

The different genetic and epigenetic alterations in PTC have been identified and associated with the pathogenesis and progression of PTC [15]. The most common mutation of PTC is BRAF V600E mutation, which occurs in 44% PTC and 24% papillary-derived anaplastic thyroid cancer (ATC). Most of them perform biological functions through MAPK and PI3K/AKT signaling pathways in PTC [16]. The mutation of BRAF and RET is able to trigger the MAPK pathway [17]. The telomerase reverse transcriptase (TERT) promoter mutations are found in 33% of the PTCs. The C228T and C250T mutations are the ones most commonly associated with aggressiveness and recurrence/distant metastasis [18]. The co-existence of BRAF and TERT is strongly associated with shorter progression-free survival [19].

In summary, we illustrate the clinical and genetic features of PTC with recurrence and metastases. The incorporation of NGS analysis aids in identifying key genetic alterations, guiding targeted therapy decisions, and potentially improving patient outcomes. Further research is warranted to optimize treatment strategies for recurrent and metastatic PTC patients.

5. Contributions

D.L. and F.Y. wrote the main manuscript text. All authors have prepared the figures and reviewed the manuscript.

6. Compliance with Ethical Standards Conflict of Interest

The authors declare that they have no conflict of interest.

7. Ethics Approval

Not applicable.

8. Informed Consent

Informed consent was obtained from all individual participants in this study.

9. Funding

None.

10. Data Availability Statement

All other data generated from this study are available upon request to the corresponding author.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2023; 73: 17-48.
2. Grogan RH, Kaplan SP, Cao H, Weiss RE, Degroot LJ, Simon CA, et al. A study of recurrence and death from papillary thyroid cancer with 27 years of median follow-up. *Surgery.* 2013; 154: 1436-1446.
3. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab.* 2005; 90: 5723-5729.
4. Zhang J, Fu C, Cui K, Ma X. Papillary thyroid carcinoma with tracheal invasion: A case report. *Medicine (Baltimore).* 2019; 98: e17033.
5. Chmielik E, Rusinek D, Oczko-Wojciechowska M, Jarzab M, Krajewska J, Czarniecka A, et al. Heterogeneity of Thyroid Cancer. *Pathobiology.* 2018; 85: 117-129.
6. Djalilian M, Beahrs OH, Devine KD, Weiland LH, DeSanto LW. Intraluminal involvement of the larynx and trachea by thyroid cancer. *Am J Surg.* 1974; 128: 500-504.
7. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. *AJCC cancer staging manual*; Springer. 2017; 1024.
8. Park JI, Venteicher AS, Hong JY, Choi J, Jun S, Shkreli M, et al. Telomerase modulates Wnt signalling by association with target gene chromatin. *Nature.* 2009; 460: 66-72.
9. Liu R, Xing M. TERT promoter mutations in thyroid cancer. *Endocr Relat Cancer.* 2016; 23: R143-155.
10. Xing M, Liu R, Liu X, Murugan AK, Zhu G, Zeiger MA, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol.* 2014; 32: 2718-2726.
11. Hemerly JP, Bastos AU, Cerutti JM. Identification of several novel non-p. R132 IDH1 variants in thyroid carcinomas. *Eur J Endocrinol.* 2010; 163: 747-755.
12. Ehninger D. From genes to cognition in tuberous sclerosis: implications for mTOR inhibitor-based treatment approaches. *Neuropharmacology.* 2013; 68: 97-105.
13. Ning L, Rao W, Yu Y, Liu X, Pan Y, Ma Y, et al. Association between the KRAS Gene Polymorphisms and Papillary Thyroid Carcinoma in a Chinese Han Population. *J Cancer.* 2016; 7: 2420-2426.
14. Li Y, Gao W, Cai X, Jin A, Shen J, Zhang Y, et al. Exploring Somatic Alteration Associating with Aggressive Behaviors of Papillary Thyroid Carcinomas by Targeted Sequencing. *Front Oncol.* 2021; 11: 722814.
15. Cancer Genome Atlas Research, N. Integrated genomic characterization of papillary thyroid carcinoma. *Cell.* 2014; 159: 676-690.
16. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer.* 2013; 13: 184-199.
17. Abdullah MI, Junit SM, Ng KL, Jayapalan JJ, Karikalan B, Hashim OH, et al. Papillary Thyroid Cancer: Genetic Alterations and Molecular Biomarker Investigations. *Int J Med Sci* 2019; 16: 450-460.
18. Liu C, Liu Z, Chen T, Zeng W, Guo Y, Huang T, et al. TERT promoter Mutation and Its Association with Clinicopathological Features and Prognosis of Papillary Thyroid Cancer: A Meta-analysis. *Sci Rep.* 2016; 6: 36990.
19. Rusinek D, Pfeifer A, Cieslicka M, Kowalska M, Pawlaczek A, Krajewska J, et al. TERT Promoter Mutations and Their Impact on Gene Expression Profile in Papillary Thyroid Carcinoma. *Cancers (Basel)* 2020; 12.