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REVIEW

Relationship between genetic alterations and clinicopathological characteristics of papillary thyroid carcinoma

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Abstract

Papillary thyroid carcinoma (PTC) is characterized by proliferation of follicular cells with distinctive nuclear features such as ground glass appearance, nuclear groove and pseudoinclusion. From the proliferation pattern, PTC is divided into several histological subtypes; conventional histology is classified as papillary type, and there are also follicular and solid variants. PTC is heterogeneous in genetic alterations. PTC with BRAF mutation presents a histology of conventional PTC, and follows an aggressive clinical course. Most cases of PTC with RAS mutation show a follicular variant, and prognosis is favorable. RET/PTC1 is observed sporadically and in young cases, and prognosis is favorable. RET/PTC3 is associated with radiation exposure, and the solid variant is frequent. ETV6-NTRK3 may be associated with radiation exposure, and the clinical course is aggressive. Mutation in the telomerase reverse transcriptase promoter is observed in PTC cases involving elderly male patients. Tumor size is large, associated with distant metastasis and advanced stage. This mutation is found concomitantly with BRAF mutation, and the clinical course is aggressive. Genetic alterations form subsets of PTC with distinct clinicopathological features. Careful assessment of clinicopathological features is considered useful in predicting clinical course and when planning treatment.

Keywords Papillary thyroid carcinoma · BRAF · RAS · RET/PTC · ETV6/NTRK3 · TERT

Introduction

Papillary thyroid carcinoma (PTC) is a malignant neoplasm of the thyroid gland. Incidence has been increasing worldwide [1]. Pathological features of PTC are distinct, and nuclear features are essential in the diagnosis of PTC.

Although PTC shows distinct histological features, genetic alterations are heterogeneous. Recent studies have revealed the presence of various mutations such as BRAF, RAS and in the promotor of telomerase reverse transcriptase (TERT), as well as gene rearrangement of RET/PTC and ETV6-NTRK. These genetic alterations are associated with the clinical and pathological characteristics of PTC. The correlation between clinicopathological characteristics and genetic alterations in PTC is reviewed.

Papillary thyroid carcinoma and morphological features

PTC is characterized by distinct nuclear features: pseudoinclusion (Fig. 1a), groove (Fig. 1b) and ground glass appearance (Fig. 1c). These nuclear features are essential for a definitive diagnosis of PTC.

Based on the proliferation pattern, PTC is categorized into several variants. The conventional type is characterized by papillary proliferation of cells with distinct nuclear features (Fig. 1d). The follicular variant is characterized by follicular proliferation of tumor cells (Fig. 1e), and the solid variant by a sheet-like proliferation of tumor cells (Fig. 1f).

Tumors usually have a thick fibrous capsule, and the tumor cells may invade into the fibrous capsule and infiltrate surrounding tissue and organs (Fig. 1g). Tumor cells may invade into lymph vessels.

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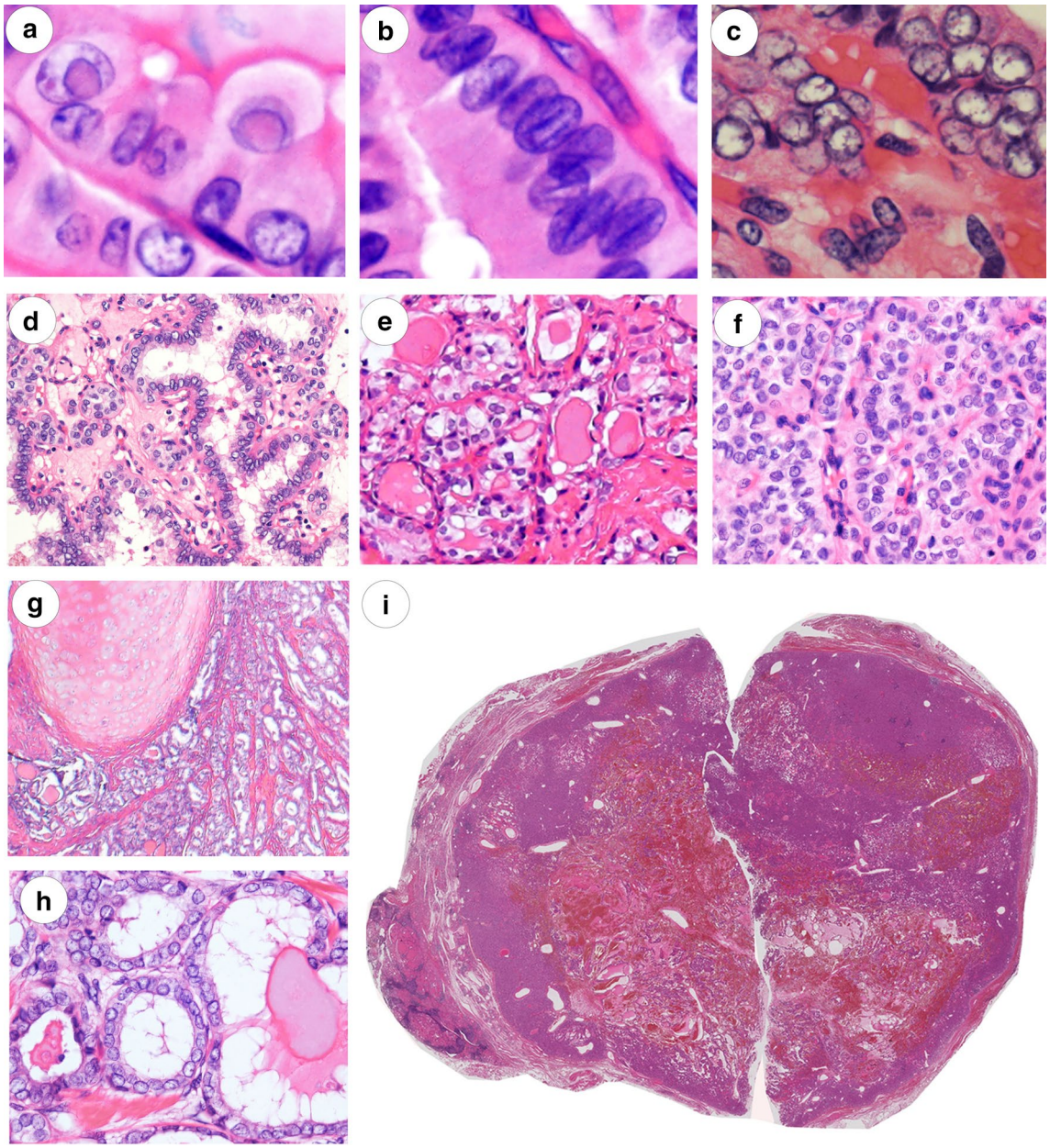

Fig. 1 The histological features of papillary thyroid cancer. Distinct nuclear features are nuclear pseudoinclusions (**a**), nuclear grooves (**b**), and ground glass appearance (**c**). Conventional papillary type of PTC is characterized by the papillary proliferation of cells with distinct nuclear features (**d**). Follicular variant is characterized by follicular pattern of proliferation (**e**). Solid variant shows a sheet-like proliferation of tumor cells (**f**). The tumor cells invade to the extrathyroidal tissue (**g**). Non-invasive follicular variant thyroid neoplasm with papillary nuclear features (NIFTP) is characterized by encapsulated follicular proliferation of tumor cells with distinct nuclear features (**h, i**)

When tumor cells have the distinct nuclear morphology of PTC but show encapsulated and follicular growth pattern, the tumor is diagnosed as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (Fig. 1h, i). It was suggested that the clinical course of NIFTP is favorable compared to that of PTC [2]. For a definitive diagnosis of NIFTP, careful histological evaluation of capsular and vascular invasion is required.

An overview of genetic alterations of PTC

Mutation of BRAF is observed in 36–83% of the cases of PTC [3]. RAS mutation is rare in conventional type PTC, but occurs in 25% of the cases of follicular variant PTC [3]. RET/PTC rearrangement is observed in 22–65% [4],

ETV6-NTRK3 fusion gene in 2–14.5% [5], and TERT promotor mutation in 8% [6] of the cases of PTC.

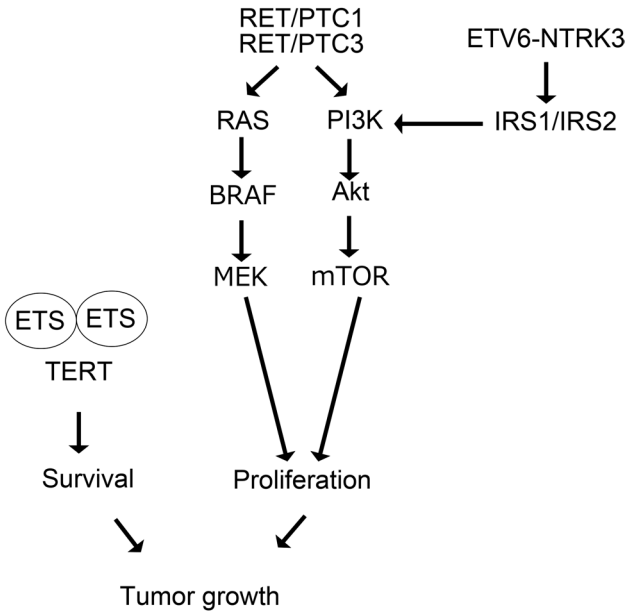

Fig. 2 The molecules involved in the carcinogenesis of PTC. The mutation of BRAF and RAS and rearrangement of RET/PTC stimulate the MAPK pathway. ETV6-NTRK3 stimulate insulin-like growth factor pathway and the PI3K/Akt pathway. These genetic alterations enhance cell growth, proliferation, apoptosis and differentiation. TERT promotor mutation induces overexpression of TERT and promotes survival of tumor cells

Molecular pathways involved in genetic alteration in PTC are illustrated in Fig. 2. Mutation of BRAF and RAS and rearrangement of RET/PTC stimulate the MAPK pathway. ETV6-NTRK3 stimulates the insulin-like growth factor pathway and the PI3K/Akt pathway. These genetic alterations encourage cell growth, proliferation, and differentiation. TERT promotor mutation induces overexpression of TERT and promotes survival of tumor cells.

Mutation of BRAF

Mutation of BRAF is observed in various malignant tumors, such as malignant melanoma, colon cancer and gastrointestinal stromal tumors [7]. Mutation of BRAF is the most common genetic alteration in PTC. While V600E mutation is the most frequent, other mutations of K601E, V600K601 delinsE and T599IV600_R603 del have also been reported [8].

PTC with BRAF mutation occurs in patients aged in their 50s [9]. Patients are predominantly male. Tumor size tends to be large [10] and tumor histology is that of conventional PTC [11]. Extrathyroidal extension, vascular invasion and lymph node metastasis are also frequent [12], and the pathological stage is usually advanced [13]. Recurrence is reported in 25% of patients [14]. Prognosis is worse than PTC with wild type of BRAF, and disease-specific death is 5% [15] (Table 1).

PTC with mutation of BRAF K601E is observed in 1.2% of the cases of PTC, and the follicular variant type is

Table 1 Genetic alterations and clinicopathological characteristics in papillary thyroid carcinoma

Genes/Promoter	Age	Gender	Background	Pathology	Clinical features
BRAF	50s	M > F		Conventional type	Large size (> 2.5 cm)
				Extrathyroidal extension	Advanced stage (> Stage III)
				Vascular invasion	Recurrence (25%)
					Lymph node metastasis (40%)
					Disease-specific mortality (5.3%)
RAS	ND	ND		Follicular variant	Favorable prognosis if encapsulated
RET/PTC1	< 18	M < F	Sporadic	Conventional type	Favorable prognosis
RET/PTC3	< 18	M = F	Radiation	Solid variant	Advanced stage (> Stage III)
					Good response for radioactive iodine
ETV6-NTRK3	> 13	M < F	Radiation	Mixed follicular and papillary pattern	Lymph node metastasis (75%)
			Hypothyroidism	Oncocytic and clear cell foci	Distant metastasis (8.3%)
				Extrathyroidal extension	
				Lymphocytic thyroiditis	
TERT promoter	50–60s	M > F	ND	ND	Large size (> 3–4 cm) Distant metastasis (17%) Advanced stage (> Stage III) Frequent recurrence (50%) Disease-free survival (10%)

ND not described

frequent. V600K601 delinsE occurs in 0.2%, which is associated with the solid variant type. BRAF T599IV600_R603 del is observed in 0.007% cases of PTC. PTC with these mutations follows a less aggressive clinical course than PTC with BRAF V600E [8].

Mutation of RAS

Among three isoforms, HRAS, NRAS, and KRAS, mutation of NRAS is the most frequent [16], and Q61R and Q61K are well reported.

Mutation of RAS is rarely observed in conventional PTC, but occurs in 25% of cases of follicular variant of PTC [3]. If the tumor is non-invasive, lymph node metastasis, distant metastasis, and recurrence are infrequent [17] (Table 1). However, prognostic significance of RAS mutation is not fully understood, due to the limited number of patients and follow-up period. Mutation of RAS is reported to be frequently observed in NIFTP [2].

RET rearrangement

RET is a receptor-type tyrosine kinase, and fusion with PTC1 and PTC3 has been reported.

RET/PTC1 is observed in cases of PTC involving young patients, less than 18 years of age [3, 18]. Correlation with radiation exposure is not observed. Conventional PTC is the most frequent histological subtype [19]. Clinical course is usually favorable.

RET/PTC3 is also observed in young patients, less than 18 years of age [20], and correlation with radiation exposure has been reported [21]. Both male and female patients are equally affected [20]. Tumors are usually in the advanced stage at the time of presentation. Regarding histological subtypes, the solid variant type is most frequent [22]. Despite advanced stage at diagnosis, survival is favorable, and tumors in this rearrangement are responsive to radioactive iodine therapy [3] (Table 1).

These rearrangements are not detected in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma. PTC with these rearrangements is not considered to transform into these aggressive carcinomas [3].

ETV6-NTRK fusion gene

ETV6-NTRK3 results from translocation t(12;15) (p13;q25). ETV6 is a transcription factor of the ETS (E26 transformation specific) family, and NTRK3 is a receptor-type tyrosine kinase.

ETV6-NTRK3 was observed in various tumors, including mammary analog secretory carcinoma in salivary glands, infantile fibrosarcoma, chronic eosinophilic leukemia, acute myelogenous leukemia and gastrointestinal stromal tumors [23, 24].

This fusion gene may be associated with radiation exposure [5]. PTC with ETV6-NTRK3 presents a mixed pattern of follicular and papillary growth, and oncocytic cell or clear cell foci are frequently observed [5, 25]. Chronic lymphocytic thyroiditis may be present in the background, and some cases clinically show hypothyroidism [5, 25]. Extrathyroidal extension and lymph node metastasis are frequent [25] (Table 1). However, the prognostic value of this fusion gene is not fully understood due to the limited number of patients [4].

Telomerase reverse transcriptase (TERT) promoter mutations

TERT is an enzyme involved in the elongation of telomeres, the nucleoprotein complex at the end of a chromosome, preserving chromosome integrity and genomic stability [6]. Overexpression of TERT is caused by a mutation of its promotor. There are two hot spots for mutation located at the − 124 and − 146 base pairs upstream from the ATG codon. Mutations of the TERT promoter are observed in tumors of the central nervous system, bladder cancer, hepatocellular carcinoma, melanoma, and thyroid cancer [26]. Overexpression promotes survival of tumor cells.

TERT promoter mutations are observed in 8% of the cases of PTC [6], and occur along with other tumors originating from the follicular epithelium of the thyroid. These mutations are not detected in normal tissue, benign lesions, or medullary thyroid carcinomas [22].

TERT promotor mutations are found in cases of PTC involving older patients in their 50s and 60s [6, 22]. Patients are predominantly male [6, 22]. Tumor size tends to be large [22]. Association with specific histological subtypes has not been reported. Distant metastasis is found in 17% of the patients [12]. Disease is usually in the advanced stages, prognosis is usually unfavorable, and the 5-year disease-free survival rate is only 10% [22] (Table 1).

It should be noted that mutations of TERT promotor may be concomitantly present with BRAF mutations [12]. Concomitant TERT and BRAF mutations are reported in elderly male patients with PTC [27]. Recurrence is reported to be 68.6% in cases of PTC with both BRAF and TERT promoter mutations, whereas recurrence was only 8.7% in cases of PTC with either one mutation [12]. Coexistence of BRAF and TERT promotor mutations, and pathologically, a Ki-67 labeling index higher than 10% is reported as a promising marker to predict recurrence of PTC [28].

Table 2 Factors assessed in pathological practice of papillary thyroid carcinoma

Age	More than 50, less than 18
Sex	Male or female
Past history	Sporadic or familial, radiation, hypothyroidism
Cytological features	Nuclear pseudoinclusion, nuclear groove, ground glass appearance Necessary for the definitive diagnosis of papillary thyroid carcinoma
Proliferation pattern	Histological subtypes: conventional papillary type, follicular variant, solid variant
Invasion	Careful assessment of capsular and lymphovascular invasion
Differential diagnosis	Papillary thyroid carcinoma, non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

Pathological practice for papillary thyroid carcinoma

The most critical factor in the diagnosis of PTC is the identification of distinct nuclear features. Next, capsular and lymphovascular invasion must be carefully evaluated. When tumor cells demonstrate the distinct nuclear features of PTC, form a follicular pattern, and evidence of capsular or lymphovascular invasion is not present, the tumor is diagnosed as NIFTP.

Genetic alterations may form subsets of PTC, with distinct clinical and pathological characteristics. Determining the genetic alteration in each case of PTC is not feasible. Instead, genetic alteration can be predicted by careful assessment of the clinical and pathological characteristics of PTC. Special attention should be given to age, sex, proliferation pattern and lymph node metastasis (Table 2).

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