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Moderate-Risk and High-Risk Thyroid Carcinomas of Follicular Cell Origin

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Abstract

Thyroid carcinoma is the most common malignancy in endocrine organs and has varied prognosis from almost benign to lethal with less than six months' survival. It is important for pathologists to recognize the moderate-risk and high-risk thyroid carcinomas because under- or over-diagnosis of these carcinomas may create serious problems in the clinical management of patients. Patients with moderate-risk or high-risk thyroid carcinoma are candidates for more aggressive treatments, such as total thyroidectomy with neck dissection followed by radioactive iodine ablation, differing from lobectomy alone for patients with benign, borderline, or low-risk thyroid carcinoma at an early stage. This review explains diagnostic histopathologic features and prognostic implications of moderate-risk and high-risk thyroid carcinomas of follicular cell origin. The moderate-risk and high-risk thyroid carcinomas are not a single disease entity but a group of carcinomas that have an aggressive clinical course between well differentiated and undifferentiated carcinomas. They are aggressive variants of papillary thyroid carcinoma, angioinvasive follicular thyroid carcinoma and well differentiated thyroid carcinoma with distant metastasis in addition to poorly differentiated carcinoma and well differentiated thyroid carcinoma with minor anaplastic component.

Keywords: Thyroid gland, follicular cell, carcinoma, prognosis, aggressiveness, diagnosis

Introduction

The classification of thyroid follicular cell neoplasms based on the traditional histopathological characteristics is shown in Table 1. Thyroid carcinomas are classified into well differentiated carcinoma (WDC), poorly differentiated carcinoma (PDC), and undifferentiated carcinoma (UC) (1, 2). WDC is usually further classified into two groups: papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC); both have an excellent prognosis with a cause-specific survival (CSS) rate after curative surgery of >95% at 20 years; whereas most patients with UC die within six months after diagnosis (3-6). Therefore, the histological diagnosis of this differentiation classification has a significant role as a prognostic factor to stratify patients postoperatively. However, it is a well-known fact that a small number of patients with WDC recur, develop distant metastasis, and eventually die of the disease (7-12). It is important for pathologists to identify and report these clinically aggressive thyroid carcinomas accurately so that clinical doctors may apply more aggressive treatments to those patients, such as total thyroidectomy with neck lymph node dissection followed by TSH suppression therapy and radioactive iodine treatment because these tumors usually retain the functions of follicular cells. This review summarizes high-risk and moderate-risk thyroid carcinomas with an aggressive clinical behavior.

Table 1: Histological classification of follicular cell neoplasms of thyroid gland

- I. Benign
  - A) Follicular adenoma
- II. Malignant
  - A) Inherited and familial (hereditary)
    1. Familial non-medullary thyroid carcinoma
  - B) Sporadic (non-hereditary)
    1. Papillary carcinoma
       a) Common type
       b) Variants
    2. Follicular carcinoma
       a) Minimally invasive
       b) Encapsulated angioinvasive
       c) Widely invasive
    3. Poorly differentiated carcinoma
    4. Undifferentiated carcinoma

The real thyroid carcinoma (genuine cancer)

Baloch et al. have described several histological types of thyroid carcinoma as 'real thyroid carcinoma' because they are associated with an aggressive clinical behavior (13). The real thyroid carcinoma in this excellent review includes aggressive variants of PTC (tall cell, columnar cell, diffuse sclerosis, solid, hobnail, and widely invasive follicular variant), PDC, and UC (13). Some of them such as diffuse sclerosing variant and follicular variant are excluded in the present review because their prognoses are eventually almost equivalent to the common type PTC in recent studies (14-17). This review focuses genuine (real and true) cancers of the thyroid follicular cell origin, including aggressive variants of PTC, angioinvasive FTC, WDC with distant metastasis in addition to PDC in the Table 2. The low-risk thyroid carcinomas and possible precancerous lesions, and the pathology, genetics and

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clinical managements of C cell (medullary) carcinomas have been reviewed elsewhere (18-22).

Table 2: Follicular cell carcinomas with an intermediate prognosis between well differentiated and undifferentiated carcinomas

1. Aggressive variants of papillary carcinoma
   a) Solid variant
   b) Tall cell variant
   c) Columnar cell variant
   d) Loss of cellular polarity/loss of cellular cohesiveness (hobnail/micropapillary)
2. Encapsulated angioinvasive follicular carcinoma
3. Well differentiated carcinoma with distant metastasis
4. Well differentiated carcinoma with focal (minor) undifferentiated carcinoma
5. Well differentiated carcinoma with squamous cell carcinoma
6. Poorly differentiated carcinoma

These carcinomas retain the functions of follicular cells and are positively stained for thyroglobulin and TTF1, while undifferentiated carcinomas and squamous cell carcinomas are usually negatively stained.

Aggressive variants of PTC

Solid variant of PTC

Solid growth pattern may be found in follicular adenoma (FA), PTC, FTC, and PDC. When a tumor exhibits solid growth and PTC-type nuclear features (more than 50% of the tumor area), a diagnosis of solid variant of PTC is made (Fig. 1). The solid variant of PTC is more commonly seen in children and its prognosis is excellent, but it shows a high risk of recurrence as reported by Collini et al. (23). Nikiforov et al. analyzed 20 PTCs with solid growth (>70%) and found that two patients died of the disease and the other two patients were alive with lung metastases. The investigators have concluded that the solid variant of PTC in adult patients has a slightly higher frequency of distant metastases and less favorable prognosis than classic PTC, however they have emphasized that the solid variant of PTC should be distinguished from PDC because PDC by WHO definition is reserved for more aggressive carcinomas (24).

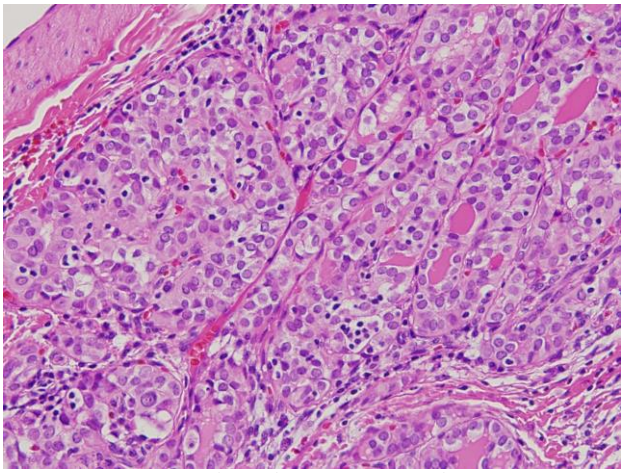

Figure 1: Solid variant of PTC from a 24-year-old female patient. Solid and trabecular growth with occasional colloid formation are seen (Hematoxylin and Eosin stain, x200).

Tall cell variant of PTC

The tall cell variant is composed predominantly of the cells whose heights are at least two times their width (1). Their cytoplasm is often eosinophilic and nuclei often show typical features of PTC (Fig. 2). The tall cell variant of PTC has a higher recurrence rate and tumor-related mortality rate than the classic PTC, and is a significant prognostic factor, independent of age, gender, extrathyroid extension, and tumor size (25-29). It is important to note that this variant is often refractory to radioactive iodine therapy, indicating less differentiation in follicular cell function (26-29). Sywak et al. reviewed the literature in 2004 and have concluded that the tall cell variant is a more aggressive thyroid carcinoma that is associated with distant metastasis in 22% of cases and has a mean tumor-related mortality of 16% (n = 209) (25). The aggressive behavior of this variant is postulated to the higher prevalence of activating point mutation of BRAF and high expression of Muc1 and matrix metalloproteinase (26, 30).

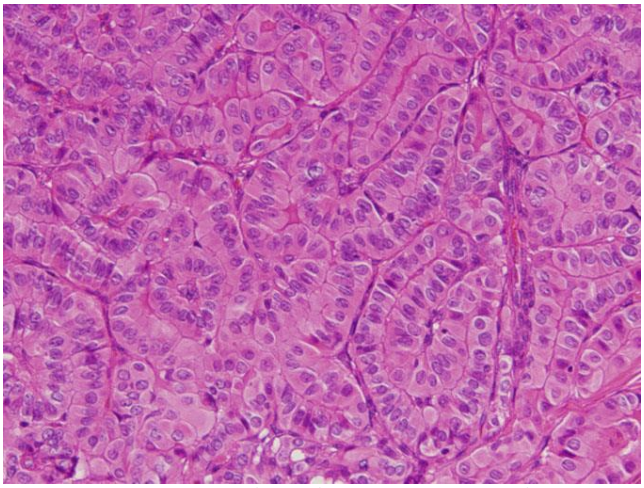

Figure 2: Tall cell variant of PTC found in a 38-year-old female patient. Note trabecular growth with elongated nuclei and eosinophilic wide cytoplasm (Hematoxylin and Eosin stain, x400).

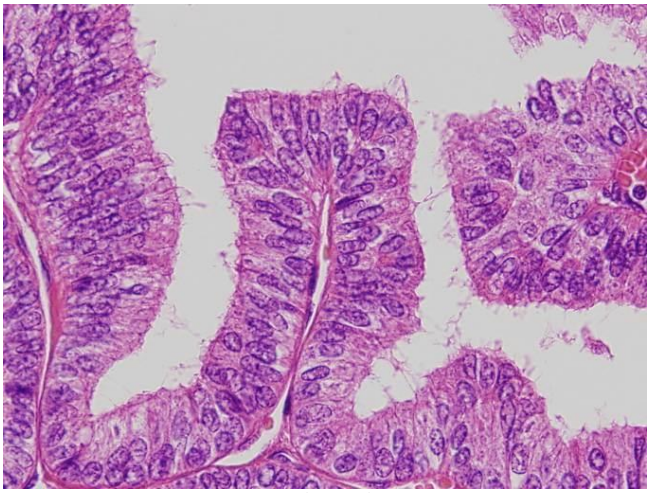

Figure 3: Columnar cell variant of PTC from a 44-year-old male patient. Pseudostratified nuclei are the characteristic feature of this variant and they do not show typical PTC type nuclear features (Hematoxylin and Eosin stain, x1000).

Columnar cell variant of PTC

The columnar cell variant is composed of pseudostratified columnar cells, which sometimes contain supra-nuclear and sub-nuclear cytoplasmic vacuoles (Fig. 3). The columnar cell variant of PTC was first reported by Evans et al. in 1986 as an aggressive variant and Sobrinho-Simoes et al. proposed that it should be included in the PDC category together with insular carcinomas, mucinous carcinomas, and mucoepidermoid carcinomas (31, 32). High rate of local recurrence and frequent distant metastasis have been reported for this variant, but an encapsulated subtype may behave differently and is indolent (33, 34). Lack of typical PTC type nuclear features in columnar cell variant may be confused with metastatic adenocarcinoma from gastrointestinal tract, but it usually has variable proportions of papillary, follicular and solid growth. CDX2, a nuclear transcription factor for intestinal development, has been reported in some cases, but its implications to carcinogenesis, morphological features and prognosis have not been clarified (35, 36).

Loss of cellular polarity/loss of cellular cohesiveness and hobnail/micropapillary variant

Loss of cellular polarity/loss of cellular cohesiveness in PTC (Fig. 4a) was first introduced from our group as a morphological feature related to poor cellular differentiation and being possible evidence of epithelial mesenchymal transition, and associated with high Ki-67 labeling index (Ki-67 LI) (37, 38). The 10-year disease-free survival (DFS) rate of the patients with this feature was found to be equivalent to that of the patients with other (solid, tall cell and columnar cell) aggressive variants (85.5% *vs*. 86.9%) (38). Motosugi et al. have emphasized hobnail growth pattern (Fig. 4b) as a variant with intermediate prognosis (39). Asioli et al. analyzed eight cases of PTC with the prominent hobnail feature and reported their aggressive clinical behavior and high rate of mortality (40). These patients developed distant metastasis in five cases and tumor related mortality in four cases. Two patients were alive with disease and two patients were alive without disease (40). Their immunohistochemical study has shown positive results on thyroglobulin, TTF1, and HBME-1 that are similar to the common type PTC, but the p53 is positive (40) and the Ki-67 LI is high (2-20%) (37,40). Lubitz et al. found $BRAF^{V600E}$ mutation in 80% of patients with this variant and RET/PTC1 rearrangement in 20% (41). The patients developed recurrence or persistent disease in four (33.3%), died in one (8.3%), and presented focal anaplastic transformation in two (16.7%) cases (41).

WDC with distant metastasis

WDCs are generally indolent tumors with only about 10% recurrence after curative surgery, and only a few patients with WDCs develop distant metastases and eventually die of the disease (7-12). Shaha et al. reported that the incidence of distant metastases at the time of initial presentation in WDC was approximately 4% and the overall prognosis was not as poor as many other human cancers, being approximately 50% (7). The 5-year CSS rate of the Japanese patients with distant metastasis has been reported to range between 65% and 95% and occupy an intermediate position between WDC and UC (8, 11, 12). We have proposed to classify WDC with distant metastasis into the category of high-risk thyroid carcinoma together with PDC in prognostic perspective (18, 19). Some of those tumors have well-differentiated follicular cell morphology and they are classed into common type PTC or FTC, which do not fit to their aggressive clinical course as if it is an under-diagnosis. However, these tumors usually have a high Ki-67 LI equivalent to those of aggressive variant of PTC, angioinvasive FTC and PDC (42, 43) and therefore we proposed to classify them into the PDC category or high-risk thyroid carcinoma category in our classification of thyroid follicular cell tumors (18, 19, 42).

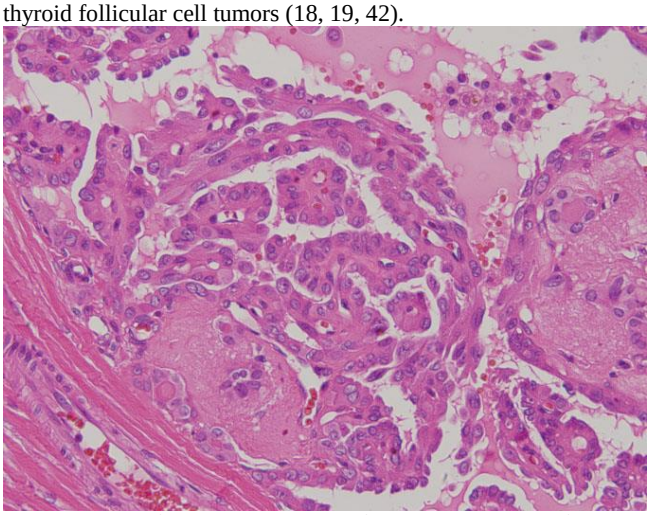

Figure 4a: Loss of cellular polarity/loss of cellular cohesiveness found in a 27-year-old male patient. Dissociated spindle cells from papillary clusters form non-glandular sheets without cellular polarity (Hematoxylin and Eosin stain, x200).

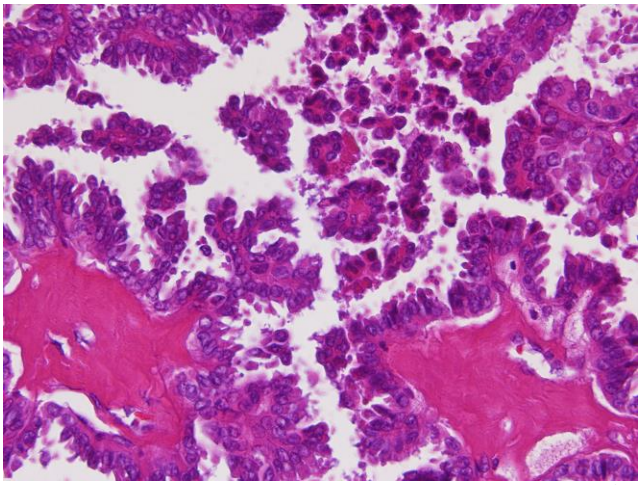

Figure 4b: Hobnail appearance and micropapillary growth pattern of the PTC in a 72-year-old female patient. Nuclear stratification and an elevated nuclear position in the cytoplasm give a hobnail appearance, and at the same time these detached cells form micropapillay clusters without vascular cores (Hematoxylin and Eosin stain, x200).

Angioinvasive follicular thyroid carcinoma

FTC is the second most common malignancy of thyroid gland and it is divided into two groups, minimally invasive FTC and widely invasive FTC based on the degree of invasiveness (1). This is because the minimally invasive FTC has a better prognosis than the widely invasive FTC (44-47). However extensive vascular invasion (>4) was reported to be a significant prognostic marker in DFS and CSS rates for the minimally invasive FTCs, in addition to the distant metastasis, older age (>45 years old), and larger tumor size (>4 cm) (48, 49). Ito et al. reported that the 10-year DFS rate of patients with extensive vascular invasion was 80% and the 10-year CSS rate of those patients was 96% (49).

Poorly differentiated carcinoma

PDC of the thyroid was first introduced in the WHO classification of thyroid tumors in the 2004 edition (1). This terminology was first introduced by Sakamoto et al. in 1983, whose histology was characterized by solid, trabecular and scirrhous growth patterns (non-follicular and non-papillary growth pattern), and later the same terminology was applied to a different histological type of thyroid carcinoma, so-called insular carcinoma, by Carcangiu et al., which has a close relationship with the PDC by Turin proposal (Fig. 5) (50-53). The prevalence of PDCs defined by three different criteria was studied in 1707 Japanese PTC patients by Ito et al.; there were 189 (11.1%) cases of PDC (Sakamoto), 15 (0.8%) of PDC (WHO) and 5 (0.3%) of PDC (Turin) (54). The three classifications of PDC overlap completely and the PDC of Sakamoto's classification is the broadest category, covering both of the WHO PDC and Turin PDC (54). The prevalence of PDC by WHO definition has been reported to differ among different geographic areas, being less than 1% in Japan, 2-3% in North America, and 15% in Italy (54-56).

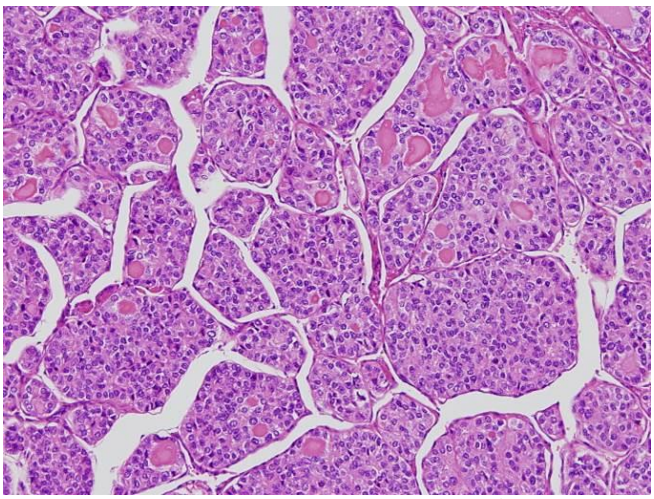

Figure 5: Insular type growth pattern (PDC in WHO definition and Turin proposal) found in a 60-year-old female patient. Well defined nests and large trabecular islands are surrounded by endothelial lining cells with vascular spaces. Small follicles with colloid substance are found in the islands. Note that the nuclear grade is usually minimal in insular carcinomas (Hematoxylin and Eosin stain, x200).

WDC with focal giant/spindle cell component

WDC with a focal giant and spindle cell component may be an early stage of UC transformed from WDC and it may be called as an incidental UC because it is found incidentally upon the postoperative histopathologic examination. Yoshida et al. analyzed 25 patients with incidental UC among a series of 675 UC patients and they reported a 1-year CSS of 71.8%, 2-year CSS of 58.3%, and median survival time of 575 days (in comparison with 110 days for common-type UC) (57). Six patients who underwent curative resection had a 1-year survival rate of 83.9%, while the 1-year CSS rate of the seven patients who underwent curative resection plus radiation was 87%. The 1-year CSS rate of the five patients who underwent curative resection plus radiation and chemotherapy was 100%, in comparison with the common-type UC that is a highly aggressive malignant tumor and has an overall 5-year survival rate ranging from 0 to 14% and a median survival of 2.5-6 months (1, 5, 6, 57-62). There are many case reports of incidental UC and curatively treated UC patients who survived more than 5 years (59, 62). It can be concluded from these observations that a UC component in WDC has a significant impact on the patient's prognosis almost equal to that of PDC (WHO or Turin definition), but not equal to the advanced stage of common-type UC patients; therefore, WDC with a focal UC component (incidental UC) should be separated from the common type UC and downgraded to a high-risk category of thyroid carcinoma from the prognostic perspective (18, 19, 42). It is also important to rule out the non-UC type (benign degenerative-type) giant and spindle cell components (42, 62-67), about which one can be confident when a Ki-67 LI of less than 5% is confirmed. The common type UC usually has a Ki-67 LI of more than 30% (42).

Conclusion

This review summarizes several types of thyroid carcinomas of follicular cell origin that usually demonstrate intermediate clinical behavior between WDC and UC. It is important for pathologists to recognize them because under- or over-diagnosis of those carcinomas may create serious problems in the clinical managements of patients. We have proposed to further risk-stratify those thyroid carcinomas into moderate-risk and high-risk carcinomas based on Ki-67 labeling index elsewhere (42).

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