Endocr Pathol (2010) 21:12–15
DOI 10.1007/s12022-010-9106-y

Papillary Carcinoma Tall Cell Variant (TCV): A Review

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Published online: 20 February 2010

Abstract Tall cell variant of papillary thyroid carcinoma is an aggressive form of thyroid cancer with a significant mortality. This review describes the pathology of this variant, compares it to its pathologic mimics and discusses its clinical pathologic features. The literature on this tumor is reviewed. A brief discussion of molecular pathologic correlates is included.

Keywords Thyroid cancer · Tall cell variant · Clinical pathologic correlations

Thyroid papillary carcinoma, the most common endocrine malignancy, is a tumor of such indolent biological and clinical behavior that the survival rate for patients with this tumor is equal or almost equal to that of individuals who never had cancer. Only a small percentage of patients with papillary carcinoma of the thyroid are affected by a tumor of considerable clinical aggressiveness. I often refer to this as "real carcinoma" of the thyroid. The most common of these subtypes is the tall cell variant of papillary carcinoma.

Tall cell variant was initially defined as an aggressive lesion by Hawk and Hazard in 1976 [1]. The definition they proposed and accepted widely by pathologists to this day includes the presence of a papillary tumor whose cells are at least twice as long (tall) as they are wide [1–3]. The tumors tend to be extremely papillary and the papillae are elongated. The papillae may coalesce and the low power appearance may simulate a trabecular pattern in parts of the tumor. The cells are large and often eosinophilic without cytoplasmic granularity so they are not true Hürthle cells. The nuclei are elongate and sometimes conform to the elongated cell in which they are contained, have prominent grooves, clearing and intranuclear inclusions (Fig. 1). Multiple inclusions may be seen and especially in fine needle aspiration preparations, these can be helpful in suggesting the tumor is a tall cell papillary carcinoma. These multiple inclusions have been likened to "soap bubbles" within the nucleus [4].

Several aspects of tall cell variant (TCV) will be discussed in this review.

> First the definition of TCV: how much of a tumor needs to show the features of TCV to be diagnosed as such?
> Secondly, what is not TCV?
> Thirdly, what are the consequences of a diagnosis of TCV?
> Finally, what are the molecular features of this group of tumors and how can this assist us in understanding the pathogenesis and behavior of this subtype of papillary carcinoma of the thyroid.

Many clinicians feel that there are significant consequences to the diagnosis of TCV. On the other hand, there appears to be confusion on the part of pathologists in recognizing this tumor or alternatively in overdiagnosing TCV. Indeed, in one study performed in a large academic center, 12% of classical PTC without extra-thyroid extension (ETE) was reclassified as TCV [5]. Hence, this group of lesions comprises a significant number of cases sent to "experts" for consultation. Thus, one needs to define the entity.

A tall cell variant of papillary thyroid carcinoma should be comprised of at least 50% TCV morphology. The literature is problematic in this regard with TCV being

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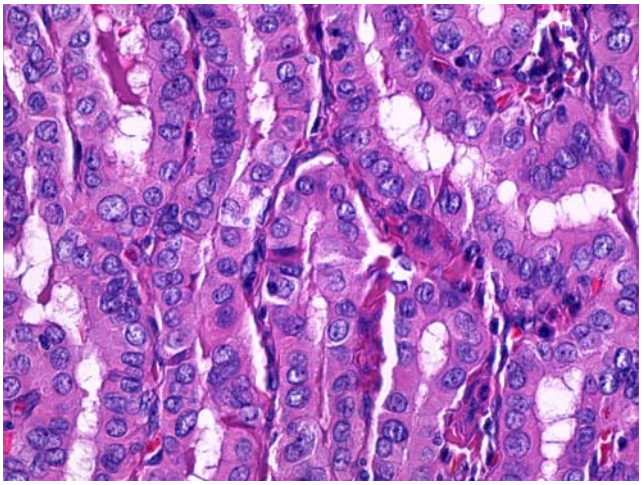

Fig. 1 An example of tall cell variant of papillary thyroid carcinoma. Note cell length and the eosinophilic cytoplasm (H&E ×40)

diagnosed in tumors having anywhere from 10% to 70% of a particular tumor [2, 6–9]. Indeed, some Japanese classifications include tall cell variant of only 10% as poorly differentiated thyroid carcinoma [10]. In my own experience, most TCV show that 75% or more of the tumor has the TCV appearance. However, many conventional papillary carcinomas will show a minor component of TCV cytology (usually 5–10%). These are not to be diagnosed as TCV papillary carcinoma, but it is my practice to mention this component since in my experience, in some of these cases, metastases or recurrences may show a higher percentage of TCV. This may indicate a more aggressive lesion is evolving from the original conventional papillary carcinoma with minor TCV areas (there is no systematic study of these cases since they are rare, but from anecdotal evidence, it appears this scenario can occur).

In order to isolate true examples of TCV, it is necessary to not include other neoplasms that may superficially resemble that tumor but do not have its prognostic implications. TCV is *not* Warthin-like papillary carcinoma [11, 12], oncocytic papillary carcinoma or its follicular variant [13, 14], nor is it any Hürthle cell tumor or nodule which may have areas of papillary growth [15].

Warthin-like papillary carcinoma is a tumor which almost always arises in a background of chronic lymphocytic thyroiditis. It is often relatively soft to palpation, circumscribed and partially cystic grossly. Microscopically, it is composed of papillae lined by oncocytic tumor cells with papillary carcinoma nuclei; the papillae are broadened centrally by an infiltrate of lymphocytes and plasma cells (similar to the infiltrate in the background thyroiditis; Fig. 2). These tumors appear to share the excellent prognostic outlook of classical or usual papillary carcinoma, and not that of TCV. Interestingly, in lymph node metastases, these tumors appear similar to the primary lesions, closely associated with inflammatory cells in the papillary cores.

It is important to note that very rarely will Warthin-like papillary carcinoma invade extrathyroidally and lose its inflammatory component, resembling TCV in the extraglandular areas. In limited experience (unpublished) with such neoplasms, these lesions seem to behave as usual papillary carcinoma and not TCV (the exception is in those lesions which show vascular invasion and even foci of necrosis in the TCV-like portion).

Oncocytic papillary carcinoma or oncocytic follicular variant of papillary carcinoma is identical microscopically and in clinical behavior to usual papillary carcinoma of similar stage [13, 14]. The cytology is eosinophilic but not granular and the nuclei resemble those of usual papillary cancer (Fig. 3).

All varieties of Hürthle cell nodules and neoplasms should not be considered TCV since the cytology is truly Hürthle cell (granular cytoplasm, round nuclei with prominent nucleoli) all different from TCV. Obviously, determining malignant from benign Hürthle cell lesions necessitates evaluation for invasive growth. Occasional examples of papillary growth can be seen in parts of Hürthle cell nodules; the cytology of Hürthle cells is maintained however. The presence of rounded calcifications superficially resembling psammoma bodies may be seen; the papillae and calcifications raise the possibility of TCV. In Hürthle cell lesions, the calcifications are found within the colloid of the Hürthle-cell-lined follicles, they are not lamellated and do not have the diagnostic implications of true psammoma bodies in the thyroid.

There is a general consensus that as a group, TCV has both a higher recurrence and death rate than classical PTC

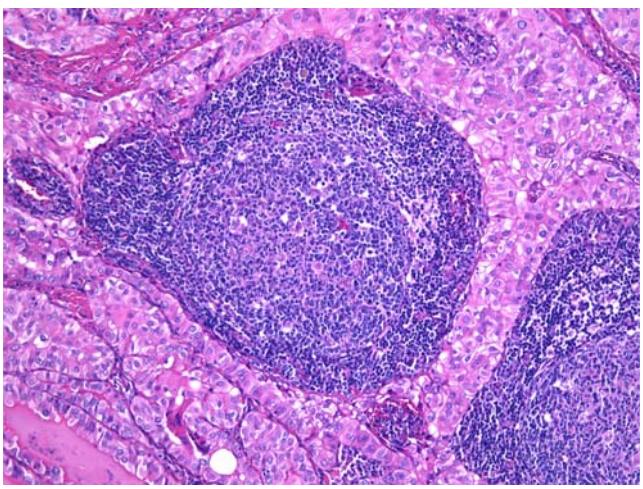

Fig. 2 A classic view of a Warthin-like papillary carcinoma. Note inflammatory cells in core of papillae (H&E ×40)

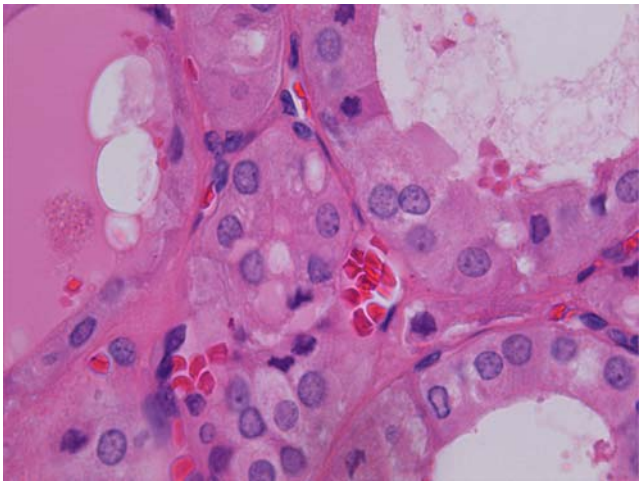

Fig. 3 An oncocytic follicular variant of papillary carcinoma is illustrated (H&E ×40)

[9, 16]. Initially, this was attributed to the fact that patients affected by TCV tumors were older at presentation and had large tumors with ETE [16]. Indeed, in one study, 80% of the TCV showed some degree of extra-thyroid extension and the mean age of presentation was 53 years [5]. However, Ghossein et al. have reported their experience that gland-confined TCV without ETE has a more aggressive behavior than conventional intra-thyroidal PTC. TCV without ETE were shown to have a significantly higher nodal metastatic rate than classical PTC without ETE independent of age, gender, and tumor size (p=0.004) [5]. In that same study, three of 47 (6%) of TCV without ETE developed distant metastases while none of the 62 classical PTC recurred at a distant site (p=0.07). It is noteworthy that the median tumor size of these TCV without ETE was 1.5 cm with one subcentimeter tumor giving rise to lung metastases 1 year after diagnosis.

The implications of tall cell micropapillary carcinoma have not been addressed in the literature as these tumors are extremely rare and long-term follow-up data on large numbers of patients are not available. Anecdotal instances of aggressive (systemic metastatic disease) clinical behavior from subcentimeter papillary carcinomas with tall cell cytology are known. Of the few cases I have personally seen, almost all have been located at the edge of the thyroid and have shown extraglandular extension; the meaning of this is, however, unknown.

At this point, no studies have addressed the prognostic impact of cervical nodal metastases comprised of tall cells in a patient whose primary tumor is of the classical type. In these cases with discrepant histology, the nodal tall cell metastasis can occur at presentation or subsequently in a recurrence. In the latter scenario, it is not uncommon to detect retrospectively a small focus of tall cells in the primary thyroidal lesion. There is also no consensus and no studies dealing with the concept of PTC with "tall cell features" and its clinical value.

Another unsettling microscopic feature is the presence of squamous areas often with associated spindle cells in zones of hemorrhage in larger TCV carcinomas. Predicting seriously aggressive behavior of such lesions prospectively is not warranted by evidence so far available. However, when one has the opportunity to examine the primary tumor in patients who develop spindle cell squamous anaplastic carcinoma arising in association with recurrent TCV, it is almost a uniform finding in the primary [17]. Since the length of time between the diagnosis and treatment of the primary lesion is often measured in years, it is unlikely that these foci represent anaplastic tumor in the initial tumor. These lesions need to be studied with genetic analysis using careful microdissection techniques.

Whether the aggressive behavior is associated with the molecular profile of these tumors, host factors or other tumor factors or tumor–host interactions is unknown. Some data seems to indicate that molecular factors intrinsic to TCV are responsible for its aggressive biologic and clinical behavior. The aggressive behavior of TCV could be related to certain factors elaborated by the tumor. The high expression of Muc1 and type IV collagenase (matrix metalloproteinase-2) [18, 19] in these tumors may allow for degradation of stroma and greater invasive properties (when compared to usual and follicular variant papillary carcinomas). The aggressive behavior of TCV may also be related to the higher prevalence of activating point mutations of the *B-RAF* in TCV when compared to classical PTC [19]. Indeed, papillary cancers of any subtype which have *B-RAF* mutations have a higher frequency of extra-glandular extension and nodal metastases, and present at a higher stage than *B-RAF* negative tumors [20].

Finally, the importance of TCV is accentuated by the fact that it is over-represented in those thyroid carcinomas that are refractory to radioactive iodine (RAI) therapy. Recently, Rivera et al. found that 20% of fluorodeoxyglucose positron-emission tomogram (FDG-PET) positive/RAI refractory tumors are tall cell variant [21]. Eighty eight percent of these RAI refractory TCV had extensive extra-thyroid extension. Clearly TCV is over-represented in these incurable tumors.

A very significant finding in almost all TCV tested to date is that they show a point mutation in the *B-RAF* proto-oncogene. Clinical trials are currently in progress to exploit this feature of papillary thyroid cancers. Chemotherapeutic agents which could inhibit B-RAF activating mutations may show promise for treatment of patients with metastatic, unresectable and/or RAI refractory thyroid cancers (www.ClinicalTrials.gov).

In conclusion, the data available to date clearly demonstrates that TCV is a biologically and clinically aggressive

form of papillary thyroid carcinoma. The presence of foci of tall cells should be mentioned in a pathology report no matter what percentage of tall cell cytology is found. As should be the case with any thyroid carcinoma, pathologists should comment in detail on the invasiveness of the tumor (number foci of vascular invasion, presence of extrathyroidal extension). A diagnosis of TCV should prompt the clinician to fully treat and carefully monitor the patient (including use of new imaging techniques). Future studies need to identify the histopathologic and molecular features that will identify those TCV that will progress to RAI refractory disease and to develop targeted therapies against these aggressive thyroid neoplasms.

References

1. Hawk WA, Hazard JB. The many appearances of papillary carcinoma of the thyroid. Clevel Clin Q. 43:207–15, 1976.
2. Johnson TL, Lloyd RV, Thompson NW, Beierwaltes WH, Sisson JC. Prognostic implications of the tall cell variant of papillary thyroid carcinoma. Am J Surg Pathol. 12:22–7, 1988.
3. DeLellis RA, Lloyd RV, Heitz PU, Eng C, editors. World Health Organization Classification of Tumours. Pathology and genetics of tumours of endocrine organs. Lyon: IARC; 2004.
4. Solomon A, Gupta PK, LiVolsi VA, Baloch ZW. Distinguishing tall cell variant of papillary thyroid carcinoma from usual variant of papillary thyroid carcinoma in cytologic specimens. Diagn Cytopathol. 27:143–8, 2002.
5. Ghossein R, Leboeuf R, Patel KN, et al. Tall cell variant of papillary thyroid carcinoma without extra-thyroid extension: biologic behavior and clinical implications. Thyroid. 17:655–61, 2007.
6. Akslen LA, LiVolsi VA. Prognostic significance of histologic grading compared with subclassification of papillary thyroid carcinoma. Cancer. 88:1902–8, 2000.
7. Ostrowski ML, Merino MJ. Tall cell variant of papillary thyroid carcinoma: a reassessment and immunohistochemical study with comparison to the usual type of papillary carcinoma of the thyroid. Am J Surg Pathol. 20:964–74, 1996.
8. Nishida T, Katayama S, Tsujimoto M, Nakamura J, Matsuda H. Clinicopathological significance of poorly differentiated thyroid carcinoma. Am J Surg Pathol. 23:205–11, 1999.
9. Ghossein R, LiVolsi VA. Papillary thyroid carcinoma tall cell variant. Thyroid. 18:1179–81, 2008.
10. Kakudo K, Bai Y, Katayama S, Hirokawa M, Ito Y, Miyauchi A, et al. Classification of follicular cell tumors of the thyroid gland: analysis involving Japanese patients from one institute. Pathol Int. 59:359–67, 2009.
11. Apel R, Asa S, LiVolsi VA. Papillary Hurthle cell carcinoma with lymphocytic stroma: "Warthin-like tumor" of the thyroid. Am J Surg Pathol. 19:810–4, 1995.
12. Baloch ZW, LiVolsi VA. Fine-needle aspiration cytology of papillary Hurthle cell carcinoma with lymphocytic stroma "Warthin-like tumor" of the thyroid. Endocrine Pathol. 9:317–23, 1998.
13. Berho M, Suster S. The oncocytic variant of papillary carcinoma of the thyroid: a clinicopathologic study of 15 cases. Hum Pathol. 28:47–53, 1997.
14. Sobrinho-Simoes M, Maximo V, Castro IV, Fonseca E, Soares P, Garcia-Rostan G, et al. Hurthle (oncocytic cell tumors of thyroid: Etiopathogenesis, diagnosis and clinical significance. Int J Surg Pathol. 13:29–35, 2005.
15. Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hurthle (oncocytic) cell and its associated pathologic conditions: a surgical pathology and cytopathology review. Arch Pathol Lab Med. 132:1241–50, 2008.
16. Michels JJ, ScI MJ, Henry-Amar M, Bardet S. Prevalence and prognostic significance of tall cell variant of papillary thyroid carcinoma. Hum Pathol. 38:212–9, 2007.
17. Bronner MP, LiVolsi VA. Spindle cell squamous carcinoma of the thyroid: An unusual tumor associated with tall cell papillary cander. Mod Pathol. 4(5):637–643, 1991.
18. Wreesmann VB, Sieczka EM, Socci ND, Hezel M, Belbin TJ, Childs G, et al. Genome-wide profiling of papillary thyroid cancer identifies MUC1 as an independent prognostic marker. Cancer Res. 64:3780–9, 2004.
19. Campo E, Merino MJ, Liotta L, Neumann R, Stetler-Stevenson W. Distribution of the 72-kd type IV collagenase in non neoplastic and neoplastic thyroid tissue. Hum Pathol. 23:1395–401, 1992.
20. Adeniran AJ, Zhu Z, Gandhi M, Steward D, Fidler JP, Giordano T, et al. Correlation between genetic alterations and microscopic features, clinical manifestations and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 30:216–22, 2006.
21. Rivera M, Ghossein RA, Schoder H, Gomez D, Larson SM, Tuttle RM. Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma. Cancer. 113:48–56, 2008.