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Brief Communication

Aggressive Histopathological Variants of Papillary Thyroid Carcinoma, Diagnostic Challenge, and Clinical Significance—A Case Series

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Abstract

Papillary thyroid carcinoma is the most common form of thyroid cancer and is usually associated with a good outcome. However, there are some aggressive variants wherein the prognosis may not be as good as for a conventional papillary thyroid carcinoma. Three cases of aggressive variants of papillary thyroid carcinoma are reported in the present series, namely, tall cell, hobnail, and columnar cell variants. This series is being reported to highlight the characteristic histopathological features which help in diagnosing these variants, especially diagnostic challenge in recognizing columnar cell variant due to lack of the classical nuclear features of papillary thyroid carcinoma in this variant. This case series also highlights the clinical importance of recognizing these variants because, according to American Thyroid Association, these variants come under intermediate risk with a poor clinical outcome, requiring aggressive management with neck dissection, radioiodine ablation, and closer disease surveillance.

Keywords: *Columnar cell, hobnail, intermediate risk, prognosis, tall cell*

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Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma and is usually associated with a good prognosis and long-term survival rate. However, some of the variants have a poor clinical outcome, which include tall cell, columnar cell, hobnail, and solid variants.[1] To designate as a variant, according to current recommendations, at least 30% of the tumor cells should show the characteristic cytologic feature.[2,3]

Three variants of PTC are reported in this series. One case each of tall cell, columnar cell, and hob-nail variant. The aggressive histopathological features observed in these cases included multifocality, infiltrative growth pattern with invasion of thyroid capsule, lympho-vascular invasion, and perineural invasion, all of which are unusual in conventional (classic) PTC.

Case 1

A 31-year-old lady presented with swelling in front of neck of three months duration. Ultrasound scan showed an ill-defined heterogeneous lesion measuring 1.8 × 1.3 cm in the right lobe and another heterogeneous lesion measuring 0.8 × 0.8 cm in left lobe. Fine needle aspiration cytology was reported as papillary thyroid carcinoma, Bethesda category VI, and she underwent total thyroidectomy. Grossly an ill-defined gray white lesion measuring 1.5 × 1.5 × 1 cm was identified in the right lobe, abutting the thyroid capsule, and another gray white area measuring 0.6 × 0.6 × 0.3 cm was noted in the left lobe. Microscopy showed multifocal papillary carcinoma with the characteristic tram-track arrangement of single layer of tall cells in most of the areas [Figure 1a]. Tall cells having a height of two to three times the width with nuclei showing crowding, overlapping, and grooving could be better appreciated in higher power [Figure 1b]. Neoplasm showed invasion of capsule. A histopathological diagnosis of multifocal tall cell variant of papillary thyroid carcinoma was given.

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Case 2

A 27-year-old lady presented with solitary thyroid nodule. Ultrasound scan showed a 2.8 × 1.4 cm hypo-echoic lesion in the right lobe of thyroid. Fine needle aspiration was done and reported as papillary thyroid carcinoma, Bethesda category VI. She underwent a total thyroidectomy. Grossly an irregular gray–white lesion measuring 2.5 × 1.8 × 1.2 cm in the right lobe abutting the external surface was identified. Microscopy shows a neoplasm composed of papillary structures lined by cells having eosinophilic cytoplasm, apically located nucleus with prominent nucleoli, and loss of cellular cohesion (hobnail morphology) in more than 30% of the tumor [Figure 1c and 1d]. Lymphovascular emboli were identified. Immunostain for thyroglobulin showed positivity in both hobnail and classical areas. A histopathological diagnosis of hobnail variant of papillary thyroid carcinoma was given.

Case 3

A 63-year-old lady presented with multiple nodules in thyroid. She complained of recent increase in the size of swelling, change in voice, and dysphagia. Guided aspiration was done and reported as papillary thyroid carcinoma, Bethesda category VI. She underwent total thyroidectomy.

Grossly the thyroid was enlarged with colloid nodules in left lobe, right lobe showing gray–white granular lesion measuring 1.2 × 1.0 × 0.5 cm [Figure 2]. Microscopy showed a neoplasm arranged in papillary pattern and glandular-like spaces lined by pseudostratified columnar cells with hyperchromatic nuclei [Figure 3a and 3b]. Neoplasm was infiltrating full thickness of the tumor capsule and invading into the thyroid parenchyma and showed perineural invasion. Immunostaining showed tumor cells to be positive for CDX2 (caudal type homeobox transcription factor 2) and TTF1 (thyroid transcription factor 1) [Figure 3c and 3d]. A histopathological diagnosis of columnar cell variant of papillary thyroid carcinoma was given.

All three patients underwent high-dose radioiodine ablation because of the intermediate risk associated with these variants and also due to adverse histological factors like lymphovascular invasion, perineural invasion, invasive nature, and multifocality. These patients are on follow-up, two patients for two years and one patient for one year. The follow-up period has been so far uneventful.

Discussion

Conventional PTC is usually associated with a good prognosis; however, there are aggressive variants of

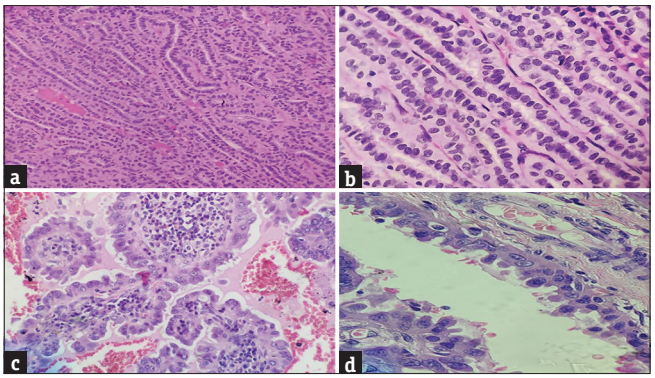


Figure 1: (a) Tram track arrangement of tall cells (H and E × 100). (b) Higher power showing tall cells with height two to three times the width (H and E × 200). (c) Papillary pattern with hob nailing of lining cells (H and E × 400). (d) Hobnail cells with apically placed nucleus and abundant eosinophilic cytoplasm (H and E × 400)

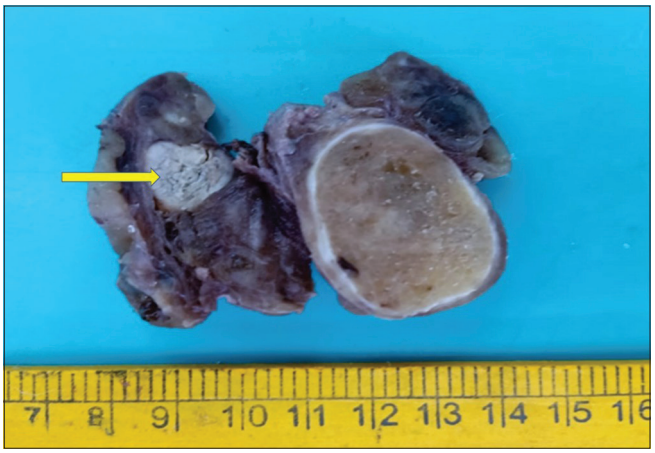


Figure 2: Thyroid enlarged with colloid nodules in left lobe, right lobe showing gray–white granular lesion measuring 1.2 × 1.0 × 0.5 cm

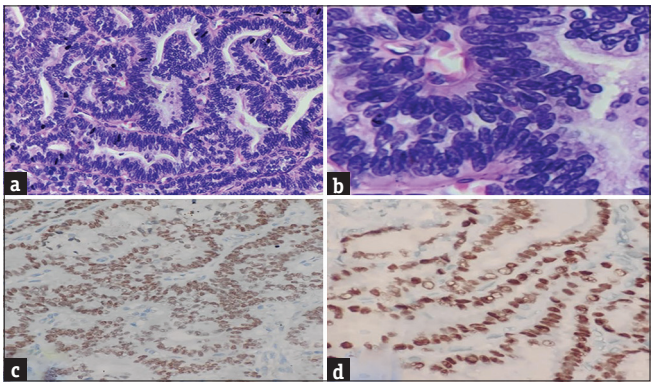


Figure 3: (a) Neoplasm showing cells arranged in papillary and glandular pattern (H and E × 200). (b) Higher power showing cells with hyperchromatic nucleus (H and E × 400). (c) Tumor cells showing nuclear positivity for CDX2. (d) Tumor cells showing nuclear positivity for TTF1

PTC, wherein the outcome may not be that favorable. Hence it is important to identify these variants for proper patient management. For making a pathological diagnosis of any variant, more than 30% of tumor cells should have the characteristic feature of the particular

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variant. However, based on evidence, we now know that even lesser percentage of variant morphology in a tumor with predominant classical areas can influence the outcome and hence needs to be mentioned in the diagnosis.[4]

The tall cell variant of papillary thyroid carcinoma was first described in 1976 by Hawk and Hazard.[5] It is the most common of the aggressive variants of papillary thyroid carcinoma. The cells of tall cell variant are two or three times as tall as they are wide and have eosinophilic cytoplasm with nuclear features of classic PTC. Tall cell variants can be refractory to radioiodine. Extra thyroidal extension and metastasis are more frequent than in classic PTC. Even when the percentage of tall cells is less than 30%, the outcome is unfavorable.[6] Beninato *et al*.[7] in their study on papillary thyroid carcinoma with tall cell areas had concluded that even with 10% tumor cells with tall cell morphology, the outcome is adversely affected. Hence it is important for the pathologist to document the presence of tall cell areas in cases of papillary thyroid carcinoma, however small the percentage of such area is. Our case showed adverse features like multifocality and invasion of thyroid capsule. BRAF mutations are present in the vast majority of tall-cell-variant tumors. TERT promoter mutations, which are associated with a worse prognosis, are also frequently found in the tall cell variant of PTC.[8]

Hobnail variant of PTC is a recently recognized aggressive variant.[9,10] It is a rare variant characterized microscopically by papillary and micropapillary structures lined by cells having eosinophilic cytoplasm, apically located nucleus with prominent nucleoli, and loss of cellular cohesion. Adverse histopathology features like necrosis, mitoses, including atypical forms which are rare in classical PTC can be associated with this variant. Angiolymphatic invasion and extrathyroidal extension are also common. Our case had also shown lymphovascular emboli. Lubitz *et al*.[3] have observed that hobnail variant as compared with follicular and tall cell variant more frequently exhibits extra-thyroidal extension and metastasis to lymph nodes.

Columnar cell variant is an uncommon variant and shows a variable behavior.[11] This variant is characterized by papillae or glandular spaces lined by pseudostratified epithelium. Cells have hyperchromatic elongated nucleus, supranuclear, and subnuclear cytoplasmic vacuolation. This morphology together with lack of conventional nuclear features of PTC can give rise to differential of metastasis from intestinal or endometrioid carcinoma. Lack of conventional nuclear features makes the diagnosis of this variant challenging for the pathologist. Immunohistochemistry helps in confirming the diagnosis. Tumor shows positivity for TTF1, thyroglobulin, and CDX2 which was seen in our case also. The morphology and CDX2 positivity can be a confusing factor in differentiating from a metastatic colorectal carcinoma as colorectal cancers are also known to express CDX2. Clinical history along with an appropriate panel of immunostains is helpful in making a diagnosis. Sujoy *et al*.[12] in their series of 10 cases of columnar cell variant, however, had observed positivity for CDX2 in only one case and had concluded that absence of CDX2 in the majority of the cases does not support the theory of CDX2 playing a role in the intestinal phenotype of this variant of PTC. Encapsulated or circumscribed tumor has an indolent behavior but those having infiltrative growth pattern and extrathyroidal extension may behave aggressively. Our case had shown infiltrative growth pattern, perineural invasion, and had the added risk factor that it was seen in an older age of 63 years.

All three of our patients underwent high-dose radioiodine ablation and first two cases are on follow-up for the past 2 years. Third case has been on follow-up for past one year. The follow-up period has been so far uneventful, possibly due to the intensive therapy given.

Conclusion

Documentation of variants of papillary thyroid carcinoma helps in building up information on clinical outcome and helps in better patient management. Hobnail and columnar cell variants are extremely rare and individual case reports can also contribute to accumulating data on the behavior. Such documentation has helped in better understanding of the clinical outcome of the relatively common tall cell variant, such that the current recommendation is to report the presence of tall cell areas irrespective of the percentage as even 10% of tall cell areas have been associated with an adverse outcome.

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Conflicts of interest

There are no conflicts of interest.

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