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Warthin-like papillary thyroid carcinoma (WL-PTC); A rare case series and review of literature

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Papillary thyroid carcinoma-Warthin (WL PTC) subtype is rare subtype of papillary thyroid carcinoma accounts for 0.2 to 1.9 % and demonstrates a strong relation with Hashimoto's thyroiditis.[1] Morphologically, WL PTC has papillary architecture composed of tumor cells with oncocytic cytoplasm, vesicular nuclei and abundant lympho-plasmacytic infiltration in the papillary cores. The term Warthin derived from similar morphological findings of Warthin's tumor in salivary gland.[2] WL PTC usually present as circumscribed or infiltrative tumor. Vascular and capsular invasion are not common in WL PTC.[3,4.]

We present two rare cases of WL PTC. The 1st case is from a patient who had a history of gluteal squamous cell carcinoma post neoadjuvant therapy. The other case is about an young male with Hashimoto's thyroiditis. These cases highlight importance of diagnosing a rare variant and subtype in PTC, as some of these may have a favorable prognosis.

Case 1

1. A 40-year male presented with swelling in neck since 2021, who had a history of diabetics on regular medication. His routine hematological and biochemical analysis were within normal limit. Fiberoptic laryngoscopy showed normal movements of vocal cords bilaterally. On physical examination, thyroid was enlarged, firm in consistency. Ultrasonography of thyroid showed well defined solid and cystic lesion with areas of microcalcification in the left lobe of thyroid measuring 12 x 6 mm. (Thyroid Image Reporting and Data system i.e. TIRAD IV). Cytological showed atypical thyroid follicular cells arranged in clusters and groups. The cells showed moderate eosinophilic cytoplasm, nuclear atypia with vesicular chromatin and nuclear clearing, background showed dense lymphocytes. Initial impression was suspicious of papillary thyroid carcinoma (Bethesda category V). (Figure 1)

Patient underwent total thyroidectomy. Macroscopic examination revealed a gray, white tumor in the left lobe of thyroid measuring 12 x 10 x 5 mm. Histomorphology showed tumor arranged in papillary architecture lined by single layer of columnar cells, moderate oncocytic cytoplasm, vesicular nuclear chromatin, intranuclear inclusion and groves. (figure 2). The papillae contained central fibrovascular core with dense lymphoplasmacytic infiltration. (Figure 2). Necrosis and mitosis were not identified. One lymph-node showed metastasis. Final impression was of papillary thyroid carcinoma,Warthin like subtype in background of Hashimoto's thyroiditis. Pathological staging (AJCC eighth edition) pT1N1.

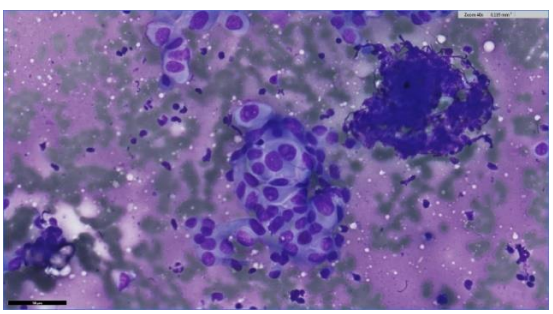

Figure 1: Fine needle aspiration cytology of the thyroid showing cells arranged in groups. These cells showed

nuclear enlargement and overlapping. The nucleus showed scattered nuclear grooves and inclusion(400x).

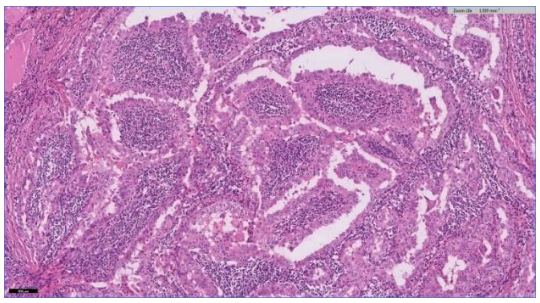

Figure 2: Microscopic H&E images showed tumour cells arranged in Papillae lined by epithelial cells having eosinophilic cytoplasm, vesicular chromatin and nuclear clearing. The papillary cores show lymphoplasmacytic infiltrate (10x).
H&E: Haematoxylin and eosin stain

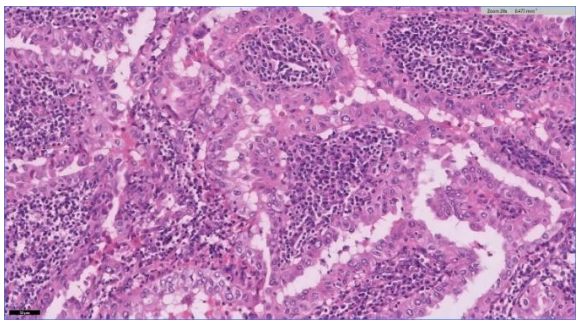

Figure 3(a): Microscopic H&E images showed tumour cells shows nuclear clearing, groves and inclusion (20x)
H&E: Haematoxylin and eosin stain

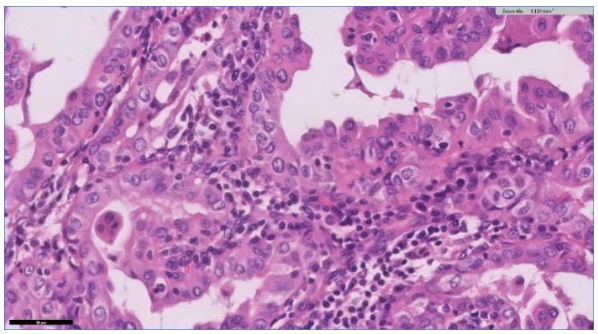

Figure 3(b): Note nuclear features of papillary carcinoma having nuclear grooves and pseudo inclusions with papillae are infiltrated by abundant lymphoplasmacytes (40x)

The papillae cores showed dense lymphoplasmacytic infiltration. (Figure 3 (a and b)). No significant mitoses or necrosis were identified. One lymph node was identified which showed metastasis. Adjacent thyroid showed lymphocytic thyroiditis. Final histopathological diagnosis was Papillary thyroid carcinoma, Warthin like subtype/

Case 2

A 42-year-old gentleman came with a complaint of swelling in the neck. Biochemical analysis was within normal limit. On fine needle aspiration reported as Bethesda category 6, papillary thyroid carcinoma. USG of thyroid showed the single left thyroid lobe nodule, already biopsy-proven papillary thyroid carcinoma measures up to 2 cm, with few sub-centimeter likely reactive lymph nodes. Thyroidectomy was performed. On gross examination, there was a well defined oval white nodule in the left lobe. Histopathological examination showed that the tumor cells were arranged in papillae with central fibrovascular core. The neoplastic cells were cuboidal to columnar cells with moderate to intense cytoplasm and showed classic nuclear features that have ground glass chromatin and inclusions. The central core showed lymphoid aggregate. Psammomatous calcification and lymphovascular invasion were seen. Seven lymph nodes were identified and they were free of tumour. Final diagnosis was Papillary thyroid carcinoma-Warthin like variant. Pathological staging: pT1b. Background thyroid showed Hashimoto's thyroiditis.

Discussion

Papillary carcinoma is the most common histological type of thyroid cancer. World Health Organization (WHO) recognises 13 subtypes: Classic PTC, encapsulated classic PTC, infiltrative follicular PTC, diffuse sclerosing PTC, solid/trabecular PTC, Warthin - like PTC, oncocytic PTC, clear cell PTC, spindle cell PTC, PTC with fibromatosis/fasciitis-like /desmoid-type stroma, tall cell PTC, hobnail PTC and columnar cell PTC.[5]

WL- PTC was first described by Apel et al[2] in a series of 13 cases and was so named due to its histological resemblance to Warthin tumour of the salivary gland.

A comprehensive review of published literature reported that WL-PTC was more common in females with a mean age of 39 years.[6] However, in this case report, the patient was a male. WL-PTC is morphologically characterized by a papillary architecture with true papillae lined by oncocytic epithelium and a lymphoplasmacytic infiltrate in the papillary cores.[7] A cytological diagnosis is possible and has been reported.[6-7] Cytological findings are those of classic PTC composed of papillary clusters and

monolayered sheets with ground glass nuclei, nuclear grooves and intranuclear pseudo-inclusions in a background of lymphocytic thyroiditis. An accurate diagnosis can be challenging for pathologists if no single dominant feature is present.[8] A review of literature regarding preoperative cytological evaluation of WL-PTC showed extensively lymphocytic smears with incorporation of thyroid follicular tumour cell clusters and frequent histiocytes. WL-PTC is associated with higher intratumorally and background lymphocytes and histiocytes compared with PTC-LT or PTC. The difference was more distinct in liquid-based cytology.[9] Our case also showed lymphoid infiltrate in the background.[10] Differential diagnosis of WL-PTC includes Hurthle cell carcinoma as well as oncocytic and tall cell variants of papillary carcinoma.[10]

WL-PTC with diffused sclerosing stroma harbouring BRAF V600E and K mutations as well as a novel germline point mutations in the RET gene, with unknown clinical and pathological significance have been reported.[8,11-13] Immunohistochemistry has no significant role in the diagnosis of WL-PTC or in differentiating it from classic and other variants of PTC, and is often not performed.[1,3]

A recent report described a case of WL-PTC in a 16-year-old female who presented with complaints of painful thyroid swelling for two years. Fine needle aspiration cytology (FNAC) from thyroid lobes showed features of lymphocytic thyroiditis with Hurthle cell change. On subsequent histopathological examination, a diagnosis of Warthin-like variant of PTC without nodal metastasis was made.[14]

Another report compared WL-PTC with classic PTC and found that WL-PTCs were more commonly associated with Hashimoto's thyroiditis (93% versus 36%, resp., $p < 0.001$)[15] and showed significantly lower rate of BRAF mutation when compared to classic PTCs (65% versus 84%, resp., $p = 0.007$).[15] When compared to classic PTC, the frequency of BRAF mutations was negatively correlated with coexisting Hashimoto's thyroiditis, but when WL-PTC and classic PTC were compared in patients with coexisting Hashimoto's thyroiditis, there were no significant differences in clinicopathologic characteristics or the BRAF mutational rate between the two groups.[16] BRAF V600E mutation was associated with more extensive disease, higher rate of recurrence and overall worse prognosis in WL-PTC.[16]

WL-PTCs like other morphological variants of papillary carcinoma, may occasionally undergo dedifferentiation. The dedifferentiated/anaplastic component is minor and may be only focally detectable. Thus, extensive sampling of all large-sized (>3 cm) papillary thyroid carcinoma is recommended. Recognition of any dedifferentiated component in a WL-PTC should be reported along with its percentage, because its presence may reflect a more aggressive clinical course.[12,17] A large cohort of 317 patients with PTC and found that 82% were females, mean age was 38 years ± 13.5 years.[12] edian follow-up period was 4 years (0.5-28.5) and most tumours were stage I with low/intermediate risk of recurrence.[11] They found no differences regarding clinico-pathological data and risk of recurrence between classic PTC and WL-PTC. WL-PTC was associated with a higher rate of anti-thyroglobulin antibodies (TgAb) (65% vs. 36%, $p = 0.016$) and lymphocytic thyroiditis compared to classic PTC (59% vs. 34%, $p = 0.03$). The rates of biochemical and structural incomplete responses were similar in both variants. WL-PTC had a lower rate of excellent response (23% vs. 54%, $p = 0.01$), which became non-significant when performing analysis by TgAb presence (50% vs. 67%, p = NS).

WL-PTC and classic PTC have similar clinical presentation and rate of recurrence. The lower rate of excellent response to treatment in WL-PTC is due to a higher frequency of anti-thyroglobulin antibodies. WL-PCT should not be considered an aggressive variant of PTC.

BRAF mutations (substitution of a valine for a glutamic acid (V599E)) have been implicated in the pathogenesis of papillary thyroid cancer and have been reported in up to 50% of the cases. They usually confer worst clinical prognosis as they are associated with a more extensive disease and a higher recurrence rate. It is interesting that BRAF mutations have been reported in approximately 75% of the patients with WL-PTC.

Vascular or capsular invasion is rare in WL-PTC.[3] However, it was reported lymphovascular invasion with metastatic lymph nodes in a WL-PTC was diagnosed in a 45-year-old female. However, patient was doing well post resection and radio-iodine therapy after four years of follow-up.

This report highlights the necessity of identifying the histologic subtype in all cases of PTC as many cases that

might be considered to be aggressive “classic variants” might turn out to be Warthin-like variants or other known aggressive subtypes of papillary thyroid cancer.[13]

Consent to Publish

Informed consent was obtained from the participant for publication in this report and any accompanying images.

Standards of Reporting

CARE guidelines and methodology were followed.

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None.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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Declared None.

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