An uncommon variant, Warthin-like papillary thyroid carcinoma: A case report

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Abstract. The most prevalent form of thyroid cancer is papillary thyroid carcinoma, of which warthin-like papillary thyroid carcinoma (WLPTC) is an uncommon variant. The symptoms, diagnosis and course of treatment for this subtype of papillary thyroid cancer are comparable to those of the classic variety. It is usually associated with Hashimoto's thyroiditis and is considered to have a favourable prognosis. In the present case report, a 40-year-old female patient was presented with multiple thyroid nodules and subclinical hypothyroidism. The female patient underwent a total thyroidectomy after a fine needle aspiration biopsy revealed an atypia of undetermined significance in one of the nodules, along with a family history of thyroid cancer. The definitive pathological assessment revealed seven thyroid nodules with four different diagnoses, one of which was WLPTC.

Introduction

In total, ~90% of thyroid malignancies are papillary thyroid carcinomas (PTCs), the most prevalent type of thyroid carcinoma (1). Tall cell, follicular and classical variations are the most prevalent types (2). Several other rare variations have also been reported, such as those with diffuse sclerosing, solid, oncocytic, columnar, cribriform, morular, and clear cell characteristics. Tall cell, follicular, diffuse sclerosing, solid, and columnar cell variants have a poorer prognosis than other variants (3,4).

The Warthin-like variant of PTC (WLPTC), considered a subtype of the oncocytic variant of PTC, is a rare subtype of papillary carcinoma constituting ~0.2-1.9% of all cases (5). Since this subtype was initially identified in 1995, <200 instances of WLPTC have been documented in the English literature (6). WLPTC resembles a Warthin tumor of the salivary gland. Histologically, the tumor demonstrates the presence of papillae lined by oncocytic cells with typical nuclear features of PTC and has prominent lymphocytic stroma in fibrovascular cores (7). Immunohistochemically, the BRAFV600 mutation was revealed in 75% of WLPTC, which is a mutation that plays a role in the pathogenesis of classical PTC. Other immunohistochemical markers detected in WLPTC are HBME-1, Galectin-3, Cyclin D1 and Cytokeratin 19 (CK19); however, these markers do not play a significant role in differential pathological diagnosis (8). The prognosis, clinical findings and demographic parameters are comparable with those of classical papillary carcinoma. In contrast to the classical variant, WLPTC usually manifests at a younger age and has a higher female prevalence (9,10). The present case report aims to raise awareness about the clinicopathologic features of WLPTC.

Case presentation

A 40-year-old female patient was presented to the outpatient clinic with complaints of fatigue and facial swelling. The patient had a history of three thyroid carcinomas in second-degree relatives. The laboratory results revealed subclinical hypothyroidism [TSH: 7.8 mIU/l (range: 0.34-5.6 mIU/l), FT3: 3.31 ng/dl (range: 2.6-4.37 ng/dl) and FT4: 0.7 ng/dl (range: 0.61-1.12 ng/dl)] with elevated levels of anti-thyroid peroxidase antibody [Anti-TPO: 816 IU/ml (range: 0-34 IU/ml)]. Neck ultrasonography (USG) revealed thyroiditis and multiple nodules with microcalcifications. The largest nodules were a 6x4 mm isoechoic-heterogeneous nodule in the right lobe and a 15x7 mm hypoechoic nodule in the left lobe. The evaluation of the bilateral central and lateral compartments revealed no pathological lymph nodes. A fine-needle aspiration (FNA) biopsy was performed for moderately suspicious nodule features. Histopathological assessment revealed an atypia of undetermined significance (AUS) for the left lobe nodule, and benign cytological findings were reported for the right lobe nodule. In addition to the patient's history and findings, total thyroidectomy was recommended on the basis of patient preference. The patient underwent total thyroidectomy, and she was discharged on postoperative day one with no postoperative

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complications. Prophylactic central lymph node dissection was not performed because no pathological lymph node was detected on preoperative USG.

The thyroidectomy sample was first examined macroscopically. Three nodules were found in the inferior pole of the left thyroid lobe, and they were measured at 9, 3 and 5 mm. Another 3-mm nodule was described in the superior pole of the left lobe. A 6x4 mm nodule was described in the inferior pole of the right lobe. Histopathological assessment of the left lobe revealed three multifocal papillary microcarcinoma lesions, two non-invasive follicular tumor papillary-like lesions, and a follicular adenoma. The 6x4-mm nodule in the right lobe was also identified as a papillary microcarcinoma. This lesion was reported as a warthin-like subtype of papillary carcinoma (Fig. 1A-D), whereas the papillary microcarcinoma foci in the left lobe were reported as an invasive subtype of follicular-type papillary microcarcinoma.

The thyroidectomy specimen was sampled after 18 h of fixation in 10% buffered formaldehyde solution at room temperature (25˚C). Following tissue processing overnight, formalin-fixed paraffin-embedded (FFPE) tissue blocks were prepared. Tissue sections of 2 μm thickness prepared from FFPE blocks were taken onto positively charged slides. All stages, including deparaffinization and antigen retrieval processes, were performed in Ventana Benchmark Ultra. As a secondary antibody, a detection kit was used, containing non-biotin horseradish peroxidase, hydrogen peroxide substrate, and 3,3'-diaminobenzidine tetra-hydroxy-chloride (DAB) chromogen (UltraView Universal DAB Detection Kit; Roche Tissue Diagnostics). Mayer's haematoxylin and bluing reagent were used for counterstaining. Detailed information about the antibodies used during immunohistochemistry is included in Table I. Microscopic evaluation was performed at x4, x100 and x400 magnifications.

In immunohistochemistry, this lesion was HMBE-1, Cytokeratin-19 and Galectin-3 positive, and the Ki-67 proliferation index was 2%. BRAF mutation was not studied. Capsule invasion was detected in one tumor focused in the right lobe and one in the left lobe. There were no signs of angioinvasion or lymphatic invasion. The thyroid tissue was compatible with Hashimoto's thyroiditis.

According to the AJCC 8th edition, the pathological stage was determined to be pT1a-Stage 1 (11). Surveillance was recommended on the basis of the patient's clinical and pathological findings. The patient remained disease-free 8 months after surgery.

Discussion

WLPTC is a rare oncocytic variant of PTC. Its demographic and clinical features resemble those of other differentiated thyroid carcinomas, especially classic PTC, which coexist with Hashimoto's thyroiditis. Similar to classic PTC, WLPTC affects women more commonly than men, and the most frequently affected age group is 30-50 years-old. Patients usually present with a painless mass in the neck (9,10,12,13). USG of the neck usually reveals a solid, hypoechoic nodule with heterogeneous parenchyma in the background. However, it may be misdiagnosed as a benign nodule or focal thyroiditis with USG (14).

There are no specific clinical or radiological findings for diagnosing WLPTC; FNA biopsy may also result in inconclusive findings. Histopathological assessment of the thyroidectomy material is crucial for a definitive diagnosis (7). The differential diagnosis of WLPTC includes Hashimoto's thyroiditis, Hurthle cell neoplasm, classical PTC arising in a thyroiditis background, tall cell variant, and the oxyphilic variant of PTC. Differential diagnosis is crucial, as some mimickers have more aggressive and unfavourable outcomes than WLPTC does. WLPTC rarely exhibits lymph node metastasis and extrathyroidal extension, thus demonstrating a low recurrence rate and a favourable outcome (9,12,13).

In the present case, the patient, who was a 40-year-old female, did not have a palpable mass on her neck and her only symptom was fatigue. A nodule that was eventually diagnosed as WLPTC was defined as a 6x4 mm isoechoic-heterogeneous nodule with microcalcifications on neck USG. USG also revealed coexisting thyroiditis, which is considered to be a common feature among patients with WLPTC. The FNA biopsy of the nodule revealed benign cytological findings. Immunohistochemical studies were not performed in FNA biopsy material.

Total thyroidectomy was recommended for patients with multiple thyroid nodules with microcalcifications, one of whom had been diagnosed with AUS, and a positive family history of thyroid carcinoma. Left hemithyroidectomy or immunohistochemical studies could have been performed as the patient's FNA biopsy revealed AUS only for the left lobe nodule. In this case, WLPTC in the right lobe would not have been diagnosed, and this could have led to a delay in treatment, also requiring a second surgery with a higher risk of complications. Another option would be a second FNA biopsy of the right lobe nodule, due to the incompatibility of pathological and radiological findings. This also could have resulted in a false negative and caused a delay in treatment. In the present case, family history of thyroid carcinoma, ultrasonographic image of microcalcifications and the patient's preference have led to total thyroidectomy without another FNA biopsy.

Even though there were no malignant findings in the cytological assessment, the definitive pathological assessment revealed four lesions of invasive thyroid carcinoma. The present case was unique in that three other foci of papillary microcarcinoma and a follicular adenoma coexisted with WLPTC.

In the present case, WLPTC could not have been diagnosed by FNA biopsy assessment before surgery; the right lobe nodule was misdiagnosed as benign with FNA biopsy and cytological evaluation. Moreover, neck USG did not reveal strong malignant features other than microcalcifications. This finding may support the idea that radiology and FNA biopsy alone are insufficient for the differential diagnosis of WLPTC.

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Table I. Antibodies used during immunohistochemistry.

Antibody	Supplier	Clone or cat. no.	Dilution	Incubation period	Temperature
CK19	Thermo Fisher Scientific, Inc.	A53-B/A2.26	1/100	32 min	56
HBME-1	Thermo Fisher Scientific, Inc.	HBME-1	1/50	60 min	56
Galectin-3	Biocare Medical, LLC	Monoclonal	1/100	32 min	56
Ki-67	Roche Tissue Diagnostics	30-9	Ready-to-use	36 min	56

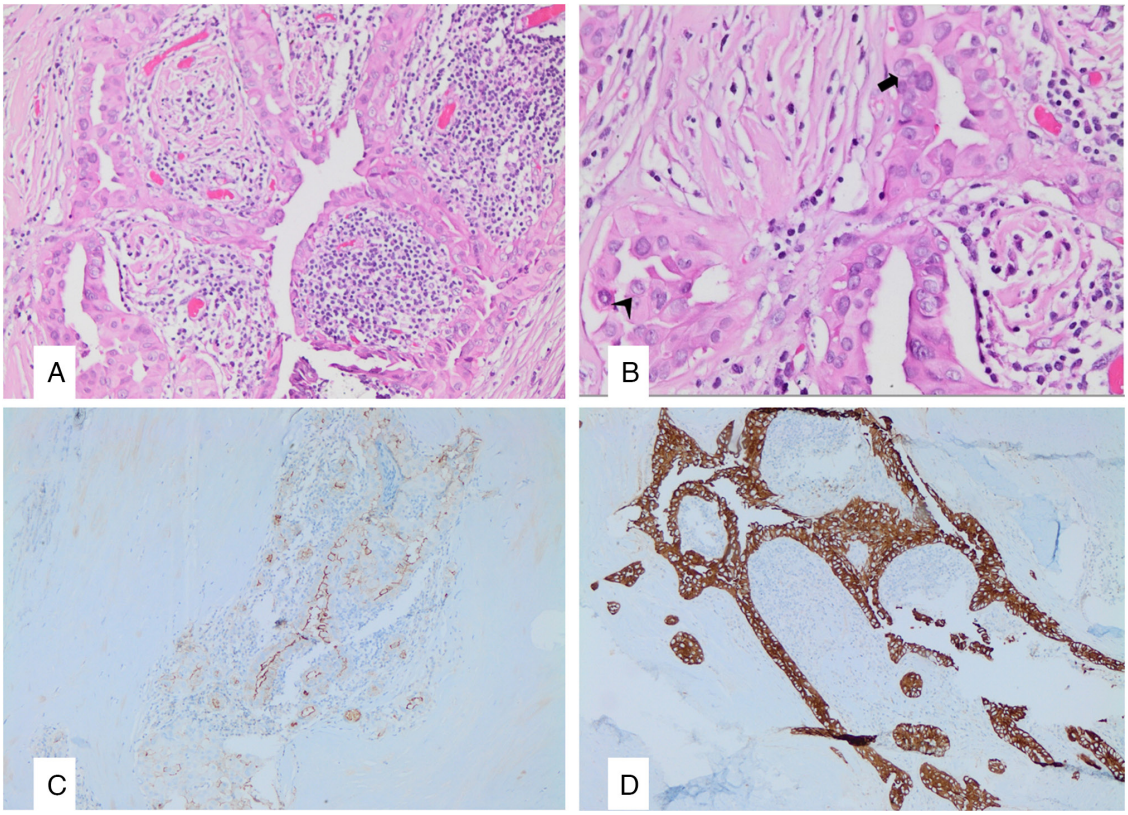

Figure 1. Microscopic findings of Warthin-like papillary carcinoma. (A) Oncocytic tumor cells lining the lymphocyte-rich stroma (H&E; magnification, x20). (B) Nuclear atypia findings specific to papillary carcinoma, such as nuclear enlargement, clarification, cleavage (arrowhead), and intranuclear pseudo-inclusion (arrow), are noteworthy (HEx40). (C) Positive HMBE1 immunohistochemical staining of tumor cells (magnification, x10). (D) Strong diffuse cytoplasmic immuno-expression of CK19 in tumor cells (magnification, x10).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

All listed authors meet the ICMJE criteria. The authors attest that all authors contributed significantly to the creation of the present study, each having fulfilled criteria as established by the ICMJE. SA, BD and ME conceptualized the present study. SA, BD, MHT, NA and ME performed the methodology. SA, BD, MHT, NA and ME investigated and analyzed the data. SA, BD, MHT, NA and ME wrote and prepared the original draft of the manuscript. SA, BD, MHT, NA and ME wrote reviewed and edtited the te manuscript. SA, BD, ME acquired the funds and obtained the resources. ME supervised the present study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

All procedures that were performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Patient consent for participation was obtained.

Patient consent for publication

Written informed consent to publish potentially identifying information, such as details of the case and associated images, was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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