Case Report

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The Warthin-like variant of papillary thyroid carcinomas: a clinicopathologic analysis report of two cases

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Abstract

Objectives: Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma, comprising various subtypes including classical PTC (accounting for approximately 55–65 % of cases) and several variants. The identified variants include papillary microcarcinoma, encapsulated variant, follicular variant, diffuse sclerosing variant, tall cell variant, columnar cell variant, cribriform-morular variant, and Warthin-like variant (WLV-PTC). WLV-PTC is a rare malignant neoplasm.

Case presentation: The present study introduced two cases of WLV-PTC from Affiliated Hospital of Chengde Medical College in retrospect. The macroscopic characteristics, histological feature, immunophenotyping, gene mutations, local invasion, and distant metastasis of the tumors were observed, and the relevant literature on WLV-PTC was reviewed. The tumor cells exhibited nuclear the characteristics similar to those of classic papillary thyroid carcinoma. Immunohistochemical analysis showed strong positivity for thyroid transcription factor 1, cytokeratin 19, Galectin-3, and CK, weak positivity for thyroglobulin, and the Ki-67 proliferation index ranging from 5 to 10 %. Gene mutation analysis revealed that Case 1 had a BRAF V600E mutation, whereas Case 2 had a wild-type mutation. WLV-PTC has histological features similar to those of Warthin tumor originating from salivary gland.

Conclusions: The prognosis of WLV-PTC is similar to that of conventional PTC of comparable size and stage.

Keywords: Warthin-like variant; papillary thyroid carcinomas; case report

Introduction

Papillary thyroid carcinoma (PTC) is the main form of thyroid carcinoma, characterized by distinctive nuclear features, papillary growth patterns, and invasiveness. The incidence of PTC is about three times higher in women than in men. While the classical phenotype is the most common histological type, several variants have been described and classified as per the WHO Endocrine Organs Classification. Some variants of PTC, such as columnar and hypercellular variants, exhibit more malignant characteristics, rendering it necessary to distinguish them from the classic type. The Warthin-like variant of PTC (WLV-PTC) was first described by Apel in 1995 [1]. It shares histological features with Warthin tumor affecting salivary glands. The tumor cells of WLV-PTC exhibit a papillary growth pattern and are infiltrated by a large number of lymphocytes, often occurring in the background of Hashimoto’s thyroiditis. WLV-PTC is a rare variant, with only about 80 cases reported in the English literature in the form of case reports. The prognosis of WLV-PTC is similar to or less aggressive than that of classical PTC. In this study, two cases of WLV-PTC were analyzed to investigate the morphological manifestation and immune phenotype of this variant. We aimed to improve the understanding of the essential pathological features for diagnosis and the biological behavior of WLV-PTC.

Case presentation

Case 1

A 60-year-old man presented with a complaint of a neck tumor. The patient did not report tenderness, polyphagia, or
emaciation. Physical examination revealed a painless mass measuring 1.5 × 1.5 cm on the left lobe of the thyroid gland; the mass had a smooth surface and moved up and down with swallowing. The right lobe of the thyroid gland appeared normal, and no vascular murmurs were detected. Thyroid ultrasound revealed diffuse lesions in the thyroid gland. Two solid nodules were detected on the left side of the thyroid, with Thyroid Imaging Reporting and Data System (TIRADS) classifications of 3 and 3–4. No abnormal lymph nodes were found on either side of the neck (Figure 1A). Laboratory test results showed increased thyroid hormone levels (151.92 nmol/L) and decreased thyroid stimulating hormone (TSH; 0.1621 nIU/L).

The patient underwent left and isthmus thyroidectomy. The tumor was sent for frozen-section pathological examination, which confirmed the presence of PTC. As per institutional guidelines, the patient then underwent left neck lymphadenectomy. A gross examination of the tumor revealed a pale white-tan nodule measuring 1 cm, with a clear boundary and medium consistency. The specimens were fixed in buffered formalin for 24 h, embedded in paraffin, cut into 4 µm slides, and stained with hematoxylin and eosin. Microscopic examination of the tumor showed two different histological structures: tumor cells in the central area exhibiting solid nests, and the surrounding papillary processes and glands. The cores of the papillae and glands contained dense lymphoid cells with focal germinal centers. At high magnification, the tumor exhibited papillary structure surrounded by a monolayer or pseudostratified epithelium. The neoplastic cells showed eosinophilic cytoplasm with characteristic cytological features of PTC, including ground glass appearance, nuclear groove, and psammoma bodies (Figure 1B and C). Immunohistochemistry analysis revealed that the tumor cells were strongly positive for cytokeratin 19 (CK19) (Figure 2A), thyroid transcription factor 1 (TTF-1) (Figure 2B), Galectin-3 (Figure 2C), Braf-V600E mutation (Figure 2D), marker MC (Figure 2E), and marker CK (data not shown). The tumor cells showed weak focal positivity for thyroglobulin (data not shown). The Ki-67 proliferative index was approximately 5% (Figure 2F). Gene mutations analysis detected a BRAF V600E mutation in the tumor (Figure 3).

Based on these results, the patient was diagnosed with WLV-PTC without lymph node metastasis. The patient had a good postoperative recovery and no obvious abnormalities were found during the 15-month follow-up consultations.

**Case 2**

In April 2022, a 47-year-old woman presented at the Surgery Department with nodules detected in bilateral thyroid glands during a physical examination. A previous examination conducted four years ago had revealed hard and regular nodules, with a maximum diameter of 1.7 cm. The patient denied experiencing weight loss, dysphagia, or hyperhidrosis. Physical examination revealed a 1.5 × 1.0 cm nodule at the supra-thyroid gland level pole of the right lobe, with a regular shape, smooth surface, and clear boundary. Ultrasound imaging revealed bilateral thyroid enlargement, with hypoechoic nodules measuring 18.8 × 13.1 × 12.3 mm and scattered multiple strong echoes. Another hypoechoic nodule measuring 15.8 × 12.0 × 6.0 mm was detected in the inferior thyroid pole of the right side (Figure 4A). Thyroid function blood tests revealed a low level of serum thyroid hormone (6.70 pg/mL).

In general, two nodules were detected on the right side and in the thyroid isthmus, measuring 1.9 × 1.4 × 1.2 × 1 cm × 1 cm, respectively. The larger nodule was tan-white in color, and the smaller one appeared yellowish. Paraffin sections revealed that the tumor exhibited a remarkable feature of papillary and glandular architectural growth pattern. Histopathological examination revealed that the papillary stalk showed dense lymphoplasmacytic infiltration (Figure 4B). The tumor cells were arranged in a pseudostratified manner
Figure 2: Immunohistochemistry (IHC) results of case 1 (IHC 100×). (A) The tumor cells were positive for CK19, (B) the tumor cells were positive for TTF-1, (C) the tumor cells were positive for Galectin-3, (D) The tumor cells were positive for Braf-V600E, (E) The tumor cells were positive for MC, (F) The IHC result shows a low Ki-67 proliferative index.

Figure 3: Detection of gene mutations BRAF V600E showed that the tumor was mutant.
and appeared eosinophilic and large. These histological features were similar to those of Warthin tumor originating from the salivary gland origin. The majority of tumor cells showed nuclear clearing and grooves (Figure 4C). Immunohistochemical analysis showed that the tumor cells were positive for CK19 (Figure 5A), TTF-1 (Figure 5B), Galectin-3 (Figure 5C), and CK (data not shown), and showed a Ki-67 proliferative index of approximately 10 % (Figure 5D). However, the tumor cells were negative for marker MC (Figure 5E) and Braf-V600E mutation (Figure 5F). Gene mutations analysis showed that the tumor was wild-type for the BRAF V600E mutation (Figure 6). Based on these findings, the patient was diagnosed with WLV-PTC without lymph node metastasis. The patient had no recurrences or metastasis at the two-month follow-up.

Discussion

The WHO has defined a total of nine different histopathological variants of PTC with different histological characteristics and varying degrees of malignancy. The oncocytic, hypercellular, and solid variants exhibit distinct features and behaviors. A different variant of PTC exhibited different histological characteristics and malignant degrees. Some variants, such as the columnar cell and hypercellular variants, show more aggressive behavior compared to others. It is necessary to understand the different variants of PTC to accurately diagnose and classify tumors. However, the rarity of some variants and the potential ambiguity in criteria could cause subjectivity and poor repeatability in subtype classifications, leading to variability in diagnoses.
among different pathologists. The Warthin-like variant has been recently recognized as an oncocytic variant in the 4th edition of the WHO classification. It is characterized by papillary architecture, oncocytic cells, and lymphoplasmacytic core infiltrates. WLV-PTC may be closely associated with Hashimoto’s thyroiditis [2, 3]. Unlike other oncocytic variants that share papillary architecture and oncocytic cells, dense lymphoplasmacytic core infiltrate is a remarkable feature of WLV-PTC [4, 5]. Owing to its rarity, only a small number of WLV-PTC cases have been reported in the literature. Interestingly, we reported two cases of WLV-PTC and studied the clinicopathological features and prognosis, which contribute to the existing data resources, and enhance the understanding of WLV-PTC among pathologists.

Clinical characteristics

Limited epidemiological data on WLV-PTC are available. WLV-PTC predominantly affects women and tends to occur at slightly older ages compared to conventional PTC with ages ranging from 19–85 years [6]. Table 1 shows these characteristics of WLV-PTC patients in the case report literature [6–13]. The WLV-PTC mainly occurs in women and is often complicated by Hashimoto’s thyroiditis. In some individual cases, IgG4-positive plasma cells have been identified in the tumor stroma of WLV-PTC [7, 14]. The presence of IgG4-positive plasma cells in the tumor stroma suggests a potential link to Hashimoto’s thyroiditis [8, 15]. In this study, although a large number of lymphocytes were found in both patients with WLV-PTC, no eosinophilic follicular epithelial cells were found, which does not meet the diagnostic criteria for Hashimoto’s thyroiditis. Importantly, the patients’ serology showed normal thyroid function.

Pathological characteristics

There are few reports on the macroscopical characteristics of WLV-PTC. Based on the summary of 79 cases of WLV-PTC in the literature, Sahoo [11] reported that the tumor size of WLV-PTC can range from 0.3 to 6.1 cm, with a median diameter of 1.5 cm. In this study, the tumor diameters of the two patients were 1.0 and 1.9 cm. The cut surface of the tumor was grayish white and grayish yellow, making it difficult to distinguish it from classic PTC based on

Figure 6: Detection of gene mutation BRAF V600E showing that the tumor was wild-type for this particular mutation.
macroscopic examination alone. Under low-power microscopy, the histological characteristics of WLV-PTC are similar to those of Warthin tumor, which originate from salivary glands [3, 9], showing papillary growth pattern. The papillary axis is accompanied by a large number of lymphoblast cells, consistent with chronic lymphocytic thyroiditis. As an autoimmune response, Hashimoto’s thyroiditis is often involved in the pathogenesis of thyroid cancer. A recent study reported a singular case of WLV-PTC in a patient with multiple sclerosis but without Hashimoto thyroiditis and hypothesized multiple sclerosis systemic autoimmune diseases may also contribute to the determination of WLV-PTC [12]. A report of three cases provided clinical, grossing, cytological, and histological correlation, revealing the feasible diagnosis of WLV-PTC based on cytomorphological aspects [13]. The tumor cells have eosinophilic cytoplasm and can be arranged in a monolayer, multilayer, or pseudo-multilayer manner. The nuclei show the typical nuclear characteristics of PTC. In Case 1 reported in this study, a predominance of diffuse eosinophilic tumor cells was observed, whereas Warthin tumor-like papillary structures rich in lymphocytic stroma were only seen in the adjacent normal thyroid tissue surrounding the tumor. Initially, metastasis from salivary gland-derived tumors was suspected, but further investigation, including an inquiry about the history of the patient’s salivary gland tumors and immunohistochemical differentiation (CD117+, p63+, TTF-1+), ruled out metastasis and confirmed the diagnosis of WLV-PTC. In Case 2, histological examination showed typical Warthin tumor-like structures and PTC-like nuclear features, enabling a clear and definitive diagnosis.

**Genetic characteristics**

Gene mutations, particularly in the PTC and BRAF genes, have been observed in WLV-PTC [10, 16]. A case report with two cases of WLV-PTC emphasized the role of histomorphology and assessment of BRAF mutation in the diagnosis of WLV-PTC [17]. The BRAF gene mutation is commonly detected in the majority of patients with the most frequent mutation site being BRAF V600E. In addition to BRAF-V600E, BRAF-V600K mutations have been detected in a few patients with WLV-PTC [18], which may have a role in promoting the occurrence and development of the condition. BRAF mutations are associated with aggressive clinical features of thyroid cancer, such as lymph node metastasis and extrathyroidal spread, higher rates of tumor recurrence, and resistance to radiiodine therapy [19]. Gene mutation analysis revealed the presence of BRAF V600E mutation in the tumor, confirming the presence of this mutation in Case 1. Here, Case 1 has BRAF V600E mutation, and Case 2 has no mutation, however, both have no lymph node metastasis and with good postoperative recovery. This emphasized the need to monitor patients for lymph node metastasis and analyze histological subtypes in all PTC cases that might be considered to be aggressive classic variants might as well be WLV-PTC.

The treatment strategy and prognosis of WLV-PTC are still controversial. Lymph node metastasis has been observed in a few cases. Furthermore, the presence of sarcoma or undifferentiated components within the tumor has been associated with a poor prognosis. The short follow-up time for the two cases in this report emphasizes the need for more extensive research and longer-term data collection for a better and more comprehensive understanding of this rare histological variant.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the Ethics Committee of Affiliated Hospital of Chengde Medical College. **Informed consent:** Informed consent was obtained from all individuals included in this study.

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Author contributions: Study conception and design: Xing Zhao, Xingbin Shen; data collection: Mingzhen Zhao; analysis and interpretation of results: Yijia Zhang, Pengyu Hao; draft manuscript preparation: Xing Zhao. All authors reviewed the results and approved the final version of the manuscript.

Competing interests: The authors declare that they have no conflicts of interest to report regarding the present study.

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References