Warthin-like Papillary Carcinoma of the Thyroid

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Background.—Warthin-like papillary carcinoma of thyroid is characterized by distinct papillary formations lined by tumor cells with oncocytic cytoplasm, nuclear features of papillary carcinoma, and brisk lymphoplasmacytic infiltrates in the papillary stalks. This tumor derives its name from its close resemblance to Warthin tumor of major salivary glands.

Oncocytic metaplasia is usually seen in both benign and malignant lesions of thyroid.1-4 The true oncocytic tumors are classified as Hürthle cell tumors, which are characterized by distinct cytology and clinical behavior.1,2,5 However, follicular cell-derived tumors and even medullary carcinoma can exhibit prominent oncocytic change.1,2,6-10 Among the follicular derived tumors, papillary carcinoma can show both focal and extensive oncocytic change.1,2,6-10

Hürthle cell variant of papillary carcinoma accounts for 1% to 11% of all papillary carcinomas. These tumors are characterized by papillary formation lined by oncocytic cells and clinically behave similarly to conventional papillary carcinoma.6,9 Apel et al reported 13 cases of a new variant of papillary carcinoma and named it Warthin-like papillary carcinoma, owing to its close histologic resemblance to a tumor encountered in salivary glands.11,12 In their series, all tumors arose in a background of lymphoid tissues and behaved in an indolent fashion.13 We report the clinicopathologic features of 17 additional cases of Warthin-like tumor of thyroid.

Materials and Methods

Fifteen cases were selected from the personal consultation files of one of the authors (V.A.L., covering years 1996-1998), and 2 additional cases were retrieved from the surgical pathology files at the University of Pennsylvania Medical Center. The cases were selected on the basis of histologic criteria described by Apel et al.11 Fine-needle aspiration (FNA) biopsies were performed in 7 cases; cytology slides were available for review in 2 cases. Hematoxylin-eosin-stained sections were available for review in each case.

The information extracted from the patient records and consultation correspondence included sex; age; clinical presentation; size of tumor; location; FNA findings, diagnosis, or both; extent of surgery (partial vs total thyroidectomy); lymph node status; and presence or absence of coexistent lymphocytic thyroiditis. Follow-up information was limited in all cases and ranged only from 1 to 1.5 years.

Results

The clinical and key pathologic features of the cases we studied are summarized in the Table. Fifteen patients were women and 2 were men. The patients’ ages ranged from 23 to 63 years. Laterality was known in 14 cases; 9 lesions were present in the right lobe, 4 in the left, and 1 in isthmus. The common presenting sign was a palpable neck mass, except in cases where the tumor was less than 1 cm and presented as an incidental finding in thyroid lobes excised for other reasons. Fine-needle aspiration biopsies were performed in 7 cases, and slides were available for review in 2 cases (details on these 2 cases have been reported previously.13 The FNA diagnoses included papillary carcinoma (n = 4), lymphocytic thyroiditis (n = 2), and atypical cells (n = 1). The surgical treatment consisted of total thyroidectomy in 11 cases and lobectomy in 6.

Each of these cases was diagnosed and treated within the past 3 years, so long-term follow-up data are not available. We are, however, aware of 2 cases (not our own material and thus not included in this series) with 6 and 9 years of follow-up; both patients did well.

Conclusions.—Warthin-like tumors can be mistaken for benign lymphoepithelial lesions of the thyroid, Hürthle cell carcinoma, and Tall cell variant of papillary carcinoma in both fine-needle aspiration and histology specimens. Follow-up information on the previously reported cases has suggested that these tumors behave similarly to usual papillary carcinoma. The extensive lymphocytic infiltration in these tumors and their association with chronic lymphocytic thyroiditis may suggest a role for immunological mechanisms in the pathogenesis of thyroid tumors.

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years of follow-up, in which no evidence of recurrent or metastatic disease was identified.

**PATHOLOGIC FINDINGS**

**Gross Findings**

The tumors ranged in size from 0.3 to 3.5 cm (mean 1.3 cm); size information was not available in 1 case. All grossly evident tumors were well circumscribed and confined to the thyroid. Cyst formation was noted in 6 cases. The uninvolved thyroid tissue in all cases varied in appearance from red-brown to tan and displayed varying degrees of nodularity.

| Clinicopathologic Features of 17 Cases of Warthin-like Tumor of the Thyroid* |
|---|---|---|---|---|---|---|
| Case No. | Sex/Age, y | Side (Lobe) | Size, cm | Lymph Node Metastases | FNA Diagnosis | Lymphocytic Thyroiditis |
| 1 | F/35 | R | 1.5 | – | Pap ca | + |
| 2 | M/23 | L | 3.0 | + | Pap ca | + |
| 3 | F/48 | ? | 1.0 | – | Pap ca | + |
| 4 | F/34 | R | 2.5 | – | Pap ca | + |
| 5 | F/45 | ? | ? | – | Lymph thy | + |
| 6 | F/59 | R | 1.0 | – | Lymph thy | + |
| 7 | F/32 | ? | 3.5 | – | Atypical cells | + |
| 8 | F/42 | Isthmus | 1.0 | – | ... | + |
| 9 | M/39 | R | 0.9 | – | ... | + |
| 10 | F/48 | ? | 0.3 | – | ... | + |
| 11 | F/38 | L | 1.0 | – | ... | + |
| 12 | F/36 | R | 0.6 | + | ... | + |
| 13 | F/45 | R | 0.6 | + | ... | + |
| 14 | F/37 | R | 0.4 | – | ... | + |
| 15 | F/45 | R | 1.0 | – | ... | + |
| 16 | F/63 | L | 1.5 | – | ... | + |
| 17 | F/53 | L | 1.7 | + | ... | + |

* R indicates right; L, left; FNA, fine-needle aspiration; Pap ca, papillary carcinoma; and Lymph thy, lymphocytic thyroiditis.

**Cytologic Findings**

Fine-needle aspiration slides were reviewed in 2 cases.14 The specimens were cellular with follicular cells arranged in 3-dimensional groups, papillary fragments, and single cells in the background of numerous reactive lymphocytes (Figure 1, A–C). The lymphocytes were found percolating between the cell groups. Both cases also showed papillary fragments with lymphocytic infiltrates filling their cores. The tumor cells consisted of abundant eosinophilic cytoplasm with enlarged eccentric nuclei with prominent nucleoli. The nuclear features of papillary cancer, that is, nuclear chromatin clearing, membrane thickening, grooves,
and inclusions, were evident in both cases. In addition, a separate population consisting of Hürthle cells with intermixed lymphocytes was also present. This feature was suggestive of a concomitant background of lymphocytic thyroiditis.

### Histologic Findings

The sections from all cases showed a circumscribed tumor with papillary architecture. Six cases showed prominent cyst formation within the main tumor mass. The papillary stalks were filled with inflammatory infiltrate, predominantly composed of plasma cells with admixed lymphocytes. These papillae were lined by tumor cells with oncocytic cytoplasm and round to oval nuclei with nuclear features of papillary carcinoma (chromatin clearing, nuclear inclusions, and grooves) (Figure 2, A–C). Seven cases also showed a concomitant papillary carcinoma (5 papillary microcarcinomas and 2 follicular variants of papillary carcinoma 2). In all cases the surrounding thyroid exhibited lymphocytic thyroiditis. All tumors were confined to the thyroid, and none revealed vascular invasion or invasive growth in the surrounding thyroid. Three cases showed regional lymph node metastases.

### Comment

We report 17 additional cases of a previously described variant of papillary thyroid carcinoma known as Warthin-like papillary carcinoma of thyroid.11,13±17 These tumors are characterized by papillary architecture and oncocytic tumor cells with nuclear features of papillary carcinoma arising in a background of lymphocytic thyroiditis.11,13±17 Apel et al. coined the designation of this tumor in regard to its close resemblance to the papillary cystadenoma lymphomatosum, or Warthin tumor of the salivary glands.11,12 These authors found that the epidemiologic features of this variant of papillary thyroid carcinoma are similar to the typical (classic) papillary carcinoma.11 Although the follow-up period in our series was limited, all tumors were of small size, confined to the thyroid, and had no evidence of vascular invasion or extrathyroidal extension. The available published data suggest these tumors behave as usual papillary thyroid carcinoma with prolonged survival and excellent long-term prognosis.11

Papillary carcinoma and its variants can exhibit different degrees of oncocytic metaplasia.1±4 Hürthle cell and tall cell variants of papillary carcinoma show prominent oncocytic change.1,2,6–10 Papillary Hürthle cell carcinomas comprise 1% to 11% of all papillary carcinomas and are characterized by papillary architecture lined by oncocytic cells with nuclear features of papillary carcinoma.6–9 However, they usually lack lymphoplasmacytic infiltrate and a strong association with lymphocytic thyroiditis, as seen in the Warthin-like variant.11,13–16 The tall cell variant of papillary carcinoma is characterized by papillary growth pattern, oncocytic elongated tumor cells with a height twice that of their width, and papillary cancer nuclei.1,2,10 Clinically, this variant of papillary cancer can behave in a more aggressive fashion and is frequently associated with extrathyroidal extension, vascular invasion, lymph node and distant metastases, and tumor recurrence.1,2

In both cytologic and histologic preparations, the Warthin-like variant of papillary carcinoma can be mistaken for the tall cell variant of papillary carcinoma owing to its oncocytic cytologic features.13–16 The distinguishing features between these 2 entities include lack of elongated cells, presence of prominent nucleoli, granular cytoplasm, and a concomitant lymphocytic infiltrate in the Warthin-like lesion.13

Some Hürthle cell lesions on histologic sections can assume a pseudopapillary architecture due to collapse and disruption of their follicular architecture.11 We believe that this feature is related to a paucity of tumor stroma in Hürthle cell lesions (benign and malignant) as compared to other follicular cell-derived tumors. This pseudopapillary pattern can be mistaken for a papillary Hürthle cell carcinoma, which can alter the clinical management since Hürthle cell carcinomas behave in a more aggressive fashion than do papillary carcinomas.1,2 It is important to not overinterpret papillary structures in Hürthle cell neoplasms as papillary thyroid carcinoma; the appropriate nuclear features of papillary thyroid carcinoma must be present to diagnose a Hürthle cell papillary cancer.

Two of the cases in this study were diagnosed as “consistent with lymphocytic thyroiditis” on FNA. The presence of Hürthle cells and lymphocytes can be seen in aspirates from lymphocytic thyroiditis.18–20 In addition, some of these cells may also show nuclear enlargement and chromatin clearing due to reactive changes, which may lead to a false-positive diagnosis.1,2,18,19 However, the tumors, especially papillary carcinoma arising in the background of lymphocytic thyroiditis, usually show 2 cell populations in cytology samples13,18,19; namely, tumor cells with nuclear features of papillary carcinoma and a background population of Hürthle cells intermixed with small and large reactive lymphocytes.13,18,19 We found a similar pattern in the FNA specimens of 2 of our cases, that is, 2 separate populations representing tumor and background thyroiditis.

Six cases in this series showed prominent cystic change in the main tumor mass. The combination of cystic lesion with a predominant lymphoid component arising in a background of lymphocytic thyroiditis can be mistaken for a benign lymphoepithelial cyst.2,21–23 These uncommon lesions are seen mainly in thyroids affected by lymphocytic thyroiditis; it has been suggested that they arise from intrathyroidal branchial remnants. Lymphoepithelial cysts usually are lined by flattened squamous or respiratory epithelium and lack intracytic papillary growth pattern.2,21–23 All of these lesions are located in the lateral lobes of the gland, whereas Warthin-like papillary thyroid cancer can arise in any area of the thyroid.11

The presence of lymphocytic infiltrate within the stalks of Warthin-like papillary carcinoma imparts a distinctive appearance to this tumor.11,13–17 Inflammatory infiltrates can be seen in association with other variants of papillary carcinoma.1,2 Some authors have suggested that this feature may be partly responsible for the indolent clinical course associated with papillary cancer.2,12 Matsubayashi et al.14 reported a favorable prognosis in patients with peritumoral or intratumoral lymphocytosis, whereas tumors that lacked such an association had higher rates of recurrence. However, other studies have found no clinical significance of lymphocytic infiltration in papillary cancer.26 In addition, it has been shown that malignant thyroid follicular cells express HLA type II antigens in response to tumor-infiltrating lymphocytes, which may play a role in the immune response against thyroid cancer.25,27,28 These studies, although they present a complex picture of tumor-host interaction, do suggest that tumor-associated lymphocytic thyroiditis plays a significant role in the inactivation of lymphocytes that may otherwise react against thyroid tumors.11,13–17
phocytes may play a role in control of thyroid cancer; this role needs to be defined further.

References