Mucoepidermoid Carcinoma Involving Warthin Tumor

A Report of Five Cases and Review of the Literature

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Key Words: Warthin tumor; Mucoepidermoid carcinoma

Abstract

We describe 5 cases of mucoepidermoid carcinoma (MEC) involving Warthin tumor (WT) of the parotid gland. The WT size ranged from 1.7 to 6.0 cm. The MECs were much smaller, 0.3 to 1.7 cm. In 3 cases, the WT completely surrounded the MEC, and in 2 cases neither WT nor MEC surrounded the other. Each MEC was low grade, 3 grade I and 2 grade II. One MEC had evidence of vascular invasion. All patients underwent partial or subtotal parotidectomy with negative resection margins. Clinical follow-up (range, 8-52 months) for 3 patients showed no evidence of recurrence. The pathogenetic relationship between WT and MEC in these cases is uncertain. In 4 cases, foci of squamous or mucous metaplasia were found in the WT component, associated with mild cytologic atypia in 3 tumors. However, a direct transition from WT to MEC was not identified. In 1 case, MEC was present 45 months before WT, suggesting that the recurrent MEC involved WT coincidentally. The small size and low grade of the MEC and the negative resection margins most likely explain the good outcome for the 3 patients with clinical follow-up data available.

Warthin tumor (WT), also known as papillary cystadenoma lymphomatosum, is the second most common benign tumor of the parotid gland, representing 10.4% of all benign parotid gland tumors at the Armed Forces Institute of Pathology. Multicentricity and bilateral involvement, which may occur in synchronous or metachronous fashion, are more common in WT than in other salivary gland neoplasms. Histologically, WT is characterized by a variable mixture of lymphoid stroma and oncocytic epithelium, and the latter is often papillary.

Carcinoma may arise rarely in WT. Nagao and colleagues reviewed the literature and identified 24 cases of carcinoma involving WT. In most instances, the carcinoma was thought to arise from WT. However, coincidental occurrence (so-called collision tumor) of WT and carcinoma is difficult to exclude. Squamous cell carcinoma is reported to be the most common type of carcinoma to arise within WT. Other types of carcinoma that have involved WT include oncocytic carcinoma, undifferentiated carcinoma, adenocarcinoma not otherwise classified, and mucoepidermoid carcinoma (MEC). To date, 5 cases of MEC arising within WT have been reported in the literature.

In this article, we describe the clinical and pathologic features of 5 additional cases of MEC involving WT.

Materials and Methods

We searched the computerized files of the Department of Pathology of the University of Texas M.D. Anderson Cancer Center, Houston, for cases of WT and MEC from 1985 through December 1999. In the time period searched, 274 cases of WT were accessioned in our department, including 86
consultation cases and 188 routinely signed out specimens. Five cases of WT with MEC of parotid gland were identified. Four cases were received in consultation, and 1 patient (case 5) underwent surgical excision at our institution.

The number of slides available for review in each case ranged from 4 to 19 (median, 5 slides). Each WT was searched systematically for areas of lining cell hyperplasia, squamous and mucous metaplasia, and areas of transition from metaplastic WT epithelium to MEC. The MEC was assessed for its relationship with WT and evidence of invasion, and each MEC was graded histologically using a system reported by others.1

Clinical information was obtained from consultation letters, communication with referring pathologists, and review of available medical records.

**Results**

**Clinical Findings**

The age of the patients ranged from 39 to 70 years. Four patients were from the United States, and 1 patient was from Korea. There were 3 men and 2 women. All patients sought medical care because of a mass that involved the parotid gland (3 right, 1 left, and 1 side not specified). All patients underwent partial (cases 1-3) or near total parotidectomy (cases 4 and 5), and the surgical margins of each specimen were negative for neoplasm.

Two patients underwent fine-needle aspiration (FNA) before surgical excision. In case 2, the FNA revealed numerous lymphocytes, immunoblasts, and benign serous acini. No oncocytic epithelium was identified. The diagnosis issued was nonspecific, but the lesion was thought to be benign. In case 5, the FNA revealed oncocytic epithelium and acute and chronic inflammation and the diagnosis of WT was established.

Two patients had a history of malignant neoplasm. One patient (case 4) had a history of MEC involving the right parotid gland 3 years earlier. Another patient (case 5) had a history of thyroid carcinoma (histologic type unknown) 19 years earlier, which at that time was treated by surgical excision and radioactive iodine ablation, with repeated radioactive iodine ablation 10 years later (9 years before excision of the parotid gland WT).

Clinical follow-up was available for 3 of 5 cases. Two patients (cases 2 and 5) were alive without evidence of disease at last follow-up, at 52 months and 8 months, respectively. In case 4, the patient had low-grade MEC 45 months before developing recurrent MEC involving WT. This patient also was alive with no evidence of tumor 30 months after surgical excision. Two patients (cases 1 and 3) were lost to follow-up.

**Pathologic Findings**

The size of the WT ranged from 1.7 to 6.0 cm (median, 3.2 cm, and mean, 3.4 cm). Each WT was histologically typical with an approximately equal mixture of oncocytic epithelium and lymphoid stroma. In all cases, prominent lymphoid follicles with secondary germinal centers were present in the lymphoid stroma. The oncocytic epithelium was double layered and focally or extensively formed papillary structures. The luminal layer was composed of columnar cells with small regular nuclei and apocrine secretions. The basal layer was composed of polygonal cells with round vesicular nuclei and small nucleoli. Mitotic figures were rare or absent. Large cystic spaces were found in each WT with eosinophilic inspissated secretions. In each tumor, epithelial lining cells exhibited foci of hyperplasia and metaplasia. In 4 (cases 1, 2, 4, and 5) and 3 (cases 2, 3, and 5) tumors, foci of squamous and mucous metaplasia were found, respectively. Squamous and mucous metaplasia were extensive in cases 3 and 5. In 3 neoplasms (cases 1, 2, and 5), metaplastic WT epithelium in proximity to MEC exhibited mild cytologic atypia.

The size of the MEC ranged from 0.3 to 1.7 cm (median, 1.5 cm, and mean, 1.1 cm). In 3 neoplasms (cases 1-3), the MEC was localized within WT. In cases 4 and 5, neither the MEC nor the WT surrounded the other. In each case, the MEC was invasive with a desmoplastic response (Images 1A and 2). A moderate to marked inflammatory response was present in 3 MECs, acute and chronic in 2 tumors (cases 1 and 5) and predominantly chronic in case 2. The MECs were composed of ducts and glands, which were focally or more extensively cystic in all tumors (Images 1B and 3C). The glands contained abundant eosinophilic or basophilic secretions. In 1 tumor (case 1), much of the MEC was solid and both blood vessel (Image 1C) and lymphatic invasion were identified. No cases had evidence of perineural invasion.

At high power, each tumor was composed of a variable mixture of intermediate, mucous, and squamous cells (Image 1B). Intermediate cells were numerous in most tumors. Clear cells were present in 2 tumors (cases 2 and 4) and prominent in case 4. Oncocytes were also numerous in case 4. Three tumors (cases 3-5) were grade I (Image 3C), and 2 neoplasms (cases 1 and 2) were grade II (Image 1B). The grade II tumors were relatively less cystic, and the tumor cells had a higher nuclear/cytoplasmic ratio and prominent nucleoli. Mitotic figures were identified but did not number greater than 4 per 10 high-power fields in any case.

In 1 neoplasm (case 5), evidence of cystic rupture, including chronic inflammation, granulation tissue, fibrosis, hemosiderin deposits, and cholesterol clefts surrounded by foreign body giant cells, was present.
Discussion

Carcinoma arising within WT is a rare occurrence. According to Nagao et al, the first description of carcinoma involving WT was by Ruebner and Bramhall in 1960. Since that time, 24 cases of carcinoma of different types have been reported to arise in WT, most commonly squamous cell carcinoma. Only 5 cases of MEC arising in WT have been reported previously. Although the 5 cases we report represent 1.8% of all WT diagnosed at our hospital, 4 of these cases were received in consultation. The true incidence of MEC involving WT is most likely much lower. Excluding the consultation cases in the present study, only 1 case of MEC involving WT occurred in the remaining 188 routinely handled specimens, for an incidence of 0.5%.

The 5 cases in this report, as well as the 5 previously reported cases, are summarized in Table 1. The median age of the patients was 59 years (range, 39-73 years). There were 6 men and 4 women. All 10 cases arose in the parotid gland, right in 4 cases, left in 4 cases, bilateral in 1 case, and unknown in 1 case. The median size of the WT was 2.4 cm (range, 1.7-6.0 cm; mean size, 3.25 cm). The MEC size is known for the 5 cases we report, with a median of 1.5 cm (range, 0.3-1.7 cm). Histologic grade was specified for 6 MECs involving WT reported (including 5 cases in the present study), and all were low grade. All 7 patients for whom clinical follow-up was available were alive at last follow-up.

The prognosis of patients with parotid gland MEC is largely dependent on tumor stage, tumor grade, and the adequacy of resection margins. The good outcome of patients with MEC involving WT is probably explained by these factors. Seven patients with MEC involving WT with clinical follow-up (including 3 patients in the present study) are included (Table 1). All 7 patients were alive, and each patient...
in whom MEC size was known had a small tumor, no larger than 1.5 cm, and no evidence of lymph node metastases. Thus, these were stage I tumors, and when adequately excised, this patient group is known to have a good prognosis.1

In addition, each MEC was low grade. Previous studies of parotid gland MECs have shown that low-grade tumors uncommonly result in patient death, usually only when the tumors are high stage.1 Although margins are not mentioned specifically in some previous reports of MEC involving WT, all 5 cases we report had negative resection margins. The simultaneous presence of WT also may have had a role in the good prognosis of MEC involving WT. The presence of the larger WT may have brought MEC to clinical attention earlier, resulting in excision when the MEC was theoretically smaller and of lower grade.

The pathogenetic relationship between the MEC and WT in these 5 cases is uncertain. In case 4, the MEC was detected and excised 45 months before the detection of WT, and thus, the presence of WT and recurrent MEC involving the parotid gland is likely to be coincidental. In the other 4 cases, the WT and MEC were intimately related to each other, suggesting that MEC arose in WT. In support of this possibility, each WT had areas of hyperplasia and squamous or mucous metaplasia. In 3 specimens (cases 1, 2, and 5), the metaplastic foci exhibited mild cytologic atypia, suggesting the possibility that these foci were a precursor lesion of MEC. However, a direct transition from WT epithelium to MEC was not identified in these cases.

The MEC in case 4 of the present study is of interest because the neoplasm had large areas of oncocytes in addition to areas diagnostic of MEC. Oncocytic differentiation in MEC is rare. We have identified 3 other cases of MEC with oncocytic differentiation involving the parotid gland in the literature.17-19 In addition, MEC with oncocytic foci involving other anatomic sites, such as lung and lacrimal gland, are reported.20,21 The presence of oncocytic differentiation in MEC is of no clinical significance. The importance of recognizing this unusual variant of MEC is in the differential diagnosis of oncocytic neoplasms.

Others have reported that previous exposure to radiation therapy increases the risk of developing salivary gland carcinoma, usually after a long latency interval.22-24 Children and adults are at risk, and the most common type of carcinoma to arise in this clinical setting is MEC.22,23 Case 5 in our study may possibly fit this profile. This 70-year-old woman had thyroid carcinoma of unknown histologic type 19 years earlier, treated by thyroidectomy and thyroid gland ablation using radioactive iodine. The patient underwent ablation 2 separate times, immediately following surgery and 10 years later, 9 years before developing MEC involving WT. Although external radiation therapy and radioactive iodine are obviously different treatment modalities, it seems reasonable to hypothesize that radioactive iodine also may increase the risk of developing salivary gland MEC. However, the risk of salivary gland neoplasms in patients who have been treated previously with radioactive iodine therapy is unknown.

The differential diagnosis of MEC involving WT of the parotid gland includes benign lesions with an extensive lymphoid reaction, WT with extensive squamous and mucous metaplasia, and metastatic carcinoma to WT.

Benign adenomas of the parotid gland can be associated with an extensive lymphoproliferative reaction, including the presence of well-developed lymphoid follicles, resembling the lymphoid stroma of WT. Auclair25 coined the term tumor-associated lymphoid proliferation (TALP) for this lymphoproliferative reaction, which has been identified in 16% of parotid gland lesions in the Salivary Gland Registry of the Armed Forces Institute of Pathology. However, benign tumors with TALP lack invasion and intermediate cells and, therefore, can be distinguished from MEC involving WT.

WT commonly has incidental foci of squamous or mucous metaplasia of oncocytic epithelium.3,26 Infrequently, WT may manifest extensive squamous or mucous metaplasia with necrosis that may be mistaken for MEC, squamous cell carcinoma, or adenocarcinoma.26 In WT cases with extensive necrosis, epithelial cells can be atypical with large nuclei, prominent nucleoli, and occasional mitotic figures, resembling necrotizing sialometaplasia of minor salivary glands.26,27
Image 3 (Case 3) Mucoepidermoid carcinoma involving Warthin tumor. A, Foci of squamous cell and mucous cell metaplasia of cyst lining in Warthin tumor (H&E, ×400). B, Small mucoepidermoid carcinoma (center) is completely surrounded by Warthin tumor (H&E, ×20). C, Higher magnification of invasive grade I mucoepidermoid carcinoma illustrating cystic glands and desmoplastic stroma (H&E, ×200).

Image 4 (Case 4) Mucoepidermoid carcinoma involving Warthin tumor (the latter not shown). The mucoepidermoid carcinoma had histologically typical areas (left) and foci of oncocytic differentiation (right) (H&E, ×200).
Furthermore, fibrosis can occur in these tumors that can mimic a desmoplastic response, as often accompanies invasive MEC. Nevertheless, WT with extensive metaplasia, necrosis, and fibrosis will not show evidence of true invasion. In addition, intermediate cells are not found in WT and are seen in MEC, although these cells can be elusive or misinterpreted.

Metastasis to WT from a previous or synchronous malignant neoplasm involving a different anatomic site can mimic MEC involving WT and always must be excluded. The most common neoplasms to metastasize to the parotid gland are squamous cell carcinoma (usually from the head and neck) and malignant melanoma.28-30 Other primary tumors that less commonly metastasize to the parotid gland include carcinomas of the lung, breast, and colon. Although MEC involving WT may histologically resemble metastatic adenocarcinoma or squamous cell carcinoma in some cases, this distinction should be possible through the clinical history and physical examination.

In summary, we have reported 5 cases of MEC involving WT. In all 5 cases, the MEC component was low grade, and in 3 cases with clinical follow-up, the patients had a good outcome, in agreement with 4 other cases reported in the literature. The small size and low grade of MEC, combined with negative surgical excision margins, probably explain the good prognosis for patients with MEC involving WT in our study. Although the number of cases of MEC involving WT is too small for definite conclusions, it seems that detection of small low-grade MEC within WT has no effect on patient outcome.

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References


Table 1
Summary of 10 Cases of Mucoepidermoid Carcinoma Involving Warthin Tumor Reported in the Literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Side</th>
<th>WT Size (cm)</th>
<th>MEC Size (cm)</th>
<th>MEC Grade</th>
<th>Clinical Follow-Up</th>
</tr>
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<tbody>
<tr>
<td>Gadient and Kalfayan,13 1975</td>
<td>60</td>
<td>M</td>
<td>Left</td>
<td>1.8</td>
<td>NA</td>
<td>NA</td>
<td>NED, 72 mo</td>
</tr>
<tr>
<td>Seifert,15 1997</td>
<td>73</td>
<td>M</td>
<td>Bilateral</td>
<td>4.0</td>
<td>NA</td>
<td>II</td>
<td>NED, time of follow-up not specified</td>
</tr>
<tr>
<td>Saku et al,14 1997</td>
<td>66</td>
<td>F</td>
<td>Left</td>
<td>2.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nagao et al,6 1998</td>
<td>58</td>
<td>M</td>
<td>Left</td>
<td>2.8</td>
<td>NA</td>
<td>NA</td>
<td>NED, 30 mo</td>
</tr>
<tr>
<td>Present study</td>
<td>54</td>
<td>F</td>
<td>Right</td>
<td>4.5</td>
<td>NA</td>
<td>NA</td>
<td>NED, 34 mo</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>Right</td>
<td>2.0</td>
<td>1.7</td>
<td>II</td>
<td>Lost to follow-up</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>M</td>
<td>Right</td>
<td>1.7</td>
<td>0.7</td>
<td>II</td>
<td>NED, 52 mo</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>M</td>
<td>NA</td>
<td>3.2</td>
<td>0.3</td>
<td>I</td>
<td>Lost to follow-up</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>Right</td>
<td>4.0</td>
<td>1.5</td>
<td>I</td>
<td>NED, 30 mo</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>Left</td>
<td>6.0</td>
<td>1.5</td>
<td>I</td>
<td>NED, 8 mo</td>
<td></td>
</tr>
</tbody>
</table>

MEC, mucoepidermoid carcinoma; NA, not available; NED, no evidence of disease; WT, Warthin tumor.


