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Diagnostic pitfalls of infarcted Warthin tumor in frozen section evaluation

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ABSTRACT

Warthin tumor (WT) is the second most common benign salivary gland neoplasm and has characteristic cytologic and histologic findings. Fine-needle aspiration is a common and useful preoperative diagnostic technique, which sometimes leads to ischemic injury resulting in the infarction of these lesions. Infarcted WT may demonstrate variable gross and histologic alterations that may render the diagnosis challenging, particularly during intraoperative frozen section evaluation.

In this study, we collected 11 resection specimens from 9 patients with infarcted WT. Seven patients were men and 2 were women, ranging from 49 to 85 years (mean, 69). All the patients had fine-needle aspiration before the resection. Macroscopically, the tumors were tan-white and contained soft, yellow, exudative material. The histologic findings were variable and included necrosis, ghosts of papillae, squamous metaplasia, cholesterol clefts, foamy macrophages, multinucleated giant cell reaction, necrotizing granulomas, and fibrosis. Each case predominantly demonstrated 1 or 2 of these histomorphologic features. In the permanent sections, additional sampling revealed foci of residual viable WT in 8 cases. Three cases were completely infarcted; however, they all had ghost-like papillae in which the architecture of WT was evident.

Infarcted WT may present a diagnostic challenge during intraoperative frozen section evaluation. Associated morphologic alterations may preclude a definitive diagnosis of WT and may mimic malignancy. Awareness of the gross and microscopic features associated with infarcted WT is important, particularly for accurate frozen section evaluation of these salivary gland tumors.

1. Introduction

Warthin tumor (WT, adenolymphoma; papillary cystadenoma lymphomatosum) is the second most common benign salivary gland neoplasm. The WT is almost exclusively limited to the parotid glands and the periparotid lymph nodes [1]. In the parotid, it usually is located in the tail of the gland and is multicentric in 10% to 20% of patients and bilateral in 5% to 15% [2,3]. The WT arising from minor salivary gland is very rare, with an incidence ranging from 0.1% to 1.2% [2,4]. Clinically, the tumor is cystic, painless, slowly growing, and firm to fluctuant at palpation. The WT has a higher incidence in older people with a mean age at diagnosis of 62 years (reported range of 12-92 years) and is strongly associated with smoking. Studies have shown that smokers had a 4- to 40-times greater risk than nonsmokers [5,6]. In the early literature, WT was reported to have a distinct male predilection, with a male-to-female ratio of 10:1. But more contemporary studies have shown that WT had a similar incidence in female and male, with a 1:1 ratio [7,9]. This change is likely largely due to the increased prevalence of smoking in women in the past few decades.

The pathogenesis of WT still remains unknown and controversial, although several theories have been proposed. The most widely accepted theory is that these tumors are caused by heterotropic salivary duct epithelium in the intra/paraparotid lymph nodes. By immunohistochemistry, the luminal and basal epithelial cells of WT have similar features as those of the striated duct cells and basal cells of the excretory duct of the salivary gland [10]. Stimuli including benzopyrene, arsenic, and N-nitrosoguandien from tobacco have been shown to irritate the ductal epithelial in the lymphoid tissue and result in oncocytic metaplasia and tumorigenesis [1].

Macroscopically, WT is an encapsulated, fluctuant soft tissue mass with smooth outer surfaces. Cut sections show multicystic dark brown spaces with motor oil-like fluid; papillary projections may be present. Microscopically, WT is composed of cysts and papillae arranged with distinct epithelial lining and underlying lymphoid tissue. The epithelial component has 2 layers of granular eosinophilic cells with prominent

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nucleoli (oncocytic epithelium). The luminal cells are nonciliated, tall columnar with nuclei aligned toward luminal aspect; the basal cells are round, cuboidal, or polygonal with vesicular nuclei. The lymphoid component is composed of mature lymphocytes with lymphoid follicles and germinal centers. The cystic spaces may contain thick secretions, cholesterol clefts, cellular debris, or corpora amylacea-like laminated bodies. Because of the unique and characteristic histologic features, WT is generally a rather straightforward salivary gland tumor to recognize by microscopy. Ancillary tests are almost never necessary. However, the luminal cells are positive for CK7 and epithelial membrane antigen. The lymphoid tissue contains mixed CD3+ T cells and CD20+ B cells.

In our practice, patients with a parotid mass routinely undergo diagnostic fine-needle aspiration (FNA) biopsy. Most salivary gland neoplasms as diagnosed by FNA are subsequently subject to intraoperative gross and microscopic evaluation with frozen sections before definitive surgery. At the time of intraoperative consultation, pathologists are called upon to diagnose the tumor as benign or malignant and, if possible, low grade or high grade to inform the surgical approach. Major surgical decision points include whether to perform a radical or marginal resection and whether or not to perform a lymph node dissection. Under usual circumstances, the diagnosis of WT is straightforward. But when variant histologic features are present, they may be misleading and can render the diagnosis very challenging, especially at the time of frozen section evaluation. Misdiagnosis with overinterpretation of reactive changes as malignant may cause unnecessary radical resection and lymph node dissection. For this study, we have collected and analyzed 11 cases of infarcted WT. We present the variable histologic findings and elaborate on a diagnostic approach.

2. Material and methods

We retrospectively studied 11 parotid WT resections from 9 patients who underwent preoperative FNA and resection at our institution from 2010 to 2016. All the cases were diagnosed as WT in the permanent sections with documented reactive changes including squamous metaplasia, necrosis, granuloma, fibrosis, or inflammation in the pathology reports. Clinical and demographic information was obtained from the electronic medical records. The gross descriptions were retrieved from the pathology reports. The FNA slides, frozen sections, and permanent sections were re-reviewed. All the histopathologic features were recorded.

3. Results

Seven patients were men and 2 were women. The average age was 67 years (range 49-85). Eight patients were smokers or former smokers. One patient denied history of smoking. Three patients were heavy alcohol users. Five patients did not use alcohol. One patient's alcohol history is unknown. Five patients had unilateral WTs, and all of them were on the right side. Two patients had bilateral WTs, and all of them were infarcted. One patient had WT in the right parotid and a lymphoepithelial lesion in the left parotid. The last patient had WT on the left side and pleomorphic adenoma on the right side. Three tumors were multinodular, and the remaining 8 presented as a single nodule. The average size of WT was 2.8 cm, ranging from 1.2 to 7.0 cm (Table).

Fine-needle aspiration was performed before resection in all patients. The biopsy preceded the resection specimen by variable amounts of time, ranging from 4 days up to 4 years. The FNA slides were diagnostic of WT in 7 cases and showed only cyst contents in 2 cases and inflammatory cells in 1 case, and the last case showed atypical epithelial cells in a cystic background, with the diagnostic consideration given to carcinoma.

After the FNA, 7 patients went through similar clinical courses. They developed facial pain, fluctuating swelling, and facial redness and warmth a few days after the FNA. Some patients had severe symptoms and were treated with a short course of antibiotics with some improvement; the others had mild pain and swelling that resolved spontaneously. Two patients did not have significant symptoms after FNA.

Partial parotidectomy was performed in all of these patients, and intraoperative frozen section evaluation was requested. Macroscopically, the tumors were well circumscribed, firm to rubbery, and solid, with or without a cystic component. Solid components were tan-white, and the cystic components contained tan-yellow, thick, exudative material. Some tumors had foci, which were dark brown and cystic. Microscopically, a range of histopathologic findings were identified including necrosis, ghosts of papillae, squamous metaplasia, cholesterol clefts, foamy macrophages, multinucleated giant cell reaction, necrotizing granulomas, and fibrosis (Fig. 1). Each case predominantly demonstrated 1 or 2 of these histomorphologic features. Five cases had ghosts of papillae with double layer of oncocytic cells and underlying lymphoid stroma, where the architecture of WT could still be appreciated (Fig. 1A). By immunohistochemistry, the infarcted stromal cells were diffusely positive for CD45, consistent with lymphocytes (Fig. 2A-C). Seven cases showed extensive squamous metaplasia with surrounding fibrosis, mimicking invasive squamous cell carcinoma (Fig. 1B). However, the cells had bland cytologic features with low nuclear/cytoplasm (N/C) ratios. Mitoses or large, hyperchromatic nuclei were not seen. Three cases showed epithelial-lined cysts; some of the epithelial cells had cytoplasmic vacuoles, mimicking low-grade mucoepidermoid carcinoma (Fig. 1C and D). Four cases showed prominent cholesterol clefts and multinucleated giant cell reaction (Fig. 1E). One case had marked necrotizing granulomas with central necrosis and surrounding palisading epithelioid histiocytes (Fig. 1F); Acid-Fast Bacillus and Grocott's Methenamine Silver (GMS) stains were performed and were negative for mycobacteria and fungi (Fig. 2D-F).

The rendered frozen section diagnosis was “WT” in 6 cases, “squamous-lined cysts” in 2 cases, “squamous cell carcinoma” in 1 case, “suspicious for low-grade mucoepidermoid carcinoma” in 1 case, and “chronic sialadenitis” in 1 case. The cases where WT was diagnosed contained viable foci of tumor on the frozen section slides. The case where a squamous cell carcinoma was considered fortunately did not result in any harm to the patient because the surgeon considered the frozen section interpretation to be significantly discrepant with his clinical impression. A conservative resection of the parotid tumor was performed without a neck dissection.

Adequate sampling with permanent sections identified viable foci of WT in 8 of the 11 cases. The remaining 3 cases were completely infarcted; however, they all had “ghosts” of papillae, and the overall architecture of WT could be appreciated.

Table
Characteristics of patients with infarcted WTs

Patient	1		2	3	4	5		6	7	8	9
Age	49		64	70	85	63		61	71	77	60
Sex	M		M	M	F	M		F	M	M	M
Tobacco	Yes		Yes	Yes	Yes	No		Yes	Yes	Yes	Yes
Ethanol	N/A		Yes	Yes	No	No		No	No	Yes	No
Laterality	Left	Right	Right	Right	Right	Left	Right	Right	Right	Right	Left
Size (cm)	2.0	N/A	1.2	1.5	7.0	3.5	1.8	2.5	3.5	2.3	2.5

Notes: Patient 1, left parotid had 2 WT masses, 2.0 and 1.4 cm in sizes; the patient also had a right parotid WT, which was resected and did not show infarction. Patient 2 had a left parotid lymphoepithelial lesion diagnosed by FNA. No resection was done on this lesion. Patient 5 had bilateral infarcted WTs.