



## Original Article

## Unreported Cytologic Characteristics of Oncocytes in Warthin's Tumors

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### Abstract

**Objective:** Warthin's tumors can contain markedly atypical or degenerated oncocytes; some have been mistaken for carcinoma or even metastatic carcinoma. To decrease the rate of false cytological diagnosis associated with this tumor, we tried to identify the characteristic cytologic features of Warthin's tumor oncocytes.

**Materials and Methods:** The clinical and pathologic features of Warthin's tumor were retrospectively reviewed in 45 cases from 1998 to 2003, in which fine-needle aspirates from 13 patients were examined.

**Results:** The male-to-female ratio was 21.5:1, the highest reported to our knowledge. Only 15 patients had a definite smoking history. Diff-Quik stained slides revealed cytologic characteristics not previously described, in which sheets of oncocytes with nuclei containing uniform, eccentric, and single pinpoint nucleoli were arranged in the same plane in all cases.

**Conclusion:** These cells with cytologic characteristics that have not been found in other lesions with oncocytes most likely derive from the basal layer of cuboid oncocytes in Warthin's tumor. They may improve the cytological diagnostic accuracy associated with Warthin's tumor. (*Tzu Chi Med J* 2010;22(3):137-140)

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## 1. Introduction

Fine-needle aspiration cytology is fairly accurate in the preoperative diagnosis of Warthin's tumor. However, when the lymphoid component, mucus, necrotic background and cystic fluid are minimal or absent, the tumors can be confused with oncocytosis (oncocytic metaplasia), oncocytoma, oncocytic carcinoma or

acinic cell carcinoma. In Warthin's tumors, the oncocytes can be markedly atypic or degenerated. Hence, in cytology, these tumors may be mistaken for oncocytic carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, squamous cell carcinoma (1,2), or even for metastatic squamous cell carcinoma or thyroid follicular carcinoma (3). Both oncocytic carcinoma and acinic cell carcinoma may have only bland oncocytic

or oncocyte-like cells (4,5). Acinic cell carcinoma can have lymphocytes and occasionally be cystic, mimicking Warthin's tumor (4). Finding cytologically characteristic features of oncocytic cells in Warthin's tumors could decrease the rate of false diagnoses of the above lesions in cytology.

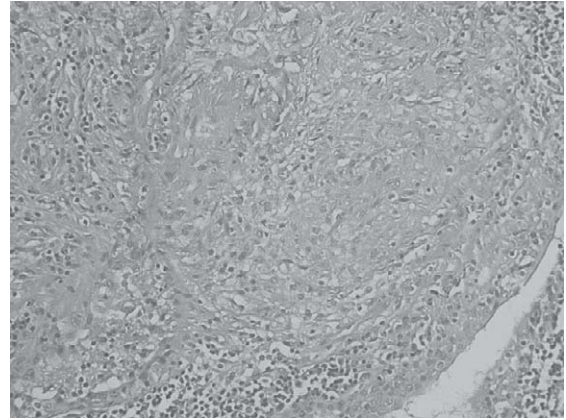
## 2. Materials and methods

The Department of Pathology database of a southern Taiwan medical center was searched for cases of Warthin's tumor (cystadenolymphoma) covering a 6-year period (1998–2003). Clinical data (sex, age, tumor location, tumor size, and smoking history) were reviewed. A positive history of smoking was defined as a more than a 5-pack-year history. Smears of fine needle aspirates stained with Papanicolaou and Diff-Quik were reviewed. Three pathologists were involved in the review.

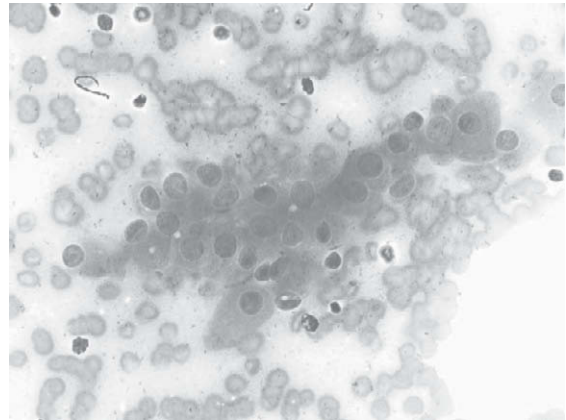
## 3. Results

Forty-five cases of Warthin's tumor were retrieved from the archives. The ratios of: male to female patients was 43/2; right side to left side disease was 20/25; parotid gland to submandibular gland tumors was 42/3; and smoking to non-smoking patients was 15/22. The smoking history was not available in eight cases. The ages of the men ranged from 35 to 83 years (mean, 60.5 years); the two female patients were 25 and 53 years old (mean, 39 years). The mean maximal tumor diameter was 3.3 cm (range, 1.5–4.5 cm). One patient had two tumor masses (2.0 cm and 2.5 cm), both in the right parotid gland. In addition to the typical features of Warthin's tumor, additional features were noted in three patients. Extensive necrosis was observed in the tumor of one patient, extensive necrosis and squamous metaplasia in another, and chronic granulomatous inflammation in the third (Fig. 1). Fine-needle aspiration histories from two of these three cases were available.

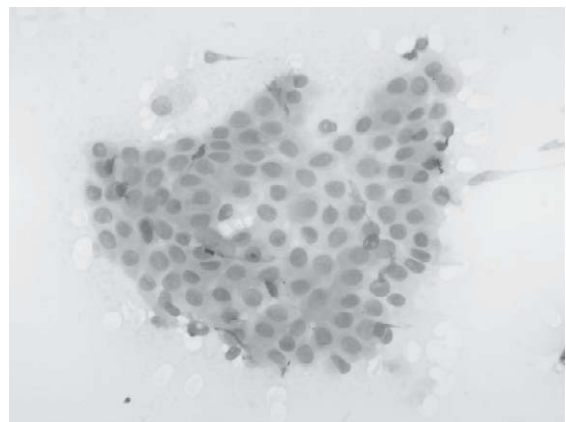
Fine-needle aspiration was performed in 13 of these 45 histologically-proven cases. In addition to the ordinary large oncocytes with abundant granular cytoplasm (Figs. 2 and 3), characteristic medium-sized oncocytes were also noted, particularly on Diff-Quik stained smears. Large or small sheets of these oncocytes with less abundant cytoplasm and nuclei containing uniform, eccentric and single pinpoint nucleoli located in the same plane were found in all cases when the focus of the microscope was adjusted (Fig. 4). These features, which we have not found in other lesions with oncocytes, have not been previously described. Ten of the 13 aspirates were diagnosed as Warthin's tumor and three as benign lesions originally.



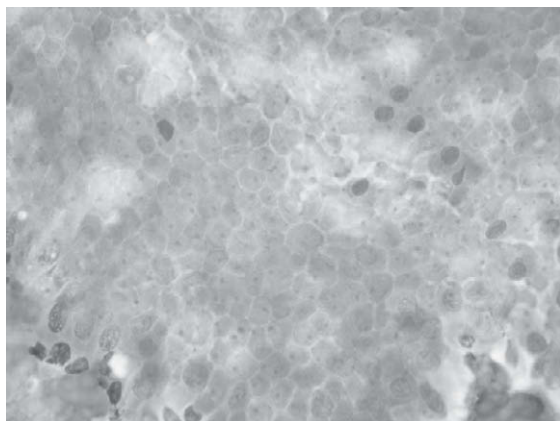
**Fig. 1 — Chronic granulomatous inflammation composed of epithelioid cells in a Warthin's tumor (hematoxylin & eosin, 400×).**



**Fig. 2 — A sheet of ordinary large oncocytes shows abundant granular cytoplasm (Diff-Quik, 400×).**



**Fig. 3 — The oncocytes have a fine granular cytoplasm (Papanicolaou stain, 400×).**



**Fig. 4 — Sheets of oncocytes contain uniform, eccentric and single pinpoint nucleoli, which are in the same plane (Diff-Quik, 400×).**

#### 4. Discussion

Smokers have an increased risk of developing Warthin's tumor (6), and smoking may provoke metaplasia of the parotid ductal epithelium (7). Most patients (85%) with Warthin's tumor smoke (8). Warthin's tumor occurs predominantly in men with a male-to-female ratio ranging from 1.6 to 5 (7,9). However, an increasing incidence among women has been noted, possibly related to an increased prevalence of smoking among women (8). The male-to-female ratio in the present study was exceedingly high (21.5:1) and, to the best of our knowledge, is the highest recorded for this disease. Twenty-two patients in this study had no smoking history; less than half (15) had a definite positive history. Further clarification is needed to determine whether other factors besides smoking predispose to this disease.

Approximately 6% of Warthin's tumors are extensively necrotic (10). It has been suggested that infarction rather than infection is the etiological factor. The pathogenesis is unknown, but it is most likely to be vascular in origin. An association with previous fine-needle aspiration has been suggested (11). The necrosis is commonly found together with squamous metaplasia. Sometimes, the metaplastic squamous cells show cytologic atypia sufficient to simulate and be misdiagnosed as squamous cell carcinoma (2) and even metastatic squamous cell carcinoma (3).

It has been reported that there is granuloma formation mimicking tuberculosis or sarcoidosis in 40% of oncocytes in Warthin's tumors (10). The pathogenesis of the granulomatous changes remains uncertain. Granuloma formation could be due to a toxic effect of the cysts' contents but probably is not a direct effect; the spread of the fluid via sinuses into the lymphatic tissue seems to be a more likely cause. It was presumed that previous fine-needle aspiration might have

some triggering effect. Granuloma formation should be included in the spectrum of secondary changes associated with Warthin's tumor. Its occurrence is not limited to metaplastic Warthin's tumors, and it can be seen in otherwise typical Warthin's tumors without any additional histologic changes (12). To avoid an incorrect diagnosis, physicians should be alert to previous fine-needle aspiration and be aware of this possible peculiar histologic change.

Warthin's tumor differs from other benign lesions. Patients with this tumor may have a somewhat increased risk of developing malignant lymphoma (13,14). Carcinomas arising from Warthin's tumors have also been reported, including mucoepidermoid carcinoma, oncocytic carcinoma, squamous cell carcinoma, and acinic cell carcinoma (15,16). Hence, it is important to differentiate Warthin's tumor from other benign lesions and from malignant lesions.

The cytologic findings in Warthin's tumor consist, in essence, of oncocytes and lymphocytes, along with the contents of the cyst (17). If aspirates of Warthin's tumors show these three components, a diagnosis is usually made without any difficulty. However, fine-needle sampling might not be representative of the whole lesion.

Although oncocytes are one of the characteristics of Warthin's tumor (18), they can also be found in aspirates in a variety of conditions affecting the salivary gland, ranging from normal glands in elderly individuals (19), reactive lesions (20), and oncocytic hyperplasia (21), to such tumors as pleomorphic adenomas and oncocytomas (benign and malignant) (19,21). The nuclei of Warthin's tumor oncocytes can be atypical (i.e., pleomorphic) and contain prominent nucleoli, and the cells can be binucleated (2,22). Nuclear pyknosis and nuclear ghosts (karyolysis) may also occur. Hence, Warthin's tumor may be mistaken for oncocytic carcinoma, acinic cell carcinoma (1,2), or even metastatic thyroid follicular carcinoma (3). Conversely, in some cases of oncocytic carcinoma, only bland oncocytic cells are seen (4). Acinic cell carcinoma can have bland oncocyte-like cells (with abundant granular cytoplasm) and lymphocytes (numerous in some cases), and can occasionally be cystic, mimicking Warthin's tumor (5). The appearance of Warthin's tumor can also be confused with that of chronic sialadenitis with oncocytosis or oncocytic metaplasia of the ducts, since oncocytes and lymphocytes are present in these conditions. Occasionally in sialadenitis, the oncocytic metaplasia can be pronounced, the chronic inflammation can be marked, and the lesion can even be cystic (20).

The cytologic features of oncocytes in Warthin's tumor are basically different from those of oncocytes or oncocyte-like cells in other salivary gland lesions. Compared with those in Warthin's tumor, the oncocytes found in the salivary glands of patients with

oncocytic metaplasia, in oncocytosis in elderly people, or in sialadenitis are smaller and cuboid. The most important clues to the diagnosis of oncocytoma are absence of a lymphoid component and background debris and the presence of oncocytic cells in sheets and groups. Oncocytes are mainly arranged in monolayered sheets in Warthin's tumor and multilayered aggregates with more variable nuclei in solid oncocytoma (17). In Pap smears, the neoplastic cells of acinic cell carcinoma can easily be confused with oncocytes, which, however, are larger, have coarser granules, and denser cytoplasm than the cells from this tumor.

In histology, the oncocytes in Warthin's tumor are mainly different from those in other related lesions, and are bilayered, with one superficial layer of columnar cells with basal-located nuclei, and one basal layer of cuboid cells. The cells with the characteristic features commonly present in smears from Warthin's tumor may be primarily derived from the superficial layer of columnar oncocytes. Therefore, they are rarely found in smears from other oncocyte-related lesions.

In our observations, the oncocytic nuclei in Warthin's tumors contained uniform, eccentric and single pinpoint nucleoli, and were arranged in the same plane in all cases, especially in Diff-Quik stain smears. Three of the cases were originally diagnosed as benign lesions. These cytological characteristic features, which we have not found in other salivary gland lesions with oncocytes or oncocyte-like cells, have not been previously reported, and most likely derive from the basal layer of cuboid oncocytes in Warthin's tumor. Hence, these characteristic features may improve the diagnostic accuracy of aspiration cytology associated with Warthin's tumor.

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