

Oncocytomas of the Submandibular Gland

A Series of 22 Cases and a Review of the Literature

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Presented at the 85th Annual Meeting of the U.S. and Canadian Academy of Pathology, Washington, DC, March 23–29, 1996.

The authors thank Ms. Robin-Anne V. Ferris, M.F.S., for her expert photography and Pamela A. Thompson, M.F.A., for her conscientious research assistance.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy, Department of the Army, or the Department of Defense.

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Received May 5, 1996; revision received July 30, 1996; accepted July 30, 1996.

BACKGROUND. Oncocytomas are benign salivary gland neoplasms that represent approximately 1.5% of all salivary gland tumors. Oncocytomas of the submandibular gland, however, are decidedly uncommon.

METHODS. Twenty-two cases of submandibular gland oncocytomas from the files of the Oral and Otolaryngic Tumor Registries of the Armed Forces Institute of Pathology were reviewed, and analysis of the histologic criteria, histochemical and immunohistochemical reactions, and ultrastructural and clinical follow-up data was performed.

RESULTS. The patients included 11 females and 11 males, age 21–88 years, with a mean age at presentation of 58.7 years. Clinically, the tumors were generally asymptomatic masses in the submandibular gland that increased in size over a period ranging from several weeks to 20 years and were occasionally associated with pain (n = 9). The tumors ranged in greatest dimension from 0.7 to 7 cm and were circumscribed to encapsulated. Histologically, the tumors were characterized by large epithelial cells with eosinophilic, granular cytoplasm. The cytoplasm stained positively with stains used to demonstrate mitochondria (phosphotungstic acid-hematoxylin, Novelli, Cresylecht violet V, and Kluver-Barrera Luxol fast blue stains). Immunohistochemical reactions demonstrated an epithelial origin (keratin and epithelial membrane antigen), whereas markers for myoepithelial derivation (S-100 protein, actin, and glial fibrillary acidic protein) were not identified. At the time this study was conducted, all patients with submandibular oncocytomas were either alive without evidence of disease or had died without evidence of recurrent disease, with surgical resection the only treatment.

CONCLUSIONS. Submandibular gland oncocytomas are rare, benign tumors. The tumor cells are filled with mitochondria, which are easily demonstrated by histochemical reactions. Complete surgical resection is adequate therapy. *Cancer* 1996; **78:2281–7**. © 1996 American Cancer Society.

KEYWORDS: submandibular gland, salivary gland, oncocytoma, oxyphilic adenoma, immunohistochemical.

Oncocytomas are benign salivary gland neoplasms that represent approximately 1.5% of all salivary gland tumors.^{1–14} Oncocytomas, comprised of oncocytes (polyhedral cells with abundant cytoplasm filled with eosinophilic granules), generally involve the parotid gland, and submandibular gland involvement is decidedly uncommon.^{2,3,8–10,13,15–23} In this article, 22 cases of submandibular gland oncocytomas are presented. The clinical information and pathologic features, including the histochemical, immunohistochemical, and ultrastructural findings, and a review of the literature are discussed.

MATERIALS AND METHODS

Twenty-two submandibular gland tumors that met the histologic criteria of oncocytoma^{1,4,10,24} were identified in the files of the Oral and

Otolaryngic Tumor Registries at the Armed Forces Institute of Pathology. Case 2 and Case 7 have been previously reported.^{16,17,22} Hematoxylin and eosin stained slides for all cases were reviewed.

Paraffin blocks or unstained slides were available in all cases. The histochemical stains performed included periodic acid-Schiff (PAS) (with and without diastase), Novelli, phosphotungstic acid-hematoxylin (PTAH), Kluver-Barrera Luxol fast blue, and Cresylecht violet V stain. The latter four stains were used to demonstrate mitochondria.

Four-micron sections were used for immunophenotypic analysis according to the avidin-biotin method of Hsu et al.²⁵ A panel of commercially available antibodies included a cytokeratin cocktail (AE1/AE3 and CK1: AE1/AE3, mouse monoclonal, 1:50 dilution [Boehringer Mannheim, Indianapolis, IN] and CK-1, mouse monoclonal, 1:200 dilution [DAKO, Carpinteria, CA]), epithelial membrane antigen (EMA) (mouse monoclonal, 1:800 dilution [DAKO]), S-100 protein (rabbit polyclonal, 1:800 dilution [Dakopatts, Glostrup, Denmark]), smooth muscle actin (SMA) (mouse monoclonal, 1:8000 dilution [Sigma Immuno Chemicals, St. Louis, MO]), and glial fibrillary acidic protein (GFAP) (rabbit polyclonal, dilution 1:2000 [DAKO]). Cytokeratin and EMA required predigestion for 3 minutes with 0.05% Protease VIII (Sigma) in a 0.1 M phosphate buffer (pH 7.8) at 37 °C. Appropriate positive and negative controls were used throughout. Electron microscopy was performed on formalin fixed, paraffin embedded tissue in one case.

RESULTS

Clinical

The patients included 11 females and 11 males (Table 1^{17,22}). Their ages ranged from 21 to 88 years, with a mean age at presentation of 58.7 years. Interestingly, the female patients had an older average age at presentation than the males (63.5 years vs. 53.9 years). Twenty-one patients were white and one was African American.

The tumors presented as masses in the submandibular gland or anterior upper neck that had increased in size over a period ranging from several weeks to 20 years. Nine patients had pain associated with the mass. There was no predilection for the right or left side because nine tumors occurred on each side (in four cases the side was not given). Follow-up ranged from 2–30 years (mean, 10.2 years). There were no recurrences or metastases in any of the patients, although in Case 13 the patient developed a second oncocytoma in the ipsilateral parotid gland 5 months later. Four years later, the patient was without evidence of a recurrence or another primary.

Pathologic Features

Grossly, the tumors were circumscribed, sometimes encapsulated by fibrous tissue of varying thickness, and confined to the submandibular gland without invasion into the salivary gland tissue or the surrounding adipose tissue. The external surface of the tumors was bosselated or lobulated and frequently had “finger-like” extensions that appeared to be invested by the same fibrous connective tissue capsule (Fig. 1). The tumors ranged in size from 0.7 to 7 cm, with an average size of 3.1 cm. Frequently demonstrating cystic degeneration (Fig. 2) with clear to brown fluid and associated hemorrhage, the excised tumors were often slightly brown to yellow. The 7 tumors that demonstrated gross cystic degeneration generally were larger tumors (average size, 4.1 cm).

Histologically, the tumor cells were arranged in solid sheets, alveoli, nests, columns, or cords that were separated by a delicate fibrovascular network. In areas, there was a pseudoacinar arrangement (Fig. 3) with a small amount of debris in the “lumen.” The cells were polyhedral to round with distinct cell borders. Abundant cytoplasm contained a varying number of fine to coarse, eosinophilic granules. In one tumor (Case 7) most of the cytoplasm was clear with a small residual rim of eosinophilic, granular material at the periphery. The cytoplasm surrounded small, round, centrally situated, pyknotic to vesicular nuclei with small to moderately large, eosinophilic, round nucleoli. Focal pleomorphism was observed, but mitotic activity, tumor necrosis, and invasive growth were not evident. Cystic structures, ranging from microscopic cysts to grossly visible cysts, often contained eosinophilic, amorphous cellular debris. A history of previous fine-needle aspiration was associated with degenerative changes (n = 6). A few lymphocytes were scattered about the periphery of the tumors, but they were never arranged in follicular structures.

Histochemistry and Immunophenotype

PTAH stain distinctly illustrated positive, small, dark-blue to black cytoplasmic granules (Fig. 4), which represented mitochondria. A PAS positive, diastase sensitive reaction confirmed the presence of glycogen. There was a strong positive reaction with the Novelli and Luxol fast blue stains (Fig. 5), whereas the Cresylecht violet reaction had the metachromatically positive granular reaction expected in mitochondria-rich cells.^{1,8,10,22–24,26–29}

All the tumors showed immunoreactivity for cytokeratin and EMA (Fig. 6). There was no reactivity documented for SMA, S-100 protein, or GFAP.

TABLE 1
Clinical Information

Case	Age (yrs)	Sex	Size (cm)	Clinical presentation	Follow-up interval
1	74	M	NS	Painless mass in upper neck, jaw region	NED, 3 yrs, LTF
2 ¹	79	M	5.5	20-year history of mass, with recent enlargement and pain	DWD, 7 yrs (MI)
3	25	M	4	Asymptomatic mass at jaw for 3 years	NED, 26 hrs, LTF
4	51	F	6	Recurrent neck swelling for 1 year	NED, 30 yrs
5	70	M	7	1-year history of intermittent swelling with tenderness	DWD, 11 yrs (shot)
6	34	M	1	3-month history of small mass, increasing in size with pain	NED, 22 yrs, LTF
7 ²²	55	F	3.4	6-month history of mass, increasing in size	NED, 15 yrs, LTF
8	56	F	2.1	Painful mass for 6–8 weeks, unresolved by antibiotics	DWD, 19 yrs (leukemia)
9	58	F	2.6	Mass with chronic pain	NED, 21 yrs
10	60	M	6	Enlarging, painful mass in upper cervical region	DWD, 2 yrs (MI)
11	54	F	5	Mass in neck	NED, 13 yrs
12	48	M	1.7	Painful mass in the neck for a number of months	NED, 13 yrs
13	59	M	2	Slowly enlarging mass for a few months	NED, 5 yrs, LTF
14	30	M	0.7	Enlarging painful mass; parotid mass 5 months later	NED, 4 yrs, LTF
15	88	F	5	Fast growing mass over a few weeks associated with pain	DWD, 9 yrs (old age)
16	50	M	1.3	Enlarging mass for 3 months	NED, 11 yrs
17	67	F	3	6-month history of painless, easily movable mass	DWD, 7 yrs (unknown)
18	87	F	1.5	Increasing size of firm nodular neck mass	NED, 8 yrs
19	21	F	2.1	6-month history of painless swelling	NED, 2 yrs, LTF
20	64	M	2.4	Enlarging painless neck mass	NED, 7 yrs
21	83	F	0.8	Enlarging mass in submandibular gland area	NED, 4 yrs, LTF
22	79	F	1.5	Mass for many years, slowly increasing in size recently	NED, 3 yrs, LTF

M: male; F: female; NS: not stated; NED: no evidence of disease; DWD: died **without** evidence of disease; LTF: lost to follow-up; MI: myocardial infarction.

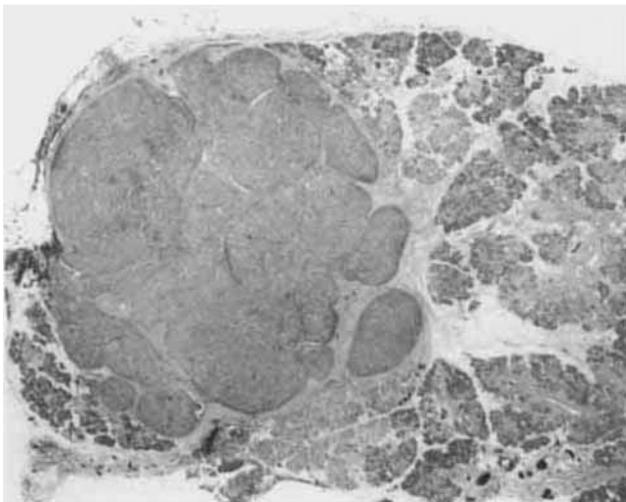


FIGURE 1. Lobulated and bosselated encapsulated oncocytoma (X7.5).

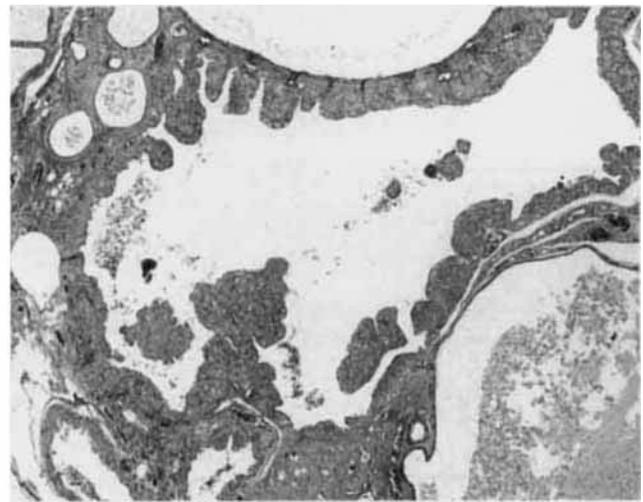


FIGURE 2. Cystic tumor with pseudopapillary formation and degenerative changes (X30).

Electron Microscopy

Electron microscopy demonstrated numerous mitochondria closely packed within the cytoplasm of the tumor cells (Fig. 7). The mitochondria were enlarged, variably shaped, and had an increased number of parallel aligned, fine, tubular, lamellar cristae. Glycogen granules were evident but not markedly increased.

DISCUSSION

Oncocytic lesions were described nearly a century ago by Schaffer when he described “granular swollen cells” in the ductal and acinar elements of salivary glands.³⁰ Although in 1927 McFarland described a tumor as an “adenoma,” without specifically calling it

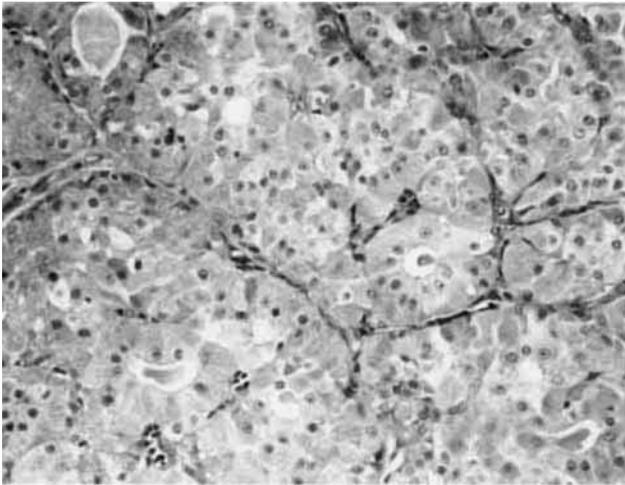


FIGURE 3. Polyhedral cells with abundant, eosinophilic, granular cytoplasm arranged in glandular groups (X300).

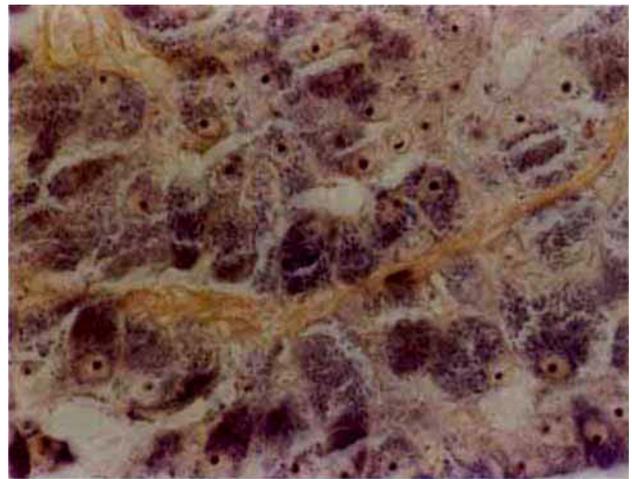


FIGURE 4. Phosphotungstic acid-hematoxylin stain with positive granules (mitochondria) (X720).

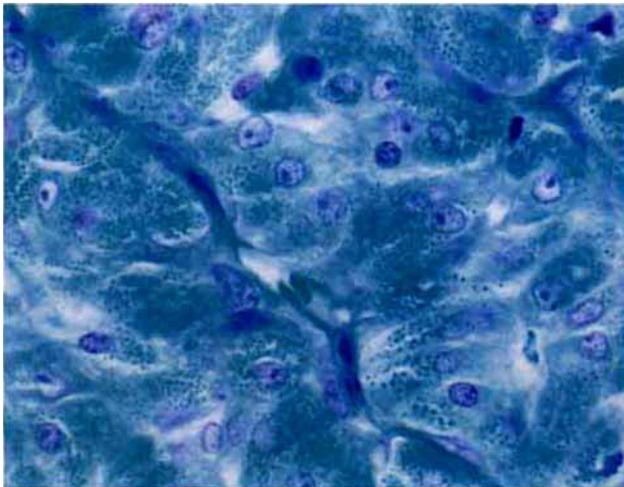


FIGURE 5. Luxol fast blue reaction demonstrating metachromatically positive granules (mitochondria) (X720).

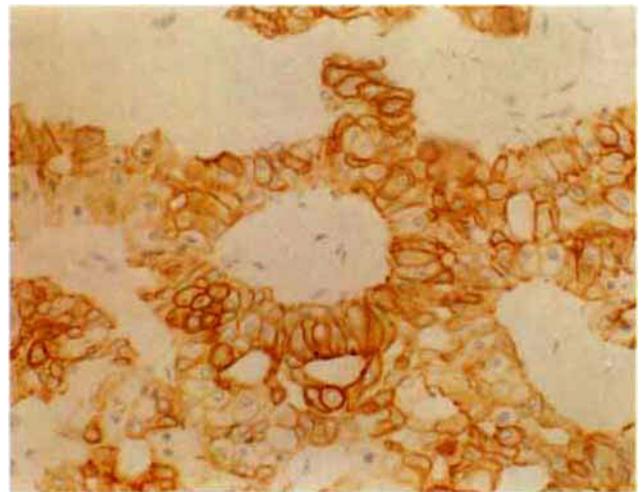


FIGURE 6. Keratin immunohistochemical reactivity of the tumor cells (X300).

an oncocytoma, the description and illustrations certainly appeared to demonstrate an oncocytoma of the parotid gland.³¹

Hamperl is considered to be the "father" of oncocytes, originally referred to as "onkocytes." He chose this word because of the Greek root word *ογκομσφαι* (onkousthai), which means "increase in bulk," swollen, enlarged, or tumor.^{10,32,33} Hamperl described oncocytes in many organs, including parotid, submaxillary, sublingual, and minor salivary glands, the thyroid, parathyroid, pituitary gland, adrenal gland, gallbladder, uterus, testicle, fallopian tube, pancreas, liver, stomach, kidney, lung, pharynx, trachea, and esopha-

gus,^{33,34} more recent publications reported oncocytes in the ovary,³⁵ lacrimal caruncle,³⁶ breast,³⁷ and thymus.³⁸ It is generally accepted that for a tumor to be called an oncocytoma, it must be comprised exclusively of oncocytes.^{1,10,24,34,39} Even though oncocytes are considered to contain abundant eosinophilic cytoplasm, one of the current study cases had clear cell changes (Case 7), which have been described in the literature.^{1,10,22,26}

There has been an active discussion in the literature as to whether oncocytomas are nodular hyperplasias or neoplasms.^{1-3,6,13,16,24,34,39-44} The large size and growth pattern of some oncocytomas, as well as the existence of malignant forms, suggest that oncocytomas are neoplasms rather than hyperplasias.

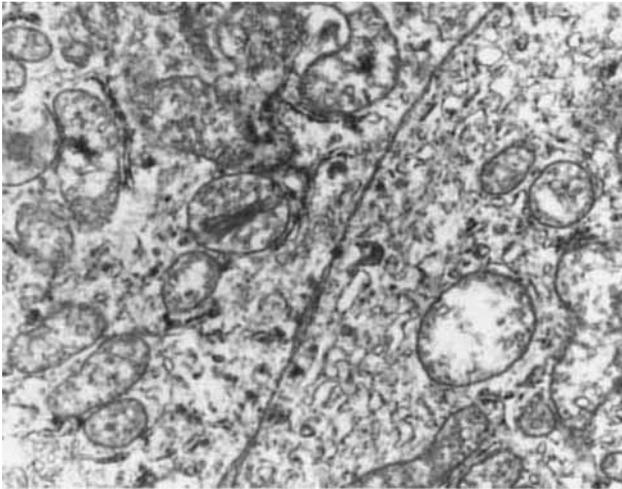


FIGURE 7. Electron microscopy demonstrating numerous mitochondria filling the cytoplasm of tumor cells (X28,000).

Oncocytes were originally thought to represent a degenerative or senescent process, especially because oncocytes can be observed in otherwise normal specimens from aging patients.^{32–34,44,45} It appears more likely they represent redifferentiation of cells with an increased, unbalanced metabolism trying to increase the output of high energy phosphate. Because mitochondria are somewhat independent organelles, another theory proposes oncocytomas may represent a neoplasm of subcellular organelles.⁴⁰ Ultrastructurally, oncocytes demonstrate mitochondrial hyperplasia with marked variability, including bizarre forms.^{1,7,21,28,46–48} The mitochondria may be angulated, semicircular, ovoid, or bulbous with closely packed central sheaves of lamellar cristae. Electron dense glycogen deposits are observed both within the cytoplasm as well as within the mitochondrial substructure. Dividing mitochondria were also noted. The fine structural features suggest a mitochondrial enzyme deficiency or alteration,^{21,46,49} which has also been demonstrated in mitochondrial enzyme studies.^{46,49} Although an increase in mitochondria has been associated with increased activity, there has been no documented specific functionality or secretion for salivary gland oncocytomas.^{6,21,29}

The first submandibular oncocytoma was reported in 1875 by DuPlay.¹⁵ There have been a number of single case reports and small series of submandibular gland oncocytomas in the literature since that time.^{2,3,8–10,13,16–23} A number of these cases have been reported more than once.^{2,3,10,16,17,22}

The clinical, histologic, histochemical, and immunophenotype data from the cases reported here conform to that in the literature. The tumor generally oc-

curs in an older age group (mean age, 58.7 years), with an equal sex predilection. Although certain patients presented with pain or tenderness ($n = 9$), the main presentation was an asymptomatic, slowly enlarging mass present over a period ranging from several weeks to many years.

There are no definitive etiologic factors for this tumor, although there has been an association with radiation in some reports.⁸

The tumors are generally circumscribed to encapsulated, although there was a lobular or bosselated growth pattern. Many reports in the literature describe multinodular,^{1,13,42,50} multifocal, and bilateral oncocytomas.^{6,8,11,13,24,42,43,50–52} Therefore, it can be difficult to discern whether a second tumor represents a new focus or recurrence of a previous tumor. One of the current study cases (Case 13) had a second oncocytoma develop in the ipsilateral parotid gland without any connection between the two tumors.

Areas of oncocytic metaplasia can often be identified surrounding oncocytomas.^{8,13,14,22,39,40,42,44,50,51,53} It appears likely that there is a spectrum of oncocytic changes that include focal hyperplasia, diffuse hyperplasia (oncocytosis), and oncocytoma.^{13,14,22,24,39,40,42,44,50,53}

Cystic degeneration, as present in some of the current study cases, has also been noted in the literature. Two possible etiologies for this are considered. Previous fine-needle aspiration is probably a factor in some cases.^{2,45,54} In addition, tumor cells that contain numerous mitochondria probably have a high oxygen tension requirement that the vascular supply may not be able to support. Oxyphilic tumors in other organs have also demonstrated a tendency toward cystic degeneration.

Complete surgical excision is recommended for all submandibular gland lesions. There have been rare examples of malignant submandibular gland oncocytic tumors,^{8,52,55} and the criteria for malignancy include capsular invasion, destructive growth, necrosis, vascular or neural invasion, lymph node and distant metastases, mitotic figures, binucleated cells, increased pleomorphism, and prominent nucleoli.^{8,24,52,55} None of the current study cases demonstrated any of these features, and long term follow-up demonstrated no recurrences or metastases.

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