Diagnosis of Salivary Gland Tumors

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The oral cavity and upper digestive tract are bathed by 1,000 to 1,500 cc. of saliva per day, providing the lubrication necessary for speech and swallowing. Some of this secretion is contributed by three large paired "major salivary glands": parotid, submaxillary and sublingual. In addition, hundreds of small glands in the submucosa of the oral and nasal cavities, paranasal sinuses, lips, tongue, hard and soft palate, pharynx and larynx constitute the "silent majority," supplying a substantial portion of the total saliva. These "minor salivary glands" histologically resemble the larger paired glands and develop from buds or oral ectoderm; they are subject to the same pathologic processes.

The nature of salivary secretion varies from the copious serous saliva of the parotid to the predominantly mucoid saliva of the sublingual, with the submaxillary glands yielding a mixed but mostly serous saliva. The minor salivary glands of the intraoral cavity produce a mixed mucous and serous secretion, whereas the glands of the pharynx and extrinsic larynx secrete a more mucoid fluid. This diversity of secretion no doubt accounts for the histologic spectrum of tumors characteristic of the major and minor salivary glands.

Indeed, salivary tissue gives rise to a more diverse range of lesions than any other organ. Almost all salivary tumors are epithelial in origin—either acinar or ductal. In addition, many benign lesions arising from interstitial tissue such as fibromas, lipomas, cysts, lymphangiomas, hemangiomas and neurofibromas are found in the salivary glands, especially the parotid. Common benign and malignant salivary gland tumors and their relative incidence are listed in Table 1.1

The incidence of cancer in the salivary glands is not proportionate to the amount of tissue present. In fact, it is the reverse: the smaller the gland, the greater the likelihood that a tumor will be malignant. For example, the incidence of cancer in the parotid gland is 25 percent; in the submaxillary gland, 50 percent; and in the minor salivary glands, approximately 75 to 80 percent. Tumors of the sublingual gland are rare, but almost all are malignant.

Clinical Recognition

Salivary tumors are usually plainly evident on careful physical examination. The chief pitfall in diagnosis is not recognizing that a tumor is of salivary gland origin.
The typical parotid tumor found below the lobule of the ear and overlying the angle of the mandible presents little diagnostic challenge. Some exceptions include lesions in peripheral tissues which appear to be separate from the body of the parotid. Failure to diagnose these lesions as salivary in nature, and attempts to excise them in the office under local anesthesia, often result in tumor recurrence or facial nerve injury. Sialography is not helpful in the diagnosis, and it is wise to suspect all lateral subcutaneous facial masses as parotid in origin. In addition, lesions in the tail of the parotid, such as Warthin's tumor, may be easily mistaken for upper cervical lymph nodes. Also, it should be remembered that tumors in the deep portion of the parotid, beneath the facial nerve, may present as retromandibular or pharyngeal submucosal masses which are entirely intraoral, without any obvious enlargement of the parotid.

The diagnosis of submaxillary tumors is generally not difficult, nor is the distinction between cancer and infection. Clinical evaluation, including the presence of pain characteristic of inflammatory disease, and sialography usually clearly point to the diagnosis. Lymph nodes can be readily distinguished from submaxillary gland enlargement by "rolling out" the nodes from under the mandible while the patient's head is flexed.

Submucosal nodules in the hard and
soft palate and intraoral surfaces are most likely to be of minor salivary gland origin; because of the high incidence of cancer, these lesions should be treated with respect. Minor salivary gland tumors must always be considered in the differential diagnosis of masses found at the base of the tongue, extrinsic larynx or paranasal sinuses.

Biopsy

Frozen section is the biopsy method of choice in the management of parotid and submaxillary tumors in all but unusual situations. A clean and unspoiled operative field is presented, eliminating the delay and possible tumor dissemination associated with a preoperative open biopsy.

Needle biopsy helps the physician decide between surgery or medical management and offers a valuable alternative to open biopsy. It also eliminates the need for surgery in patients with such conditions as Sjögren’s syndrome, sialadenitis, sarcoidosis, tuberculosis, lymphoma or an inflammatory disease. Of course, a negative biopsy is never accepted as a final diagnosis. If a tumor is suspected but cannot be confirmed, surgical excision and frozen section should be performed.

Excisional biopsy is the preferred procedure when enlargements of the minor salivary glands are small and easily accessible. If the tumor is benign, no more need be done. If the tumor is malignant, large and inaccessible such as the base of the tongue, the antrum or the hard palate, a carefully placed open biopsy, sometimes done by punch, helps in planning a future operative procedure. A methodical approach may reduce the high local recurrence rate noted in malignant minor salivary gland tumors.

Benign Salivary Gland Tumors

Mixed Tumor

Mixed tumors constitute about 85 percent of all benign salivary lesions. Minck introduced the term in 1874 to denote the epithelial and mesenchymal origin of mixed tumors; today, however, it is almost universally accepted that they are only of epithelial origin. Even cartilaginous material found in these lesions has been identified as mucins of epithelial origin. It is suggested that myoepithelial cells, undergoing metaplastic change, have the capacity to act as facultative chondrocytes, elaborating a matrix of mesenchymal components similar to hyaline cartilage.

Mixed tumors have elicited great interest over the years. They fascinate the pathologist because of their bizarre and unusual array of histologic components, including epithelial, chondroid, myxomatous and hyalinized mesenchymal elements. They frustrate and challenge the surgeon because simple excision of these benign tumors has resulted in a high rate of recurrence, often with multiple seeding. In the past, mixed tumors, particularly of the parotid, were shelled
or spooned out to avoid injury to the facial nerve; multiple recurrent tumors usually developed. In 1943 McFarland advised watchful waiting as the treatment of choice for these "mysterious tumors." 5

Because of a marked tendency to recur, mixed tumors were thought to be multicentric in origin. There is little evidence to support this view. 6 In a study of 500 cases, Foote and Frazell found "... not a single example of multicentricity; in every case the mass was solitary." 7 In contrast, recurrent mixed tumors were characterized as "poorly defined aggregations of multiple nodules." 8 Tiny excrescences on the surface projected beyond the main body of the tumor through a thin and often incomplete capsule; what appeared to be a separate focus was actually an extension of the tumor itself. Thus the very capsule, which facilitates surgical enucleation, traps tumor buds and leaves behind the seeds of future, frequently multiple recurrences.

It was also thought that highly cellular mixed tumors had a higher recurrence rate. Again, this has not been proven; Foote and Frazell 9 and Eneroth 10 found no significant difference in the recurrence rate between tumors with high and poor cellularity. Thus, the 30 percent recurrence rate of mixed tumors treated by enucleation must be accepted as the result of seeding at original surgery. As enucleation and simple excision were replaced by en bloc excision of the tumors, such recurrences have become rare.

Clinically, mixed tumors are asymptomatic and slow growing. Although they can reach enormous size in the parotid, they do not invade the facial nerve or infiltrate the skin.

Papillary Cystadenoma Lymphomatosum (Warthin's Tumor)

Warthin's tumor accounts for about 10 percent of all benign salivary lesions. The histologic origin is still debated; it is proposed, however, that the tumor evolves from heterotopic salivary epithelium within the lymph nodes.

Warthin's tumor develops almost exclusively in the parotid gland and rarely in the submaxillary glands, lacrimal glands and minor salivary glands of the palate. The characteristic soft, almost fluctuant, consistency of this tumor, its frequent location in the tail of the parotid (sometimes entirely separated from the main body of the gland), its tendency to bilaterality, its preponderance in men in a ratio of 9:1 and its infrequent occurrence in Negroes often enable the informed observer to make the diagnosis on physical examination. It has recently been reported that Warthin's tumor, alone among salivary tumors, will concentrate technetium-99m, making preoperative identification possible. 11 The tumor is frequently multicentric in origin and tends to recur after local excision. Malignant transformation is unknown.
Oxyphilic Adenoma (Oncocytoma)

Oncocytomas are unilateral, slow-growing, benign solid tumors which arise from duct epithelium and are almost always found in the parotid gland. They are unicentric, encapsulated and consist of distinctive large cells with eosinophilic cytoplasm, often resembling those of the liver and adrenal cortex. Oncocytomas often mimic mixed tumors in clinical presentation. Recurrence after adequate excision is unusual as is the development of cancer.

Benign Lymphoepithelial Lesions

Occasionally a parotid tumor contains lymphoid infiltration and epithelial proliferation. Godwin described a group of such cases and stressed the benign nature of the process. Benign lymphoepithelial lesions may present as individual nodules, scattered foci or they may diffusely infiltrate the parotid. It has been postulated that these lesions represent a stage in the development of Sjögren's syndrome.

Malignant Salivary Gland Tumors

There are three major classifications of malignant salivary gland tumors: mucoepidermoid carcinoma, malignant mixed tumors and adenocarcinoma. (Table 2.) These occur with roughly equal frequency and comprise 80 to 90 percent of salivary gland cancers. Squamous cell carcinomas comprise an additional five to 10 percent.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinomas account for a third of all malignant salivary gland tumors. These circumscribed, nonencapsulated lesions arise from salivary duct epithelium and, as the name implies, contain both mucus-secreting and epidermoid cells, as well as intermediate types of basal or nonmucus-secreting cells. Sixty to 70 percent occur in the parotid; 15 to 20 percent in the minor salivary glands of the oral cavity, often in the hard and soft palate; and 10 percent in the submaxillary gland.

Most patients with mucoepidermoid carcinoma have an excellent prognosis with a five-year survival rate approaching 90 percent. However, the remaining 10 percent of patients have a highly malignant disease, and a much less favorable prognosis. In an attempt to predict which tumors would follow the more aggressive course, Stewart, Foote and Becker divided mucoepidermoid tumors into "high" and "low" grade groups. Epidermoid and intermediate cells predominate in highly aggressive tumors; mucus-secreting and intermediate cells are found in low-grade tumors. Two-thirds of patients with high-grade tumors develop regional node metastases; a third have distant metastases over a five-year period. In contrast, patients with low-grade tumors follow a clinical course similar to that of benign mixed tumors. In a series of 100 cases from the Mayo Clinic followed more than five years...
years (median time: 12 years), there was only one death in the 86 patients with low-grade tumors, while there were eight deaths in the 14 patients with high-grade tumors. Although most surgeons find a definite correlation between histologic grade and the clinical course of mucoepidermoid tumors, a low-grade appearance does not guarantee a nonaggressive course.

Malignant Mixed Tumor

Malignant mixed tumors comprise 20 to 30 percent of salivary gland cancers and occur twice as often in women as in men. Most involve the parotid gland, fewer the submaxillary gland and the minor salivary glands.

The question of whether malignant mixed tumors are cancerous from onset, or whether benign mixed tumors un-

### Table 2. Malignant Salivary Gland Tumors

| Mucopidermoid Tumors | Characteristics |
|-----------------------|-----------------|
| Circumscribed, nonencapsulated lesions arising from salivary duct epithelium |
| 60-70% located in the parotid; 15-20% in the minor salivary glands (often in the hard and soft palate); 10% in the submaxillary glands |
| A five-year survival rate approaching 90% |

| Malignant Mixed Tumors | Characteristics |
|------------------------|-----------------|
| Most involve the parotid, fewer the submaxillary gland and minor salivary glands |
| Probably evolve from benign mixed lesions |
| An excellent prognosis for focal cancers; poor prognosis in extensive or recurrent cancers |

| Adenocarcinomas: Adenocystic Carcinomas (Cylindromas) | Characteristics |
|-------------------------------------------------------|-----------------|
| Found in submaxillary and minor salivary glands |
| Probably originate from canaliculi and intercalated ducts of the peripheral duct systems |
| Five-year cure rate of 75%; 10- to 20-year cure rate drops to 15-20% |

| Acinic Cell Carcinomas | Characteristics |
|------------------------|-----------------|
| Peculiar to the parotid (rarely occur in submaxillary and minor salivary glands) |
| 70% occur in women |
| Five-year cure rate of 90%; 25-year cure rate of 50% |
Adenocarcinoma

Adenocarcinomas constitute approximately one-third of all malignant salivary tumors, and may present in several forms, each of which has a unique histologic appearance and clinical course.

Adenocystic Carcinoma (Cylindroma)

Cylindromas can occur in all salivary glands but are found most often in the submaxillary and minor salivary glands. Indeed, these unusual tumors are the most frequently encountered cancer in the minor salivary glands.

The term cylindroma graphically portrays the structural pattern of these tumors; the enclosure of mucin or hyaline cylinders within epithelial islands. Often the small, darkly stained cells appear as anastomosing cords lying in a mucoid or hyaline stroma. Although usually classified as adenocarcinomas, cylindromas most probably originate from the canaliculi and intercalated ducts of the peripheral duct system.

The clinical presentation of adenocystic carcinoma mimics that of a mixed tumor, which is often the preoperative diagnosis. Local pain is a prominent feature in 50 percent of patients. The presence of facial paralysis is an ominous sign. In a review of 35 patients with parotid adenocystic carcinoma, all 10 with facial nerve paresis died within eight years. These cancers are not encapsulated and are deceptively slow growing. Failure to control the disease locally occurs in more than half the cases. Adenocystic carcinoma tends to infiltrate the perineural spaces of lymphatic vessels; lung, bone, visceral and regional lymph node metastases are common in the late stages.

While most investigators have not been able to correlate the microscopic appearance of adenocystic carcinoma with length of survival, some suggest that the clinical course is more rapid and fulminant in tumors with a solid histologic pattern of a larger cell type with areas of necrosis. The five-year cure rate is approximately 75 percent; the 10- to 20-year rate drops to 15-20 percent.

Acinic Cell Carcinoma

Acinic cell carcinomas appear to be peculiar to the parotid gland. Only five percent occur in the submaxillary gland, and even fewer in the minor salivary glands. Seventy percent of acinic cell tumors are found in women.

The clinical presentation of acinic cell carcinomas may also mimic mixed salivary tumors. These low-grade carcinomas recur locally and produce distant metastases; regional nodes are infrequently involved. In one study the deter-
minate five-year cure rate was 90 percent; it was 50 percent in 25 years. 20

Other forms of adenocarcinomas are classified according to histologic appearance, including solid undifferentiated, anaplastic, trabecular and mucous-cell carcinomas. These tumors are highly aggressive with a marked tendency for local recurrence, as well as lung and bone metastasis. The five-year survival rate is only 30 percent.

Squamous Carcinoma

Squamous carcinomas comprise perhaps five to 10 percent of all salivary tumors and occur most frequently in the parotid and submaxillary glands. Whether these tumors represent de novo squamous carcinomas of ductal origin or a mucopidermoid carcinoma in which the epidermoid element has become predominant is subject for speculation. Epidermoid carcinomas arising elsewhere in the body may also lodge in the parotid gland and may be erroneously interpreted as salivary in origin.

Squamous carcinoma of the salivary glands is a rapidly progressing disease; 50 percent of the patients reviewed in one study died within a year. 21 The five-year survival rate is 10 to 20 percent.

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