Rev Esp Patol 1999; Vol. 32, N~ 3: 43 1-435

Short Course 9

Update on salivary gland tumors

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Head and neck pathology incorporates aspects of anatomical and surgical pathology, otorhinolaryngology, as well as oral surgery, medicine and pathology. Over the past few years immunohistochemistry and molecular biology have contributed to greater understanding in this area, especially in the classification and prognostic evaluation of salivary gland tumors. Therefore, this short course will review some practical diagnostic problems and give insights into the relevance of molecular biology in this field. The main topics will be:

- Criteria for the diagnosis of malignancy in pleomorphic adenoma.
- Characteristics to distinguish between the different types of clear cell tumors.
- Oncocytic lesions and squamous differentiation in salivary gland tumors.
- The progression of low-grade carcinomas to high-grade neoplasms.
- Relevant recent advances in molecular biology and immunohistochemistry.

References

- Dardick I. Color Atlas/text of Salivary Gland Tumor Pathology. Igaku-Shoin Med Pubi, New York 1996.
- Ellis GL, Auclair PL, Gnepp DR. Surgical Pathology of the salivary Glands. WB Saunders, Philadelphia 1991.
- Ellis GL, Auclair PL. Atlas of Tumor Pathology: Third series, Fascicle 17 Tumors of the Salivary Glands. AFIP, Washington, DC, 1996.
- Seitert G. Pathologie der Speicheldriisen. 2nd ed. Springer-Verlag, Berlin 1996.
- Seitert G, Sobin LH. World Health Organization International Histological Classification of Tumours: Histological Typing of Salivary Gland Tumours. 2nd ed. Springer-Verlag, Berlin 1991.

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Malignancy in pleomorphic adenoma

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Introduction

Pleomorphic adenoma (PA) (benign mixed tumor) of the salivary glands is clinically and pathologically benign but the concept of malignancy in it is much more complex than appears at first sight. The multinodular and pseudoinfiltrative growth pattern can make complete surgical excision difficult and can lead to recurrences. Microscopically, benign PA may display hypercellularity, cellular atypia, necrosis and capsular and vascular invasion (1), whereas there are PAs that contain genuine histological evidence of malignancy, either *in situ* or minimally invasive, but which behave in a benign fashion after excision.

Incidence

The frequency of malignancy in a PA *(i.e.,* malignant mixed tumor) varies in different surveys (2, 3); the average of several large series was 3.6% of all salivary tumors, 11.7% of malignancies and 6.2% of PAs (range 1.9-23.3%).

Forms of malignancy in a pleomorohic adenoma

Three entities are recognized (in order of frequency): carcinoma in pleomorphic adenoma, carcinosarcoma (true malignant mixed tumor) and metastasizing pleomorphic adenoma.

Carcinoma in a oleomorphic adenoma

This typically presents with a long history of a salivary gland nodule that suddenly gets bigger. The incidence of malignancy increases with the length of history of the PA but the time interval can still be short (2). The main histological finding is the simultaneous presence of a benign PA and a carcinoma. The proportion of the malignant component varies from minute foci to major parts of the PA. The most common types of carcinoma are poorly differentiated adenocarcinoma and undifferentiated carcinoma [many ot which were found to be myoepithelial by K. Nagao *et al.* (2), and also by us in Milan (4)], but others can occur, *e.g.,* squamous, mucoepidermoid, polymorphous low grade adenocarcinoma and ductal carcinoma (3).

The criteria for a diagnosis of malignancy are capsular invasion, infiltration into neighboring tissues, vascular involvement and abnormal mitotic figures (2). Minor findings are the presence of hyalinization, necrosis and increased mitotic activity, with occasional transitional changes made up of cells sharing features intermediate between frank malignancy and PA. A recent practical development may be the use of the proliferation marker Ki-67 (MIBi); carcinoma within a PA usually shows a markedly increased MIBi index.

Once a carcinoma has been identified in a PA, it is important to assess its relationship to the capsule of the PA. If the malignant element has invaded into the capsule but does not extend beyond it, the prognosis should be similar to that of ordinary benign PA – this is minimal capsular invasion. This is the case even when the malignant component is an aggressive neoplasm, such as salivary duct carcinoma, provided there is no extension through the capsule (1). However, there are practical problems when the capsule is incomplete or inadequately sampled. When a carcinoma invades beyond the capsule, its extent is important: Tortoledo *et al.* (3) found that

none of the patients whose tumor penetrated 6 mm or less beyond the capsule died of the disease but that all patients with invasion of 8 mm or more had a fatal outcome.

Carcinosarcoma in a eleomorehic adenoma (true malignant mixed tumor)

Carcinosarcoma is exceedingly rare (5). Many arise in a preexisting PA but they can also develop *de novo.* Microscopy shows that it is a biphasic tumor, composed of epithelial and mesenchymal components. The epithelial component is generally a poorly differentiated (adeno)carcinoma or salivary duct carcktoma. The mesenchymal element is usually a chondrosarcoma but osteogenic sarcoma, fibrosarcoma, malignant fibrous histiocytoma and pleomorphic rhabdomyosarcoma have also been described (3). It has still not been resolved whether myoepithelial cells have a role in the genesis of the multiple tissue differentiation; some immunocytochemical results support a myoepithelial histogenesis while others do not. In analogous neoplasms in the breast, there is experimental evidence that the sarcomatous elements derive from myoepithelial cells and the carcinoma from the epithelial cells.

Metastasizing oleomorohic adenoma

Metastasizing pleomorphic adenoma (MPA) (6) is histologically indistinguishable from benign PA but it metastasizes widely to distant sites and can kill the patient. It remains histologically "benign" in the primary site, local recurrences and metastatic deposits. The reported cases (<100) shared several similarities, such as long time intervals (up to 50 years) between the primary tumor and metastases, and simultaneous local recurrences and distant metastases. The recurrences are usually multiple, and although their morphology and that of the metastases are almost identical, they seem to play an important role in the genesis of systemic spread. This suggests that surgical manipulation may favor vascular implantation or invasion eventually leading to metastases but in many cases of MPA it was not possible histologically to demonstrate actual vascular permeation.

References

1. Brandwejn M, Huvos AG, Oardick I et al. *Noninvasive and minimally invasive carcinoma ex mixed tumor A olinicopathologic and ploidy Study of 12 patients with major salivary tumors of low (or no?) malignant potential.* Oral Surg Oral Med Oral Pathol 1996; 81: 665-664.
2. *Nagao* K, Matauzaki O, Saiga H at al. *Histopathologic studies on carcinoma in pleomorphic adenoma of the parotid gland.* Cancer 1981; 48: 113-121.
3. Tortoledo ME, Luna MA, Batsakis JO. *Carcinomas ex pleomorphic adenoma and malignant mixed tumors: Histomorphologic indexes.* Arch Otolaryngol 1984; 110: 172-1 76.
4. Eli Palms S. Guzzo M. *Malignant myoepithelioma of salivary glands: Clinicopathologic features of ten cases.* Virchow Archiv A Pathol Anat 1993; 423: 389-396.
5. Gnepp OR. *Malignant mixed tumors of salivary glands: A review* Pathol Annual 1993; 28(ptl): 279-328.
6. Wenig BM, Hitchcock CL, Ellis GL at al. *Metastasizing mixed tumor of salivary glands: A clinicopathologic and flow cytometrc analysis.* Am J Surg Pathol 1992; 16: 845-858.

Clear cell tumors

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Introduction

The unqualified term "clear cell tumor" (or carcinoma) is not a diagnostic category but a description of one of several neoplasms and tumor-like lesions of the salivary glands histologically characterized by a significant population of cells possessing clear cytoplasm. In Exeter they comprised 2.3% (14/608) of all salivary tumors over the last 21 years. Most salivary tumors can be diagnosed purely on hematoxylin and eosin morphology but clear cell tumors are an exception and generally require special stains, immunohistochemistry and even electron microscopy.

Table 1. Classification of clear cell tumors of the salivary glands.

Benign
Pleomorphic adenoma, myoepithelioma, sebaceous adenoma, oncocytoma and oncocytic hyperplasia (MNOH)
Malignant, primary
a) Carcinomas not usually characterized by clear cells, but with rare clear cell variants; *e.g.,* mucoepidermoid and acinic cell carcinomas
b) Carcinomas usually characterized by clear cells
i) Dimorphic epithelial-myoepithelial carcinoma
ii) Monomorphic hyalinizing clear cell carcinoma
clear cell malignant myoepithelioma (myoepithelial carcinoma)
Malignant metastatic
Carcinomas, especially kidney, thyroid. Also melanoma
MNOH = multifocal nodular oncocytic hyperplasia

Individual tumor tyDes

Pie omorohic adenoma and benign mygevithelioma

These are variants of the same tumor but only rarely are clear cells (usually myoepithelial) a significant component. Generally, there are areas of typical pleomorphic adenoma or other forms of myoepithelial cells.

Oncocvtoma and multifocal nodular oncocytic hyperolasia

Oncocytes sometimes have clear cytoplasm. This is often the case in multifocal nodular oncocytic hyperplasia, which may be bilateral. The cytoplasm shows granular positivity with phosphotungstic acid hematoxylin (PTAH) and antimitochondrial antibody, and large numbers of mitochondria are seen on ultrastructural examination.

Sebaceous adenoma and carcinoma

These are especially rare and resemble sebaceous neoplasms of the skin. Their cytoplasm has a "foamy" appearance due to lipid. The carcinomas may also include basaloid areas.

Acinic cell carcinoma

The clear cell variant is uncommon (6% in one large series), and even then they are never pure, and cells with the characteristic periodic acid-Schiff-positive and diastase-resistant cytoplasmic zymogen granules are also present. Their behavior is the same as that of other acinic cell carcinomas.

Mucoevidermoid carcinoma

The clear cell variant is generally low grade; true epidermoid and mucous cells may be few.

Adenoid cystic carcinoma

Clear cells are sometimes seen, usually due to myoepithelial cell participation.