Necrotizing sialometaplasia

Necrotizing sialometaplasia is a benign self-limiting ulcer or swelling, typically on the palate, thought to be due to salivary gland infarction resulting from ischemic injury. Microscopic examination shows lobular necrosis of the minor glands with regenerative hyperplasia of the adjacent salivary ducts and pseudoepitheliomatous hyperplasia of the overlying epithelium, mimicking squamous or mucoepidermoid carcinoma.

Sauamous metaplasia in salivary aland tumors

Squamous metaplasia (with or without keratin pearls) is common in pleomorphic adenomas, particularly of the lip. It also occurs in Warthin's tumors that have undergone extensive necrosis, probably due to infarction, but possibly also following tine needle aspiration. Squamous metaplasia can occasionally be seen in otherwise typical adenoid cystic carcinomas.

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma has a variety of cell types: squamous, mucous, intermediate and clear. Low-grade tumors tend to be largely cystic with many mucous cells and scanty others. The squamous cells show little pleomorphism and few mitoses; dyskeratosis and keratinization are uncommon. High-grade tumors tend to be solid, have many fewer mucous cells, and often the squamous element shows cellular pleomorphism, neural involvement and necrosis.

Sauamous cell carcinoma

This uncommon primary salivary tumor is often poorly differentiated and carries a bad prognosis (5). It is important to distinguish it from metastatic squamous carcinoma. All such tumors should be stained for mucus to exclude mucoepidermoid carcinoma.

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Progression to low-grade and high-grade salivary gland tumors

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Salivary gland neoplasms have two major pathways of biological progression: firstly, benign tumors that evolve to malignancy of either low or high grade and secondly, low-grade carcinomas that undergo transformation to high-grade lesions.

Pleomorphic adenoma is the commonest benign salivary tumor in which a carcinomatous component can arise but myoepitheliomas and basal cell adenomas may also become malignant, usually with features of low-grade histology. Two clinical settings are claimed to be more frequently associated with such progression: a long-standing lesion and also when there have been multiple recurrences of a benign tumor, eventually associated with incomplete excision or capsule disruption.

Low-grade to high-grade progression has been documented in anecdotal cases of low-grade salivary carcinomas either with or without myoepithelial differentiation. The development of adenocarcinomatous or undifferentiated components in an otherwise typical acinic cell carcinoma is exceedingly rare and such transformation is associated with a less favorable outcome of the disease, *i.e.,* frequent recurrences. Stanley *et al.* (1) coined the term "dedifferentiated acinic cell carcinoma" to designate such cases. The glandular component has no specific histological features, displaying a tubuloductal arrangement of an adenocarcinoma NOS, frequently with abundant sclerotic stroma. This concept of dedifferentiation is controversial and some authors do not accept that an adenocarcinomatous or undifferentiated component in an otherwise typical acinic cell carcinoma is a sequential event in the process of neoplastic progression.

Epithelial-myoepithelial carcinoma has also been reported to be associated with an anaplastic component (2). Simpson *etal.* (3) described dedifferentiated areas in the recurrence of their case 3. In a series of 22 such carcinomas, Fonseca and Soares (4) found nuclear atypia of more than 20% of the tumor cells to be a criterion that worsens the prognosis.

The processes underlying dedifferentiation of salivary gland neoplasms remain to be established and no identified factors have been implicated. As a rule, the vast majority of well-differentiated low-grade tumors do not undergo such transformation. Accumulation of genetic mutations underlying either oncogene activation or loss of tumor suppressor gene activity are thought to be involved in the stepwise progression from adenoma to carcinoma exadenoma and eventually from low-grade *vs.* high-grade carcinoma areas. Activation of *c-myc* and *ras* p21 protooncogenes and p53 mutations were demonstrated to play important roles in the malignant transformation of pleomorphic adenomas (5).

It seems that c-erbB-2 is not involved in the genesis of salivary gland neoplasms with evidence of myoepithelial lineage, but in contrast, it is overtly expressed by high-grade carcinomas (5), suggesting distinct molecular mechanisms in salivary gland carcinogenesis. There is some variation in the literature regarding the frequency of p53 alterations but it is accepted that progression to high-grade malignancy is related to p53 mutations and alterations of the growth factor receptor encoded by c-erbB-2. It is also known that DNA aneuploidy and chromosomal aneusomy characterizes tumors with aggressive features, which also indicate their contribution to the low-grade cases that evolve to high-grade carcinomas. Alterations at 8q and 6q regions suggest an association between these events and the development and/or progression to carcinoma in pleomorphic adenoma. Likewise, it appears that alterations on the short arm of chromosome 17 may represent an event related to tumor progression.

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Molecular biology and immunohistochemistry

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Several salivary tumors show microscopically recognizable subtypes, which may be related to the grade of malignancy. It is tempting to believe that the relatively poor prognosis higher grade subtype arises from one or more of the lower grade subtypes via a series of consecutive, partly independent, molecular progression events in certain genes. The most commonly involved gene families in epithelial malignancies are *p53, myc, ras,* and *neu,* whilst *raf, myb, fur and lun,* and genes that code for epidermal growth factor-R (EGF-R) and platelet-derived growth factor (POGE) are less common. Pleomorphic adenoma (PA) is characterized by recurrent chromosome rearrangements, reciprocal translocations in particular, with breakpoints at 8q12, 3p2I, and 12q13-15. The most common abnormality in PA is a reciprocal t(3;8)(p21 ;q21); this results in promoter swapping between the gene for Il-catenin and PLAGi, a novel zinc finger gene at 8q12 (1). This finding indicates that PLAGi activation due to promoter swapping is very likely to be a crucial event in salivary gland tumourigenesis.

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The presence of p53 gene abnormalities has been analyzed [bothby polymerase chain reaction (PCR)-based assays and immunohistochemistry (IHO)] in *e.g.,* PA and carcinoma in pleomorphic adenoma (CPA). Loss ot heterozygosity (LOH) of the p53 gene occurs in approximately 50% of PAs and in more than 85% of CPAs. The p53 oncoprotein is overexpressed in some 10% of adenomas and 75% of carcinomas, and tumors with overexpression of p53 protein demonstrate LOH. Investigation (fluorescence *in situ* hybridization) of numeric aberrations of chromosome 17 in PA and CPA revealed that loss of chromosome 17 may occur in PA betore its transformation to CPA. p53 expression is frequently associated with deletion of the p53 gene, and polysomy 17 is more frequent in CPA than PA, and associated with mutation of p53. In agreement, other reports suggest that alterations on the short arm of chromosome 17 may represent an event related to salivary gland tumor progression.

Adenoid cystic carcinomas (AdCC) also show a relatively high incidence of LOH at the p53 gene, and also at the Rb gene. The number of mutations (both LOH and microsatellite alterations) at either gene is greater in histologically high-grade foci than low. AdCCs show no K-ras mutations at the sites suspected of harboring recessive oncoganes. In contrast, a single type of p53 point mutation has been demonstrated in recurrent AdCCs, but not in the primaries (tissue PCR amplified for p53 exons S to 8, and direct sequencing). The presence of p53 oncoprotein positive tumor cells and the point mutations in recurrent AdCC suggest that p53 alterations are involved in late rather than early stages of tumor progression. In dedifferentiated acinic cell carcinoma, both low- and high-grade components were negative for p53 oncoprotein expression, and POR and single-strand conformation polymorphism analyses were consistent with a germ line configuration of the p53 gene in both elements of this tumor. In agreement, p53 protein accumulation seems to be unrelated to tumor recurrence (2). These findings suggest that p53 is far from always an early event in the malignant transformation and progression of salivary gland tumors.

myc. ras. Rb. c-erbB and others

The synergistic interaction of the amplified *c-myc* oncogene with transformation growth factor-ct (TGF-ct) *in vitro* to promote phenotypic transformation of mammary epithelial cells, apparently also takes place in mouse salivary gland tumorigenesis. Investigation of salivary adenocarcinomas for mutational activation of H-ras, K-ras and N-ras has shown an unusual ras mutation in 3 of 13 cases (A:T to G:C transition at the second position of codon 51 of the *H-ras* gene). C-erbB-2 oncoprotein is rarely expressed in salivary tumors. Bcl-2 is present in a wide variety of non-Hodgkin's lymphomas and the oncoprotein is also expressed in several salivary carcinomas, and reactive conditions of salivary gland mucosa-associated lymphatic tissue. It was recently shown that PAs have few areas of allelic loss, and that many salivary carcinomas displayed allelic loss patterns different from many other human tumor types (3). This latter finding and the diversity in p53 mutations (see above), suggest distinct genetic pathways in the progression of salivary gland tumors.

Immunohistochemistry

Single and coexpression of many gene products have been studied in relation to histological type, histogenesis, tumor stage, cell proliferation, etc.. Reduced expression of E-cadherin in AdCC correlates with unfavorable prognosis (4), while *e.g.,* expression of oncoprotein p53 in carcinomas appears to be unrelated to prognosis. The few typical' immunoprofiles of some salivary gland tumors are present usually only when the diagnosis already can be made on ordinary hematoxylin and eosin stained sections. Certain tumors have cells that are positive for prostate-specific antigen, which can cause erroneous diagnosis of metastatic disease. Salivary duct carcinoma often expresses c-erbB-2 protein, is positive for androgen receptor and gross cystic disease fluid protein-is, and is usually estrogen and progesterone receptor negative, but this immunophenotype does not totally exclude matastatic breast cancer. Assessment of proliferation by Ki-67 can be of value, *e.g.,* in differentiating difficult cases of AdCC from polymorphous low-grade adenocarcinoma. IHC has limited use in diagnostic salivary pathology and is best appreciated in relation to differentiating primary *vs.* metastatic disease, and in certain rare tumors such as small cell neuroendocrine carcinoma, primitive neuroectodermal tumors, sarcomas, etc.

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