

Eq/the/al-rn voevithellal carcinoma

Clear cells are usually part of the myoepithelial component and form a mantle around an inner layer of small cuboidal epithelial cells. This dimorphic pattern can be highlighted immunohistochemically. This tumor generally behaves as a low-grade malignancy.

Hyalinizina clear cell carcinoma

Monomorphic clear cell carcinomas are either epithelial or myoepithelial; the former, hyalinizing clear cell carcinoma, usually arises in the minor glands and is of low-grade malignancy. Microscopically, there are groups and trabeculae of polygonal glycogen rich cells separated by dense collagen bands. At times, particularly in the deeper parts of the tumors, the cells may lose their clarity when their cytoplasm appears weakly eosinophilic. Immunohistochemistry reveals positivity with cytokeratins but myoepithelial markers [S-100 protein and a smooth muscle actin (SMA)] are negative.

Clear cell malignant mvoeoithelioma (mvoeoithelial carcinoma)

The other form of monomorphic clear cell carcinoma is myoepithelial; relatively few cases have been described, mainly in the major glands. Microscopically, it is composed of sheets of clear cells, sometimes mixed with spindle shaped and other myoepithelial cells. Collagenous spherules and areas of necrosis are usual. The cells usually express cytokeratins, 5-100 protein and rSMA. It is too early to comment on behavior but distant metastases and death due to disease have been reported.

Metastatic renal cell carcinoma

Metastases composed of clear cells in the salivary glands include especially renal carcinoma. There are no specific markers as yet and it is best diagnosed (or excluded) by imaging the kidneys.

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Squamous and oncocytic metaplasia in salivary gland tumors

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Oncocytic lesions of salivary glands

Oncocytic change is where cells develop intensely eosinophilic granular cytoplasm due, typically, to increased numbers of mitochondria (1). Most oncocytic lesions show two types of cells: light

and dark. The former are large and round or polygonal and have finely granular, pink cytoplasm and a vesicular nucleus. The dark cells are usually more sparse and have deeply eosinophilic, compressed cytoplasm and densely hyperchromatic nuclei.

Benign lesions

Focal and diffuse oncocytosis

Foci of oncocytosis, usually of ducts but sometimes also acini, are increasingly common with advancing age. Diffuse oncocytosis of the parotid is rare and can involve the whole gland.

Ductal oncocytosis

Extensive oncocytic metaplasia of ducts, often with cystic dilation, is seen mainly in the larynx and rarely elsewhere. These lesions can be regarded as oncocytic papillary cystadenomas. Microscopically, they resemble Warthin's tumor without lymphoid stroma. A similar appearance is seen in cheilitis glandularis (stomatitis glandularis).

Multifocal nodular oncocytic hyperplasia

Multifocal nodular oncocytic hyperplasia (MNOH) comprises nodules of oncocytes, often with clear cytoplasm. The nodules may appear to engulf normal acinar tissue, giving a false impression of invasion.

Oncocytoma

This tumor is rare and 50% are associated with MNOH. It comprises a well-demarcated mass of light and dark oncocytic cells with a solid, trabecular, or tubular configuration. A fibrous capsule may be incomplete, and there is little internal fibrous stroma. A rare clear cell variant typically consists of a circumscribed mass of polyhedral cells with clear cytoplasm and small eccentric hyperchromatic nuclei; phosphotungstic acid hematoxylin (PTAH) staining may be unreliable.

Warthin's tumor

Warthin's tumor has several variants, one being the stroma poor type with sparse lymphoid stroma; it forms a solid nodule of oncocytic cells rather than a papillary cystic lesion (2).

Oncocytic tumor metaplasia

Oncocytic metaplasia in other benign salivary gland tumors (mainly pleomorphic and basal cell adenomas) is more common than oncocytoma itself (3).

Malignant oncocytic tumors

Mucoepidermoid carcinoma

Oncocytic change, either focal or diffuse, is a rare feature of mucoepidermoid carcinoma.

Oncocytic carcinoma

Oncocytic carcinoma is a rare tumor, found mainly in the parotid gland. The histological features are dysplastic, mitotically active oncocytic cells with soft tissue, perineural and vascular invasion. It is aggressive, and over half of the reviewed cases either died from the tumor or were alive with active disease, although this may not always be so, even in lesions with perineural invasion (4).

Squamous metaplasia and tumors of salivary glands

Squamous differentiation is common in reactive salivary gland lesions and can be seen in several tumors, either as metaplasia, or as an integral feature of the tumor.

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.

Squamous metaplasia in salivary gland 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 fine 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.

Squamous 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 myoepithe-

liomas 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 *et al.* (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.

References

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