

# Solid Tumour Section

## Review

## Head and neck: Salivary gland tumors: an overview

Audrey Rousseau, Cécile Badoual

Universite Rene Descartes Paris 5, Service d'anatomie Pathologique - Hopital Europeen Georges Pompidou - 20 rue Leblanc - 75015 Paris - France (AR, CB)

Published in Atlas Database: September 2010

Online updated version : <http://AtlasGeneticsOncology.org/Tumors/SalivGlandOverviewID5328.html>  
DOI: 10.4267/2042/45043

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2011 *Atlas of Genetics and Cytogenetics in Oncology and Haematology*

### Classification

The 2005 World Health Organization (WHO) classification of SGTs is complex and comprises 10 benign and 23 malignant entities of epithelial origin. Non epithelial neoplasms are rare, representing about 2-5% of SGTs, and will not be discussed herein. They include, among others, haemangioma, lymphangioma, schwannoma, neurofibroma, lipoma, sarcoma, lymphoma, and metastatic lesions (which develop preferentially in the parotid glands, and are most often of squamous cell origin). The diversity of epithelial SGTs as well as their rarity and varied morphological aspects often makes diagnosing such neoplasms difficult. Most primary epithelial SGTs occur in the parotid glands; about 10% occur in the submandibular glands, and less than 1% develops in the sublingual glands. Minor glands are involved in 9-23% of SGT cases. Between 54 and 79% of all tumors are benign, and 21 to 46% are malignant. Most SGTs occurring in the sublingual glands are malignant (70-90%). Fifteen to 32% of parotid tumors, and about 40% of submandibular lesions are carcinomas. Finally, 50% of minor gland neoplasms are cancers. Notably, SGTs of the tongue, floor of the mouth and retromolar areas are most often malignant. Overall, pleomorphic adenoma is the most frequent SGT, comprising about 50-60% of cases. The second most frequent benign SGT is Warthin tumor. Mucoepidermoid carcinoma is the most common malignant SGT. Histological types vary in frequency according to location. Pleomorphic adenoma, Warthin tumor, and mucoepidermoid carcinoma are commonly found in the parotid glands whereas polymorphous low-grade adenocarcinoma usually arises in minor glands.

2005 WHO classification of epithelial SGTs

- Benign epithelial tumors
  - Pleomorphic adenoma
  - Myoepithelioma
  - Basal cell adenoma
  - Warthin tumor
  - Oncocytoma
  - Canalicular adenoma
  - Sebaceous adenoma
  - Lymphadenoma
  - Ductal papilloma
  - Cystadenoma
- Malignant epithelial tumors
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Polymorphous low-grade adenocarcinoma
  - Epithelial-myoepithelial carcinoma
  - Clear cell carcinoma, not otherwise specified
  - Basal cell adenocarcinoma
  - Malignant sebaceous tumors
  - Cystadenocarcinoma
  - Low-grade cribriform cystadenocarcinoma
  - Mucinous adenocarcinoma
  - Oncocytic carcinoma
  - Salivary duct carcinoma
  - Adenocarcinoma, not otherwise specified
  - Myoepithelial carcinoma
  - Carcinoma ex pleomorphic adenoma
  - Carcinosarcoma
  - Metastasizing pleomorphic adenoma
  - Squamous cell carcinoma
  - Small cell carcinoma
  - Large cell carcinoma
  - Lymphoepithelial carcinoma
  - Sialoblastoma

Because of the morphological diversity of SGTs and the rarity of some subtypes, only the most frequent entities (i.e. pleomorphic adenoma, Warthin tumor, and mucoepidermoid carcinoma) will be discussed in detail herein. Other less frequent entities will be mentioned briefly.

## Clinics and pathology

### Disease

Salivary gland tumors (SGTs)

#### Note

The salivary glands comprise the three paired major glands (the parotid, the submandibular and sublingual) and the minor glands (located in the palate, lips, buccal mucosa...). Salivary gland tumors (SGTs) are rare neoplasms accounting for 0.4-13.5 cases per 100000 people. Malignant SGTs represent 6% of head and neck cancers and 0.3% of all cancers in the US. Still in the US, carcinomas of the major salivary glands comprise 11% of oropharyngeal neoplasms. On the whole, SGTs predominantly arise in female patients, but the sex ratio varies according to tumor type. The average age of patients with SGT is about 45 years old. The peak incidence of most specific types is in the 6<sup>th</sup> and 7<sup>th</sup> decades. However, the highest incidence of pleomorphic adenoma (PA), mucoepidermoid carcinoma (MEC), and acinic cell carcinoma is in the third and fourth decades. In the pediatric population, the most common malignant SGT is mucoepidermoid carcinoma. Mesenchymal neoplasms are more frequent in this age group compared to the adult population and epithelial tumors are more often malignant.

### Etiology

The etiology of SGTs is so far unknown. Putative risk factors include cigarette smoking, genetic predisposition, viral infections, rubber manufacturing, plumbing, some types of woodworking, as well as asbestos mining, exposure to nickel compounds, and cellular phone use. The only well-established risk factor is ionizing radiation. Atomic bomb survivors and cancer patients treated by radiation present with a substantially higher risk of developing SGTs. However, there is a strong association between Warthin tumor (WT) and cigarette smoking, with WT occurring 8 times more often in smokers than in non-smokers. Irritants in tobacco smoke may cause metaplasia in the parotid gland. The association with tobacco use may explain the higher incidence of WT in males.

### Cytogenetics

A growing number of both benign and malignant SGTs are characterized by recurrent genetic alterations, particularly chromosome translocations. Specific chromosomal rearrangements are commonly found in malignant hematopoietic proliferations as well as in sarcomas, but less than 1% of all epithelial cancers are characterized by such distinct, recurrent genomic anomalies. Those anomalies may serve as diagnostic,

prognostic and/or predictive markers in SGTs and their identification may complement the morphologic evaluation. Chromosome translocations in SGTs result in pathogenetically relevant fusion oncogenes. Those genes encode novel fusion proteins as well as ectopically expressed normal or truncated proteins that may play a role in tumor initiation and/or progression.

### Treatment

Radical surgical excision is the cornerstone treatment of SGTs.

### Prognosis

Prognosis correlates most strongly with clinical stage, emphasizing the importance of early diagnosis. Optimal initial surgery minimizes the risk of local recurrence, hence the risk of distant metastases.

The tumor type and microscopic grade have been shown to be independent predictors of behavior. Acinic cell carcinoma, basal cell adenocarcinoma, clear cell adenocarcinoma, and epithelial-myoepithelial carcinoma are all low-grade neoplasms whereas salivary duct carcinoma, oncocytic carcinoma, primitive epidermoid carcinoma, and undifferentiated carcinoma are high-grade tumors. The site of occurrence is also an important prognostic factor. Patients with MEC of the parotid gland have a better prognosis than those with submandibular gland tumors of the same grade. With some other tumor types, both a younger age and female gender are associated with a better outcome. Facial nerve paralysis appears to predict both recurrence and decreased survival.

### Disease

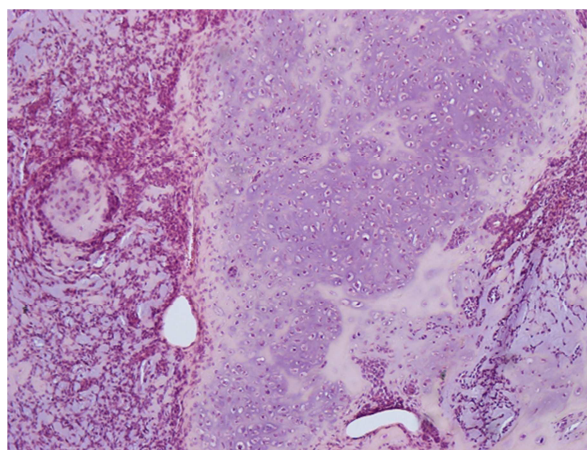
Pleomorphic adenoma (PA)

#### Clinics

PA is typically a slowly growing, asymptomatic, discrete nodule most often located in the superficial lobe of the parotid gland. It is usually mobile with palpation, and rarely causes facial paralysis due to extrinsic compression of the VII cranial nerve.

#### Pathology

Pleomorphic adenoma is a benign epithelial tumor most often arising in the parotid gland.



Pleomorphic adenoma HEX100.

It may also occur in the submandibular and minor salivary glands. Microscopically, PA is characterized by its morphological diversity. It comprises epithelial and myoepithelial cells variably arranged in a mucoid, myxoid or chondroid background. Epithelial cell types observed in PA include cuboidal, basaloid, squamous, clear, and spindle cells. The epithelial component may predominate and in this instance the lesion is called "cellular PA". The myoepithelial component may form a fine reticular pattern or sheets of spindle cells. The mesenchymal tissue is mucoid, myxoid or chondroid, and predominates in some instances. Osseous metaplasia or lipomatous differentiation may be seen. PA usually presents with a variably thick capsule that on serial sectioning may be focally absent. The lesion typically harbors few mitoses and cytological atypia. Although PA is a benign tumor, it may recur and/or undergo malignant transformation.

**Histogenesis:** PA has been shown to be of monoclonal origin. A common single cell may give rise to epithelial and modified myoepithelial cells, as well as mesenchymal elements. The two components may share a common origin from a single uncommitted cell (e.g. pluripotent intercalated duct cell) that may differentiate along epithelial and mesenchymal cell lines. Alternatively, PA could develop from committed progenitor cells, e.g. epithelial basal ductal cells. Upon neoplastic transformation, some of those cells may undergo divergent differentiation and acquire a mesenchymal phenotype.

### **Cytogenetics**

Pleomorphic adenoma presents with a highly specific and recurrent pattern of chromosome abnormalities. Four major cytogenetic subgroups have been defined: rearrangements involving 8q12 (39%), with the t(3;8)(p21;q12) translocation representing about half the cases; rearrangements of 12q13-15 (8%); sporadic clonal changes involving chromosomal segments other than 8q12 or 12q13-15 (23%), and an apparently normal karyotype (30%).

Rearrangements of chromosome 8q12 in PA most often involve the 5' non-coding region of PLAG1 (pleomorphic adenoma gene-1). Translocations involving 8q12 result in promoter swapping between PLAG1 and an ubiquitously expressed gene, leading to activation of PLAG1 expression. The translocation partners most often involved are CTNNB1 (encoding beta-1 catenin) and LIFR (leukemia inhibitory factor receptor), resulting from translocations t(3;8)(p21;q12) and t(5;8)(p13;q12), respectively.

PLAG1 is a developmentally regulated zinc finger gene that maps to 8q12. It is not expressed in normal salivary gland parenchyma. The gene product is a nuclear protein that functions as a DNA-binding transcription factor. Potential PLAG1 binding sites have been found in promoter 3 of the IGF-II (insulin-like growth factor II) gene. It was shown that PLAG1 bound IGF-II promoter 3 and stimulated its activity.

IGF-II was highly expressed in PAs with up-regulated PLAG1 gene. Conversely, IGF-II up-regulation was neither detected in PAs without abnormal PLAG1 expression, nor in normal salivary gland parenchyma. Thus, IGF-II is a potential PLAG1 target gene. PLAG1 may play a role in PA pathogenesis by inducing growth factor production, hence cell proliferation. It was demonstrated by Western blot and immunohistochemical analyses that PLAG1 expression was up-regulated in epithelial and myoepithelial cells, as well as in the mesenchymal component of PA.

Another mechanism of gene fusion involving PLAG1 is formation of chromosome 8 rings harboring amplification of a pericentromeric segment with breakpoints in the FGFR1 gene at 8p12 and in the PLAG1 gene at 8q12.1. Such r(8)(p12q12.1) rings result in a novel FGFR1-PLAG1 gene fusion. The breakpoints occur in the 5' non coding regions of both genes, leading to promoter substitution and activation of PLAG1 expression.

Cryptic, intrachromosomal 8q rearrangements have been reported in PAs with an apparently normal karyotype. In PLAG1-CHCHD7 gene fusions, exon 1 of CHCHD7 (coiled-coil-helix-coiled-coil-helix domain 7) was fused to either exons 3-4 or 2-4 of PLAG1, resulting in up-regulated PLAG1 protein expression. CHCHD7 maps to chromosome 8q12, 500 bp telomeric to PLAG1. It is a newly identified member of a multifamily of proteins containing a conserved coiled-coil-helix-coiled-coil-helix domain. CHCHD7 gene is ubiquitously expressed and its function has yet to be discovered.

TCEA1 (transcription elongation factor A 1, also known as SII) is another potential fusion partner of PLAG1 in cryptic 8q rearrangements. The TCEA1-PLAG1 fusion transcript is formed by fusion of exon 1 of TCEA1 to exon 2 or 3 of PLAG1. TCEA1 is an intronless, ubiquitously expressed pseudogene that maps to chromosome 3p21.3-22 (to the same region as CTNNB1). Transcription elongation factors are involved in the regulation of the transcription of most protein-coding genes. TCEA1 releases RNA polymerase II from transcriptional arrest due to specific DNA sequences or DNA-binding proteins.

The mechanism of such cryptic 8q rearrangements may be a promoter substitution resulting from a nonreciprocal rearrangement such as an insertion.

The target gene in 12q13-15 rearrangements is HMGA2 (high motility group 2, also known as HMGIC). It maps to 12q14.3 and encodes a small non-histone, chromatin-associated protein that can modulate transcription by altering the chromatin architecture. The highest expression levels of HMGA2 gene are detected in fetal tissues whereas gene expression is undetectable in normal adult tissues. The translocations involving 12q13-15 generate gene fusions in which the 5' part of HMGA2 (encoding the three DNA-binding domains) are linked to various fusion partner genes. Two fusion genes, HMGA2-NFIB (nuclear factor I B

gene) and HMGA2-FHIT (fragile histidine triad gene), have been identified in PAs with  $\text{ins}(9;12)(\text{p}23;\text{q}12-15)$  and  $\text{t}(3;12)(\text{p}14.2;\text{q}14)$  respectively. Such rearrangements lead to separation of the DNA-binding domains from the spacer, the carboxy-terminal acidic domain, and the entire 3' UTR with its miRNA complementary sites. Those sites are targets for the miRNA let-7 and their loss through chromosomal translocation/truncation disrupts repression of HMGA2, leading to increased expression. Such loss of regulatory sequences has been demonstrated to promote anchorage independent-growth. Thus, HMGA2 gene rearrangements may promote tumorigenesis in PA.

A third fusion partner gene identified in PA is WIF1 (wnt inhibitory factor 1). Since HMGA2 and WIF1 genes are located in opposite orientation 0.7 Mb apart, the recurrent HMGA2-WIF1 fusions are likely to result from a cryptic paracentric inversion.

Other complex HMGA2 alterations have been identified in PA, such as amplifications involving an apparently intact HMGA2 sequence, a disrupted gene or the HMGA2-WIF1 fusion gene. Amplification in addition to gene fusion is a novel mechanism of HMGA2 activation. Moreover, high-level expression of HMGA2 resulting from gene amplification has been suggested to contribute to malignant transformation of PA.

HMGA2 plays an important role in mammalian growth (mutations of the mouse gene causes the "pygmy" phenotype) and may be a key player in PA development and progression. PLAG1 gene exerts oncogenic effects by inducing growth factor production. In opposition, the pathogenetic relevance of the fusion partners of those genes remains to be elucidated. The diversity in chromosomal segments that participate in the translocations and the absence of a common structural or functional denominator in those segments suggest that their role may be merely to provide the necessary elements for proper translation of the fusion transcripts.

The PLAG1- and HMGA2-containing fusion genes may be used as diagnostic markers in PA. Detection of such genetic hallmarks using RT-PCR or FISH technique could help diagnose morphologically ambiguous cases.

### **Treatment**

Because of the risk of recurrence and malignant transformation, radical surgical excision is required. Still, whether to perform superficial parotidectomy or extra-capsular dissection remains debated. Additional surgery in case of recurrence exposes to an increased risk of facial nerve injury.

### **Prognosis**

The prognosis of pleomorphic adenoma is excellent if completely removed. Recurrence rates at 5 year- and 10 year-follow-up are 3.4% and 6.8%, respectively.

## **Disease**

Carcinoma ex pleomorphic adenoma

### **Clinics**

Patients present with rapid growth and/or ulceration of a known, untreated PA. The mass is usually painless but about one third of patients have pain or facial nerve paralysis. The lesion may be fixed to underlying soft tissues.

### **Pathology**

Carcinoma ex PA is a malignant epithelial cell proliferation arising in an authentic PA. According to the AFIP (Armed Forces Institute of Pathology), it represents about 6% of malignant SGTs and develops in 9.5% of PAs. Similarly to PA, carcinoma ex PA mainly occurs in the parotid gland; it usually develops a decade later compared to PA. It may result from accumulation of genetic alterations in long-standing tumors. Indeed, the risk of malignant transformation increases with time. The malignant component may totally replace the benign portion of the tumor. It may correspond to poorly differentiated adenocarcinoma, undifferentiated carcinoma or any other type of epithelial malignancy.

### **Cytogenetics**

Genomic alterations in carcinoma ex PA are identical to those found in PA. Alterations at 12q13-15 with amplification of HMGA2 and MDM2 genes have been reported. MDM2 (at 12q14-15) is one of the most frequently co-amplified genes together with HMGA2, suggesting a pathogenetic role for MDM2 in carcinoma ex PA. The genes were co-amplified in the same homogeneously staining regions and double minute chromosomes in a case of carcinoma ex PA with a  $\text{del}(5)(\text{q}22-23\text{q}32-33)$  and  $\text{t}(10;12)(\text{p}15;\text{q}15)$ . However, there was little MDM2 protein expression, as assessed by immunohistochemistry, compared to high HMGA2 expression levels in the carcinomatous parts of the tumor.

Cerb-B2 surexpression has been detected in one third of carcinoma ex PA and could help distinguish it from atypical PA. Mutation and overexpression of TP53 are also frequent events in carcinoma ex pleomorphic adenoma.

### **Treatment**

In carcinoma ex PA, the recommended therapy is wide local excision with lymph node dissection, followed by radiation therapy for widely invasive tumors.

### **Prognosis**

The prognosis of carcinoma ex PA depends on its extension. Prognosis is excellent when the malignant component is confined to the PA nodule whereas it may be dismal when carcinoma extends beyond the capsule and infiltrates into adjacent soft tissues. Capsular penetration of more than 1.5 mm and a high-

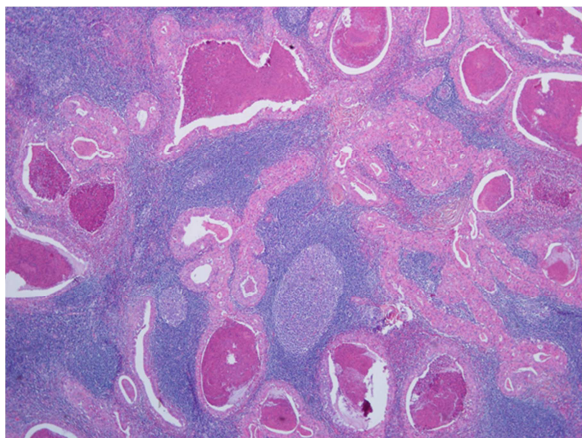
grade carcinomatous component are associated with poor prognosis. Survival rates at 5, 10, 15, and 20 years range from 25-65%, 18-50%, 10-35%, and 0-38%, respectively.

### **Disease**

Warthin tumor (WT)

### **Clinics**

WT presents as an asymptomatic, slowly growing, and fluctuant mass located in the lower pole of the parotid gland. It is clinically multicentric in 12-20% of patients, and is bilateral in 5-14%. Additional subclinical lesions are found microscopically in 50% of cases. WT usually occurs in patients in their seventh decade and is rare before age 40. Pain occurs in about 10% of cases, and facial paralysis is very unusual, resulting from inflammation and fibrosis.



Warthin tumor HEx100.

### **Pathology**

WT is composed of glandular and often cystic structures, sometimes presenting with papillae, lined by a bilayered epithelium, comprising inner columnar eosinophilic or oncocytic cells and outer smaller basal cells. The stroma often contains dense lymphoid tissue that may harbor germinal centres and mantle zones. WT is also known as cystadenolymphoma, but this term should not be used in order to avoid confusion with malignant lymphomas. It is almost exclusively found in the parotid glands and the periparotid lymph nodes. WT is well demarcated by a thin capsule. The lesion usually harbors no significant nuclear atypia or mitotic activity. Malignant change is rare, at about 1%, and may involve the epithelial or lymphoid component. The epithelial component may degenerate into squamous cell carcinoma, and occasionally into mucoepidermoid carcinoma, adenocarcinoma or undifferentiated carcinoma. Lymphoma, especially of the nodal type, may develop from the lymphoid component of WT.

Histogenesis: WT is thought by some to originate from heterotopic salivary ductal inclusions in intra- or periparotid lymph nodes. This hypothesis may explain why

WT is not observed in salivary glands without incorporated lymph nodes. Other authors posit that WT is a benign epithelial neoplasm that attracts a marked lymphoid reaction, similar to that seen in other salivary gland neoplasms. The immunoprofile of the lymphocyte subsets is similar to that of lymphocytes in normal or reactive lymph nodes. Analysis of the X chromosome-linked human androgen receptor gene showed that WT is non-clonal, and thus likely to be non-neoplastic. According to some, WT may result from induction of cystic changes in branchial cleft epithelium by an inflammatory infiltrate.

### **Cytogenetics**

Three distinct groups of WT have been defined based on cytogenetic aberrations: one with a normal karyotype, a second with numerical changes only (loss of Y chromosome or trisomy or monosomy 5), and a third group involving structural changes with one or two reciprocal translocations. Two neoplasms have been reported to carry a t(11;19)(q21;p13) translocation, suggesting a link to mucoepidermoid carcinoma. The translocation was present either as the sole karyotypic anomaly or as part of a more complex karyotype. The case displaying a complex karyotype carried a MECT1-MAML2 fusion transcript. In another series, 4 out of 11 WT cases (36%) also harbored that fusion transcript. A recent independent study reported that 2 out of 48 cases (4%) expressed the MECT1-MAML2 fusion transcript, and that both cases were metaplastic variants of WT. But, on review, the tumors were reclassified by the same investigators as highly suspect for MEC. The remaining 46 neoplasms were definitely classic WTs and none displayed the fusion transcript. Hence, morphologically ambiguous cases of WT exhibiting the MECT1-MAML2 chimeric gene should be regarded with caution.

### **Treatment**

In Warthin tumor, radical surgical excision (either superficial parotidectomy or enucleation) is curative.

### **Prognosis**

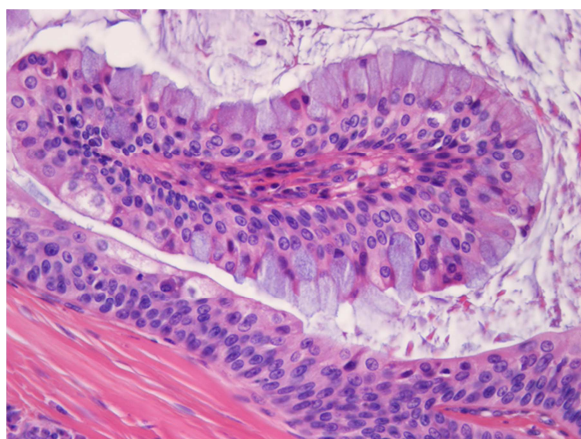
Recurrence rates are low, at about 2-5.5%; recurrence presumably results from multifocality.

### **Disease**

Mucoepidermoid carcinoma (MEC)

### **Clinics**

In the major salivary glands, MEC usually presents as a solitary painless lesion. Similarly to other malignant neoplasms, over 50% of patients have been aware of the tumor for less than 6 months. Two thirds of individuals are asymptomatic. Some patients report rapid growth of the mass; others experience pain, dysphagia, trismus, and facial paralysis. In minor salivary glands, 40% of patients are symptomatic, suffering from pain, numbness of teeth, dysphagia, ulceration, and haemorrhage.



Mucoepidermoid carcinoma HEx400.

### Pathology

MEC is the most common type of malignant SGTs, accounting for about 35% of salivary gland cancers. About 50% arise in the major salivary glands. MEC comprises epidermoid cells, mucus-producing cells, and so-called intermediate cells. It is usually multicystic with a solid component. Cystic spaces are lined by mucous cells associated with a variable number of intermediate cells and a few epidermoid cells. Intermediate cells usually predominate and form clusters or solid sheets. Keratinisation is rarely seen. The borders of the lesion may appear well-defined but infiltration of adjacent gland parenchyma is most often obvious.

MECs are classified as low-, intermediate- or high-grade tumors depending on the presence or absence of the following criteria: 1) neural invasion, 2) necrosis, 3) anaplasia, 4)  $\geq 4$  mitoses per 10 high power fields, and 5) less than 20% cystic spaces relative to solid areas. All these histopathological features are indicative of a more aggressive neoplasm.

Histogenesis: Mucoepidermoid carcinoma may originate from excretory duct reserve cells, but the issue remains moot.

### Cytogenetics

Even though MEC is the most common type of malignant SGTs, its pathogenesis and the key molecular events leading to its development are yet to unravel. At least two partially overlapping cytogenetic subgroups have been identified, i.e. MECs with t(11;19)(q21;p13) or variants thereof, and MECs with single or multiple trisomies, either observed as the sole abnormality or in combination with structural rearrangements.

A recurrent t(11;19)(q21;p13) translocation has been identified in MECs of both salivary gland and bronchopulmonary origin. Such a translocation leads to the fusion of exon 1 from a gene of unknown function at 19p13, termed mucoepidermoid carcinoma translocated 1 (MECT1, also known as CTCRC1, TORC1, or WAMTP1), with exons 2-5 of a member of mastermind-like gene family, MAML2, at 11q21. It has

been demonstrated that the resultant fusion transcript MECT1-MAML2 activated transcription of the Notch target gene HES1 independently of ligand stimulation. The translocation t(11;19)(q21;p13) and the MECT1-MAML2 fusion transcript have been detected in 38-81% of MEC cases. The translocation is shared by acute leukemia, and an apparently identical rearrangement has been identified in WT. Apart from WT, it has not been demonstrated in any other salivary gland tumor. Immunohistochemistry using an MECT1-MAML2 antibody in fusion-positive MECs resulted in nuclear staining of all three major cell types, i.e. mucus-producing, epidermoid, and intermediate cells. However, stromal cells did not express the fusion protein. Expression of the hybrid gene in all cell types suggests that it may play a role early in tumor initiation. Such a distinct translocation and resulting fusion transcript may be a useful tool in diagnosing morphologically ambiguous MEC. In addition, there is an association between transcript expression and tumor stage, with fusion-positive tumors behaving in a less aggressive fashion. Fusion-positive patients had a significantly lower risk of local recurrence, metastases, or tumor-related death compared to fusion-negative ones (median survival of more than 10 years compared to 1.6 years). In addition, there was a preponderance of highly differentiated low-grade tumors in fusion-positive patients compared to the fusion-negative group.

In one study, more than 55% of the MEC cases expressed the MECT1-MAML2 fusion transcript, indicating that the fusion is more common than suggested by conventional cytogenetic analysis. Not all fusion-positive tumors carried the translocation t(11;19), meaning that other cryptic translocations may contribute to the disease in such cases. Several cases displayed cryptic 11;19 rearrangements and MECT1-MAML2 gene fusions. Fusions may thus be found in MECs with complex 11;19 rearrangements and in tumors with variant translocations such as t(11;17) and t(11;13), as well as in tumors with apparently normal karyotypes and trisomies.

The second most common chromosomal abnormality was single or multiple trisomies, observed in 7 of 21 MECs in one series. Trisomies were mostly observed in cases not harboring a t(11;19). The most frequently encountered trisomies were +7, +8, and +X. Other recurrent abnormalities found were deletions of the terminal part of 6q. Apart from these abnormalities, the t(11;19)-negative MECs showed a heterogeneous pattern of rearrangements with no obvious recurrent aberrations.

Very recently, deletions of CDKN2A gene have been shown to be associated with poor prognosis in MECT1-MAML2 fusion-positive MECs. In the same study, neither activating EGFR mutations nor copy number gains at the EGFR locus was detected in fusion-positive and fusion-negative cases. Finally, detection of HER-2 overexpression by immunohistochemistry has been

correlated to adverse clinicopathologic features in several studies.

### **Treatment**

Mucoepidermoid carcinoma is treated by wide local surgical excision, followed by radiation therapy in case of inadequate surgical margins or pejorative microscopic features (e.g. neural invasion). Classification into high-grade and low-grade tumors guides treatment but the behavior of intermediate-grade neoplasms remains difficult to predict.

### **Prognosis**

The 5- and 10-year survival rates are about 35% and 10-20%, respectively. Presence of distant metastases portends poor prognosis.

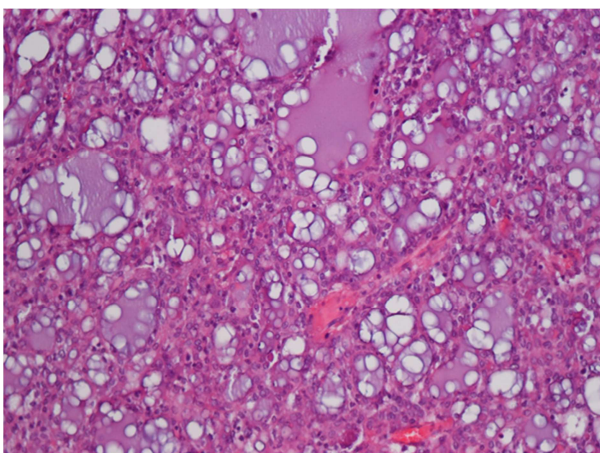
### **Disease**

Acinic cell carcinoma

### **Clinics**

Acinic cell carcinoma is a low-grade malignant neoplasm that constitutes approximately 17% of SGTs and mostly develops in the parotid gland (80%). Seventeen percent arise in the intraoral minor salivary glands (buccal mucosa, upper lip); 4% develop in the submandibular glands and less

than 1%, in the sublingual glands. It is the second most common epithelial malignancy of salivary glands after mucoepidermoid carcinoma. Women are more often affected than men. All age groups can be affected with an even distribution of patients from the second to the seventh decade. It usually presents as a slowly enlarging mass 1 to 3 cm in greatest dimension. It may rarely be multinodular or fixed to skin or adjacent soft tissues. Acinic cell carcinoma is the malignancy of salivary glands that most often occurs bilaterally. About 30% of patients experience pain and less than 10% develop facial paralysis. At the time of diagnosis, signs and symptoms have usually been present for less than a year.



Acinic cell carcinoma HEx200.

### **Pathology**

Acinic cell carcinoma is a malignant neoplasm demonstrating serous acinar cell differentiation which is characterized by cytoplasmic zymogen secretory granules. Acinar cells are large, polygonal with lightly basophilic, granular cytoplasm and round, eccentric nucleus. The cytoplasmic zymogen secretory granules are PAS-positive, resistant to diastase digestion, and non-reactive or only weakly reactive to mucicarmine stain. Several cell types and growth patterns can be observed: acinar, intercalated ductal, vacuolated, clear, and non-specific glandular and solid/lobular, microcystic, papillary-cystic, and follicular growth patterns. Even though one component may predominate (usually acinar cells and intercalated duct-like cells), many tumors harbor a combination of different cell types and architectures. In the follicular pattern, thyroid follicle-like structures filled with an eosinophilic proteinaceous material are present. Some features have been associated with a more aggressive biological behavior such as cellular pleomorphism, frequent mitoses, focal necrosis, neural invasion, infiltration, and stromal hyalinisation.

Histogenesis: Acinic cell carcinoma may arise from neoplastic transformation of the terminal duct cells (intercalated duct cells) with differentiation toward serous acinar cells. Another theory posits that it could arise from transformation of terminally differentiated serous acinar cells.

### **Cytogenetics**

Multiple structural and numerical aberrations have been described in acinic cell carcinoma but no specific alteration has been identified. Loss of Y and trisomy 7, 8, and 21 have been reported. In the largest study to date, 21 (84%) of the 25 acinic cell carcinomas showed LOH (loss of heterozygosity) in at least one of the 20 loci tested on chromosomes 1, 4, 5, 6, and 17. Chromosomal arms 4p, 5q, 6p, and 17p were the most frequently altered, with 4p15-16, 6p25-qter, and 17p11 regions showing the highest rate of abnormalities. In another study, analysis of different samples from a single case found evidence of polyclonality.

### **Treatment**

Surgical excision is the mainstay of treatment in acinic cell carcinoma. Radiation therapy may be indicated in some cases.

### **Prognosis**

Acinic cell carcinoma tends to recur (35% of cases) and metastasize to cervical lymph nodes and later in the disease, to the lungs. Large size, incomplete resection, multiple recurrences, and lymph node metastases are associated with a poor prognosis. The rate of disease-associated death is about 16%. While tumors in the submandibular gland are more aggressive than those in

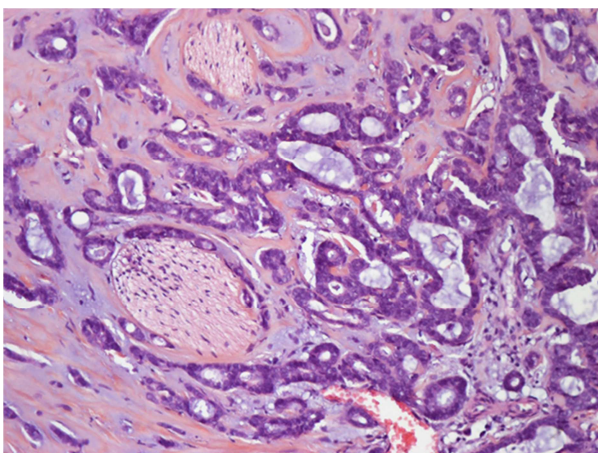
the parotid gland, acinic cell carcinomas in minor salivary glands are less aggressive than those in the major salivary glands.

### Disease

Adenoid cystic carcinoma

### Clinics

Adenoid cystic carcinoma manifests as a slowly growing mass often accompanied by pain and in some cases, facial paralysis.



Adenoid cystic carcinoma HEx200.

### Pathology

Adenoid cystic carcinoma is an epithelial malignancy composed of epithelial and myoepithelial cells variably arranged in tubular, cribriform, and solid patterns. The cribriform pattern, which is the most common, is characterized by nests of cells containing small, circular cyst-like spaces. The solid pattern is associated with a poor prognosis compared to the tubular and cribriform architecture. Neural invasion is a hallmark of this entity, and often extends beyond the main tumor mass. Infiltration of adjacent soft tissues is also characteristic of adenoid cystic carcinoma.

### Cytogenetics

Adenoid cystic carcinoma is characterized by a t(6;9)(q22-23;p23-24) translocation. The translocation fuses exon 14 of MYB gene, on chromosome 6q22-23, to the last coding exons of NFIB gene, on chromosome 9p23-24. Most breakpoints occur in intron 14 of MYB and intron 8 of NFIB. The minimal common part of MYB that is deleted is exon 15 including the 3'-UTR which contains several highly conserved target sites for miR15a/16 and miR-150 microRNAs. These microRNAs are known to negatively regulate MYB expression. Deletion of these target sites may lead to overexpression of MYB-NFIB transcript and activation of MYB targets, including genes associated with apoptosis, cell cycle control, cell growth/angiogenesis, and cell adhesion. Deregulation of expression of MYB and its target genes may be a key oncogenic event in the pathogenesis of adenoid cystic carcinoma.

Mutations in the c-kit gene have recently been described in adenoid cystic carcinoma, but their occurrence is rare, and they most probably do not represent driver mutations in this entity.

### Treatment

Treatment of adenoid cystic carcinoma consists of wide local and radical surgical resection with or without radiation therapy, but the disease is usually relentless.

### Prognosis

Most patients (80-90%) die of disease within 10 to 15 years. The solid pattern is associated with a worse prognosis compared to the tubular or cribriform architecture. The prognostic value of neural invasion is debated.

## References

- Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer (2010).. Mitelman F, Johansson B, Mertens F (Eds.). <http://cgap.nci.nih.gov/Chromosomes/Mitelman>.
- Geurts JM, Schoenmakers EF, Röijer E, Stenman G, Van de Ven WJ. Expression of reciprocal hybrid transcripts of HMGIC and FHIT in a pleomorphic adenoma of the parotid gland. *Cancer Res.* 1997 Jan 1;57(1):13-7
- el-Naggar AK, Abdul-Karim FW, Hurr K, Callender D, Luna MA, Batsakis JG. Genetic alterations in acinic cell carcinoma of the parotid gland determined by microsatellite analysis. *Cancer Genet Cytogenet.* 1998 Apr 1;102(1):19-24
- Geurts JM, Schoenmakers EF, Röijer E, Aström AK, Stenman G, van de Ven WJ. Identification of NFIB as recurrent translocation partner gene of HMGIC in pleomorphic adenomas. *Oncogene.* 1998 Feb 19;16(7):865-72
- Jin C, Jin Y, Höglund M, Wennerberg J, Akervall J, Willén R, Dictor M, Mandahl N, Mitelman F, Mertens F. Cytogenetic and molecular genetic demonstration of polyclonality in an acinic cell carcinoma. *Br J Cancer.* 1998 Aug;78(3):292-5
- Aström AK, Voz ML, Kas K, Röijer E, Wedell B, Mandahl N, Van de Ven W, Mark J, Stenman G. Conserved mechanism of PLAG1 activation in salivary gland tumors with and without chromosome 8q12 abnormalities: identification of SII as a new fusion partner gene. *Cancer Res.* 1999 Feb 15;59(4):918-23
- Holst VA, Marshall CE, Moskaluk CA, Frierson HF Jr. KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. *Mod Pathol.* 1999 Oct;12(10):956-60
- Lee PS, Sabbath-Solitare M, Redondo TC, Ongcapin EH. Molecular evidence that the stromal and epithelial cells in pleomorphic adenomas of salivary gland arise from the same origin: clonal analysis using human androgen receptor gene (HUMARA) assay. *Hum Pathol.* 2000 Apr;31(4):498-503
- Voz ML, Van de Ven WJ, Kas K. First insights into the molecular basis of pleomorphic adenomas of the salivary glands. *Adv Dent Res.* 2000 Dec;14:81-3
- Debiec-Rychter M, Van Valckenborgh I, Van den Broeck C, Hagemeyer A, Van de Ven WJ, Kas K, Van Damme B, Voz ML. Histologic localization of PLAG1 (pleomorphic adenoma gene 1) in pleomorphic adenoma of the salivary gland: cytogenetic evidence of common origin of phenotypically diverse cells. *Lab Invest.* 2001 Sep;81(9):1289-97
- Röijer E, Nordkvist A, Ström AK, Ryd W, Behrendt M, Bullerdiek J, Mark J, Stenman G. Translocation,



- deletion/amplification, and expression of HMGIC and MDM2 in a carcinoma ex pleomorphic adenoma. *Am J Pathol.* 2002 Feb;160(2):433-40
- Tonon G, Modi S, Wu L, Kubo A, Coxon AB, Komiya T, O'Neil K, Stover K, El-Naggar A, Griffin JD, Kirsch IR, Kaye FJ. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. *Nat Genet.* 2003 Feb;33(2):208-13
- Tonon G, Gehlhaus KS, Yonescu R, Kaye FJ, Kirsch IR. Multiple reciprocal translocations in salivary gland mucoepidermoid carcinomas. *Cancer Genet Cytogenet.* 2004 Jul 1;152(1):15-22
- Voz ML, Mathys J, Hensen K, Pendeville H, Van Valckenborgh I, Van Huffel C, Chavez M, Van Damme B, De Moor B, Moreau Y, Van de Ven WJ. Microarray screening for target genes of the proto-oncogene PLAG1. *Oncogene.* 2004 Jan 8;23(1):179-91
- Barnes L, Eveson JW, Reichart P, Sidransky D. Pathology and Genetics of Head and Neck Tumours. World Health Organization Classification of Tumours. IARC Press Lyon, 2005.
- Martins C, Fonseca I, Roque L, Pereira T, Ribeiro C, Bullerdiek J, Soares J. PLAG1 gene alterations in salivary gland pleomorphic adenoma and carcinoma ex-pleomorphic adenoma: a combined study using chromosome banding, in situ hybridization and immunocytochemistry. *Mod Pathol.* 2005 Aug;18(8):1048-55
- Stenman G. Fusion oncogenes and tumor type specificity--insights from salivary gland tumors. *Semin Cancer Biol.* 2005 Jun;15(3):224-35
- Asp J, Persson F, Kost-Alimova M, Stenman G. CHCHD7-PLAG1 and TCEA1-PLAG1 gene fusions resulting from cryptic, intrachromosomal 8q rearrangements in pleomorphic salivary gland adenomas. *Genes Chromosomes Cancer.* 2006 Sep;45(9):820-8
- Behboudi A, Enlund F, Winnes M, Andrén Y, Nordkvist A, Leivo I, Flaberg E, Szekely L, Mäkitie A, Grenman R, Mark J, Stenman G. Molecular classification of mucoepidermoid carcinomas-prognostic significance of the MECT1-MAML2 fusion oncogene. *Genes Chromosomes Cancer.* 2006 May;45(5):470-81
- Okabe M, Miyabe S, Nagatsuka H, Terada A, Hanai N, Yokoi M, Shimozato K, Eimoto T, Nakamura S, Nagai N, Hasegawa Y, Inagaki H. MECT1-MAML2 fusion transcript defines a favorable subset of mucoepidermoid carcinoma. *Clin Cancer Res.* 2006 Jul 1;12(13):3902-7
- Asp J, Stenman G. Head and Neck: pleomorphic salivary gland adenoma with inv(8)(q12;q11) (CHCHD7-PLAG1). *Atlas Genet Cytogenet Oncol Haematol.* April 2007.
- Asp J, Stenman G. Head and Neck: pleomorphic salivary gland adenoma with ins(8)(q12;q11q11) (TCEA1-PLAG1). *Atlas Genet Cytogenet Oncol Haematol.* April 2007.
- Mayr C, Hemann MT, Bartel DP. Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. *Science.* 2007 Mar 16;315(5818):1576-9
- Tirado Y, Williams MD, Hanna EY, Kaye FJ, Batsakis JG, El-Naggar AK. CRTC1/MAML2 fusion transcript in high grade mucoepidermoid carcinomas of salivary and thyroid glands and Warthin's tumors: implications for histogenesis and biologic behavior. *Genes Chromosomes Cancer.* 2007 Jul;46(7):708-15
- Ellis GL, Auclair PL. Tumors of the Salivary Glands. Atlas of Tumor Pathology Fourth Series Fascicle 9. Washington, DC: Armed Forces Institute of Pathology, 2008.
- Fehr A, Röser K, Belge G, Löning T, Bullerdiek J. A closer look at Warthin tumors and the t(11;19). *Cancer Genet Cytogenet.* 2008 Jan 15;180(2):135-9
- Just PA, Miranda L, Elouaret Y, Meatchi T, Hans S, Badoual C. [Classification of salivary gland tumors]. *Ann Otolaryngol Chir Cervicofac.* 2008 Dec;125(6):331-40
- Persson F, Winnes M, Andrén Y, Wedell B, Dahlenfors R, Asp J, Mark J, Enlund F, Stenman G. High-resolution array CGH analysis of salivary gland tumors reveals fusion and amplification of the FGFR1 and PLAG1 genes in ring chromosomes. *Oncogene.* 2008 May 8;27(21):3072-80
- Sadetzki S, Chetrit A, Jarus-Hakak A, Cardis E, Deutch Y, Duvedvani S, Zultan A, Novikov I, Freedman L, Wolf M. Cellular phone use and risk of benign and malignant parotid gland tumors--a nationwide case-control study. *Am J Epidemiol.* 2008 Feb 15;167(4):457-67
- Teymoortash A. Head and Neck: Salivary gland: Warthin's tumors. *Atlas Genet Cytogenet Oncol Haematol.* April 2008.
- Boukheris H, Curtis RE, Land CE, Dores GM. Incidence of carcinoma of the major salivary glands according to the WHO classification, 1992 to 2006: a population-based study in the United States. *Cancer Epidemiology, Biomarkers and Prevention* 2009;18(11):2899-906.
- O'Neill ID. t(11;19) translocation and CRTC1-MAML2 fusion oncogene in mucoepidermoid carcinoma. *Oral Oncol.* 2009 Jan;45(1):2-9
- Persson F, Andrén Y, Winnes M, Wedell B, Nordkvist A, Gudnadottir G, Dahlenfors R, Sjögren H, Mark J, Stenman G. High-resolution genomic profiling of adenomas and carcinomas of the salivary glands reveals amplification, rearrangement, and fusion of HMGA2. *Genes Chromosomes Cancer.* 2009 Jan;48(1):69-82
- Persson M, Andrén Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. *Proc Natl Acad Sci U S A.* 2009 Nov 3;106(44):18740-4
- Uro-Coste E. Tumeurs des glandes salivaires. Etat des lieux en 2009. *Annales de pathologie* 2009 ;29 :274-85.
- Vila L, Liu H, Al-Quran SZ, Coco DP, Dong HJ, Liu C. Identification of c-kit gene mutations in primary adenoid cystic carcinoma of the salivary gland. *Mod Pathol.* 2009 Oct;22(10):1296-302
- Anzick SL, Chen WD, Park Y, Meltzer P, Bell D, El-Naggar AK, Kaye FJ. Unfavorable prognosis of CRTC1-MAML2 positive mucoepidermoid tumors with CDKN2A deletions. *Genes Chromosomes Cancer.* 2010 Jan;49(1):59-69
- Moskaluk CA, Frierson HF Jr, El-Naggar AK, Futreal PA. C-kit gene mutations in adenoid cystic carcinoma are rare. *Mod Pathol.* 2010 Jun;23(6):905-6; author reply 906-7

---

*This article should be referenced as such:*

Rousseau A, Badoual C. Head and neck: Salivary gland tumors: an overview. *Atlas Genet Cytogenet Oncol Haematol.* 2011; 15(6):533-541.

---