REVIEW

Immunohistochemistry Markers for Salivary Gland Tumours – A Review

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Abstract

Introduction: Salivary gland tumours (SGTs) are a diverse, rare group of tumours that pose a diagnostic difficulty due to their varied histological features in single lesions and overlapping histological patterns similar to those seen in different tumour entities.

Aim: This present review provides comprehension of the recent concepts of immunohistochemical markers to increase the diagnostic accuracy for salivary gland neoplasms.

Materials and Methods: Relevant articles were collected and reviewed.

Discussion: Although haematoxylin and eosin are still the gold standard methods for diagnosis, immunohistochemistry (IHC) studies can assist in diagnosis, mainly in cases with overlapping morphology and in differentiating between luminal and abluminal cells, as well as in understanding the heterogeneous architecture of SGTs. This helps in diagnosis.

Conclusion: Despite several advances in diagnosis, SGTs still remain a heterogeneous group of tumors that challenge both pathologists and clinicians alike. Immunohistochemistry (IHC) can be a helpful and effective tool to increase accuracy, particularly in cases that cannot be assessed by histological examination alone.

Keywords: IHC Markers, Diagnosis, Luminal Cell Markers, Myoepithelial Cell Markers, GFAP, Cd117, Ki 67, Polymorphous Adenocarcinoma, Pleomorphic Adenoma, Adenoid Cystic Carcinoma.

Introduction

The salivary gland tumours (SGTs) comprise less than 1% of total tumours and 3-5% of head and neck tumours.[1] Among the SGTs, pleomorphic adenoma is the most common; yet its morphological heterogeneity could suggest many other tumours, particularly polymorphous adenocarcinoma, epithelial myoepithelial carcinoma, myoepithelioma, and adenoid cystic carcinoma, especially in a tiny incisional biopsy. Furthermore, polymorphous adenocarcinoma shares features with adenoid cystic carcinoma (ADCC), pleomorphic adenoma (PA), and canalicular adenoma.[2] Although haematoxylin and eosin are still the gold standard methods for diagnosis, immunohistochemistry (IHC) studies can assist in diagnosis, particularly in cases of overlapping morphology. IHC can be advantageous for evaluating cell nature, differentiation, proliferation, tumour protein expression, and in differentiating between luminal and abluminal cells, as well as in understanding the heterogeneous architecture of SGTs, thereby aiding in diagnosis.[3]

Histogenesis

(In Greek, "histos" means "tissue" and "genesis" means "production") is the development of tissues from undifferentiated cells of an embryo. In pathology, the term "histology" refers to the "cell of origin" for a neoplasm rather than the tumour's developmental phase. Four theories have been hypothesized for histogenetic concepts.[4]

Basal Reserve Cell Theory: According to this theory, basal cells of the excretory and intercalated ducts function as reserve cells for more highly differentiated components of the functional salivary gland units.[4]

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How to cite the article: Akalya P, Sahana NS, Suresh T, Chavan NV, Shiragur SS, Anjana K. Immunohistochemistry Markers for Salivary Gland Tumours – A Review. Oral Maxillofac Pathol J 2025; 16(1); 57-64.

Source of Support: Nil

Conflict of Interest: None

Pluripotent Unicellular Reserve Cell Theory: This theory states that basal cells of excretory ducts are responsible for the development of all salivary gland units.

Semi-Pluripotent Bicellular Reserve Cell Theory: This is the most accepted theory. Two cells, the excretory duct reserve cell and the intercalated duct reserve cell, are presented as the hypothetical cells of origin for salivary gland neoplasms.[5] The basal cells of the excretory duct (excretory duct reserve cells) produce squamous or mucin-producing columnar cells, while those from the intercalated ducts (intercalated duct reserve cells) are responsible for the development of intercalated, striated, and acinar elements. According to this theory, excretory duct reserve cells give rise to squamous cell carcinomas (SCC) and mucoepidermoid carcinomas, while the intercalated duct reserve cells give rise to all others.

Multicellular Theory: Recent evidence suggests that all mature cell types, including acinar and basal cells in salivary gland tissue, are capable of proliferation. This theory presumes that SGTs originate from differentiated or adult cell counterparts within the functional salivary ducto-acinar complex.[6,7]

Morphogenesis Concepts

(Greek: morphe – form; genesis – to produce) refers to the development of the shape of an organ. In pathology, it refers to the process of differentiation in tumours and the resulting histomorphological characteristics of that particular tumour. Apart from the cell of origin, a pathologist typically considers the differentiation process and arrangement of tumour cells as crucial when classifying the neoplasm.[8,9]

Histologically, the salivary gland basically comprises acini and ducts. The acinar and duct cells are located near the lumen of the ducts, thus called luminal cells, while myoepithelial cells and basal cells are positioned away from the lumen, referred to as abluminal cells.

Secretory acini are wrapped by myoepithelial cells. The intercalated duct is surrounded by myoepithelial and basal cells. Striated ducts and downstream conducting units are lined by simple or pseudostratified columnar epithelium, which gradually transforms into stratified squamous epithelium and is supported by basal cells.

Classification of Salivary Gland Tumours Based on Morphogenesis Concepts:

A. Tumor composed of both luminal and myoepithelial cells.

B. Tumor composed of only luminal cells.

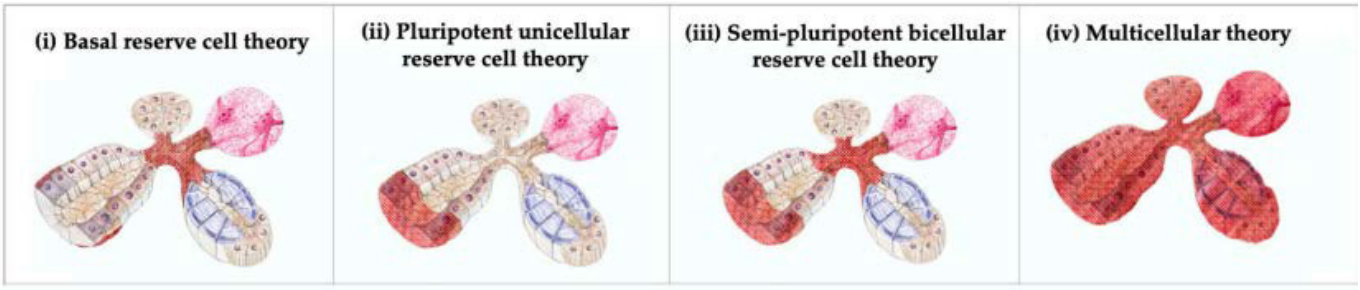

Fig.1: Histogenetic Concepts

(IMAGE COURTESY: Iyer, J; An Overview on the Histogenesis and Morphogenesis of Salivary Gland Neoplasms and Evolving Diagnostic Approaches. Cancers 2021, 13, 3910)

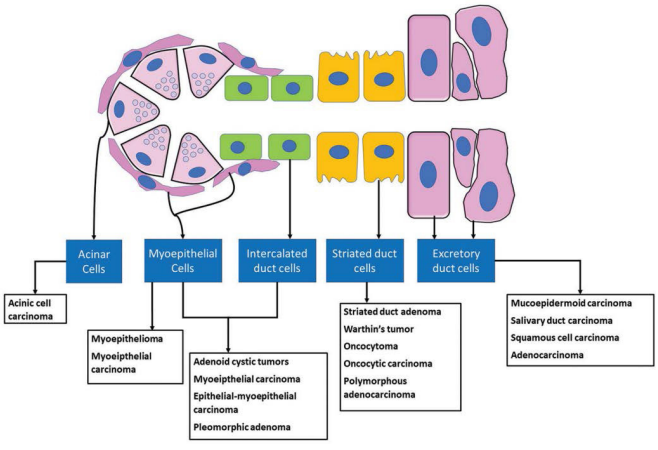

Fig.2: Multicellular Histogenesis Concept of Salivary Gland Tumours

(IMAGE COURTESY: Sonawane SG, Pathogenesis of salivary gland neoplasms: The concepts of histogenesis and morphogenesis. J Global Oral Health 2023; 6:59-65)

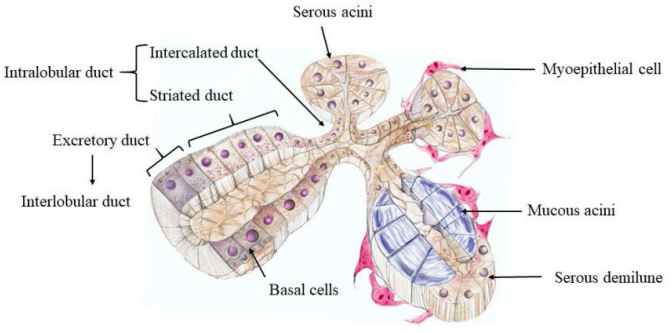

Fig.3: Schematic Representation of the Histology of Salivary Glands

(Image courtesy: Tran, O.N.; Chapter 14—Stem Cell–Based Restoration of Salivary Gland Function. In A Roadmap to Non-Hematopoietic Stem Cell-Based Therapeutics, 2018.)

Fig. 4: a. Luminal and myoepithelial cells, b. Luminal cell, c. myoepithelial or basic cells
Image Courtesy: Text book on salivary gland tumour pathology – by Dardick

C. Tumor composed of only myoepithelial cells/ basal cells.

Although many tumors are thought to contain both luminal and myoepithelial cells, the histologic difference are due to various forms and distribution of luminal and abluminal cells.

Cells (cuboidal/columnar, sheets, islands, and duct like).

Various forms of myoepithelial cells (Spindle, Plasmacytoid, Clear cells).

The ratio of the Ductal: Myoepithelial cells.[9]

1: Markers for Cellular Differentiation

1.1: Markers for Luminal Cells:

The acinar cells show diffuse positivity to cytokeratins with low molecular weight, weak positivity for cytokeratins with high molecular weight, diffuse positivity to α-amylase and DOG1, and weak positivity for lactoferrin, lysozyme, carcinoembryonic antigen (CEA), and epithelial membrane antigen (EMA).4 CEA (functions include signal transduction, cooperation with proto-oncogenes in cellular transformation, and inhibition of proliferation of epithelial tumors) immunoreactivity is generally detected in the cytoplasm of epithelial cells and luminal contents of neoplastic glands.[10]

The ductal cells show diffuse positivity for high molecular

Morphogenetic Classification of Salivary Gland Tumours:

CLASSIFICATION	SUBCLASSIFICATION	BENIGN	MALIGNANT
1)Luminal and myoepithelial cells	With extracellular matrix	• Pleomorphic adenoma • Basal cell adenoma	• Carcinoma ex pleomorphic adenoma • Adenoid cystic carcinoma • Basal cell adenocarcinoma • Polymorphous adenocarcinoma • Mucoepidermoid carcinoma • Epithelial myoepithelial carcinoma
	Without extracellular matrix	• Basal cell adenoma (solid) • Cellular Pleomorphic adenoma • Warthin's tumour	
2) Primarily myoepithelial/basal cells	-	Myoepithelioma	Myoepithelial Carcinoma
3)Primarily of luminal/ acinar cells	-	Canalicular adenoma, ductal papilloma, cystadenoma, oncocytoma	Acinic cell carcinoma, Salivary duct carcinoma, Adenocarcinoma, Oncocytic carcinoma, Intercalated duct adenoma, Striated duct adenoma
Undifferentiated cells			Undifferentiated carcinoma

TABLE 1: Morphogenetic Classification Of Salivary Gland Tumours

weight cytokeratins and weak positivity for EMA and CEA.[9,10]

1.2: Markers for Abluminal Cells:

Abluminal cells are positive for high molecular weight cytokeratins (such as CK14) and myoepithelial cells (ME cells). Myoepithelial cells show positivity for muscle proteins such as smooth muscle actin (SMA), muscle-specific actin (MSA), and calponin).[11] Myoepithelial and basal cells are CK14 and p63-positive and negative for CEA and EMA.

The neoplastic ME cells exhibit morphological variations, including epithelioid, spindle, plasmacytoid, and clear cell features, and often produce mucinous or basement membrane-like extracellular matrix. Neoplastic myoepithelial cells can occasionally be visualized by H&E staining, but immunohistochemical (IHC) analysis is generally necessary for more accurate identification.[12]

Various ME cell markers are available, with calponin and smooth muscle actin being more specific. S-100 is not a specific marker for myoepithelial cells and can sometimes be detected in ductal cells as well.[13] Glial fibrillary acidic protein (GFAP) is a myoepithelial marker (low sensitivity), but it is most advantageous in pleomorphic adenomas and myoepitheliomas, where it shows intense positivity. GFAP is useful for differentiating these from polymorphous adenocarcinoma or adenoid cystic carcinoma (in which GFAP is negative).[14,15]

Recent studies show that WT1 (Wilms tumour gene 1) is a sensitive marker for neoplastic myoepithelial cells in pleomorphic adenomas and is not expressed in normal myoepithelial cells.[11,14]

The staining properties of myoepithelial markers depend on the antibodies and cell types used. Staining for α-SMA, MSA, and calponin is usually seen diffusely in spindle cells, whereas positive cells are focally detected in epithelioid and clear cell types. Plasmacytoid cells are usually calponin-positive but negative for α-SMA and MSA.15

It is always better to use a panel of antibodies to visualize myoepithelial cells, especially in neoplastic myoepithelial cells. Pan-CK, calponin, α-SMA, and p63 (or CK14) are useful markers for myoepithelial cell differentiation.

1.3 Markers for Oncocytic and Sebaceous Differentiation:

Oncocytes are epithelial cells that present with abundant granular, eosinophilic cytoplasm, a central pyknotic nucleus, and ultrastructurally show a greater number of mitochondria of different sizes. Oncocytic cells typically represent a metaplastic change associated with aging.[16]

Oncocytomas and oncocytic carcinoma are salivary gland tumours in which oncocytes are predominantly seen. Focal areas of oncocytes are noted in a few salivary gland neoplasms (SGNs) such as Warthin's tumour, pleomorphic adenoma, myoepithelioma, polymorphous adenocarcinoma, basal cell adenoma, acinic cell carcinoma, mucoepidermoid carcinoma, and myoepithelioma.[17,18]

These oncocytes show strong positivity for anti-mitochondria antibodies (AMA).[15] Additionally, sebaceous differentiation is seen in sebaceous adenoma and sebaceous carcinoma. Epithelial membrane antigen (EMA) (with a characteristic bubbly pattern), adipophilin, and perilipin are positive for sebaceous differentiation. [19,20,21]

2: Markers to Differentiate Benign and Malignant Counterparts:

Tumours such as basal cell adenoma and basal cell adenocarcinoma, myoepithelioma and myoepithelial carcinoma, and oncocytoma and oncocytic carcinoma have basic histological appearances that closely resemble each other in terms of structures, patterns, and cellular features. The malignant counterparts are distinguished from benign tumours by histological hallmarks such as invasive outgrowth (the most important diagnostic feature), perineural and vascular invasion, necrosis, and mitosis. However, in cases of small incisional biopsies, the morphological appearance is not sufficient to confirm malignant features.[11]

Ki-67 is a useful marker for malignancy and aggressiveness. The Ki-67 index in benign neoplasms of the salivary glands is

ANTIGEN	LUMINAL CELLS		ABLUMINAL CELLS	
	ACINAR	DUCTAL	ME CELLS	BASAL
PAN CYTOKERATIN(AE1/AE3)	+VE	+VE	+VE	+VE
EPITHELIAL MEMBRANE ANTIGEN	+VE	+VE	-VE	-VE
CARCINOEMBRYONIC ANTIGEN	+VE	+VE	-VE	-VE
CK 14	-VE	-VE	+VE	+VE
P63	-VE	-VE	+VE	+VE
SMOOTH MUSCLE ACTIN			+VE	-VE
CALPONIN			+VE	-VE
MUSCLE SPECIFIC ACTIN			+VE	-VE
VIMENTIN			+VE	-VE
GFAP(Glial fibrillary acidic protein)			+VE	-VE
S100	VARIABLE	VARIABLE	VARIABLE	VARIABLE

TABLE 2: Markers for Luminal and Abluminal Cell(+ve : positive ; -ve : Negative)

5% or less. High expression is associated with high-grade lesions; in contrast, the mucoepidermoid carcinoma of low grade had a Ki-67 index of 2.2%, while a higher value of 8% was observed in mucoepidermoid carcinoma of high grade.[11,22]

Other indexes, such as an apoptotic index of >0.4% as determined by the TUNEL method, along with strong expression of p53 and EGFR, and loss of bcl-2 expression, may be diagnostic for malignant tumours.[23]

3.Markers for Most Commonly Encountered Salivary Gland Tumour:

3.1. Pleomorphic Adenoma:

Pleomorphic adenoma (PA) is a mixed benign tumour and the most common salivary gland neoplasm. The reserve cell of the intercalated duct is the cell of origin, which has the ability to differentiate into both epithelial and myoepithelial cells.24 Because of its morphological diversity, it mimics other tumours. PA shows positivity for both luminal and myoepithelial cell markers.

This tumour shows positivity for CK7, CEA, and EMA (luminal cell markers), as well as myoepithelial cell markers like SMA, MSA, calponin, p63, CK14, S100, vimentin, Wilms tumour 1 (WT1), GFAP, and PLAG1 (pleomorphic adenoma gene 1).

The major differential diagnoses include myoepithelioma, basal cell adenoma, adenoid cystic carcinoma (ACC), and polymorphous adenocarcinoma (PAC).[28] Myoepithelioma shows only myoepithelial cell differentiation, while luminal cell markers are negative.[25]

Adenoid cystic carcinoma is invasive, shows perineural invasion, and contains glycosaminoglycan material. It is characterized by small, uniform cells with an angulated shape and hyperchromatic nuclei. GFAP tends to be absent, whereas CD117 highlights the inner ductal cells more strongly. The Ki-67 proliferative index is greater than 10%, compared to pleomorphic adenoma (benign), where it shows 5% or less.[26]

Polymorphous adenocarcinoma (PAC) develops only in the minor salivary glands. It exhibits prominent perineural invasion and has more uniform cells, oval nuclei, and delicate, fine vesicular nuclear chromatin. It shows weak GFAP and p63 expression. [27,28]

3.2: Basal Cell Adenoma:

Basal cell adenomas are benign salivary gland tumours comprised of inner ductal cells, outer nests, and cords of small, isomorphic basaloid cells with a distinct basement membrane-like structure. They lack the myxochondroid stroma of pleomorphic adenomas. The basaloid cells are monotonous, with dense chromatin and inconspicuous nucleoli, and show scant cytoplasm.[29,30]

Immunohistochemistry shows that basal-myoepithelial cells are positive for CK14, p63, and SOX10. The ductules are positive for CK7 and EMA.[31,32]

3.3. Adenoid Cystic Carcinoma(Adcc):

Adenoid cystic carcinoma (ADCC) is a malignant salivary gland tumour characterized by the neoplastic differentiation of salivary acinar-type and myoepithelial cells, producing a mucinous or basement membrane-like extracellular matrix.[33]

ADCC is positive for ductal and myoepithelial/basal markers such as CK7, calponin, SMA, smooth muscle myosin heavy chain (SMMHC), p63, SOX10, and S100.[33,34] Immunochemical stains like smooth muscle actin, S100, and SMMHC highlight myoepithelial differentiation around pseudocysts.

The pseudocyst lumens stain for basement membrane components, including type IV collagen and laminin. ADCC is strongly positive for C-kit (CD117), with significant expression in the inner cell layer. This helps distinguish ADCC from polymorphous adenocarcinoma (PAC), as ADCC shows over 50% positivity, while PAC shows less than 50% or none.[35,36]

The Ki-67 index is always above 10% in ADCC, particularly high in the solid variant, which has a worse prognosis. Increased p53 expression also indicates poor prognosis.

Differential diagnoses for ADCC include pleomorphic adenoma, PAC, and basal cell adenoma. Pleomorphic adenoma can be differentiated from ADCC using immunohistochemical markers; GFAP is less sensitive but helpful. PLAG1 does not play a role in ADCC tumorigenesis and is overexpressed in pleomorphic adenoma.[37]

PAC typically occurs in minor salivary glands and lacks ductal and myoepithelial cell populations. The c-kit marker distinguishes ADCC from PAC, with ADCC showing over 50% positivity. [37,38]

MARKERS	BENIGN TUMOURS	MALIGNANT TUMOURS
Ki-67(cell cycle marker G1/ G2/S/M)	Mostly less than 5%.	Shown to always be >10%, except in MEC where ki 67 index is less than 5 %
Apoptotic index	<0.4% as determined by TUNEL method	>0.4% as determined by the TUNEL method
MCM2(cell cycle marker (G1/ G2/S)	Shown always less than 10%	shown always greater than 10%
BCL 2		Loss of BCL-2
P53 AND EGFR		strong expression of p53 and EGFR

MCM2 – Mini chromosome maintenance -2; BCL 2-B cell lymphoma 2; EGFR- Epidermal growth factor receptor.

TABLE 3: Markers to Differentiate Between Benign and Malignant Tumours

In basal cell adenoma, the Ki-67 index is below 2%, supporting the diagnosis alongside strong S100-positive spindle-shaped stromal cells.[38]

3.4. Acinic Cell Carcinoma(Acc):

Acinic cell carcinoma (ACC) is a low-grade malignant salivary gland tumour that demonstrates serous acinar differentiation. Although α-amylase, a specific marker for normal acinar cells, is not always detected in ACC, recent studies indicate that DOG1 staining serves as a marker for salivary acinar cells, and strong staining can aid in diagnosing acinic cell carcinoma.[3,9] Immunohistochemistry for S100, mammaglobin, DOG1, and SOX10 helps differentiate between acinic cell carcinoma and secretory carcinoma.

Secretory carcinoma exhibits strong positivity for S100 (while acinic cell carcinomas are negative or only show patchy positivity) and mammaglobin but is largely negative for DOG1.[39] Acinic cell carcinomas display diffuse strong positivity for DOG1 and SOX10 on the luminal aspect of acini, and are negative for S100 and mammaglobin.[39]

3.5. Polymorphous Adenocarcinoma:

Polymorphous adenocarcinoma (PAC) is the second most common intraoral malignant salivary gland tumour, with approximately 60% occurring in the palate. These tumours are histologically characterized by cytological uniformity, morphological diversity, and an infiltrative growth pattern. A notable feature is the wide variation in morphological configuration, with common perineural involvement.[40]

Before the 2017 WHO classification, PAC was referred to as polymorphous low-grade adenocarcinoma. The term "low grade" has been removed in the recent classification; it is now simply called polymorphous adenocarcinoma.[40,41] This change reflects the unpredictable behavior of this lesion, as some do not exhibit low-grade characteristics.[42]

Due to its morphological diversity, PAC can mimic pleomorphic adenoma and adenoid cystic carcinoma histologically. Immunohistochemically, PAC shows positivity for pan-cytokeratin (CK) (97.3%), CK7 (96.8%), E-cadherin (90.0%), vimentin (92.5%), S100 (97.0%), p63 (91.7%), and SOX10 (100%), while little to no positivity is observed for CK20 (0.0%), p40 (0.0%), and GFAP (5.0%).

The antibody p40, an isotype of p63, shows uniform negativity in PAC, indicating a lack of true myoepithelial differentiation. The Ki-67 proliferation index is typically low, at less than 10%. However, an elevated Ki-67 index (more than 10%) is seen in 10%–20% of cases. GFAP shows diffuse positivity in pleomorphic adenoma, while both p63 and p40 are positive, and CD117 shows positivity in the inner luminal cell layer in adenoid cystic carcinoma.[43]

CK7+/CK20−, p63+/p40−, S100+, Vimentin+, and GFAP− immunophenotype have diagnostic value for PAC.

3.6. Mucoepidermoid Carcinoma:

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy and the most prevalent salivary gland neoplasm in children. The tumour can arise in major or minor salivary glands and is histomorphologically characterized by varying degrees of an admixture of epidermoid (squamoid), mucous, and intermediate cells.

Diagnosis is primarily based on morphology, with ancillary mucin stains or immunohistochemistry as needed. Diagnosing high-grade tumours, clear cell variants of MEC, and MEC with significant oncocytic components in small biopsy specimens can be challenging.

Differential diagnoses may include poorly differentiated squamous cell carcinoma, salivary duct carcinoma, or metastatic carcinoma. MEC must also be differentiated from acinic cell carcinoma, retention cysts, papillary cystadenoma, and oncocytoma.[44]

Immunohistochemistry shows CK7 positivity in mucinous cells. Intermediate, squamoid, and basaloid cells are positive for high-molecular-weight keratins (CK14 and CK5/6) and p63. P63 is a useful marker to differentiate acinic cell carcinoma from MEC; ACC is negative for p63, while all MEC are strongly positive for it.[45] The p63 immunostaining pattern can help distinguish low-grade MEC from retention cysts and papillary cystadenomas. In mucus retention cysts and papillary cystadenomas, p63 expression is limited to the basal layers of the cystic spaces, whereas in low-grade MEC, p63 is strongly expressed in the suprabasal layers of the epidermoid component of the tumour.[46]

MEC expresses various membrane-bound mucins, including MUC1, MUC4, MUC5AC, and MUC5B, in varying proportions. High MUC1 expression is associated with high histological grade, a high rate of recurrence and metastasis, and a short disease-free interval. Positive staining for MUC5AC is also helpful in differentiating high-grade MEC from squamous cell carcinoma.[47]

3.7. Salivary Duct Carcinoma:

Salivary duct carcinoma (SDC) is a high-grade malignancy, most commonly arising in the parotid gland, with a poor short-term prognosis.[48]

Histopathologically, it exhibits features similar to ductal breast carcinoma, presenting both intraductal and invasive components. Studied markers include Ki-67, proliferating cell nuclear antigen, c-erbB-2, and p53. The androgen receptor (AR) shows strong positivity in SDC, akin to ductal breast carcinoma, while estrogen receptor and progesterone receptor expressions may be negative, aiding in the differentiation from breast metastasis.[44,45] More than 20% of tumors demonstrate diffuse and strong membranous staining for HER2/neu, typically seen in high-grade malignancies. The Ki-67 proliferative index is often greater than 10%.[49]

3.8. Epithelial Myoepithelial Carcinoma(EMC):

Epithelial-myoepithelial carcinoma (EMC) is a biphasic tumour consisting of an inner layer of duct lining cells and an outer layer of clear cells, which form double-layered duct-like structures. Clear cells, of myoepithelial origin, often predominate in number.[50] EMC shows positivity for both luminal and myoepithelial cell markers. Immunohistochemistry reveals positivity for CK AE1/AE3 and CK7 in the small cuboidal, eosinophilic epithelial cells surrounding luminal spaces arranged in ductal structures. Myoepithelial cells are strongly reactive for p63, smooth muscle actin, vimentin, and S-100 protein.[51]

Conclusion:

Despite several advances in diagnosis, SGTs remain a heterogeneous group of tumors, challenging both pathologists and clinicians. While IHC plays a limited but important role in diagnosing salivary gland tumors, H and E staining remains the gold standard. It is essential to understand that IHC should be viewed as a method to assist in the final diagnosis, rather than as a means to alter the H&E-based diagnosis.

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