REVIEW ARTICLE

A Systemic Review on Similarities between Salivary and Mammary Gland Neoplasms and the Role of Antihormonal Therapy in Salivary Gland Tumors

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Abstract

Objective: The present review focuses on the morphological, pathological, and molecular level resemblance of salivary and mammary gland neoplasms with emphasis on the current status of hormonal therapy strategies in salivary gland tumors.

Methods: Literature review developed in compliance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and data collected from PubMed, Cochrane, Wiley library, and other related reference articles.

Results: The expression of hormonal receptors was found to be demonstrated frequently in salivary duct carcinoma, followed by a few other malignant tumors like carcinoma ex pleomorphic adenoma (PA), adenocarcinoma not otherwise specified (NOS) and mucoepidermoid carcinoma (MEC).

Conclusion: The similarities in the morphology, biology, and molecular changes between the salivary gland and breast tumors form the basis for the detection of hormonal receptors and the use of antihormonal therapies. The novel treatment strategies of antihuman epidermal growth factor receptor 2 (anti-HER2) and anti-androgen receptor (AR) are currently found to be effective in unresectable/rapidly progressive tumors and in multiple tumor recurrence cases for a few salivary gland tumor histologies.

Keywords: Acinic cell carcinoma, Adenoid cystic carcinoma, Androgen receptor, Epidermal growth factor receptor, Estrogen receptor, Mucoepidermoid carcinoma, Progesterone receptor, Salivary duct carcinoma.

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Introduction

Salivary glands are complex tubuloacinar exocrine or merocrine glands mainly secrete saliva. The parotid gland is ectodermal, while submandibular and sublingual glands are endodermal in origin. All the minor salivary glands have mixed origins with both ectodermal and endodermal components. The epithelial cells determine the type of secretion produced by the gland and the mesenchymal cells contribute to the morphology of the gland.[1] Each developed gland consists of parenchyma, glandular secretory tissue, and stroma. The secretory units contain secretory cells which organize to form clusters called acini. These units can be either of the three types—mucinous, serous, and seromucinous. The secretions pass through the intercalated ducts, striated, excretory duct, and finally main excretory duct opening into the oral cavity.[2]

The mammary gland contains both ectodermal and mesodermal components. The ectoderm forms a mammary line which resolves into placodes. These placodes invaginate into the mesenchyme and form the rudimentary ductal structure. The embryonic mammary mesenchyme provides the key signals for epithelial cell differentiation. This epithelial differentiation was demonstrated in reciprocal tissue recombination experiments in which 12 and 16th-day-old embryonic mammary epithelium was combined with salivary mesenchyme and grown in culture. These tissue recombinants produced epithelium that was morphologically resembling salivary glands. The rudimentary ductal system forms the terminal end buds which later differentiate to form myoepithelial cells. This system will develop into terminal ductolobular units with acini which are mainly mediated by hormones.[3]

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The matured salivary gland contains two types of cells, both luminal and abluminal cells. The luminal cells include acinar and ductal cells. The abluminal cells are myoepithelial and basal cells.[4] Unlike salivary glands, mammary glands undergo complex epithelial remodeling throughout puberty, pregnancy, lactation, and weaning. The mammary gland is a highly branched ductal structure having luminal cells and myoepithelial cells.[5] Each cell type in both mammary and salivary glands express a variety of markers that helps in the identification and characterization (Table 1) and (Table 2).[6–8]

Salivary gland tumors are distinct in their wide variety of subcategorization and rarity in occurrence. The two most widely

Table 1: Important immunohistochemical markers for salivary gland cell types[6]

Antigen	*Luminal cell*	*Myoepithelial cell*	*Basal cell*
AE1/AE3	+	–	–
CK5/6	–	+	+
CK14	–	+	+
P63	–	+	+
α-SMA	–	+	+
Vimentin	–	+	+
CK19	+	+	+
Calponin	–	+	–

CK, cytokeratin; SMA, smooth muscle actin

Table 2: Important immunohistochemical markers for mammary gland cell types[7,8]

Antigen	*Luminal cells*		*Abluminal cells*	
	Acinar	Ductal	Myoepithelial	Basal
CK (AE1,AE3)	+	+	+	+
EMA	+	+	–	–
CEA	+	+	–	–
CK14	–	–	+	+
P63	–	–	+	+
α-amylase	+	–	–	–
α-SMA	–	–	+	–
Muscle specific actin	–	–	+	–
Calponin	–	–	+	–
Podoplanin	–	–	+	–
Vimentin	–	–	+	–
S-100	Variable	Variable	Variable	Variable
GFAP			Variable	

CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; GFAP: glial fibrillary acidic protein; SMA, smooth muscle actin

accepted theories for the development of salivary gland tumors are the bicellular reserve cell theory and the multicellular histogenetic concept. Bicellular reserve cell theory states the two major reserve cells, also known as pluripotent cells like excretory duct reserve cells and intercalated duct reserve cells, will undergo altered differentiation. The tumors considered as excretory duct reserve cell origin are MEC, primary squamous cell carcinoma (SCC), and salivary duct carcinoma, whereas intercalated ductal origins are polymorphous adenocarcinoma, basal cell adenocarcinoma, adenoid cystic carcinoma (ADCC), and acinic cell carcinoma (ACC). Adenocarcinoma not specified is postulated to arise from any of these reserve cells and carcinoma ex-PA is considered to have uncertain histogenesis. The multicellular theory defines tumorogenesis as the multiplicity of any cell type giving rise to a wide variety of histologies.[9]

The tumors of the breast most commonly arise from the luminal epithelial components of the terminal duct lobular unit. The role of myoepithelial cells is studied in both salivary and breast tumors. These cells are considered tumor suppressors and are seen in many premalignant and *in situ* lesions which in turn will turn into low-grade tumors.[10] In salivary gland tumors, these cells can undergo various morphological changes due to metaplasia, dedifferentiation, and transdifferentiation to form modified or neoplastic myoepithelial cells. But similar to the breast, these cells will lead to low-grade tumors with low metastatic potential.

The most common salivary gland tumors are glandular origin, while mammary gland tumors are ductal origin. Boecker et al. proposed a lineage differentiation model for the common tumors of both glands. According to their study, the ducts of both the glands normally contain keratin (K5/K14) and p63-positive progenitor cells, which get differentiated to glandular cells, which are K8/K18 positive and myoepithelial cells which are positive for smooth muscle actin (SMA). The progenitor cells are located in the interlobular ducts of mammary glands and striated ducts of salivary glands. All the morphologically similar tumors are hence derived from these progenitor cells, which undergo both myoepithelial, glandular, and mesenchymal differentiation.[11]

Most of the studies on salivary gland-like tumors of the breast are done by Foschini et al. and they divided these tumors into three categories:[12]

- Tumors with pure myoepithelial differentiation—benign and malignant myoepithelioma.
- Tumors with mixed epithelial and myoepithelial differentiation—PA, adenomyoepithelioma, ADCC.
- Tumors with pure epithelial differentiation—ACC, MEC, oncocytoma, polymorphous adenocarcinoma.

Most of the salivary gland-like tumors of the breast are triple-negative tumors with the absence of expression of progesterone receptor (PR), estrogen receptor (ER), and HER2 receptors. Hence these tumors are clinically aggressive.

Most malignant salivary gland tumors have a high rate of locoregional recurrences resulting in a grave outcome, while most breast tumors are resectable, completely resulting in a better outcome. The complexity of head and neck spaces with variable neural anatomy associated with these tumor sites results in an incomplete clearance of tumor cells in contrast to breast tumors, where the resection is simple and straightforward with the sparing of adjacent structures. The first line of treatment for salivary gland tumors is surgical excision with or without adjuvant treatment. In unresectable or rapidly progressive metastatic tumors and in cases with multiple recurrences, systemic adjuvant therapies are necessary. Adjuvant therapy is currently limited to radiotherapy. There are studies showing the role of antihormonal therapy in adjuvant settings causing cessation of tumor progression or resolution of tumor size with improved quality of life for the patients.

In this review, we categorized the tumors occurring in both salivary and mammary glands into benign and malignant groups.

Salivary gland-like tumors of the breast can be classified as

- BENIGN TUMORS:
  - Pleomorphic adenoma
  - Adenomyoepithelioma
  - Microglandular adenosis
  - Myoepithelioma
- MALIGNANT TUMORS:
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Acinic cell carcinoma
  - Salivary duct carcinoma
  - Secretory carcinoma
  - Low-grade adenosquamous carcinoma
  - Basal cell adenocarcinoma
  - Malignant myoepithelioma
  - Adenomyoepithelioma
  - Oncocytic carcinoma
  - Polymorphous carcinoma
  - Carcinoma expleomorphic adenoma

Methodology

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines of reporting were followed:

Eligibility: Inclusion criteria-studies allowed in our review were observational, *in vitro* and *in vivo* prospective and retrospective studies. The comparison of mammary and salivary glands was analyzed in a systemic way using data search keywords salivary gland-like tumors of breast or morphological similarities between salivary and mammary glands. The studies examining salivary gland tissue for hormone receptor expressions by all the methods (*in situ* hybridization/immunohistochemistry), which includes HER2, androgen, estrogen, and PRs were analyzed. PubMed, Cochrane, Wiley library were searched from the year 2020 using the search string salivary gland-like tumors of breast or HER2/erythroblastic oncogene B, androgen, estrogen and PR expression in salivary gland tumors or role of tamoxifen/trastuzumab/combined androgen blockade (CAB) in salivary gland cancers. In addition to this, the reference list of obtained articles was also analyzed.

Exclusion criteria: Studies reported in languages other than English, unpublished studies, studies not publishing the tumor histology subtypes, and hormone receptor expression studies published before the year 2000 were excluded. The above criteria fulfilling studies were screened and assessed. The information gathered was sorted out for individual histological subtypes and represented in tables. The comparative studies on both mammary and salivary gland tumors were analyzed and reviewed in a systemic manner.

Pleomorphic Adenoma: Pleomorphic adenoma (PA) is also known as a benign mixed tumor, the most common salivary gland neoplasm. The cell of origin is the uncommitted reserve cell of the intercalated duct that has the potential to differentiate into both epithelial and myoepithelial cells. It constitutes 75% of benign salivary gland tumors and most commonly occurs in parotid (80%). It mainly affects the 4th and 5th decade population and has no sex predilection.[13]

Pathologically they are solitary firm round masses. The major histological feature has both epithelial and myoepithelial components. The presence of hyalinized stroma is the most important histological predictor of malignant change. Almost all PAs have a thin capsule with pseudopodia or satellite nodules in nearly 25% of cases. In around 70% of cases, either of the cytogenetic changes, like 8q12 rearrangements/12q13–15 rearrangements, were noted.[14]

Regarding the hormonal receptor status in PA, few studies were found in the literature. In a study by Larbcharoensub et al., metastasizing PA showed expression of PRs and they provided evidence for the role of the hormonal receptors in the pathogenesis and treatment of metastasizing PA.[14] Glas et al. demonstrated intense immunostaining with PR in recurrent PA while some authors considered ER status mainly ER β-expression has a role in PA.[15] All three receptor expression was studied by Souza and colleagues and stated that ER, PR and HER2 expression is not linked with the progression, recurrence, and malignant transformation of PA.[16]

Contrary to these findings in carcinoma ex-PA, 31–38% shows amplification of HER2.[17] Di et al. reported overexpression of HER2 in carcinoma ex-PA, which is considered as the initial event in malignant change.[18] Di and colleagues presented a case of carcinoma ex-PA successfully treated with trastuzumab and radiotherapy. Several authors also demonstrated the HER2 expression in malignant luminal cells and its involvement in the progression from the intraductal to the extracapsular stage. A similar event was also reported in the breast, where high-grade ductal carcinoma *in situ* with HER2 overexpression often progresses to invasive ductal carcinoma. The hormone receptor expression in PA is shown in the following table (Table 3).

Carcinoma Expleomorphic Adenoma

Carcinoma ex-PA is a mixed tumor with both epithelial and myoepithelial components arising from longstanding or recurrent PA. The malignancy rate in recurrent PA is 7–16%. The transformation occurs through different phases of progression, such as carcinoma *in situ* (retained myoepithelial layer), intracapsular tumor (abnormal proliferation within and between existing ducts), minimally invasive (breach of capsule), and widely invasive (extending to the gland and soft tissue).[19]

Pleomorphic adenoma (PA) of the breast is a salivary-type tumor with both epithelial and myoepithelial proliferations. A total of <100 cases have been reported in English literature so far. The first case was reported in 1906. The myoepithelial cells are located abundantly around the subareolar region and their proliferation is considered to be a key factor in histogenesis.[20,21] Histologically, it is composed of epithelial and myoepithelial components in the myxoid/chondroid and osteoid matrix. Immunohistochemistry (IHC) findings are similar to salivary glands, except in a few studies,

Table 3: Summarizes the hormone receptor expression in PA

Study	*No of cases*	*PR*	*ER*	*AR*
Moriki et al. (2001)[21]	3	–	–	+
Glas et al. (2002)[17]	69	+	–	NA
Nasser et al. (2003)[22]	4	NA	NA	–
Larbcharoensub et al. (2009)[16]		+	–	NA
Wong et al. (2009)[23]		NA	+	NA
Ito et al. (2009)[24]	41	–	–	+
Nakajima et al. (2009)[25]	23	NA	NA	+
Can et al. (2017)[26]	91	+	+	+
Aquino et al. (2018)[27]	18	–	+	+

AR, androgen receptor; ER: estrogen receptor, NA, not assessed; PR, progesterone receptor

the ER was positive. Malignant change in PA is very rarely reported in the literature. Hayes et al. reported a case series of three cases of carcinoma ex-PA of the breast and all three tumors met the diagnostic criteria defined for their salivary gland counterpart, including strong positivity to p53, but none of the three cases showed HER2 positivity.[32]

The breast PA has a thin incomplete pseudocapsule with pseudopodia with a high rate of recurrence similar to salivary tumors mandating a minimum of 3 mm adequate margin for excision.

Myoepithelioma

They are rare, benign salivary gland tumors most commonly occurring on the palate and parotid. Pathologically they have plasmacytoid or spindled myoepithelial components, and ductal structures are extremely rare. Most of the time, they are benign tumors, but malignant transformation can occur in recurrent cases.[13]

Myoepithelioma breast is also a rare tumor with pure myoepithelial cell differentiation. IHC is similar to salivary glands demonstrating features of myoepithelial cells. Aquino et al. demonstrated demonstrate AR positivity 28% of myoepithelioma patients showed AR positivity.[27]

Sclerosing Polycystic Adenosis (SPA)

Sclerosing polycystic adenosis (SPA) was originally described as a nonneoplastic condition analog to fibrocystic changes of the breast. It is a rare benign salivary gland lesion that commonly arises in the parotid gland. It is a well-encapsulated circumscribed lesion with low chances of recurrence, around 11%.[23] Most of the cases contain the proliferated apocrine ductal cells and nuclear atypia that is similar to apocrine intraductal neoplasia of the breast. SPA is characterized by genetic alterations in the phosphoinositide 3-kinase pathway and phosphatase and tensin homolog deleted on chromosome 10 expression. This molecular profile is similar to salivary duct carcinoma and the apocrine variant of intraductal carcinoma. One case of salivary duct carcinoma arising in recurrent adenosis has been reported so far.[24] Rico et al. reported a case of salivary gland-type mammary carcinoma arising in microglandular adenosis. Microglandular adenosis of the breast is an uncommon benign proliferative lesion. Even though it is a benign lesion, it can progress into atypical microglandular adenosis with increased cellularity and atypia, or in around 27% of cases, it gets converted into invasive carcinoma. The epithelial cells of this benign lesion are negative for both ER, PR, and HER2 receptors. Salivary gland-type carcinomas represent the second most common morphology after invasive ductal carcinoma in microglandular adenosis. The most commonly reported is ADCC.[25]

Both sclerosing polycystic adenosis and microglanduar adenosis can be considered preneoplastic conditions.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common salivary gland malignancy. Pathologically have both solid and cystic components. The hallmark in histology is the presence of three cell types—mucous, squamoid, and intermediate. Clinical staging, histological grade, and location of the tumor are the most important parameters determining the prognosis. There are various grading schemes described for MEC and the most accepted is Auclair grading, which was later modified by Brandwein et al. The most consistent finding is translocation t(11;19) (q21;p13) seen in >50% of MECs, which forms a fusion gene mastermind-like protein 2:MEC translocated gene 1.[13]

Mucoepidermoid carcinoma (MEC) of the breast is a rare malignancy occurring with an incidence of 0.2%. The morphology and histology are similar to salivary MEC ranging from high to low grade. The clinical behavior is based on histological grading. The genetic alteration in breast MEC is similar to the salivary gland with t(11;19) and disrupts the neurogenic locus notch homolog protein 1 (Notch 1) signaling pathway.[12] These translocations are mainly observed in low and intermediate-grade tumors and are associated with favorable outcomes, whereas p53 is the most frequently mutated gene in high-grade MECs.[26]

So far, only 28 cases of MEC breast have been reported and the results show that the histomorphological features, biology, and clinical behavior is similar to salivary glands (Table 4).

In most of the studies of MEC assessing the hormone status, the expression of both PR and ER is either negative or weakly positive. In general, around 30% of cases of MECs show HER2 overexpression. All cases of MEC were negative for ER in a study by Pires et al. around 136 cases of MECs were assessed in that study.[48] In another analysis of 16 cases by Can and colleagues, HER2 overexpression with negative AR was found in two high-grade tumors.[26] Glisson and colleagues evaluated HER2 status in high-grade salivary gland carcinomas, which showed a positivity of 21% for MEC and on trastuzumab therapy, one out of three cases showed partial response.[39] Gibbson and colleagues concluded a significant therapeutic role of HER2 receptors in MEC.[37]

Adenoid Cystic Carcinoma (ADCC)

Adenoid cystic carcinoma (ADCC) is a slowly progressing infiltrative type of tumor with a protracted course of duration. Adenoid cystic

carcinomas are more reported in minor salivary gland tumors and three growth patterns are identified: tubular, cribriform, and solid. Grading based on this tumor growth pattern carries the prognostic information. Grade III, with >30% solid pattern, carries a bad prognosis. Lung metastasis which is indolent for many years and perineural invasion are the classic features. The most consistent molecular translocation found is t (6;9), which involves myeloblastosis and nuclear factor I B genes. Immunohistochemical study shows positivity to the cluster of differentiation 34 and also receptor tyrosine kinase (c-KIT) is detected in around 80–94% of cases. Surgical resection is the treatment of choice in ADCC, followed by adjuvant treatment. 10 and 20-year overall survival is 39–55% and 21–25%, respectively.[15]

Adenoid cystic carcinoma (ADCC) of the breast accounts for <0.1% of breast carcinomas and microscopically, the features mimic ADCC salivary glands with three growth patterns. c-KIT overexpression is found in almost all ADCC breast cases and it shares the common translocation of t (6;9) at the molecular level. This marker can be used in targeted therapy for both tumors. In contrary to salivary ADCC, breast ADCC carries a favorable prognosis with fewer chances of lymph node and distant metastasis. The incidence of perineural invasion is very rare in the breast. Based on the grade of tumor, mastectomy with or without axillary dissection is recommended. 10-year overall survival for breast ADCC is >90% (Table 5).[49]

In a study comprised of exclusively ADCC for HER2 expression, only 16% (5/32) showed positivity limiting the clinical utility of this target. Overexpression of HER2 was variable in older studies ranging from 0 to 58–100%.[55] It has been shown in one study that HER2 expression was associated with significantly lower disease-free intervals.[56] The incidence of estrogen and progesterone receptors also shows variable results, with 0–75% in ER and 0–50% in PR positivity. However, a case report has mentioned a partial response of parotid ADCC with tamoxifen (ER antagonist).[57] AR status analysis shows only a small subset of tumor (5–15%) with weak AR expression.[58]

Acinic Cell Carcinoma (ACC)

Acinic cell carcinoma (ACC) is an uncommon tumor constituting around 10% of malignant tumors. Microscopically four different

Table 4: Summarizes the hormone receptor expression in MEC

Study	*Cases*	*PR*	*ER*	*HER2*	*AR*
Gibbons et al. (2001)[37]	22	NA	NA	+	NA
Weed et al. (2002)[38]	28	NA	NA	+	NA
Nasser et al. (2003)[22]	10	+	+	NA	+
Glisson et al. (2004)[39]	14	NA	NA	+	NA
Shang et al. (2008)[40]	46	NA	NA	+	NA
Ito et al. (2009)[24]	30	–	–	NA	+
Clauditz et al. (2011)[41]	319	NA	NA	+	NA
Ettl et al. (2012)[42]	28	NA	NA	+	NA
Nakano et al. (2013)[43]	31	NA	NA	+	NA
Lemound et al. (2016)[44]	10	+	–	–	+
Hashimoto et al. (2017)[45]	34	NA	NA	+	NA
Can et al. (2017)[26]	16	+	+	+	–
Aquino et al. (2018)[27]	13	–	+	NA	+
Szewczyk et al. (2019)[46]	16	+	+	–	+
Hsieh et al. (2020)[47]	24	NA	NA	+	NA

AR, androgen receptor; ER, estrogen receptor; NA: not assessed; PR, progesterone receptor

Table 5: Summarizes the hormone receptor expression in ADCC

Study	*Cases*	*PR*	*ER*	*HER2*	*AR*
Dori et al. (2000)[50]	27	+	–	NA	NA
Gibbons et al. (2001)[37]	6	NA	NA	+	NA
Glisson et al. (2004)[39]	70	NA	NA	+	NA
Dori S et al. (2002)[51]	32	NA	NA	+	NA
Nasser et al. (2003)[22]	10	–	–	NA	+
Barrera et al. (2008)[52]	47	+	+	NA	NA
Ito et al. (2009)[24]	30	–	–	NA	+
Riad et al. (2009)[53]	11	+	–	NA	+
Luo et al. (2009)[54]	17	NA	+	NA	NA
Can et al. (2017)[26]	26	+	+	NA	+
Szewczyk et al. (2019)[46]	33	–	–	–	+

AR: androgen receptor; ER: estrogen receptor; NA, not assessed; PR, progesterone receptor

patterns are seen—solid/lobular, microcystic, papillary-cystic, and follicular. The presence of acinic cells and dense lymphoid infiltration with germinal centers are classical features. ACC, in general, has the best survival except for the bad histological variant papillary cystic.[15]

Acinic cell carcinoma (ACC) of the breast shows serous differentiation similar to salivary glands. It is similar to salivary glands regarding the morphological, immunohistochemical, and ultrastructural aspects. The prognosis of breast ACC is reported as good with a low rate of recurrences and distant metastasis.[49] Very few studies evaluated the hormone receptor status of ACC and none had shown positivity to PR, but few cases were weakly positive to other receptors.[26]

Salivary Duct Carcinoma (SDC)

It is one of the most aggressive salivary gland tumor subtypes accounting for <10% of salivary gland tumors. Around 90% of the cases arise in the parotid gland. Microscopically most of the SDCs have large prominent ductal carcinoma *in situ* components with a cribriform pattern. Immunohistochemical analysis shows positivity to cytokeratins. AR, carcinoembryonic antigen, and HER2 receptors.[15]

Histologically SDC is similar to invasive ductal carcinoma of the breast. The morphology of SDC salivary glands is characterized by distinct ducts and acini with comedo-type necrosis. These features are analogous to the comedocarcinoma subtype of invasive mammary ductal carcinoma. At the molecular level also, similar alterations were found in the chromosomal arms 6,16q,17p, and 17q. Both tumors have similar aggressive biological behavior with a high rate of metastsis (Table 6).[49]

Recently a lot of studies evaluated the presence of hormone receptor status of SDC. The most widely studied and expressed is HER2 receptors showing variable results ranging from 25–100% in salivary glands and 20–25% in mammary glands. HER2 expression is associated with histological grade in both organs. In a recent meta-analysis by Egebjerg et al., the prevalence of HER2 positivity was found to be 43% in SDC.[59] Expression of AR is reported in around 29–46% of cases over various studies. Fan et al. suggested a potential role of AR in the pathogenesis of SDC through the epidermal growth factor receptor and transforming growth α-factor.[61] There is a wide disparity in the expression of ER and PR is least significant in most of the studies. Both HER2 and AR have a potential role in the pathogenesis of SDC and hence can be used as a target for therapeutic intervention.

Secretory Carcinoma

Secretory carcinoma of salivary glands was first described in 2010 by Skalava et al. they described a series of 16 cases resembling both salivary ACC and low-grade cystadenocarcinoma. The most distinct feature was strong similarities with secretory carcinoma of the breast in both morphology and IHC panel. The presence of translocation t (12;15) (p13:q25) with the ETS variant transcription factor 6 and neurotrophic receptor tyrosine kinase 3 fusion gene is specific for secretory carcinoma breast. IHC markers that are positive include S100, vimentin and mammaglobin, and negative for discovered on gastrointestinal stromal tumor 1 (DOG1). They are low-grade tumors with an indolent course.[91]

Similar to breast secretory carcinoma, mammary analog secretory carcinoma of salivary glands are classified as a triple negative disease with the absence of expression of ER, PR, and HER2 receptors.

Low-grade Adenosquamous Carcinoma

This was originally described in 1987 as a variant of metaplastic carcinoma breast. It is a tumor of uncertain histogenesis but morphologically similar to syringomatous carcinoma of salivary glands. Syringomatous adenocarcinoma, similar to adnexal carcinoma of the skin is now considered a newer emerging entity termed sclerosing microcystic adenocarcinoma of salivary glands. Sclerosing microcystic adenocarcinoma has exclusively been reported in minor salivary glands, including the tongue, lip, the floor of the mouth, buccal mucosa, and nasopharynx. SMA has relatively good outcome without locoregional recurrences or distant metastasis.[89]

The mammary counterpart of SMA is clinically present as a palpable mass in the upper lateral quadrant. Microscopically these are similar to SMA, with glandular structures filled with amorphous material and embedded in the abundant stroma. They are also composed of both glandular cells and myoepithelial cells. Low-grade adenosquamous carcinoma breast is negative for hormonal receptors and usually has an indolent behavior with relatively good outcome.[90]

Basal Cell Adenocarcinoma

Basal cell adenocarcinoma is rare and constitutes only 1–2% of salivary gland malignancy and almost always occurs in the parotid gland. Basal cell adenocarcinoma shows indolent behavior but is locally aggressive, with chances of recurrence in about 30% of cases. Regional and distant metastasis rates are 8–12% and 2–4%, respectively.[15,94]

Basal cell adenocarcinoma is a rarely reported entity in literature. In 2012, Flynn et al. published a case series of three cases of basal cell adenocarcinoma arising in salivary gland metaplasia of the breast. Microscopically made of solid nests of basaloid neoplastic cells with salivary gland-like acini.[91] Walls et al. reported a literature review with 11 patients of basaloid salivary gland analog tumors of the breast.[92] All tumors displayed malignant basal cells forming glands and solid nests. There are a few other case series by shin et al. and Lamovec et al. reporting basaloid tumors of the breast. But due to the paucity of literature, it is difficult to conclude the prognosis and outcome of these tumors.[93,94]

Very few studies evaluated the hormone receptor status of basal cell adenocarcinoma. Nasser et al. showed few cases having positivity to AR.[23] The recent meta-analysis by Egebjerg et al. reported five studies of basal cell adenocarcinoma, but all had HER2 negative status.[59]

Benign and Malignant Myoepithelioma

Myoepitheliomas are rare benign salivary gland tumors composed of plasmacytoid or spindled myoepithelial cells, most commonly affecting the palate and parotid. Myoepithelial carcinoma is a malignant counterpart that is also very uncommon and frequently occurs in parotid glands. They have irregular borders with infiltrative growth patterns and follow the rule of 30. A total of 30% of patients will have multiple local recurrences, 30% will die of metastatic disease, and 30% will be disease-free after resection.[15]

Benign and malignant myoepithelioma of the breast is extremely rare. Similar to a salivary gland tumor, it is entirely made of myoepithelial cells. Prognosis is poor, with a high rate of distant and local failure.[96]

The hormone receptor expression was rarely studied in myoepithelial tumors due to the rarity of the lesion. Aquino and

Table 6: Summarizes the hormone receptor expression in SDC

Study	*Cases*	*PR*	*ER*	*HER2*	*AR*
Fan et al. (2000)[60]	13	–	–	NA	+
Fan et al. (2001)[61]	12	–	–	NA	+
Skalova et al. (2001)[62]	15	NA	NA	+	NA
Nasser et al. (2003)[22]	10	–	–	NA	+
Skalova et al. (2003)[63]	11	NA	NA	+	NA
Glisson et al. (2004)[39]	12	NA	NA	+	NA
Jaehne et al. (2005)[64]	50	NA	NA	+	NA
Williams et al. (2007)[65]	84	NA	NA	NA	+
Cornolti et al. (2007)[66]	13	NA	NA	+	NA
Nabili et al. (2007)[67]	7	NA	NA	+	NA
Sygut et al. (2008)[68]	4	NA	NA	NA	+
Ettl et al. (2008)[72]	12	NA	NA	+	NA
Locati et al. (2009)[70]	25	–	–	+	+
Williams et al. (2010)[68]	66	NA	NA	+	NA
Clauditz et al. (2011)[41]	14	NA	NA	+	NA
Dipalma et al. (2012)[71]	42	–	–	+	+
Suzuki et al. (2012)[72]	12	NA	NA	+	NA
Cros et al. (2013)[73]	3	–	–	+	+
Nardi et al. (2013)[74]	27	NA	NA	+	NA
Kondo et al. (2014)[75]	13	NA	NA	+	NA
Masubuchi et al. (2014)[76]	32	NA	NA	+	+
Han et al. (2015)[77]	25	NA	NA	+	NA
Luk et al. (2016)[78]	119	NA	NA	+	+
Kusafuka et al. (2016)[79]	101	NA	NA	+	+
Lemound et al. (2016)[44]	38	+	+	+	+
Can et al. (2017)[27]	25	+	+	+	+
Takase et al. (2017)[80]	151	NA	NA	+	+
Hashimoto et al. (2017)[45]	32	NA	NA	+	NA
Khoo et al. (2017)[81]	15	NA	NA	+	+
Boon et al. (2018)[82]	177	NA	NA	+	+
Beck et al. (2018)[83]	15	NA	NA	+	NA
Ryu et al. (2018)[84]	28	NA	NA	+	–
Kanazawa et al. (2018)[85]	34	NA	+	+	+
Liang et al. (2019)[86]	75	NA	+	+	+
Santana et al. (2019)[87]	25	NA	NA	+	+
Szewczyk et al. (2019)[46]	16	–	–	+	+
Villepelet et al. (2019)[88]	61	NA	NA	+	+

Contd…

Contd…

Study	*Cases*	*PR*	*ER*	*HER2*	*AR*
Gargano et al. (2019)[89]	28	NA	NA	+	+
Chatzopoulos et al. (2020)[90]	16	NA	NA	+	+

AR, androgen receptor; ER, estrogen receptor; NA, not assessed; PR, progesterone receptor

colleagues reported 28% of cases of benign myoepithelioma with AR expression.[27] ER and PR expression were not found to be significant in the available studies. A total of 4.3% is the prevalence of HER2 positivity in the recent meta-analysis by Egebjerg et al.[59]

Adenomyoepithelioma

It is a biphasic tumor morphologically similar to epithelial, myoepithelial carcinoma of salivary glands with a fairly good outcome.[96]

In the breast, it occurs as adenomyoepithelioma, histologically made of dual cell proliferation lining the glandular lumen. The prognosis of adenomyoepithelioma breast is good, with chances of recurrence on incomplete primary excision.[95]

The prevalence of HER2 positivity in epithelial, myoepithelial carcinoma corresponds to 1.8%, according to a recent meta-analysis.[56] The status of hormonal receptors is the least studied in this entity.

Oncocytic Carcinoma

Oncocytic lesions are usually benign in salivary glands. They are extremely rare and are characterized by malignant oncocytes with adenocarcinomatous differentiation with features of locoregional and distant invasion. Most of the reported cases are high-grade with increased rates of locoregional and distant failure.[95]

Oncocytic tumor of the breast occurs in elderly females and are composed of >70% oncocytes. These are extremely rare variants of breast carcinoma with variable expression of hormone receptors.[96] HER2 receptor expression was not identified in studies, including oncocytic carcinoma while AR was found positive in a few studies.[27]

Polymorphous Adenocarcinoma

It is the second most common intraoral malignant salivary gland tumor, with approximately 60% occurring in the palate. These tumors are histologically characterized by cytological uniformity, morphological diversity, and infiltrative growth pattern. A salient feature is the wide variation of morphological configuration and perineural involvement is common. The prognosis is relatively good.[15]

Polymorphous carcinoma of the breast morphologically resembles low-grade adenocarcinoma salivary glands composed of the proliferation of monotonous neoplastic cells arranged in an Indian file pattern. IHC shows strong positivity to B-cell leukemia/lymphoma 2 protein.[98] Only a few cases have been reported so far. HER2 expression is not found in adenocarcinomas and few studies show expression of ERs.[26]

Current Role of Hormone Receptor Status in Treatment of Salivary Gland Tumors

Tumors originating from the excretory ducts (MEC, SCC, and SDC) may show higher rates of HER2 overexpression than tumors originating from intercalated ducts (ADCC, ACC, adenocarcinoma NOS, myoepithelial carcinoma).

Human epidermal growth factor receptor 2 (HER2) belongs to the class of the epidermal growth factor receptor. It possesses a tyrosine kinase activity gene and is involved in signal transduction of cell growth. HER2 overexpression can be measured semiquantitatively by immunohistochemistry and gene amplification can be measured by fluorescent *in situ* hybridization technique. HER2 overexpression or amplification is linked to the response to trastuzumab in breast cancers. HER2 receptor status acts as a therapeutic target and a prognostic factor in breast carcinoma. HER2 expression is associated with the worst prognosis and using monoclonal antibody trastuzumab for patients exhibiting HER2 overexpression is the standard of care in breast carcinoma now.[101] The morphological similarity of salivary duct carcinoma to invasive carcinoma of the breast and molecular resemblance to apocrine breast cancer makes HER2 a novel target for therapeutic intervention in salivary glands. HER2 expression is most frequently found in this subtype in most of the studies. HER2 scoring system used for breast cancer is applied for salivary gland carcinoma. Treatment of HER2 positive cases may include monoclonal antibodies (trastuzumab and pertuzumab) or HER2 tyrosine kinase inhibitors (lapatinib). The present evidence offers HER2 targeted therapies (trastuzumab plus taxane, pertuzumab plus trastuzumab, or ado-trastuzumab emtansine) as first-line or subsequent-line therapies for HER2 positive salivary gland carcinoma.[102] Recent two trials with HER2 targeted therapies showed a good response rate of 90 and 60% with ado-trastuzumab emtansine and a combination of trastuzumab and pertuzumab, respectively. In an open-label phase IIa basket trial, complete response was observed in SDC and partial response most commonly was seen in the adenocarcinoma subtype.[103] In the National Cancer Institute Molecular Analysis for Therapy Choice trial with ado-trastuzumab emtansine for HER2 amplified pathologies, two out of three salivary gland carcinomas with MEC and SCC subtypes showed partial response.[104]

Androgen, estrogen, and PRs are members of the nuclear hormone receptor family of transcription factors. Androgens bond to AR, resulting in the promotion of certain genes and pathways involved in tumor cell growth and resistance. AR is expressed in the majority of SCCs and a minority of other subtypes, such as adenocarcinoma NOS.[58]

For patients with AR-positive salivary gland cancer, CAB may be offered.[36] AR-positive cases treated using leuprorelin acetate and bicalutamide showed an overall response rate of 42% in a phase II study. 94% of cases were SDC and the rest were adenocarcinoma NOS.[105] There are few retrospective studies demonstrating response to androgen deprivation therapy, either single-agent or CAB [lutenizing hormone releasing hormone (LHRH) LHRH analog plus bicalutamide].[106–108] The first prospective trial on AR-positive salivary tumors, single agent enzalutamide showed stable disease in more than half the patients.[109]

Several studies observed ER and PR receptor expression in salivary gland tumors, but there is a vast disparity in the results ranging from 0–86% and 0–50% for both ER and PR, respectively. Williams et al. described the expression of ER-β in most of the tumors of the breast and salivary glands. The absence of ER-β is associated with local recurrences. ER-β inhibit cell proliferation through the cyclin D1 pathway and apoptotic pathway.[36,65] Several strategies are used in breast cancer for targeting ER-positive tumors, like ovarian suppression drugs, estrogen production blockage with aromatase inhibitors, and, most commonly, selective estrogen receptor modulators like tamoxifen.[110] There are a few case reports of the use of tamoxifen for ADCC showing stable disease.[111] Another case report of SDC parotid treated with tamoxifen and anastrozole (aromatase inhibitor) showed an objective response with long-term disease stability.[112]

The role of PR was extensively studied by Yoshimura et al. in human ADCC cell lines. Progesterone was found to markedly inhibit cell proliferation. In both salivary and mammary glands, this inhibitory effect was observed. In both types of cancers, Id-1 and cellular Myc was downregulated and p21 was upregulated after progesterone treatment. Hence progesterone is homeostatic for both cancers and triggers a tumor dormancy state.[113] Selective PR modulators have significant activity against breast cancer in clinical trials, but due to cross-reactivity with glucocorticoids, it is less tolerated by patients. Targeted ER/PR therapy is currently not being used in the treatment of salivary gland carcinomas, likely due to the lower frequency of positive receptor status and less likely benefit of targeting these receptors.

Conclusion

The resemblance of mammary and salivary gland tumors is the basis for the newer concept of antihormonal therapies in salivary gland tumors. Even though these tumors differ in incidence, most of them show similar clinical behavior and biology. Based on the expression of hormone receptors in breast cancer, similar tumors of salivary glands can be evaluated for targeting these receptors. A wide range of receptor expression is observed in a wide variety of subgroups of salivary gland tumors. It could also be due to variability in antibody clones, fixation processes, scoring systems, and observer variability. Current evidence manages relevant information regarding the status of HER2 and ER expression of tumors. These receptors are significantly expressed more in salivary duct carcinoma and in the minority of carcinoma ex PA, adenocarcinoma NOS, and MEC. The novel treatment strategies of anti-HER2 and anti-AR therapies are currently found useful mainly for SDC and a few cases of adenocarcinoma NOS and MEC. The wide range of protein expression and the vast diversity of salivary gland tumors mandates more accurate data from multi-institutional prospective trials to establish the role of hormonal therapies in salivary gland tumors.

Limitations

The statistical analysis of the prevalence of each receptor status on individual histological subtypes was not done.

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