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CLINICOPATHOLOGICAL STUDY ON RARE MALIGNANT TUMORS OF PAROTID GLAND AND COMPREHENSIVE REVIEW ON NEWER ENTITIES OF SALIVARY GLAND TUMORS

Oncology

Veena B Ganga* Senior Resident, Kidwai Memorial Institute Of Oncology, Bangalore, 560002 India. *Corresponding Author

Krishnappa Professor, Kidwai Memorial Institute Of Oncology, Bangalore, 560002, India.

ABSTRACT

Salivary gland tumors are a heterogeneous group of tumors in the head and neck; most of the malignant tumors have a poor prognosis and limited long-term survival. The recent 2017 WHO classification had made few changes in the sub-categorization and modified some terms. More studies are underway in the field of molecular level changes and responses to targeted therapies in these tumors. These researches have shown some resemblance in the behavior of salivary gland and breast carcinomas, leading to a new line of thinking in terms of hormonal therapy. This study outlines 14 cases of rare parotid tumors reported in our institute during the time period of 2018 to 2020 and a comprehensive review on salivary gland tumors, newer entities added, and newer treatment strategies.

KEYWORDS

salivary gland tumors, IHC(immunohistochemistry),ACC(Acinic cell carcinoma), SDC (salivary duct carcinoma), MEC(mucoepidermoid carcinoma), SCC (squamous cell carcinoma)

1. INTRODUCTION

In the past few years, improvement in molecular testing, immunohistochemical panel studies and newer mutational sequencing has facilitated a more precise classification of salivary gland tumors. 2005 WHO classification of salivary gland tumors had 24 different entities, since then newer subtypes were studied and added in the modified WHO list with 28 separate entities.[1]

Salivary gland tumors most commonly occur in the parotid gland and most of the tumors are benign in nature. About 1 in 4 parotid tumors are malignant. Radiation exposure including low dose radioiodine and cellular telephone use are described as risk factors for parotid carcinoma.[1] The clinical features of a rapid increase in size, facial nerve palsy, cervical lymphadenopathy, fixity to surrounding structures are the factors predicting the odds towards malignancy. Conventional MRI and FNAC are supplementary aids in the diagnosis of benign and malignant tumors. Diffusion weighted MRI is found to have better accuracy in distinguishing malignant and benign lesions based on the specific diffusion pattern. The role of PET CT scan is to exclude distant metastasis.[2]

The histology and architecture of salivary glands are important to understand the type of cells undergoing malignant transformation. All the salivary glands have common embryogenesis, they develop from two distinct structures; oral epithelium and underlying mesenchyme. Parotid glands are the first to develop at around 6 weeks of intrauterine life.[3] Two types of cells constitute the glandular structure mainly the luminal and abluminal cells. Luminal cells are epithelial in origin which are ductal and acinar cells and lines the lumen, while abluminal cells include myoepithelial and pluripotent basal cells. Abluminal cells are not in contact with the lumen. The gland is organized into several lobules which contain acini. These acini are connected to the ductal system which follows the order of intercalated ducts, striated ducts, and excretory ducts in increasing diameter.

There are four theories proposed to explain the tumourigenesis in salivary glands[4]

1. The multicellular theory proposed by Dardick et al where the entire ductoacinar unit undergoes a transformation from differentiated cells to dedifferentiated cells with a deranged growth pattern.
2. Pluripotent unicellular reserve cell theory: basal cells of the excretory duct are responsible for all the remaining salivary gland units.
3. Semi-pluripotent bicellular reserve cell theory: developed by Eversole 1971 and modified by Batasakis et al. According to this theory, the outer basal cells give rise to inner luminal cells. They proposed that the intercalated ducts develop from the excretory ducts.
4. Bicellular reserve cell theory stated that the derangement happens when the pluripotent basal cells undergo differentiation. Hence earlier the change happens, it results in more undifferentiated and high grade tumors.[2] This is the most widely accepted theory. The excretory duct reserve cells and intercalated duct reserve cells are considered as hypothetical cells of origin. The tumors considered as excretory duct reserve cell origin are mucoepidermoid carcinoma, primary squamous cell carcinoma, and salivary duct carcinoma whereas intercalated ductal origins are polymorphous adenocarcinoma, basal cell adenocarcinoma, adenoid cystic carcinoma, and acinic cell carcinoma.

Adenocarcinoma not specified is postulated to arise from any of these reserve cells and carcinoma expleomorphic adenoma is considered to have uncertain histogenesis.

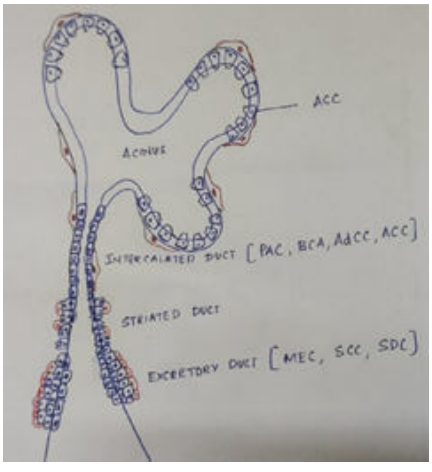

Figure 1: DUCTOACINAR UNIT

Showing sites of origin of the tumor
Luminal cells of acini - Acinic cell carcinoma (ACC). Reserve cells of intercalated duct – polymorphous adenocarcinoma (PAC), basal cell adenocarcinoma (BCA), adenoid cystic carcinoma(AdCC). Reserve cells of striated duct – mucoepidermoid carcinoma (MEC), squamous cell carcinoma (SCC), salivary duct carcinoma (SDC).

Each cell expresses different markers which help in tumor characterization and identification of subtypes. Unlike in the other subsites of head and neck neoplasms, the histological typing of salivary gland tumors is not based on the cell of origin. The type of cellular differentiation, tumor cell organization, materials secreted by tumor cell are the factors which help in diagnosis.The cell differentiation results in three basic tumor structures for salivary gland neoplasm.

1. Dual population with both luminal and abluminal cell differentiation

2. Cell population resembling glandular/ acinar cells.
3. Cell population similar to myoepithelial/ basal cells

Immunohistochemistry has a limited role in the diagnosis of salivary gland neoplasms. It is useful for 2 purposes, the first is to identify the type of cell differentiation and the second is to identify the Ki67 index to differentiate between adenoma and carcinoma.

Despite newer molecular diagnostic techniques, salivary gland tumor still creates a challenge in distinguishing malignant and benign entities as they are the most heterogeneous variety of cancers. Moreover, the rarity of the disease, limited experience of the pathologist, and vast morphological diversity create a diagnostic dilemma in tumor typing. Tumor grade and histology are the most important prognostic factors for locoregional and distant failure. In most cases, the final characterization of the tumor can be confirmed only after surgical excision and biopsy. Almost all the high grade tumors require multimodality treatment and carries poor prognosis. In this study, a clinicopathological analysis of fourteen rare parotid tumors treated during the period 2018 to 2020 (3 years) was carried out.

2. MATERIALS AND METHODS

A retrospective analysis was conducted at Kidwai Institute of Oncology, Bangalore on rare parotid tumor cases that underwent treatment during the time period of 3 years between 2018 to 2020 in the department of head and neck surgery. Inclusion criteria included both malignant and benign tumors of parotid which are the rarest subtypes. The data regarding clinical presentations, staging, fine needle aspiration cytology, CECT findings, type of treatment (curative / palliative), final histopathology findings, and outcome were analyzed.

2.1 Objective of the study

To focus on the clinicopathological features of rare parotid tumors presented to the department of head and neck surgery during the study period.

2.2 Methodology

The data included in the study were selected cases of rare parotid tumors according to the final histopathology report for those patients who underwent surgical modality of treatment and fine needle aspiration cytology report for those cases who underwent palliative treatment. Clinical data were collected from medical records which included the patient's age, gender, clinical and radiological features, type of treatment the patient underwent, biopsy result, final histopathology reports, and the last follow-up disease status.

3. RESULTS

A total of 14 cases were reviewed.

Table: 1 The histology of these tumors are represented in table 1

TUMOUR CHARACTERISTICS AND MANAGEMENT:

Histological type	No of cases
Salivary duct carcinoma	4
Squamous cell carcinoma	2
Adenocarcinoma	2
Acinic cell carcinoma	1
Carcinoma expleomorphic adenoma	1
Secretory carcinoma	1
Carcinosarcoma	1
Lymphoma	1
Haemangiopericytoma	1

14 case records of patients diagnosed with rare parotid tumors who presented to the Department of Head and Neck during the study period were selected. Of the 14 cases, 4 were female. All the cases presented to us with a history of long standing parotid swelling. All patients had grade 3 to 4 facial palsy except for the lymphoma case. All cases underwent radiological assessment during evaluation. Fine needle aspiration cytology was done as a routine workup, but most of the preliminary FNAC report did not correlate with the final histopathology sub-categorization. The common subtype obtained on histology was salivary duct carcinoma (n=4), followed by squamous cell carcinoma (n=2) and Adenocarcinoma (n=2). Both the cases of squamous cell carcinoma had involvement of the external auditory canal.

Lymphoma and adenocarcinoma patients underwent trucut biopsy and immunohistochemistry panel. The histology type of lymphoma on IHC was suggestive of MALT(mucosa associated lymphoid tissue) lymphoma with CD19, CD 20. CD22 and kappa light chain positive. This case was managed with radiotherapy as it was a limited stage disease.

Two cases reported as adenocarcinomas were high grade tumors and T4a stage tumors. Both were female patients, one case had N1 nodal status positive for malignancy and underwent total parotidectomy with modified neck dissection and adjuvant radiotherapy. The other adenocarcinoma case was the only case that could not be surgically salvageable in our study as the tumor was T4a disease with lung metastasis and with the tumor extending up to the zygomatic arch, getting a complete negative surgical margin was not possible. The case was referred for palliative chemotherapy.

The only benign tumor included in our study was haemangi opericytoma, which was seen in a 30 year old male with a history of recurrent parotid tumor and initially diagnosed as a solitary fibrous tumor on fine needle aspiration cytology.

Total parotidectomy along with sacrificing the facial nerve was carried out as the tumor mass was encasing the nerve. Final pathology and IHC report showed CD 34 and STAT6 positivity with ki67 index 5 to 6 % confirming haemangi opericytoma.

We had 3 cases of salivary duct carcinomas presenting in the T4a stage with facial nerve palsy, two patients were female and one patient was male. All the 3 patients underwent radical parotidectomy with neck dissection and reconstruction with PMMC flap (2)/ submental flap (1) followed by adjuvant radiotherapy. Histopathology report confirmed high grade SDC showing perineural invasion with carcinoma insitu changes in the parotid duct. IHC revealed Her2 positivity and focal positivity for androgen and progesterone receptors.

The single unique case we encountered in this study was that of a 42 year old male who presented with parotid swelling with intact facial nerve function. He subsequently underwent conservative parotidectomy with sparing of the facial nerve. Histology of the surgical specimen confirmed the diagnosis of low grade secretory carcinoma, positive for s100 and mammoglobulin on IHC

The single reported case of acinic cell carcinoma was that of a 56 year old female with parotid swelling and facial nerve palsy. After radical parotidectomy and neck dissection, she underwent free flap reconstruction with an anterolateral free flap which failed, and later PMMC flap was done. The final report confirmed an aggressive variant of the acinic cell, papillary cystic type.

We had a case of a 62 year old male presenting with facial nerve palsy and right parotid swelling, FNAC of the tumor reported as carcinoma expleomorphic adenoma. MRI revealed an extensive lesion involving infratemporal fossa with suspected perineural spread and level 2 lymph nodes adherent to the internal jugular vein. Radical parotidectomy with hemimadibulectomy and modified radical neck dissection with reconstruction were done.

The final pathology report was in favor of carcinoma expleomorphic with adenocarcinoma component. The patient received adjuvant radiotherapy but within one year of follow-up, he developed distant metastasis.

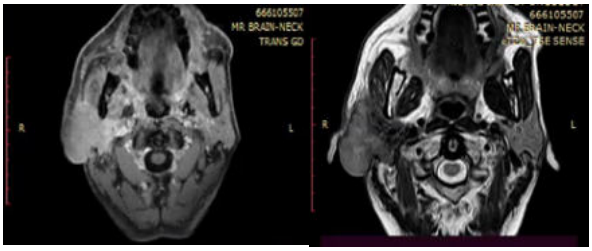

Figure: 2a Preoperative photo of long standing right parotid swelling presenting with facial nerve palsy, 2b Radical parotidectomy with neck dissection and PMMC flap reconstruction.

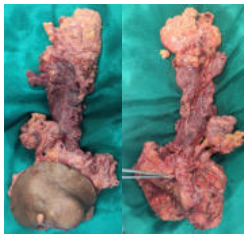

Figure 3a and 3b: Contrast enhanced T1 and T2 weighted MRI images showing contrast enhancement of tumor in both superficial and deep lobes

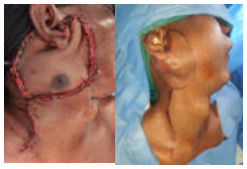

Figure 4a and 4b: Radical parotidectomy and neck dissection specimen with forceps pointing on the resected proximal end of the facial nerve.

Two cases of squamous cell carcinoma and a single case of adenocarcinoma also were reviewed. Both SCC cases had involvement of the external auditory canal in addition to facial nerve palsy and underwent sleeve resection also.

Another aggressive malignant tumor encountered was a 30 year old female with previous history of two excisions done presented with a fumigating bleeding tumor with facial nerve palsy. PETCT was done as a part of metastatic workup which was showing FDG avid large parotid lesion involving both deep and superficial part with largest dimension of 10 cm infiltrating the masseter muscle. The medial carotid space was free. A few FDG avid level II, III, V lymph nodes also noted. Fine Needle aspiration cytology was showing poorly differentiated tumor. Radical parotidectomy with modified radical neck dissection and PMMC flap reconstruction was done. The final histopathology report was showing carcinosarcoma with carcinoma component pancytokeratin positive and sarcoma component negative for cytokerakin.

S100, desmin, SMA, CD34 and EMA but positive for vimentin. Microscopically it was composed of pleomorphic spindle cells with high mitotic rate. The Ki 67 index was more than 30% in both the components. Postoperatively patient took adjuvant radiotherapy also.

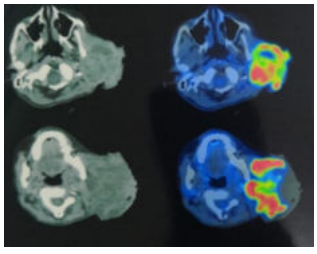

Fig 5: PET CT scan showing FDG avid lesion involving both superficial and deep lobes with extensive skin involvement and fungation.

Almost all the malignant tumors were reported as high grade in cytology and all these cases had either skin involvement or stretched out skin. Hence they underwent multimodality treatment with radical parotidectomy, neck dissection with reconstruction followed by adjuvant radiotherapy.

OUTCOME

Among the malignant tumors treated, four cases had recurrence within the first year of completion of treatment and had an average survival period of 6.4 months. The rest of the cases had recurrence free survival till the date of the last follow-up. The mean follow-up period was 11.8 months. Recurrence was found in high grade histology variants of salivary duct carcinoma (2), SCC (1), acinic cell carcinoma (1) and carcinosarcoma(1). Three out of five recurrent parotid cases died during the study period and all the three cases had distant metastasis in lung or liver.

4. DISCUSSION

The newer molecular level diagnostic tools and mutation specific antibodies have facilitated a more specific categorization of salivary gland tumors. WHO classification of salivary gland tumors has undergone a lot of changes leading to more tumor subtype variants identification. The recent 2017 WHO classification includes 13 benign and 23 malignant tumors.[5] Salivary gland tumors can be also be categorized as high grade, intermediate, and low grade tumors. Most of the rare tumors of parotid we encountered were high grade tumors. The following table shows tumor grading classification.

Table 2

Low grade	Intermediate	High grade
Low grade mucoepidemoid carcinoma	Cribriform variant Adcc	High grade mucoepidermoid carcinoma
Acinic cell carcinoma	Epithelial myoepithelial carcinoma	Salivary duct carcinoma
Tubular variant of Adcc		Carcinoma expleomorphic adenoma
Low grade adenocarcinoma		Adenocarcinoma NOS
Polymorphic low grade adenocarcinoma		Squamous cell carcinoma
Mucinous adenocarcinoma		Undifferentiated carcinoma
Clear cell carcinoma		Small cell and large cell carcinoma
Mammary analogue secretory carcinoma		Oncocytic carcinoma
Basal cell adenocarcinoma		carcinosarcoma
Sebaceous adenocarcinoma		
Intraductal carcinoma		

This grade classification does not always parallel with the clinical behavior, but still, almost all the high grade tumors exhibited highly aggressive clinical courses. The major histological subtypes we came across will be enumerated in detail

SALIVARY DUCT CARCINOMA:

These are rare, highly aggressive salivary gland malignancies with high mortality and morbidity. It accounts for 10% of all salivary gland tumors. It has a male predisposition and affects elderly people. It resembles highly aggressive ductal carcinoma of the breast. It frequently involves the parotid with a propensity for perineural invasion; microscopically it has intraductal and invasive components. Even though IHC is not useful for diagnosis, it is to be highlighted that constant overexpression of HER2, androgen receptor, and prostate specific antigen expression opens up newer avenues for molecular research and targeted therapy in the future. High ki67 index along with HER2 positivity indicates aggressive behavior.[6] In 2017 Osborn et al did a large sample study on 495 cases of SDC and he concluded that currently there is no proper treatment guideline for this aggressive tumor and adjuvant treatments do not have any impact on the overall survival. One of the treatment drugs under investigation is trastuzumab based on HER2 overexpression.[7]

SECRETORY CARCINOMA:

This subtype was first described in 2010 by Skalava et al. they described a series of 16 cases resembling both salivary acinic cell carcinoma and low grade cystaden ocarcinoma. The most distinct feature was strong similarities with secretory carcinoma of the breast in both morphology and IHC panel. They identified the presence of translocation t (12;15) (p13:q25) with the ETV6 NTRK3 fusion gene which is specific for secretory carcinoma breast. IHC markers that are positive include S100, vimentin, and mammoglobulin and negative for DOG1. They described it as a mammary analogue of secretory carcinoma. They are low grade tumors with an indolent course, pathologically they have a microcystic honeycomb appearance with multiple small cysts combining to form large cysts but acinar cells are absent.[8]

An Indian case series by Nisar Z et al included three cases in 1 year

period and is the first study in Indian literature. In this study, there was a female preponderance.[9]

The mean age of presentation is 46.5 years with a male to female ratio of 1:1. Before its description in 2010 it was described as zymogen poor acinic cell carcinoma and was included in acinic cell carcinomas, but in 2017 WHO classified secretory carcinoma as a separate entity. To date around 289 cases are reported.

SQUAMOUS CELL CARCINOMA:

Primary SCC of salivary glands is rare (0.3 to 1.5%) and most commonly it occurs due to metastasis of cutaneous SCC to intra and periparotid nodes. Cases of primary SCC is reported only in parotid till now. Primary SCC can arise following longstanding ductal obstruction, lithiasis, squamous metaplasia, and dysplasia. 66 parotid SCC cases were reviewed in a study by Ying Y et al in 2005, where more than 50% of cases were metastasis most commonly from cutaneous tumors. The clinical outcome was similar in both metastasis and primary.[10]

ADENOCARCINOMA NOT OTHERWISE SPECIFIED:

ANOS is a malignant neoplasm exhibiting both glandular or ductal differentiation but lacks histomorphological features of carcinomas.it is usually a diagnosis of exclusion and typically occurs in older adults. The majority of ANOS is high grade with a 15 year survival rate of only 3%. The grading system is based on the extent of primary gland formation having the following features of nuclear atypia, high mitotic rate, atypical mitotic figures, necrosis, perineural invasion, bony invasion, angiolymphatic invasion, and aggressive pattern of invasion.[11]

CARCINOMA EXPLEOMORPHIC CARCINOMA (malignant mixed tumor):

it's a mixed tumor with both epithelial and myoepithelial components arising from longstanding or recurrent pleomorphic adenoma. The incidence is increasing with 1.5% at 5 years and 10% at 15 years, most commonly arises in the parotid. The malignancy rate in recurrent pleomorphic adenoma is 7 to 16%. Carcinoma expleomorphic adenoma is not a standalone diagnosis. The type and extent of the carcinoma component impact the management. Most of the tumors are high grade adenocarcinoma, SDC, or low grade myoepithelial carcinoma. The concept of stratification by the extent of invasion was introduced previously but it is expanded in the new WHO classification.

The transformation occurs through different phases of progression 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). This histological progression is very important as the prognosis depends upon the stage of this progression. Initially, there is a malignant change in the ductal luminal cells of pleomorphic adenoma but the abluminal myoepithelial cells are intact. In the next phase, these malignant cells break the abluminal myoepithelial cell sheath and invade the stroma of pleomorphic adenoma but the capsule is intact and in the third phase these cells will break the capsule and become extracapsular and invasive. The last phase is divided into minimally invasive and widely invasive.[12,13] The cutoff value for this is controversial. 2005 WHO classification took 1.5mm as the minimum cut off according to Brandwein et al[14], but several other studies have justified different values ranging from 8mm (Toryoledo et al[15]) to 5mm (Olsen et al[16], Weiler et al[13]). Hence current WHO edition suggests further studies for a validated cutoff point.

Palma et al proposed a classification for carcinoma expleomorphic adenoma which includes 4 subcategories [17]

1. Non invasive/Insitu/intratubular/intraductal
2. invasive but still intracapsular
3. minimally invasive < 1.5mm
4. Invasive up to 6mm.

The prognosis is bad when it arises in a recurrent pleomorphic adenoma compared to carcinoma arising in a primary pleomorphic adenoma. This is basically due to its size and clinical features which give primary big lesion more time to stay in the intracapsular stage which allows early diagnosis before it becomes extracapsular. The malignant component is often a high grade carcinoma typically SDC/ ADC. These tumors are found to have fusion genes PLAG1 and HMG2, chromosomal aberrationsHER2, MIB-1, and p53. The overexpression of Her 2 is important to identify patients eligible for Trastuzumab therapy if the patient develops distant metastasis. Studies conducted in pleomorphic adenoma identified two types of Carcinomas composed of a different group of malignant cells. One group is CK 7, CK 8, Ck19 positive cells similar to luminal cells and the second one is both luminal and Ck14 positive myoepithelial or basal cells. Carcinoma expleomorphic adenoma is highly aggressive with distant metastasis and recurrence in around 70% of cases. The risk is comparatively less in the intracapsular and minimally invasive phase.[1]

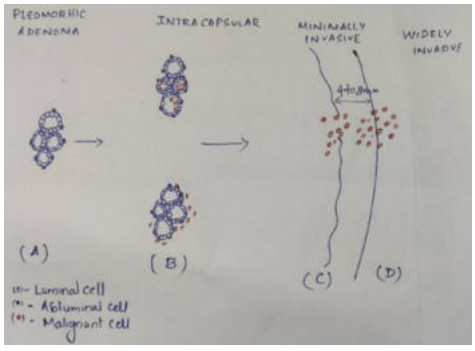

Figure 6: Demonstrates stages of progression of carcinoma expleomorphic adenoma,(A) – pleomorphic adenoma precursor lesion, luminal cells- CK7, CK18+, abluminal (myoepithelial cells)- CK14, p63, SMA + (B)- abnormal luminal or abluminal cell proliferation, (C)- breach of the capsule by malignant cells (D) extending into the surrounding gland and soft tissue.

ACINIC CELL CARCINOMA: These are low grade salivary gland tumors and constitute 15 to 17 % of parotid tumors. They tend to occur in the younger age group compared to other malignancies and it is the second most common malignancy of salivary glands[18]. In children, these tumors arise from acinic cells and serous acinar cell differentiation is the hallmark. The histopathological variants of ACC include solid microcystic, papillary cystic, and follicular. Papillary cystic is a high grade variant associated with a poor prognosis. The other factors indicating poor survival includes large tumor size, involvement of the deep lobe of the parotid, and incomplete surgical excision. Immunonegativity for mammoglobulin differentiates it from secretory carcinoma. The natural course of the disease is long and the cure rate gradually drops from 76% at 5 years to 55% at 15years.

LYMPHOMA: salivary gland lymphoma constitutes <2% of lymphomas and 12% of extranodal lymphomas of the head and neck. It commonly affects the parotid gland followed by submandibular, minor salivary glands, and sublingual glands. The most common histology includes MALT lymphomas (60 to 70%) and DLBCL(20 to 30%). Around 30% of MALT lymphomas have involvement of multiple salivary glands at the time of diagnosis. In addition to that, there are reports of involvement of nonsalivary sites like the stomach hence upper gastrointestinal endoscopic examination is required in addition to imaging. Management is nonsurgical with radiotherapy/ chemoradiotherapy.[19]

HAEMANGIOPERICYTOMA:

it is an uncommon mesenchymal vascular tumor arising from the capillary pericytes. It can be found anywhere in the body with 13 to 25% in the head and neck region. According to the 2013 WHO classification, haemangiopericytoma has been unified with solitary fibrous tumor. Around 40 cases have been reported so far and 34 were reported to be from the parotid gland. Diagnosis is based on morphological and immunohistochemical features. CD34 is the most specific marker. In addition to that, studies have already shown bcl2 and CD 99 also as markers in SFT. Immunoreactivity to STAST6 is highly sensitive and specific. The factors which differentiate between benign and malignant types include the presence of prominent mitotic activity (4 or more per 10 HPF), hemorrhage, necrosis, anaplasia, and increased cellularity. Surgical excision with adequate margins is important due to the high chance of recurrence. The role of radiotherapy is limited to incomplete resection, improving survival, and treating inoperable metastatic disease.[20]

NEWER ENTITIES INCLUDED IN WHO CLASSIFICATION:

The fourth edition of the WHO classification made few changes in nomenclature and added few newer entities. Two separate new entities included are secretory carcinoma and intraductal carcinoma. Intraductal tumors have intraductal or intracystic growth of neoplastic epithelium. The subtypes low grade cribriform cystadenocarcinoma (low grade SDC) and conventional SDC insitu are categorized together in this group. Intraductal carcinoma can be low, intermediate, or high grade based on the cytological features. Low grade lesions are more common and occur mostly in the parotid gland. It shows immunoreactivity to S100 but AR negative. High grade tumors have the same phenotype as SDC and these tumors are positive for AR and negative for S100. It can be differentiated from SDC by IHC which is positive for AR and HER 2 but negative for S100. Skalova et al in 2018 reported 17 cases of intraductal carcinoma. They identified the presence of NCOA4-RET as the dominant fusion gene in the intercalated type of intraductal carcinoma and a novel TRIM27-RET fusion in the apocrine variant.[21]

Another notable change in the new classification is the terminology low grade polymorphous adenocarcinoma got changed to polymorphous adenocarcinoma. It was initially described by Evans et al as an infiltrative salivary gland tumor with a variety of growth patterns. It occurs exclusively in minor salivary glands. It shows different histological patterns like tubular, fascicular, cribriform, and papillary/solid. At the base of the tongue, a distinctive cribriform appearance with clear nuclei similar to papillary thyroid carcinoma was identified and named as cribriform adenocarcinoma of the tongue and later as cribriform adenocarcinoma of minor salivary glands. The growth pattern of this tumor is actually papillary glomeruloid. Recent studies identified PRKDgene rearrangements (PRKD1, PRKD2, PRKD3 WITH ARIDA AND DDX3X) in 80 % of cases. WHO 2017 classification defines CAMSG as a variant of polymorphous adenocarcinoma and hence included in that category. Even though the vast majority of cases are low grade, there is no structured evidence for the grading scheme and it should be done on an individual case basis, this could be the reason for editing the low grade.[22,23]

The novel and consistent finding in hyalinizing clear cell carcinoma is the EWSR1-ATS1 fusion gene, these characteristics of gene alteration and typical morphological appearance removed the suffix not otherwise specified from clear cell carcinoma.

Salivary glands and mammary glands have similarities in their architecture. This could be the reason behind the resemblance of many of the tumor entities of both glands on a closer look.[24] Another change made in the latest classification is the addition of a rare lesion sclerosing polycystic adenosis under the category of other epithelial lesions. It is a benign lesion morphologically similar to fibrocystic and sclerosing adenosis of the breast. Only 60 cases have been reported so far and commonly involve the parotid gland. Studies have suggested that this entity occurs through a clonal process and hence should be reconsidered whether to be included in the neoplastic category. The recurrence rate is 11% and occurs usually due to incomplete surgical resection. Only a single case of SDC arising in this condition has been reported till now.[11]

Some of the recent studies have shown few points of resemblance between mammary gland tumors and salivary gland tumors. There are obvious similarities even in the anatomy including ectodermal origin, branching architectural pattern, and segmental differentiation. Both are exocrine glands with similar morphology. Even though incidence differs, there are a few tumors in both groups found to share common biological and molecular changes.[25,26]

1. Mucoepidermoid carcinoma: MEC in the breast is a rare entity and it was described by Patchefsky et al and because of the similarity with salivary MEC, the same grading system was used. They both share the same specific translocation of t (11; 19) (MAML2: MECT) creating a fusion protein that is found to be associated with a reduced risk of death in both groups.
2. Adenoid cystic carcinoma: AdCC also occurs in the breast but it is very rare. Unlike the AdCC of salivary glands, these tumors have more than 90% overall survival with nodal and distant metastasis chances being rare. Both the tumors are characterized by c-KIT expression and share a common translocation t(6,9) leading to a fusion gene MYB-NFIB. This fusion product is more expressed in proliferating cells and hence can provide a new therapeutic approach for the management.
3. Salivary duct carcinoma: these are rare aggressive tumors histologically representing features of invasive ductal carcinoma of the breast. The morphology of SDC is very similar to comedocarcinoma of the breast. In addition, they have similar clinical behavior and highly metastatic features with poor prognosis. Similar biological marker Her2 is identified in SDC and breast carcinoma. Her2 also enhances androgen receptor function and hence antiandrogen therapy may be effective. There are studies demonstrating EGFR promoting tumorigenesis. Both the gene targets Her 2 and EGFR could guide as targets for newer therapeutic options.
4. Secretory carcinoma is another such subtype closely resembling breast carcinoma

The resemblance of salivary gland and breast carcinomas pave a way for research in hormonal therapies in salivary gland neoplasms. The sex steroid hormone receptors are extensively studied for the diagnosis and treatment of breast carcinoma.SDC commonly express androgen receptors in 92 to 100% cases and in these cases, androgen deprivation therapy can produce clinical benefit which more effective and less toxic compared to chemotherapy Williams et al described in his study about estrogen receptor beta in many breast and salivary gland tumors and lack of this receptor expression was associated with a high recurrence rate. These receptors can be a target for management.[27] Murase R et did few studies on hormone receptors in salivary gland tumors and they could demonstrate that as a part of malignant transformation these cells will be deprived of hormone receptors and hence hormone receptor overexpression need not be a criteria in hormone therapy.[25] There are case reports showing tamoxifen reactivating estrogen receptor expression. Progesterone could also suppress the proliferation and invasion of salivary gland tumor cells. There can be some common pathways and mechanisms in both salivary and breast carcinomas which will be altered with progesterone therapy.[28]

5. CONCLUSION

Salivary gland tumors are a heterogeneous group of tumors with a vast variety of tumor entities that still need to be investigated. Several grading schemes exist in literature with their own limitations. Optimal grading criteria for each subtype are lacking. All high grade tumors need not be aggressive all the time and intermediate grade doesn't have clear cut specifications. The application of molecular changes and genomic studies are now revealing the characteristics of sequencing and more knowledge into their subentities. The treatment strategy for salivary gland tumors is surgery followed by adjuvant radiotherapy for high grade tumors but still, long term survival is poor. Most of the time adjuvant treatments will be a palliative treatment option. But there are cases like adenoid cystic carcinoma and few low grade tumors even with metastasis they have long survival. Even though there are some unanswered questions and no clear-cut benefits in these targeted approaches, adoption of it will be an option compared to chemotherapy inducing toxicities. The prognosis of most salivary gland tumors can be altered with delay in progression of tumors and a novel treatment approach can be expected in the future.

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