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(Mucoepidermoid Carcinoma Of Salivary Gland)

A literature Review

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Certification of the Supervisor

I certify that this project entitled "**Mucoepidermoid Carcinoma Of Salivary Gland: A Literature Review**" was prepared by fifth year student (**Batoul Saad Dawd)** under my supervision at the College of Dentistry / University of Baghdad in partial fulfillment of the graduation requirements for the bachelor degree in dentistry.

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Dedication

To the one who lit the lamps of science and knowledge in my heart, to the symbol of manhood and loyalty, to my first teacher, To the first love, to the closest friend, to the kindest heart, to the truest word, and the most beautiful years, to the beloved of life, today and tomorrow ' my father

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Primarily I would like to thank the supreme power the Almighty God for everything in my life, for being able to complete this project with success.

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List of abbreviations

Abbreviation phrase

MECs	**Mucoepidermoid carcinoma**
MRI	Magnetic resonance imaging
CAT	Computerized Axial Tomography
MSGTs	Malignant salivary gland tumor
SGCs	salivary gland carcinoma
AFIP	Armed Forces Institute of Pathology
AdCC	adenoid cystic carcinoma
SDC	salivary duct carcinoma
NSM	necrotizing sialometaplasia
SPA	sclerosing polycystic adenosis
MECT1	Mucoepidermoid carcinoma translocated gene 1
MAML2	Mastermind-like gene family
ck	cytokeratin
PAS	periodic acid-Schiff

Introduction

Mucoepidermoid carcinoma (MEC) is the oral cavity epithelial salivary gland neoplasm **(Dossani et al., 2016).** This malignancy exhibits varying degrees of differentiation and histologic grade as well as widely diverse biologic behavior.

Mucoepidermoid carcinoma (MEC) is defined by the WHO as "a distinctive salivary gland malignancy composed of mucinous, intermediate (clear cell) and squamoid tumor cells, forming cystic and solid patterns. It has an annual incidence of 0.44 per 100,000 persons. It is the commonest primary salivary carcinoma worldwide, and accounts for 2.8% to 16% of all salivary gland tumors,12% to 30% of malignant salivary gland tumors, and 6.5% to 41% of minor salivary gland tumors, representing the most common type of minor salivary gland malignancy in most series**.(Gnepp et al,2021)** Histopathological, MECs are divided into low ,middle ,high grade tumor **(Nance et al., 2008)**Approximately one-half of these tumors (53%–56%) arise in the major salivary glands, with 85% to 88% of these (45% of all MECs) occurring in the parotid gland, 8% to 13% in the submandibular gland, and 2% to 4% involving the sublingual gland **(Brandwein et al,2017)**

In the minor salivary glands, MEC most commonly occurs on the palate, but a significant number may also be found in the retromolar area, foor of the mouth, buccal mucosa, lip and the tongue(**Barcellos et al,20008)**

It may also rarely arise primarily within the body of the mandible or maxilla, where it is the most common central salivary gland tumor of the jaws(**Pontes et al, 2018)**

There is a wide age distribution with a mean of 47 years (range 3–95 years). Interestingly, patients with palate MECs tend to be younger than those with floor of mouth, lip, or tongue lesions. It is the most common malignant salivary gland tumor to arise in children and adolescents younger than 20 years of age, but is unusual in the first decade of . For all ages, MEC has a slight 3:2 female predominance **(Gnepp et al ,2021)**

Chapter one

Review of literature

1.1 Malignant salivary gland tumor

Salivary gland tissues (SG) are found throughout the upper aerodigestive tract. The parotid, submandibular, and sublingual glands are the three major salivary glands. Minor salivary glands can be found in a variety of locations, including the lips, gingiva, cheek, palate, tongue, oropharynx, paranasal sinuses, and parapharyngeal space **(Tian et al., 2010).**

Malignant Salivary gland tumors (MSGTs) are rare lesions with a wide range of clinical, histological, and biological characteristics (**da Silva et al., 2018).** Furthermore, due to their morphological similarities, these lesions frequently pose a diagnostic challenge for pathologists **(Rooper and Pathology, 2019)**

In general, they are arising from the major and those arising from the minor salivary glands. Parotid glands are more affected site by SGCs, than submandibular and sublingual glands. Also, minor salivary glands are the source of SGCs, representing for 9-23%of all malignant salivary gland tumors **(Ito et al., 2005, Wang et al., 2017).**

Tumors of the saliva glands represented a variety of neoplasm **(Nagarajan et al., 2020).** These are unusual tumors that are medically and morphologically diverse unlike other head and neck cancers **(Zhao et al.,2011)**. Salivary gland cancers, classified as head and neck cancers, establish approximately 6% of head and neck cancer diagnoses depend on presented by American Head and Neck Society **(Lin et al., 2018).**

Salivary gland carcinomas (SGCs) are relatively rare. The most common histopathologic types are as follows: Oncocytic carcinoma, Oncocytic tumor metaplasia ,Mucoepidermoid carcinoma ,Acinic cell carcinoma, Epithelial myoepithelial carcinoma, Salivary duct carcinoma, Papillary cystadenocarcinoma**.(Gnepp et al,2021**)

The median age of occurrence for(MSGTs)was 45 years old, with the incidence peaked in the 7th **(de Oliveira et al., 2009**) Salivary gland

carcinomas were more common in women, with a male: female ratio of 1:1.5 **(Al-Khateeb et al., 2007).**

So yet, the etiology of MSGTs is unknown. Cigarette smoking, virus infections, rubber factory employees, DNA, and so forth are all potential risk factors. Ionizing radiation is the only well-established risk factor. MSGTs are much more likely to develop in atomic bomb survivors and radiation therapy patients **(Rousseau et al., 2011).**

1.2 Mucoepidermoid Carcinoma Of Salivary Gland

Mucoepidermoid carcinoma (MECs) is the oral cavity epithelial salivary gland neoplasm **(Dossani et al., 2016).**

It accounts for 5%–10% of all tumors and 30% of all salivary gland malignancies, while Iraqi national study found that the incidence of MECs was (31.40 %) of malignant SGT and (7.90 %) of all tumors**(Raid 2021)**

Approximately 5% of these tumors occur in patients younger than 18 years of age with mostly affected women **(Garde et al., 2016)**

MECs IS one of the most common salivary gland malignancies In1945,Stewart et al.were the first to describe this neoplasm as‘ ‘mucoepidermoid tumor’ ’They divided this tumor into two varieties ‘‘relatively favorable(benign)and highly unfavorable(malignant**).(Maloth 2015)**

In 1953, Frazell and Foote reported the development of distant metastases **(Bai et al., 2013)** in some patients with "relatively favorable" tumors included in the previous quotation. Nevertheless, the 2nd edition of the WHO Histopathological Categorization of neoplasm of the Salivary Gland, published in 2015, retained the term mucoepidermoid tumor, for the reason that only a minority do eventually metastasize and in only a very few does invasiveness assume a serious degree, though these tumors must be regarded as potentially malignant **(Kessler and Bhatt, 2018)** Currently, all of these tumors are considered to be malignant with the capability to recur or

metastasize to regional lymph nodes or to distant viscera, regardless of their macroscopic or microscopic appearances.

Later, Jakobsson and many other authors proposed categorizing MECs as low, intermediate, or high **(Capodiferro et al., 2020).**

This comprises mucus-producing, squamous, and intermediate form as its name implies **(Daryani et al., 2012)**

Nearly two-thirds exist within the parotid gland, and one-third occur within the minor salivary glands. It can be found on the palate, retromolar region,, buccal mucosa, lips, and tongue when MECs arises in salivary glands.Laryngeal, lacrimal, nasal, paranasal, tracheal, or pulmonary tumor **(Barcellos et al, 2008)**

Rarely, it originates in the mandible and maxilla as an intraosseous tumor, referred to as ‘‘central mucoepidermoid carcinoma **(Moghadam and Moghadam, 2014)**

The histogenesis of central mucoepidermoid carcinoma remains controversial, but one highly possible theory is that this malignancy arises from the lining epithelium of odontogenic cysts During the fifth and sixth decades of life, it develops most often in adolescents. While rare in children, it is the primary malignant salivary gland tumor and affects women more frequently than men (3:2) **(Maloth et al 2015)**

This malignancy exhibits varying degrees of differentiation and histologic grade as well as widely diverse biologic behavior .

1.3 Etiology of mucoepidermoid carcinoma

1.3.1 Radiation

The most common etiologic factor that has been implicated in the development of MECs is radiation, with MECs developing in as many as 44% of patients with a history of a radiation- associated adenocarcinoma; latency periods in this group ranged from 7 to 64 years. Land and colleagues reviewed data on 145 major and minor salivary gland tumors, from atomic bomb survivors exposed to radiation from Hiroshima and Nagasaki, and found an increased relative risk of 9.3 for patients with MECs, with the proportion of MECs increasing with increasing doses of radiation. At 2006 study described 12 salivary gland neoplasms occurring in survivors of childhood cancers treated with chemotherapy and radiotherapy of these tumors were MECs.(**Gnepp et al, 2021**)

1.3.2 Genetic background of MEC:

One significant genetic abnormality in MECs is the translocation of chromosomes t (11;19) (q21; p13), which has been proposed as an early event in the disease's pathogenesis. This translocation, which has been reported in more than 50% of MECs tumors results in the fusion of the MECT1 and MAML2 genes, resulting in a fusion protein that disrupts cell cycle regulation and differentiation **(Bell et al., 2013).**

When compared to high-grade tumors, low-grade tumors have a higher incidence of fusion, and patients with fusion-positive cancer have improved survival with a significantly lower risk of local recurrence, metastases, or cancer-related mortality **(Behboudi et al., 2006, Jee et al., 2013, Kang et al., 2017)**. Previous data demonstrate that the MECT1/MAML2 translocation may be the main oncogenic driver in MEC.

In tumors without the translocation, the TP53 mutation may act as an alternate mechanism of tumorigenesis **(Kang et al., 2017).**

In addition, POU6F2 mutations may act as drivers of oncogenesis in low-grade tumors. Also, they found somatic mutations in a number of other

genes not previously implicated in MEC that may serve as therapeutic targets. These findings should be further investigated for their therapeutic potential **(Kang et al., 2017)**

1.4 clinical and Radiographic feature of mucoepidermoid carcinoma

Mucoepidermoid carcinoma is the most common malignant salivary gland tumor in both major and minor salivary gland sites; In the major salivary glands Primarily affecting the parotid (89.6%), submandibular (8.4%), and sublingual (0.4%) glands. Its appearance at a primary bone site is much rarer, accounting for only 2% to 4% of all MEC **(Johnson et al., 2008).**

The palate is the most frequently involved minor salivary gland site, but the buccal mucosa, upper and lower lips, retromolar region, and tongue may be affected **(Ellis and Auclair et al.,1996; Spiro et al.,1978)**

Affecting age range from 3rd to 7th decades of life, with a peak incidence from the 5th to 6th decades of life **(Choi et al., 2001, Ito et al.,7 2009)**

The average age of onset is 55 years, and it is the most common malignant salivary gland tumor in young people **(Triantafillidou et al., 2006**).

MEC typically manifests as a painless, variable-fixed, rubbery or soft mass. Intraoral tumors, due to their superficial location, may appear as a blue-red tinged swelling, similar to a mucocele or other vascular tumors **(Pires et al., 2007, Awni et al., 2017).**

Low-grade tumor – the tumor of low-grade malignancy usually appears as a slowly enlarging, painless mass.It seldom exceeds 5 cm in diameter**.(Ellis et al., 2008,Rajendran, 2009)**

High-grade malignancy –the tumor of high-grade malignancy grows rapidly and does produce pain as an early symptom. rapidly enlarging mass accompanied by pain, fixation,otorrhea, paresthesia

facial nerve palsy, dysphagia,hemorrhage, or trismus **(Rajendran, 2009)**as you seen in figure (1)

Minor gland tumor-it appears asymptomatic tumors that are located in the palatal tumors appear as fluctuant, bluish, smooth-surfaced swellings resembling mucoceles**(Ranganath et a 2011)**

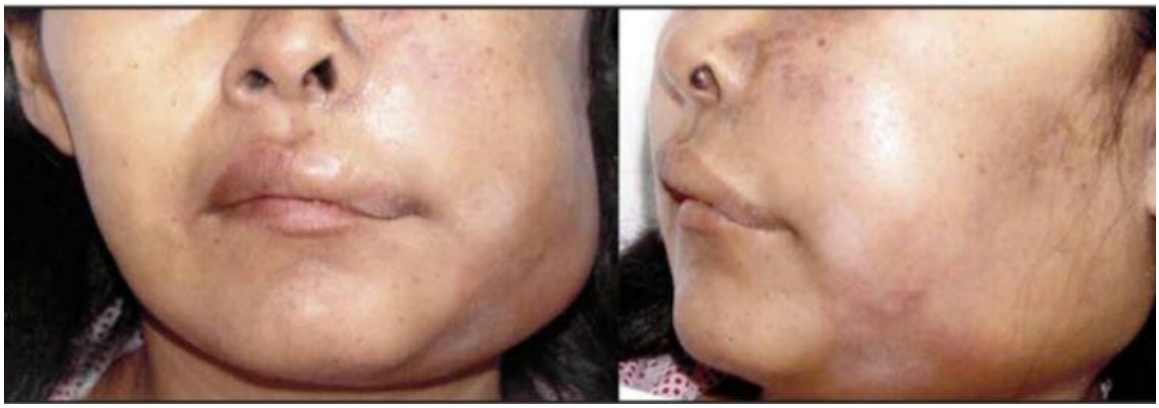

Figure.(1): Female patient, 30 years old. Tumorous lesion in left parotid gland. Patient complained of pain and paresthesia. One year of illness with slow, progressive growth. Diagnosed with high grade MC and died six months later, after radiation treatment

Radiographic features

Radiographic appearances largely depend on grade, making preoperative imaging important in planning and counseling. **(Yousem et al,2000)**

-in Ultrasound typically a well-circumscribed hypoechoic lesion, with a partial or completely cystic appearance. The lesion stands out against the relatively hyperechoic normal parotid gland.

-in CT Low-grade tumors appear as well-circumscribed masses, usually with cystic components. As you seen in figure(2)
The solid components enhance, and calcification is sometimes seen. High-grade tumors, on the other hand, have poorly defined margins, infiltrate locally and appear solid.

–in MRI
Again, imaging is dependent on grade. Low-grade tumors have similar appearances to pleomorphic adenomas:

T1: low to intermediate signal; low signal cystic spaces
T2: intermediate to high signal; cystic areas will be high signal
T1 C+ (Gd): heterogeneous enhancement of solid components

High-grade tumors, on the other hand, have lower signal on T2 and poorly defined margins, and infrequent cystic areas:

T1: low to an intermediate signal
T2: intermediate to low signal

It is essential to image the cranial nerves with fat-saturated post-contrast T1 sequences to assess for perineural spread, and as such the base of the skull should be imaged up to and including the cavernous sinus and inner ear**.(Som et al, 2003)**

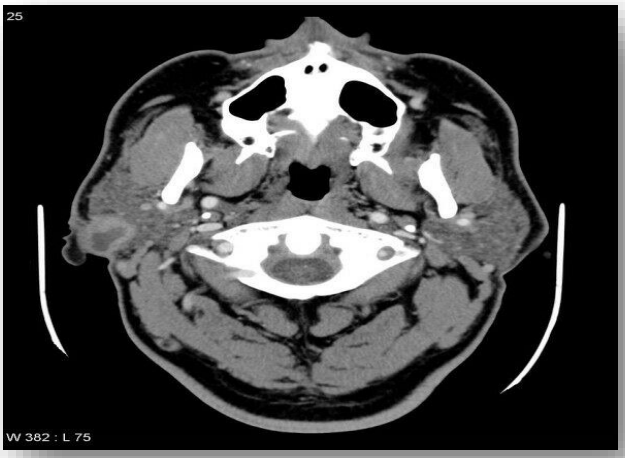

Figure (2) Single CT slice at the level of the parotid glands demonstrates a single mass with central low density cystic component in the posterolateral aspect of the right parotid.(curtin 2003)

1.5 Macroscopic feature of mucoepidermoid carcinoma

Mucoepidermoid carcinoma is a most common SGCs with distinct histology that account for half of all parotid malignancies **(Hu et al., 2019)**

mucoepidermoid carcinoma typically manifests as acircumscribed but unencapsulated or incompletely capsulated, firm mass.

High-grade tumors are poorly circumscribed and have infiltrative borders, often with fixation to the adjacent tissue.

The cut surface commonly has conspicuous cystic structures accompanied by grayish-white to tan solid areas as you see in figure (3) . Cystic spaces may contain brownish and mucinous material. Hemorrhage or necrosis is frequently present in high-grade tumors, and these tumors tend to be solid. The tumor size ranges from less than 1 cm to over 12 cm in the major salivary glands and as large as 5 cm in the minor salivary glands **(Ellis and Auclair et al., 1996).**

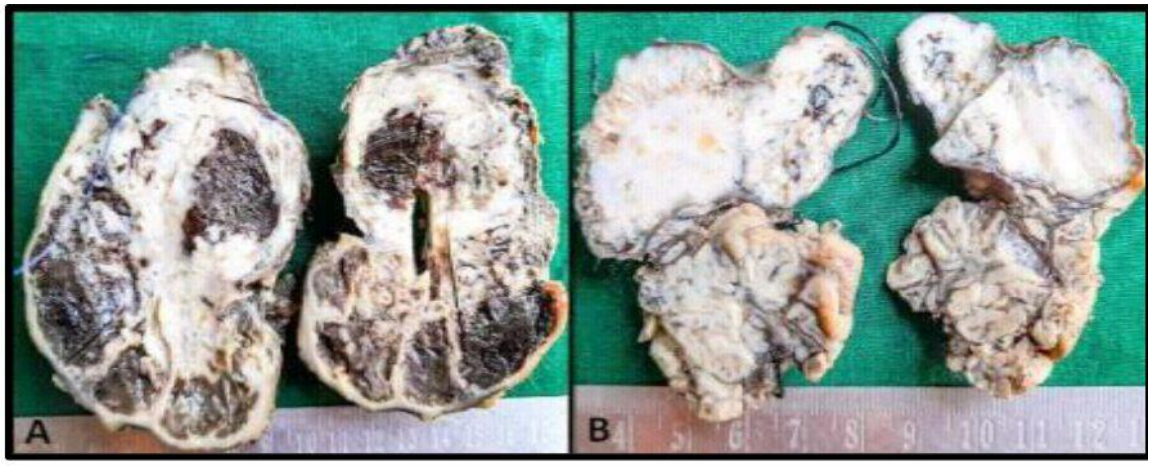

Figure (3) Gross appearance of MEC (A): Showing areas of cyst formation. (B): Shows entirely solid tumor, commonly seen in low-grade lesions with an adjoining normal salivary gland (Pachori et al., 2019).

1.6 Microscopic feature of mucoepidermoid carcinoma :

Mucoepidermoid carcinoma is believed to originate from the pluripotent reserve cells of excretory ducts that are capable of differentiating into mucus-secreting cells, epidermoid-type (squamous) cells, and intermediate cells, which are cells of intermediate diferentiation between the other two cell types **(moyer et al 2007)**

Epidermoid cells have abundant eosinophilic cytoplasm and vesicular nuclei. They are only occasionally associated with individual cell keratinization or keratin pearl formation. Epidermoid cells are negative for mucicarmine but may show a faint positive for PAS stain.

The intermediate cells include smaller basal cells (maternal cells) and larger cells that are differentiating toward epidermoid and mucus-secreting cells. These are ovoid with scanty cytoplasm, and the size ranges from small, resembling basal cells, to about three times larger than lymphocytes. These cells exhibit a small, centrally located, darkly stained nucleus and pale eosinophilic cytoplasm, which is negative for mucin stains.

The mucous cells are cuboidal, columnar, or goblet-like, and tumors frequently form solid masses containing scattered mucin positive cells and/or single or multilobulated cysts, with varying numbers of simple to markedly thickened stratifed squamous epithelium and varying numbers of mucocytes, which may be prominent. The mucocytes are large and pale and typically have a well-defined cell membrane. The cytoplasm is foamy or reticular and shows variable basophilia; it exhibits positive staining with mucicarmine and Alcian blue. The nuclei are usually hyperchromatic and peripherally placed. Mucinous cells tend to be more numerous in MECs with cyst formation.

Clear cells are large and round or polyhedral, and their nuclei may be centrally or peripherally located. Many of these contain glycogen but only occasionally mucin, or both**.(Gnepp et al,2021)**

1.6.1Grading System of Mucoeppidermoid Carcinoma

All MECs are malignant with a metastatic potential,regardless of their microscopic appearance. Nevertheless, certain features can predict outcome to some degree and MECs are histologically classified as low, intermediate, and high grade. Suggested grading criteria have included the relative proportion of cell types, the degree of tumor invasiveness, anaplasia, the pattern of invasion, the degree of maturation of the various cellular components, mitotic rates, presence or absence of necrosis, neural or vascular invasion, and the proportion of tumor composed of cystic spaces relative to solid growth, one study particularly emphasized the importance of any necrosis**(Katabi et al,2014)**

Low-grade MECs are usually well circumscribed and typically have a prominent cystic or microcystic component, lined with intermediate, epidermoid, or mucous cells as you seen in figure (4) . More solid elements are less conspicuous and commonly develop a nesting pattern with multiple, well-circumscribed epidermoid nests containing numerous clear cells, some of which contain intracytoplasmic mucin. Many low-grade tumors, especially in the minor salivary glands, contain a prominent mucus-secreting component, composed of columnar cells lining cystic spaces. Nuclear atypia, mitotic activity, and an infltrative growth pattern are not usually features of low-grade tumors. However, differentiation (high- grade transformation) in a low-grade MEC has been reported.

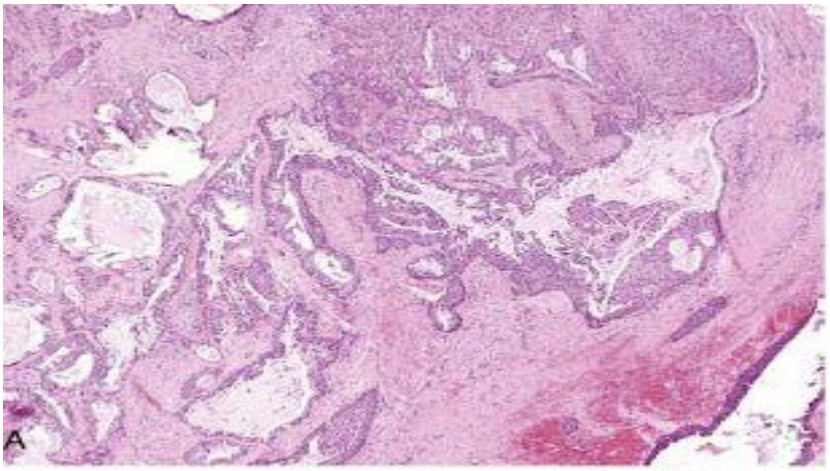

Figure (4) Low-grade mucoepidermoid carcinoma with a promi- nent cystic component. The tumor contains goblet, intermediate, and squamous cells.(Gnepp et al,2021)

Intermediate-grade tumors are less cystic and show a greater tendency to form larger, more irregular solid nests or sheets of squamous cells, and ofen have more prominent intermediate cell population. A minor degree of nuclear atypia and mitotic activity may be present, and an infltrative component is usually noted.

High-grade tumors are predominantly solid and infltrative with greater degrees of atypia; they are usually very similar to squamous cell carcinoma, but rarely show keratinization. There is usually scant mucin production, and careful searching and special stains to identify intracellular mucus may be required.as you see in figure (5).

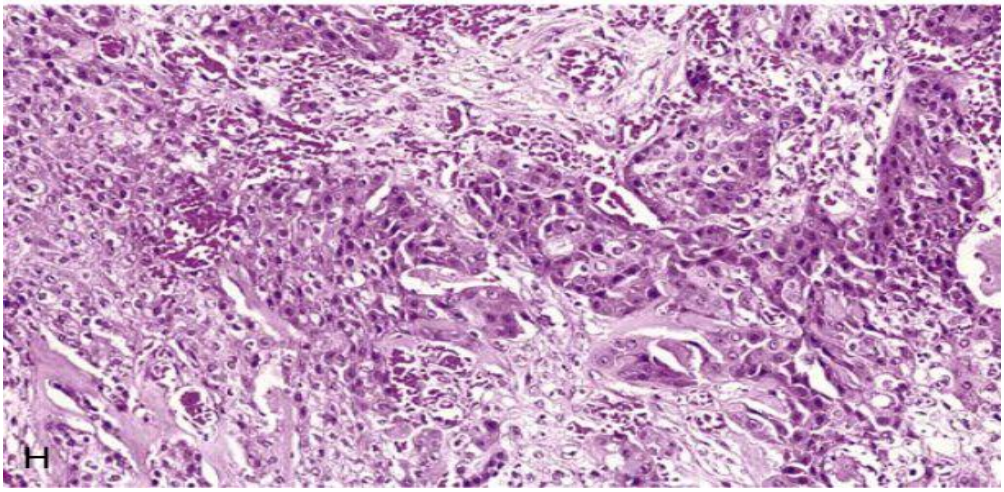

Figure (5) High-grade tumor is composed of poorly differentiated, irregular nests of infltrating tumor cells. This tumor demonstrated only very focal mucinous differentiation (Gnepp et al 2021)

Grading MEC is subjective, with different criteria used in various series, and there is no universally accepted grading system**.(Ellis et al, 2008)**. There is no consensus defining the individual histologic grading criteria, and stage appears to be a better prognostic indicator than grade. Early systems advocated a two-level system, with high-grade MEC defined by the presence of invasion(blanck 198) or predominantly solid tumor. However, more recently, three- level systems of dividing tumors into low, intermediate, and high grades have become more widely used. Because of wide interobserver

variability using these systems, Ellis and Auclair proposed a numerical grading scheme based on weighted histologic criteria (Table -1-) The histopathologic features that were most useful in indicating aggressive behavior were a cystic component of less than 20% of tumor area, four or more mitotic figures per 10 high-power fields, nerve invasion, tumor necrosis, and the presence of cellular anaplasia (cellular and nuclear pleomorphism, increased nucleocytoplasmic ratio, prominent or multiple nucleoli, and hyperchromasia). Each of these parameters was assigned a point value, and the total sum of points for the five variables determined the tumor grade (see Table -1-). This scheme from the Armed Forces Institute of Pathology (AFIP) generally shows good correlation with clinical outcome and is reproducible.

TABLE 1	**Armed Forces Institute of Pathology Grading Parameters and Point Values for Mucoepidermoid Carcinoma**
Parameter	Point Value
Cystic component of <20%	+2
Neural invasion	+2
Necrosis	+3
≥4 mitoses per 10 high-power fields	+3
Anaplasia	+4
Grade	Point Score
Low	0–4
Intermediate	5–6
High	7–14

Modifed from Ellis, G.L., Auclair, P.L., 1996. Atlas of Tumor Pathology: Tumors of the Salivary Glands, 3rd Series, Fascicle 17. Armed Forces Institute of Pathology, Washington, DC, p. 155–175.

1.6.2 VARIANT OF MUCOEPIDERMOID CARCINOMA

A-Sclerosing mucoepidermoid carcinoma

Although mucoepidermoid carcinoma is the most common primary malignancy of the salivary glands, the sclerosing morphologic variant of this tumor is extremely rare, with only six reported cases. As its name suggests, sclerosing mucoepidermoid carcinoma is characterized by an intense central sclerosis that occupies the entirety of an otherwise typical tumor, frequently with an inflammatory infiltrate of plasma cells, eosinophils, and/or lymphocytes at its peripheral regions. As you see in figure (6)The sclerosis associated with these tumors may obscure their typical morphologic features and result in diagnostic difficulties. Tumor infarction and extravasation of mucin resulting in reactive fibrosis are two mechanisms that have been suggested as the cause of this morphologic variant **(Neville et al , 2015)**

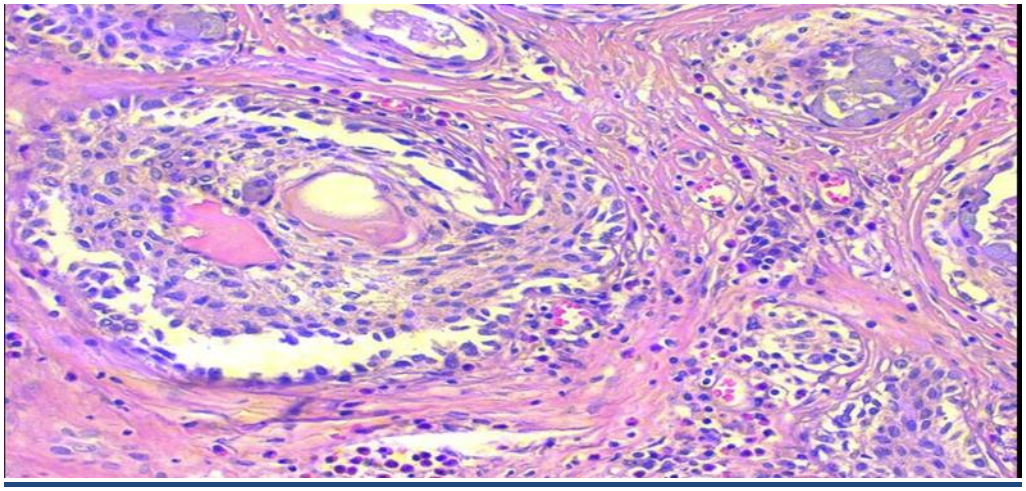

figure (6) Sclerosing mucoepidermoid carcinoma with eosinophilia composed of variably sized tumor nests within a fibrohyaline stroma that is replete with eosinophils. Scattered goblet cells are also present in the tumor nests. The tumor cells have oval nuclei with prominent nucleoli and eosinophilic cytoplasm (Gnepp et al , 2015)

B-Oncocytic variant

Oncocytic differentiation may be a focal feature of some mmucoepidermoid carcinomas, but it is rarely an extensive "oncocytic variant," with a limited No. of cases reported**(Brannon RB et al. 2003; Corcione L et al. 2007)**as you seen in figure(7) . The majority of oncocytic mucoepidermoid carcinoma are low-grade tumors and should not be misdiagnosed as oncocytoma. Also, a few cases of intraoral mucoepidermoid carcinoma have been associated with melanin pigmentation **(Takeda et al. 2006)**

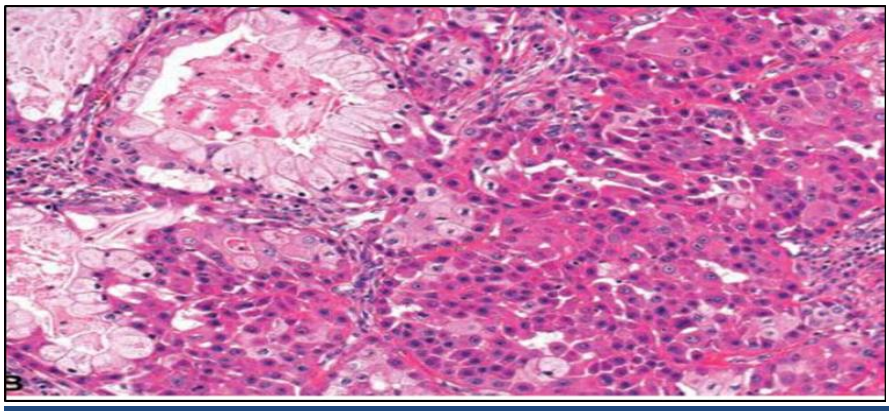

figure (7) Oncocytic variant of mucoepidermoid carcinoma. Cells have abundant dense granular cytoplasm. (Cell block, H&E). (Corcione L et al. 2007)

C-Tumor associate lymoid infiltration

MECs may have e xtensive secondary lymphoid cell infiltration, referred to as tumor-associated lymphoid proliferation as you see in figure (8**)**
(Auclair et al.,1994), is commonly present the feature that may be confused with metastasis to or origin from ectopic salivary gland tissue in intra parotid lymph nodes.

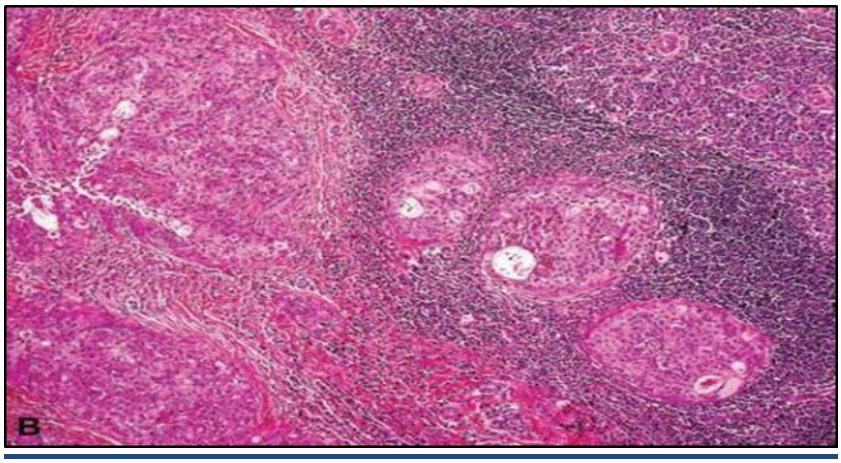

figure (8) Extensive secondary lymphoid cell infiltration, referred to as tumor-associated lymphoid proliferation (Auclair et al.,1994)

D- clear cell variant

when the clear cells prominent over other cells type this called clear cell variant of MECs as you see in figure (9) **(Ogawa I et al. 1992; Ellis GL et al.,1998)**

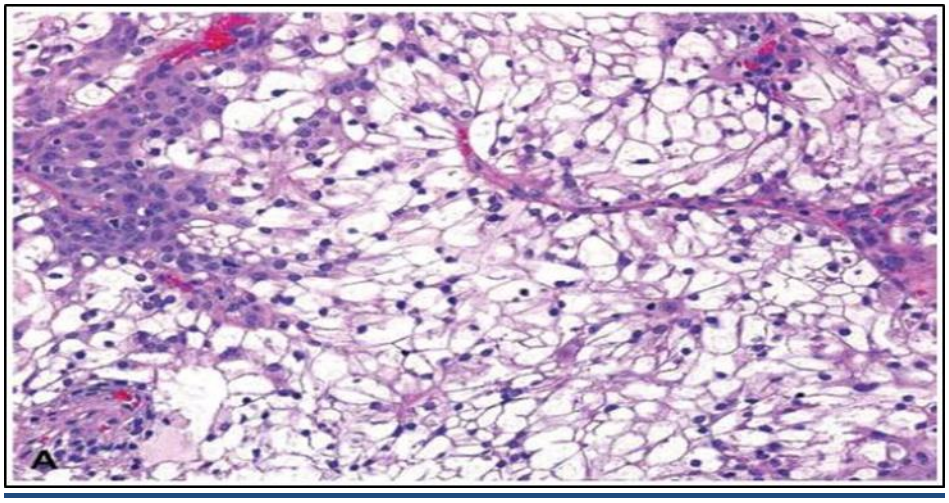

figure (9) Mucoepidermoid carcinoma , Clear cell variant (Ellis gl et al,1998)

1.6.3 Immunohistochemistry of MECs

In most instances of MEC, special stains and immunohistochemistry are not necessary for diagnosis. However, in cases where mucinous cells are few, PAS- diastase and mucicarmine stains usually will highlight the mucocytes. Similarly, if epidermoid cells are sparse, high- molecular-weight cytokeratin stains (e.g., 34βE12, CK14, CK5/6), as well as p40 and p63 stains, can help identify them. Other immunohistochemical findings are that staining with mammaglobin can be extensive, but S100 protein reactivity is relatively rare.(**patel et al,2013)** Luminal and mucous cell brush borders often show some positivity with DOG-1.A single case has been reported showing melanocytic marker (S100 protein, HMB-45, Melan-A, SOX10) expression**.(Gnepp et al,2021)**

Marker

MECs appear positive for CK5, CK6, CK7, CK8, CK14, CK18, CK19, EMA, CEA, and p63.
Similarly, they are negative for CK20, SMA, MSA, and S100.(**Gnepp et al ,2021)**

1.6.4 cytology

Cytology description
Most often graded as low grade or high grade on FNA

Low to intermediate grade:

Can be acellular or hypocellular smears,Extracellular mucin may be the prominent feature,Cystic background,Aggregates of epidermoid cells, intermediate cells and mucocytes,the epidermoid cells appear as bland cohesive flat sheets with squamoid / dense cytoplasm and well defined cellular borders,Predominantly mucus cells floating in extracellular mucin (low grade),No keratinization seen,Lympocytes present in about 20% of cases and are abundant **(Diagn et al,2017)**

High grade:

Highly cellular aspirates,High grade nuclear features with pleomorphic nuclei, prominent nucleoli,Intermediate cells and mucous cells are rare Increased mitosis,Necrotic background**(cibase ,2020)**

1.7 Differential Diagnosis

The differential diagnosisof MECs consists of necrotizing sialometaplasia (NSM), cheilitis glandularis, inverted duct papillomas, sclerosing polycystic adenosis (SPA), cystadenoma and cystadenocarcinoma, Warthin tumor (metaplastic variant), metastatic squamous cell carcinoma (SCC; for high-grade tumors), several primary salivary gland carcinomas and other clear cell tumors, adenosquamous carcinoma, and rarely, pleomorphic adenoma (PA**).(Gnepp et al,2021)**

NSM can rarely simulate low-grade MEC; however, NSM retains the lobular architecture of the normal gland and shows ghost outlines of necrotic acinar elements, and the squamous cell nests have a smooth outline. It lacks the cystic growth typical of low-grade MEC, and intermediate-type cells are not found. Inverted duct papillomas also have both epidermoid and mucus cells. However, the characteristic endophytic nature of inverted duct papilloma with its central cavity, blunt papillary ingrowths, and broad pushing margins contrasts with the multicystic, multinodular, and more obviously infltrative character of MEC. SPA may superfcially resemble MEC, but lacks obvious epidermoid diferentiation. The finding of characteristic large acinar granules is diagnostic of SPA, and in addition, the cysts and spaces are lined by epithelium surrounded by myoepithelial cells, as confrmed by appropriate immunomarkers. In both cystadenoma and cystadenocarcinoma, there is usually less stroma between the cysts compared with MEC, there is typically a papillary component, and the epidermoid component of MEC is not seen; the pattern of p63 expression may also help in cystadenoma, it is restricted to just the basal layer, whereas it is more extensive in MEC.**(lanzel et al ,2016)**

MEC with a prominent lymphoid component and oncocytic cells can be morphologically indistinguishable from Warthin tumor (especially the metaplastic variant) – in such cases, the only reliable way to separate them is to demonstrate the presence of the CRTC1-MAML2 fusion

Metastatic SCC typically has more keratin production than MEC and it does not contain any cells with intracellular mucin, whereas high- grade MEC will always contain at least a few mucocytes, with careful histologic sampling, and mucin staining on at least two tissue blocks. Staining for MUC5AC may also aid the distinction, Prominent nuclear pleomorphism is unusual in MEC. If noted, a metastatic SCC or another high-grade tumor needs to be ruled out.(**Bia et al,2013**)

Acinic cell and secretory carcinomas may contain plentiful mucin, but p63 staining will be at most, minimal, unlike in MECs . Sebaceous carcinoma does not usually contain intracellular mucin in the clear cell population and lacks intermediate-type cells and mucocytes. Hyalinizing clear cell carcinoma can contain (usually) small amounts of mucin and may thus mimic MEC; they can be separated in most cases by fuorescent in situ hybridization (FISH) studies which will show rearrangements of EWSR1 in the former, and MAML2 in the latter

High-grade MEC can be distinguished from salivary duct carcinoma, as most cases of the latter are androgen receptor positive**.(Spellman et al,2018)**

Adenosquamous carcinoma is included in the diferential diagnosis primarily for minor gland tumors. It can usually be separated from MEC because it has two distinctly separate components, squamous and glandular, and shows a more intimate involvement of the mucosal surface, sometimes including dysplasia and carcinoma in situ; however, rare MECs may arise from the surface mucosa. In contrast, in MEC, the squamous and mucinous components, together with intermediate cells, are usually closely associated with each other in the same tumor nests. Rarely, a PA may have areas of prominent (epithelial) mucinous or mucoepidermoid- type metaplasia. Mucinous metaplasia may or may not be associated with squamous areas of a PA and is typically focal and limited in extent. However, on very rare occasions, both the squamous and mucinous elements may be abundant and cause diagnostic difficulty.

Finding myxoid stroma containing myoepithelial cells, which MEC does not have, and the lack of destructive overgrowth of the PA elements will

establish the correct diagnosis. In addition, MEC can very occasionally arise as the malignant component of a carcinoma-ex-PA. Careful histologic sampling will allow separation of these two features. MEC arising as a component of carcinoma-ex-PA is usually more widespread and may show evidence of invasion into surrounding tissue and/or destructive overgrowth of the benign pleomorphic adenoma tumor element

1.8 Intraosseous Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma may originate within the jaws. This tumor type is known as central mucoepidermoid carcinoma. It is thought to form by the malignant transformation of the epithelial lining of odontogenic cysts. The most frequent presenting symptom is cortical swelling , although some lesions may be discovered as incidental findings on radiographs.Pain, trismus,and paresthesia are reported less frequently. Radiographs usually reveal either a unilocular or multilocular radiolucency with well-defined borders as you seen in figure (10), However, some examples are characterized by more irregular and ill-defined areas of bone destruction. Some cases are associated with an unerupted tooth and. therefore. clinically may suggest an odontogenic cyst or tumor.The mandible is three times more commonly affected than the maxilla**.(Neville et al,2015)**

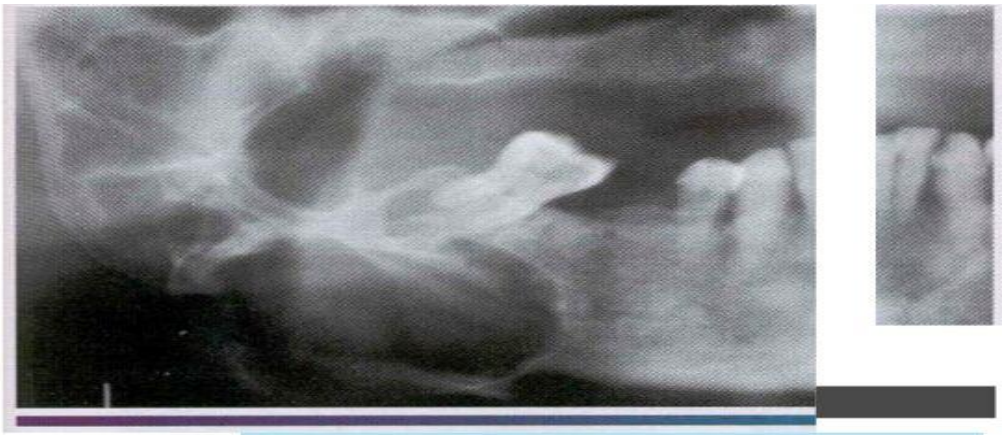

figure (10)Intraosseous mucoepidermoid carcinoma. Mul- tilocular lesion of the posterior mandible (Neville et al , 2015)

1.9 Treatment and Prognosis

Complete surgical excision is the treatment of choice for MEC. Adequate excision is important in all grades of tumor, with much higher recurrence rates reported with positive surgical margins (on the order of 50% for low- and intermediate-grade tumors, and slightly more than 80% for high-grade tumors**).(Gnepp et al,2021)**

Radiation therapy should be added in high-grade tumors and in patients with residual microscopic disease at the surgical margins. In contrast, a more recent series found that among patients with low-grade MECs, with close or positive margins on initial resection, additional treatment had no impact on survival or recurrence, and suggested that observation might be a reasonable alternative management in this select group of patients**.(Bhattacharyya ,2004)**

The prognosis predicted by clinical stage , histopathologic grade ,positive surgical margin ,location ,perinural invasion **(Laine et al., 2002 and Schu"z et al., 2006).**

In patients with low-grade tumors, the survival rate is 90% to 100(with exception the submandibular gland), these tumors rarely recur or metastasize. Data from the AFIP indicated that 5% of major gland and 2.5% of minor gland low-grade MECs metastasized to regional lymph nodes or resulted in death**.(Ellis et al,2008)**, This may be explained by tumor stage at presentation. The metastasis rate for high-grade tumors was 55% for the major glands and 80% for those of minor salivary gland origin.

Metastasis, recurrence, and death rates for patients with low-grade submandibular gland tumors were 13%, 9%, and 13%, respectively

Several patients in this latter series, with small (low stage) low-grade tumors with adequate treatment, inexplicably died of the disease. Spiro and colleagues also found more frequent metastases with submandibular gland MEC than from other major gland sites. A 2004 study reported similar

results, reinforcing the fact that MEC of the submandibular gland, irrespective of grade, should be treated aggressively, In addition, floor of mouth and tongue are sites of MECs with more aggressive and less predictable behavior.

Survival is better with tumors occurring in younger patients and among females, whereas survival is adversely affected in patients older than 60 years of age**.(Morales et al,2017)**

Intermediate- and high-grade tumors have a greater tendency to infiltrate, recur, and metastasize, with reported disease-free rates at 5, 10, and 15 years of 49%, 42%, and 33%, respectively.

In a study from Milan, the overall 5- and 10-year survival rates were 60.6% and 51.2%, respectively. However, the 5-year disease-free survival rate decreased dramatically from 88.9% in low-grade tumors to only 27.8% in high-grade tumors

Chapter two conclusion

Conclusion

The mucoepidermoid carcinoma is one the most common salivary gland malignancies.This malignancy exhibits varying degrees of differentiation and histologic grade swell as widely diverse biologic behavior,Approximately one-half of these tumors (53%–56%) arise in the major salivary glands, with 85% to 88% of these (45% of all MECs) occurring in the parotid gland, 8% to 13% in the submandibular gland, and 2% to 4% involving the sublingual gland,It may also rarely arise primarily within the body of the mandible or maxilla, where it is the most common central salivary gland tumor of the jaws

Histopathologically, MECs composed of mucinous, intermediate (clear cell) and squamoid tumor cells, forming cystic and solid patterns, are divided into low ,middle ,high grade tumor.

The most common etiologic factor that has been implicated in the development of MEC is radiation, also the translocation of chromosomes (11;19) (q21; p13), which has been proposed as an early event in the disease's pathogenesis and POU6F2 mutations may act as drivers of oncogenesis in low-grade tumors.

MEC typically manifests as a painless, variable-fixed, rubbery or soft mass. Intraoral tumors, due to their superficial location, may appear as a blue-red tinged swelling, similar to a mucocele or other vascular tumors

Complete surgical excision is the treatment of choice for MEC. Adequate excision is important in all grades of tumor.

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