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CLEAR CELL SALIVARY GLAND TUMORS- AN OVERVIEW

Dental Science

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ABSTRACT

The salivary glands are the site of origin of a wide variety of neoplasms. The histopathology of these tumors is said to be the most complex and diverse of any organ in the body. Although infrequent, salivary gland tumors with a dominant population of clear staining cells present problems in differential diagnosis. When clear cells predominate the tumor cell population arriving at a particular diagnosis is difficult. Hence this review focuses on this heterogenous group of clear cell neoplasms of salivary gland and attempts to shed light on some of the characteristics that help distinguish one neoplasm from another.

KEYWORDS

Clear cell, neoplasm, Salivary gland tumor

INTRODUCTION

It only takes one biological cell to create an organism. A single cell is able to keep itself functional by owing a series of 'miniature machines' known as organelles. Cells can become specialized to perform a particular function within an organism. [1]

Clear cells as the name suggests are cells having a clear halo around their nuclei.Clear cells are either epithelial or mesenchymal cells composed of pale or clear cytoplasm with distinct nucleus. [2] Presence of clear cells are attributable to various factors including artifactual changes, improper cellular preservation and hydropic degeneration of organelles, or due to the accumulation of glycogen, mucopolysaccharides, lipid, mucin, or phagocytized foreign body material in the cytoplasm of tumor cells. [1] Clear cells are present in both physiologic and pathologic conditions. [2] The rich glycogen content of the cytoplasm gives a clear cell appearance in remnants of dental lamina, rests of Malassez and eccrine sweat glands. Clear cell tumors of the head and neck constitute a heterogenous group of lesions. They may be observed in almost any benign or malignant tumor of epithelial, mesenchymal, melanocytic or hematopoeitic derivation. [1] The presence of clear cell in odontogenic cysts and tumor is because of their origin from dental lamina.Focal clear cell change in a tumor may become more extensive with tumor progression or it may appear secondarily, reflecting clonal evolution in that tumor. These factors may collectively make the diagnosis of clear cell tumors difficult and challenging. With few exceptions, most neoplasms with a clear cell component show sufficient original characteristic histomorphological features that would enable the pathologist to render a precise and accurate diagnosis. [2,3,4] Nevertheless, these changes can potentially lead to difficulties and delays in establishing the diagnosis. [5] These tumors are reported in various sites including the skin, salivary glands, neck, thyroid gland, mastoid bone, middle ear, and jawbones. [1]

Here is a classification of the clear cell tumors of the head and neck region [2] :

- Clear cell odontogenic lesions
- Odontogenic cysts
- Gingival cysts of adults
- Lateral periodontal cyst
- Clear cell calcifying odontogenic cyst
- Odontogenic tumors
- Clear cell odontogenic carcinoma
- Clear cell odontogenic ghost cell tumor
- Clear cell calcifying epithelial odontogenic tumor
- Clear cell salivary gland tumors
- Clear cell Myoepithelioma
- Clear cell oncocytoma
- Clear cell Mucoepidermoid carcinoma
- Clear cell acinic cell carcinoma
- Clear cell myoepithelial carcinoma
- Epithelial myoepithelial carcinoma
- Hyalinising clear cell carcinoma
- Clear cell metastatic tumors including carcinomas arising from
- Kidney
- Liver
- Thyroid
- Prostrate
- Large bowel
- Clear cell keratinocytic tumors
- Clear cell variant of squamous cell carcinoma
- Clear cell variant of basal cell carcinoma
- Clear cell melanocytic tumors
- Baloon cell nevus
- Baloon cell melanoma
- Clear cell bone and cartilaginous tumors
- Clear cell Chondrosarcoma
- Clear cell Osteosarcoma
- Adipose tumors
- Lipoma
- Liposarcoma
- Clear cell tumors arising from skin adnex
- Tricholemomma
- Clear cell acanthoma
- Sebaceous adenoma
- Sebaceous carcinoma
- Syringoma
- Eccrinespiradenoma
- Clear cell hiradenoma
- Miscellaneous clear cell conditions
- Storage disease- Hurler's syndrome
- Viral disease - koilocytes
- Alveolar soft part sarcoma
- Ganglioma

This review will provide an overview of the various salivary gland lesions associated with clear cel

HYALINISING CLEAR CELL CARCINOMA

Clear cell carcinoma is a rare low-grade carcinoma that occurs almost exclusively in the intra-oral minor salivary glands. Occasional cases have been reported in other sites. Various terms applied to this tumour reflect its histological diversity.The tumor cells are characteristically clear and the stroma has areas of hyalinization. Various terminologies used are hyalinizing clear cell carcinoma, clear cell carcinoma, clear cell Adenocarcinoma. The recognition and consequent reporting of this neoplasm increased significantly after the report by Milchgrub et al. It is of interest to note that this tumour has been included as a distinct entity in the third World Health Organization (WHO) classification. [1]

The origin of the clear cells in salivary glands is controversial. It is believed that these tumors originate in the intercalated duct cells or that the myoepithelial cells are the progenitor of the clear cells. They are attributable to various factors including artifactual changes, improper cellular preservation and hydropic degeneration of organelles, or due to the accumulation of glycogen, mucopolysaccharides, lipid, mucin, or phagocytized foreign body material in the cytoplasm of tumor cells. Hydrotropic degeneration in the squamous cells of mucoepidermoid carcinoma can produce areas of clear cells and occasionally these are the predominant feature (clear cell variant). Sebaceous carcinomas may include clear cells but these contain lipid droplets giving the cytoplasm a 'foamy appearance'. [6]

Clear cell tumors of salivary gland could be recognized as primary clear cell tumors or those that are associated with other salivary gland tumors.

PRIMARY CLEAR CELL CARCINOMA

Primary clear cell tumours of salivary origin fall into 2 distinct lineage restrictions – those that require evidence of myoepithelial differentiation and those that do not. Clear cell carcinoma is a classic and distinct entity that represents the latter differentiation pathway. By definition, clear cell carcinoma contains a significant proportion of clear cells, but it does not fit into any other recognized neoplastic entities. Although non-lipid and non-mucin, but glycogen-rich clear cell tumours in salivary glands have long been recognized, they were only recently included in the third WHO classification as a distinct low-grade carcinoma. Most of these tumours have been reported as sporadic cases with the exception of a few well documented series. The natural course is an indolent, painless, submucosal mass that occurs predominantly in the minor salivary glands of elderly women. [1]

Histological features (Figure 1)

The microscopic feature of clear cell carcinoma is distinctive. Individual tumour cells are principally characterised by optically clear cytoplasm with well-defined borders and a centrally placed nucleus, organized in trabeculae, cords, or solid nests. The stroma is typically hyaline although dense fibrous, and loose myxoid or mucoid may be found. Because of the characteristic hyaline stroma of the clear cell carcinoma, it is often termed hyalinising clear cell carcinoma, but this is not a constant feature. Some tumours may be relatively solid, and thus may be referred to as clear cell carcinoma. This term is also preferred by the third WHO classification, whether or not there is significant hyalinisation. The hyaline stroma does not represent the basement membrane type of material found in tumours of myoepithelial lineage. The diagnosis of clear cell carcinoma is usually apparent in H & E sections, but it is imperative to perform special and immunohistochemical stains to exclude other salivary gland tumours with a clear cell component. [7]

Differential Diagnosis

Although clear cells are found in a number of salivary gland tumours, most can be excluded based on other typical cellular or growth phenotypes. The distinction from epithelial-myoepithelial carcinoma is, however, quite difficult, especially the solid form without any discernible double-layered cytology. The presence of PAS-positive and Congo-red negative stroma in clear cell carcinoma may help in the differentiation between this and other clear cell tumours. **(Figure 2)** The cytoplasmic clarity in clear cell carcinoma is due to glycogen; it reacts variably with PAS and is mainly attributed to water. Alternatively, it may result from the loss of organelles, storage of substances or fixation artifacts. Therefore, a negative result for PAS staining does not preclude a diagnosis of clear cell carcinoma, unless myoepithelial markers are likewise negative, as found in this case. Though clear cell carcinoma characteristically infiltrates adjacent structures, and even extends to the overlying epithelium, there has been no report of surface epithelial dysplasia. [8,9]

Immunohistochemistry

Immunohistochemistry may be helpful in revealing the cell of origin of the tumour. The immunohistochemical pattern of the tumor is characterized by immunoreactivity for low molecular weight cytokeratins, epithelial membrane antigen (EMA), and carcinoembrionic antigen (CEA). Vimentin, Smooth-muscle actin, Muscle-specific actin, and calponin are not expressed. It should be noted that S100 protein, which is one of the markers of myoepithelial cells, is rarely positive in clear cell carcinoma while other markers of myoepithelial lineages are invariably negative. [10]

Treatment

Wide excision is the treatment of choice for most clear cell carcinoma, although neck dissection and radiotherapy have been performed in a few cases. Adverse biologic behaviour ranges from multiple recurrences to local nodal or distant disease. The decision to include node dissection or radiotherapy is generally based on the presence of positive margins, high grade histology, invasion (vascular/neural) or positive neck nodes. While these prognostic factors also apply to clear cell carcinoma, an additional factor correlated with nodal metastasis is the presence of mitotic activity. Follow-up is therefore important. [11]

Prognosis

The local recurrence rate is 17% (Wang et al., 2002); multiple recurrences have only been occasionally reported (Tang et al.,1995).The rare cases with local and lung metastases have been sensitive to chemotherapy, with favourable clinical behavior and no recurrences during follow up (Wang et al., 2002; Grenevicki et al., 2001). To date, only one case of HCCC with more aggressive behaviour, quick tumour growth, diffuse metastases and unfortunate prognosis, a few months, has been reported (O'Regan et al., 2004)

Clear Cell Carcinoma Associated With Other Salivary Gland Tumors

Diagnostic dilemmas and controversies are recognised in the classification salivary gland neoplasms associated with clear cells. A proper classification is important and is usually established on the basis of typical features that are apparent. In most of the cases clear cells constitute only a minor component of cellular constituency. But in some tumors they constitute the major component where the diagnosis is a real challenge. It is important to differentiate Hyalinising Clear Cell Carcinoma from other tumors with clear cell features because of their differences in treatment and clinical outcome. [12]

Clear cell myoepithelioma (Figure 3)

Myoepithelial cells are components of several salivary gland neoplasms, tumors in which all or virtually all the neoplastic cell exhibits a myoepithelial phenotype may be aptly designated myoepithelioma. The clear cell variant can occur in both major and minor glands but is relatively rare. It is composed of a bland uniform population of epitheliod tumor cellswith moderate amounts of clear cytoplasm. [13]

Clear cell myoepithelial carcinoma

Clear cell myoepithelial carcinoma accounts for about 16% of all myoepithelial carcinomas. It is important to distinguish this salivary gland tumor with clear cell components as it tends to behave more aggressively with a 50% recurrence rate and 40% metastatic rate. Immunohistochemistry shows positivity with anti S-100 protein, vitamin and high molecular weight cytokeratin, muscle specific actin (MSA), (HHF-35) and alpha smooth muscle actin (SMA). [1]

Clear cell oncocytoma (Figure 4)

Oncocytomas, including the clear cell variant are composed of large polyhedral eosinophilic epithelial cells with characteristic granular cytoplasm and small dark nuclei separated by thin vascular fibrous septae. The oncoytomas and their clear cell variants stain strongly positively for phosphotungstic acid hematoxylin (PTAH) and negatively for myoepithelial markers. Clear-cell oncocytoma of the salivary gland shows excellent prognosis. [14]

Clear cell Mucoepidermoid carcinoma (Figure 5)

MEC has three distinct cell populations (epidermoid, mucous and

intermediate cells) arranged in variable patterns. Approximately 10% of the tumor population may be clear cells but may occasionally form a large population of the tumor cells. Clear cells are much more frequently encountered in mucoepidermoid carcinoma when compared to acinic cell carcinoma. The clear cells in MEC stain positively with PAS; often with the absence or diminish intensity of staining after digestion with diastase confirming its glycogen content. [1]

Clear cell acinic cell carcinoma (Figure 6)

Clear cells exist in approximately 6% of acinic cell carcinomas (ACC) but in almost 1%, they constitute the major population of tumor cells. The clear cells in ACC do not contain glycogen and the cytoplasmic clearing is most probably related to fixation artifacts, reduction in the numbers of organelles, or may reflect transformation of neoplastic acinar cells. The PAS positive diastase resistant zymogen cytoplasmic granules help in establishing the diagnosis especially when the typical histological features are only focally recognised. [1]

Epithelial myoepithelial carcinoma (Figure 7)

Epithelial–myoepithelial carcinoma typically shows duct-like structures of solid, cystic, spindle, tubular, papillary, or cribriform tumor patterns. These carcinomas comprise characteristically two cell types; ductal, cuboidal, intercalated duct like eosinophilic cells typically surrounding a small lumen, and larger polygonal clear cells presenting myoepithelial differentiation. Immunohistochemistry staining with anti S-100 protein can easily distinguish these cells. [13]

Clear cell metastatic tumors

Renal cell carcinoma which often demonstrates clear cell changes shows the greatest tendency to metastasize to various sites. Metastasis of these tumors to the head and neck are also noted in about 15-16% cases. Metastasis to the parotid gland is even more rarely encountered and metastasis to the oral soft tissues is also rarely seen. [1]

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Differential diagnosis of clear cell lesions of salivary gland origin [15]

Tumor	Clear cell oncocytoma	Clear cell carcinoma	Mucoepidermoidcarcioma	Epithelial-Myoepithelioma carcinoma	Clear cell myoepithelioma and myoepithelial carcinoma	Acinic cell carcinoma	Metastatic renal cell carcinoma
Nature of clear cell	Oncocytes	Ductal cells	Intermediate cells, mucinous cells	Myoepithelial cells	Myoepithelial cells	Acinic cell	Neoplastic renal epithelial cells
Cause of cytoplasmic clearing	Encapsulated or circumscribed; trabeculae or packets	Infiltrative; solid or trabecular; sclerotic or hylanizedstroma	Glycogen and mucinrepectively	Glycogen	Glycogen	Tissue-processing artifact	Glycogen and lipid
Growth pattern	Encapsulated or circumscribed; trabeculae or packets	Infiltrative; solid or trabecular; sclerotic or hyalinizedstroma	Infiltrative; inflammed fibrous stroma; islands of epidermoid, intermediate and mucinous cells; some cystic spaces	Infiltrative;ductal structures lined by inner cuboidal cells and outer clear myoepithelial cells	Lobules, nests, trabeculae, and fascicles; may have collagenous spherules	Infiltration in board fronts; microcystic pattern	Prominent sinosoids; hemorrhage and hemosiderin deposition; some glandular structure
Cytologic features of clear cells	Centrally located round nuclei; pheripheral rim of cytoplasm may retain pink granularity	Polygonal cells with water-clear cytoplasm; nuclei central or eccentric	Intermediate clear cells are large cells with water-clear cytoplasm; mucinous cells have flocculent cytoplasm	Polygonal cells, with basally located or central nuclei; water-clear cytoplasm	Cells polygonal or spindly; variable degrees of nuclear atypia; often admixed with a population of cells with eosinophlic cytoplasm	Pheripherally located nuclei; sparse basophillic granules in some cells	Water-clear cytoplasm; varibale nuclear atypia
Staining properties	PTAH+ Mitocondrial +	CK+, EMA+	PAS+, PSAD-, Mucin- for intermediate clear cells; PAS+, PASD+, MUCIN+ from mucinous cells	S-100, Actin+, calponin+, p63+	S-100, Actin+, calponin+, p63+	PASD+ Granules, amylase+	Lipid +, PAS+, PASD-, CK+,EMA+, myoepitheilal markers

CONCLUSION

Clear cell lesions and tumors of salivary gland are assorted group with the presence of common entity "clear cell ". Distinction between all these lesions becomes perplexing due to similar histopathologic appearance. Biologic behaviour of these lesion may vary from being slothful to aggressive. Hence the appropriate distinction of these tumours is essential to arrive at the right diagnosis.

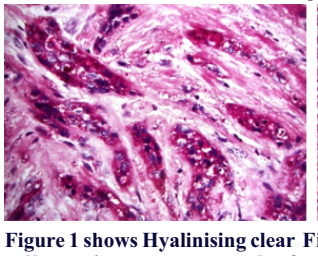

Figure 1 shows Hyalinising clear cell carcinoma composed of infiltrating thin cords of bland clear cells in a densely hyalinised stroma [13]

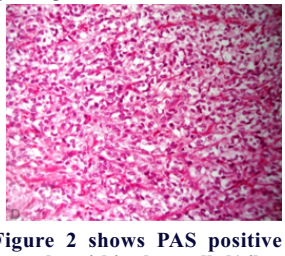

Figure 2 shows PAS positive granules within clear cells [16]

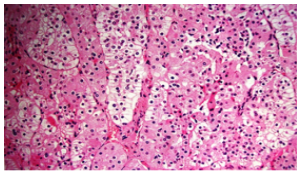

Figure 3 shows neoplastic cells arranged in sheets with moderate amount of clear cytoplasm [13]

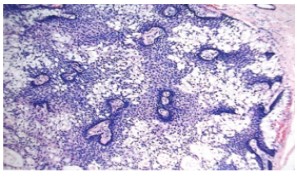

Figure 4 shows oncocytoma composed predominantly of clear cells with focal area of typical oncocytic cells [13]

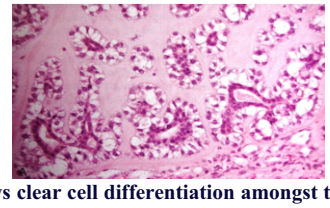

Figure 5 shows clear cell differentiation amongst the epidermoid cells of mucoepidermoid carcinoma [17]

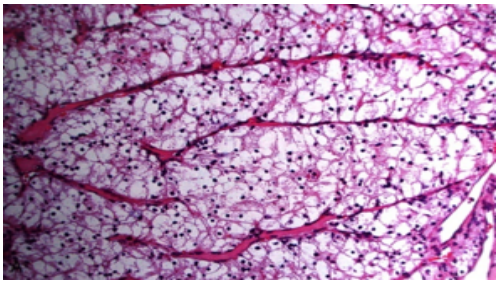

Figure 6 shows clear cell variant of acinic cell carcinoma composed of sheets of clear cells with slightly pleomorphic eccentrically located nuclei and abundant clear cytoplasm [13]

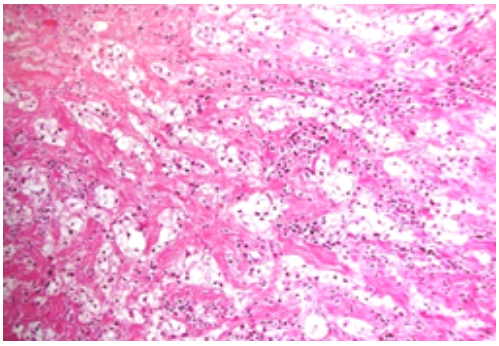

Figure 7 shows epithelial myoepithelial carcinoma demonstrating irregular nests of tumor cells composed of intercalated duct like structure surrounded by clear myoepithelial cells [13]

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