Review Article

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Dentistry Section

Molecular Characterization of Clear Cell Lesions of Head and Neck

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ABSTRACT

The salivary glands, oral mucosa and jaws constitute a group of lesions which are heterogeneous in nature and are odontogenic, salivary or metastatic in origin. This group of tumours is termed as Clear Cell Tumours. Fixation artifacts are one of the most important reasons for the cell to appear clear but clearing of cells may also result from cytoplasmic accumulation of water, presence of glycogen within the cell, intermediate filaments, immature zymogen granules, or a paucity of cellular organelles. Clear cell Odontogenic neoplasms predominantly include odontogenic carcinoma, ameloblastoma and calcifying epithelial odontogenic tumour. Clear cell tumours of salivary gland origin are almost invariably malignant in nature but they do include two benign lesions. Very frequently, surgical pathologist encounters clear cells in many malignant neoplasms, the nature and sources of which are undetermined on the basis of conventional histopathology. This review will selectively discuss the clinicopathological features of neoplasms which at times may pose a diagnostic challenge and dilemma due to clear cell changes.

Keywords: Artifact, Fixation, Metastatic, Odontogenic, Salivary

INTRODUCTION

The term clear cells refer to cells having a clear halo around their nuclei, which may be due to abundant glycogen or other material that is not stained by Haematoxylin or Eosin [1].

At the time of tooth development the primitive oral cavity or stomodaeum is lined by ectoderm, which consists of a basal layer of cuboidal to low columnar cells and a surface layer of flattened squamous cells. The cytoplasm of these cells is glycogen rich which gives them an empty appearance (clear cell). Therefore clear cells are considered to be the typical feature of cellular remnants of the primitive oral cavity or stomodaeum. These cells are found to contain a large quantity of PAS positive diastases labile material indicative of glycogen [2].

Types of Clear Cells

1. Physiologic Clear Cells
2. Pathologic Clear Cells

Physiologic Clear Cells

Cells having clear halo around the nuclei and are widely distributed in the body are termed as physiologic clear cells. These can be observed in the histological sections of epithelium. They are also referred to as Non keratinocytes.

1. Pigment producing cells (melanocytes)
2. Langerhans cells
3. Merkel cells

These cells together constitute 10% of the cell population in the oral epithelium. These non keratinocytes lack desmosomal attachment to adjacent keratinocytes. During histological processing the cytoplasm shrinks around the nucleus and produces the clear halo. Merkel cells though are non-keratinocytes but they possess dendritic processes and have keratin tonofilaments and occasional desmosomes linking them to adjacent cells. As a result, they do not always resemble the other clear cells in histologic sections. None of these cells contains the large number of tonofilament and desmosomes seen in epithelial keratinocytes, and none participate in the process of maturation seen in oral epithelia [1].

Pathologic Clear Cells

Tumours composed exclusively or predominantly of clear cells are rare in the salivary gland, jaws and oral mucosa, and represents only 1% to 2% of all tumours in such locations. More frequently, clear cells represent a minor element in otherwise typical tumours [3]. Clear cells may be observed in almost any benign or malignant tumour of epithelial, mesenchymal, melanocytic or hematopoietic derivation [4]. In the maxillofacial area, clear cell neoplasms can be schematically subdivided in to at least three categories, according to their putative origins. These include tumours of the salivary gland, odontogenic neoplasms, and metastatic clear cell tumours. The first two of the mentioned groups represent at least 90% of all the clear cell tumours in the maxillofacial region [3].

Origin of Clear Cells

In the maxillofacial area, clear cells are found in many different tumours which are usually salivary, odontogenic or metastatic in origin, and in these tumours clear cells most often result from artifacts of fixation but in some instances they may be a reflection of peculiar functional states of the tumour cells as reported especially in salivary gland tumours; scarcity of organelles in cells of salivary ducts which give them an empty appearance; intracellular accumulation of various substances such as glycogen in myoepithelial cells, accumulation of mucin in mucous cells, lipids in sebaceous cells, tonofilaments in epidermoid clear cells, immature zymogen granules in clear acinar cells [3].

Diagnostic Dilemma of Clear Cell Lesions

A common problem for the surgical pathologist is represented by the image of cytologically malignant neoplasms that are composed entirely or predominantly of polygonal cells with clear cytoplasm. Sometimes, the clinical and radiographic details pertaining to these masses will allow for a confident diagnosis to be made. However, disclaimers are often employed in initial reports on clear cell lesions, such as “this is an undifferentiated malignancy with extensive clear cell change; further electron microscopic or immunological analyses will be necessary to obtain a more definitive interpretation” [Table/Fig-1].

Clear cell lesions	Histopathological pattern	Special stains	IHC	Differential Diagnosis
1. Clear Cell Myoepithelial Carcinoma	Arranged in various patterns including plasmacytoid, epithelioid and clear cells	Positive for PAS	Show positivity for S-100, high molecular weight cytokeratin, MSA, alpha SMA	Clear cell Oncocytoma, MEC, Acinic cell carcinoma, Clear cell Carcinoma
2. Epithelial-Myoepithelial Carcinoma	Arranged in various pattern including tubular, cibriform, solid and spindle cell areas	Positive for PAS and susceptible to diastase digestion, Positive for Methanamine silver, Mucicarmine and Alcian blue	Highlighted by Pancytokeratin, EMA, S-100, SMA, P63 and Vimentin	Myoepithelial carcinoma, Clear cell Carcinoma, Pleomorphic Adenoma
3. Hyalinizing Clear Cell Carcinoma	Clear cells arranged in anastomosing cords, sheets, trabeculae, nests and solid sheets	Positive for PAS and negative for congo-red amyloid staining, myoepithelial antigen and mucin	Highlighted by S-100, MSA, and SMA	Pleomorphic Adenoma and Metastatic Renal Cell Carcinoma
Odontogenic Tumours				
4. Clear Cell Odontogenic Carcinoma	Arranged in 3 histological patterns-biphasic pattern, monophasic pattern and clear cell nest with ameloblastoid palisading	Positive for PAS	Highlighted by S-100 protein, Melanoma associated antigen	Clear cell variant of CEOT, Metastatic Renal Cell Carcinoma
5. Clear Cell Calcifying Epithelial Odontogenic Tumour	Arranged in irregular strands, cords, nests of polyhedral epithelial cells	Positivity for PAS reaction	Highlighted by S-100	CCOT, CCA, Metastatic Renal Cell Carcinoma, Oncocytoma
Metastatic clear cell lesions				
6. Clear Cell Renal Cell Carcinoma	Characterized by solid nests of epithelial cells with clear cytoplasm and small round hyperchromatic nuclei	Positivity for PAS reaction	Positive for focal cytokeratin	Clear Cell Malignancy of Salivary Gland

[Table/Fig-1]: Immunohistochemical Profiling of Various Clear Cell Lesions

Varying Modes of Clear Cell Presentation in Clear Cell Lesions

1. Neoplastic proliferation of diverse lineage may manifest a virtually identical clear cell appearance, regardless of whether they are benign or malignant in nature [5]. Thus, the *Modus operandi* for a surgical pathologist lies in further electron microscopic or immunological analyses.
2. Tumour progression can lead to extensive clear cell changes, perhaps as a secondary phenomenon or as a result of clonal evaluation.
3. Identification of origin and differentiation of tumour becomes increasingly difficult in cases where clear cell changes have noticed in primary neoplasms example clear cell variant of renal cell carcinomas metastasizing to oral cavity and other organs of body
4. Artifacts that may cause clear cell changes in the first place may also diminish or abrogate the immunoreactivity sought in immunohistological assessments. This effect is potentially irremediable, even after so-called "antigen-retrieval" methods have been applied to the tissues in question [5].

History

Merkel cells were first described as ''*Helle Zellen" (clear cells)* located in the basal layer of the epidermis at certain distinct areas of mammalian hairy skin by Merkel, 1875 [1]. In 1945 Waldron and Mustoe demonstrated clear cells in Mucoepidermoid carcinoma [6]. Clear cell sarcoma (CCS) is a recently described variant of sarcoma and was first described by Dr. Franz M. Erzinger in 1965 [7]. First case of Clear cell calcifying epithelial odontogenic tumour was reported by Abrams and Howell in 1967 [8]. Epithelial myoepithelial carcinoma was first described by Donath et al., in 1972 and because of the presence of the clear cell component initially epithelial myoepithelial carcinoma was described as glycogen-rich or clear cell adenoma [9]. In 1980 *Batsaki* described a term Clear cell carcinoma of the salivary gland [10]. Paul Grawitz in 1883 described clear cells in Renal Cell Carcinoma [11]. In 1985 Hansen et al., reported a locally aggressive odontogenic neoplasm and named it as a Clear cell odontogenic tumour [12].

WORKING CLASSIFICATION

Clear cell tumours, both benign and malignant can be classified on the basis of tissue of origin-

1. Epithelium
2. Mesenchymal
3. Miscellaneous

- Epithelium
  - a) Glandular
  - b) Non glandular
    - Odontogenic
    - Non odontogenic

I. EPITHELIUM

A. PRIMARY

a. Glandular

1 Predominantly clear cell tumours
- Clear cell myoepithelioma
- Epithelial myoepithelial carcinoma
- Hyalinizing clear cell carcinoma

2 Clear cell variant of salivary gland tumours
- Oncocytoma (clear cell variant)
- Mucoepidermoid carcinoma (clear cell variant)
- Acinic cell adenocarcinoma (clear cell variant)
- Clear cell variant of sebaceous adenoma and lymphadenoma

b. Non glandular

1 Odontogenic epithelium
- Cysts
- Glandular cyst
- Gingival cysts
- Lateral Periodontal cyst
- Botryoid odontogenic cysts
- Tumours
- Clear cell odontogenic tumour
- Clear cell calcifying epithelial odontogenic tumour
- Clear cell ameloblastoma

2 Non odontogenic epithelium

1. Cutaneous adnexa

a) Melanocytic lesions
- Nevocellular nevi (basilar melanocytes)
- Balloon cell nevus

- Melanomas
  - Superficial spreading
  - Nodular invasive

b) **Trichilemmoma**
- Clear cell acanthoma
- Sebaceous adenoma and carcinoma

c) **Syringomas**
- Eccrine Spiradenoma
- Clear cell Hidradenoma

2. **Tumours of Keratinocytes**
- Basal cell carcinoma
- Squamous cell carcinoma

B. METASTATIC
- Renal cell carcinoma
- Liver
- Large bowel
- Prostrate
- Thyroid

II. MESENCHYMAL
- Derived from cartilage- Clear cell variant of chondrosarcoma
- Derived from adipocytes- Lipoma and Liposarcoma
- Ewing's Sarcoma & Primitive neuroectodermal tumour
- Alveolar soft part sarcoma
- Rhabdomyosarcoma
- Clear cell sarcoma

III MISCELLANEOUS
1. Storage Diseases
   - Hurler's disease
   - Hand-Schuller's disease
2. Viral Infections
   a) Squamous papilloma
   b) Verruca vulgaris
   c) Condyloma acuminatum

CLEAR CELL LESIONS
Clear cell tumours of the oral mucosa, jaws, and salivary glands constitute a heterogeneous group of lesions which may be either salivary gland, odontogenic, or metastatic in origin [3]. Most frequently, clear cells represent a minor element and often result from artifacts of fixation but in some instances they may be reflection of peculiar functional states of the tumour cells, as reported especially in salivary gland tumours. Focal clear cell change in a tumour may appear secondarily, reflecting clonal evolution and the presence of clear cells may become more extensive with tumour progression. These factors may collectively make the diagnosis of clear cell tumours difficult and challenging. Clear cells of salivary gland and odontogenic origin may constitute at least 90% of all clear cell tumours in the maxillofacial region [13].

Intraosseous salivary gland tumours may be derived either from ectopic salivary tissue, may arise from the neoplastic transformation of the mucous cells, or from embryonic remnants of submandibular glands, or from bony entrapment of mucous cells of the retromolar pad during embryogenesis or theoretically, from salivary tissue present in lingual cortical defect of the mandible. Clear cells are observed in any type of benign and malignant salivary gland tumours, including benign mixed tumours, myoepithelioma/ myoepithelial carcinoma, oncocytoma/oncocytic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, polymorphous low-grade adenocarcinoma, and adenoid cystic carcinoma. Primary central clear cell carcinoma of salivary origin is extremely rare and it must be included in the differential diagnosis of central clear cell tumours and tumour- like conditions of bone. Between 15–35% of all parotid gland tumours are malignant and 21– 42% of these represents metastatic disease. The majority of metastatic parotid tumours are of cutaneous origin, primarily squamous cell carcinomas and melanomas [4].

A) Glandular
- **Predominantly clear cell tumours**

1. Clear Cell Myoepithelial Carcinoma (CCMC)

Myoepitheliomas are tumours arising from myoepithelial cells lacking ductal differentiation and exhibiting both epithelial and smooth muscle cell characteristics. Benign myoepithelial tumours are seen mostly in extremities and head-neck region, while their malignant counterparts mostly occur in the salivary glands.

The tumour generally presents a benign clinical course; common presentation being a non-painful swelling or mass. The masses may range from 1.5-4 cm in their greatest dimension. The most common sites of myoepithelial carcinoma lie in the parotid gland as well as the nasopharynx, paranasal sinus and nasal cavity of head-neck region. Both benign myoepithelioma and its malignant counterpart myoepithelial carcinoma are comprised exclusively of myoepithelial cells that may be arranged in various patterns including plasmacytoid, epithelioid, and clear cell patterns. CCMC comprises about 16% of all myoepithelial carcinomas. Its distinction from other salivary gland tumours with clear cell components is important since CCMC tends to behave more aggressively with a 50% recurrence rate and 40% metastatic rate [3].

This tumour characteristically reacts positively with anti S-100 protein, vimentin, high molecular weight cytokeratin, muscle specific actin (MSA) and alpha smooth muscle actin (SMA) immunohistochemical stain [14]. Calponin is the most sensitive and specific marker to identify myoepithelial differentiation in myoepithelial carcinoma and thought to be superior to MSA and SMA in delineating the myoepithelial cells [14].

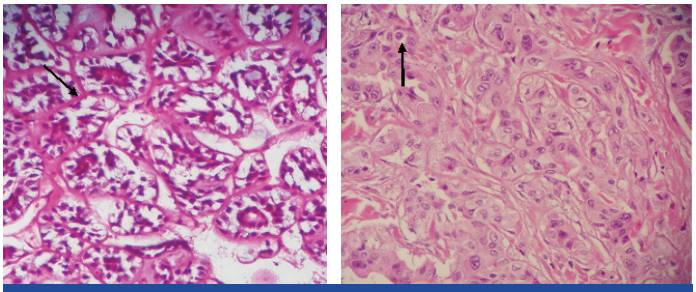
2. Hyalinizing clear cell carcinoma

Clear cell carcinoma of salivary gland has been described in 1980 by Batsakis. Salivary gland neoplasms composed predominantly of clear cells include lesions such as MEC, acinic cell carcinoma, myoepithelioma and oncocytoma but they can be recognized by their specific histological features. Chen classified clear cell carcinomas according to their morphology into two subgroups: a) a biphasic variant composed of eosinophilic cells and clear cells with a double layer arrangement; b) a monophasic variant composed solely of clear cells. Recently Milchgrub et al., designated the latter subgroup as hyalinizing clear cell carcinoma [10,13].

In WHO classification of salivary gland tumours hyalinizing clear cell carcinoma (HCCC) is indicated as being a variant of clear cell epithelial-myoepithelial carcinoma, many researchers now think it should be a separate entity with its own characteristic histological findings. Microscopically, the HCCC shows clear cells, arranged in anastomosing thick trabeculae, cords, nests, or solid sheets surrounded by hyalinized bands with foci of myxohyaline stroma. They show infiltrative borders with minimal nuclear pleomorphism and a very low mitotic index [Table/Fig-2]. Immunohistochemically the tumour cells are cytokeratins and epithelial membrane antigen (EMA) positive [15].

Clear Cell Variants of Salivary Gland Tumours.
1. Clear Cell Variant of Mucoepidermoid Carcinoma (MEC)

Clear cells approximately constitute 10% of the tumour population



[Table/Fig-2]: Histopathological picture showing nests of clear cells surrounded by hyalinized band at X400 magnification (black arrow).
[Table/Fig-3]: Histopathological picture shows areas of clear cells which are large polygonal and having distinct outline X400 magnification (black arrow).

in Mucoepidermoid carcinoma which is one of the most common malignant salivary gland neoplasm sometimes clear cells form a large population of tumour cells. In addition to the typical features of MEC such as cystic spaces lined by mucus cells and epidermoid cells, there is also a presence of clear cells. Clear cells may be a predominant component or rare finding in salivary gland tumours. Clear cells appear as large, polygonal cells with distinct outlines and a hydropic, watery clear cytoplasm. The nuclei are small, vesicular or pyknotic, and centrally placed [Table/Fig-3]. The origin of these clear cells in MEC has been debated. The presence of clear cytoplasm can be due to three basic factors. First, due to intracellular accumulation of components like glycogen, lipid, or mucin. Second, due to scarcity of cytoplasmic organelles like mitochondria, and thirdly due to a fixation artifact. The presence of clear cells does not affect the grading of mucoepidermoid carcinoma, it has been noted that clear cells usually predominate in high-grade tumours and make the prognosis of solid mucoepidermoid carcinoma poor. Clear cells in MEC typically stain positively with PAS; often with the absence or diminished intensity of staining after digestion with diastase confirmating its glycogen content [4,6].

2. Clear Cell Variant of Oncocytoma

Oncocytomas are benign salivary gland neoplasms that represent approximately 1.5% of all salivary gland tumours. Ten cases of clear cell variant of oncocytoma have been reported by Ellis [3]. Oncocytic lesions can be described as a “granular swollen cells” in the ductal and acinar elements of salivary glands. Although in 1927, the tumour was described as an “adenoma”. The presence of oncocytes was originally thought to represent a degenerative or senescent process, as these cells are observed in otherwise normal specimens from aging patient. It is hypothesized that they represent redifferentiation of cells with an increased, unbalanced metabolism trying to increase output of high energy phosphate. Though, mitochondria are somewhat independent organelles, another theory proposed that oncocytomas have granular appearance and these granules represents a neoplasm of subcellular organelle. These lesions are composed of well-circumscribed masses of large polyhedral cells arranged in an organoid fashion with thin fibrous vascular septa. Most of the tumour cells tend to be completely clear, whereas others have variable amount of eosinophilic granular cytoplasm. Transition from typical eosinophilic oncocytes to clear cells forms can be seen [3]. Tumours show immunoreactivity for cytokeratin and EMA. There is no reactivity documented for SMA, S-100 protein, or GFAP [16].

B) Non Glandular

i) Odontogenic Epithelium

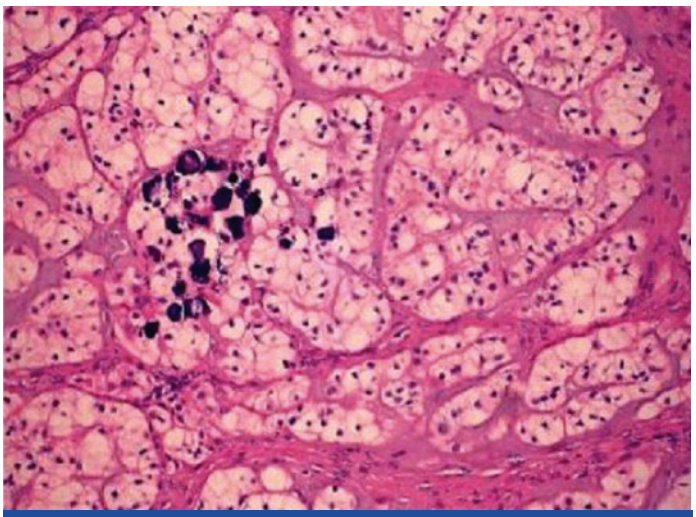
- **Tumours**

1. Clear Cell Odontogenic Carcinoma (CCOC)

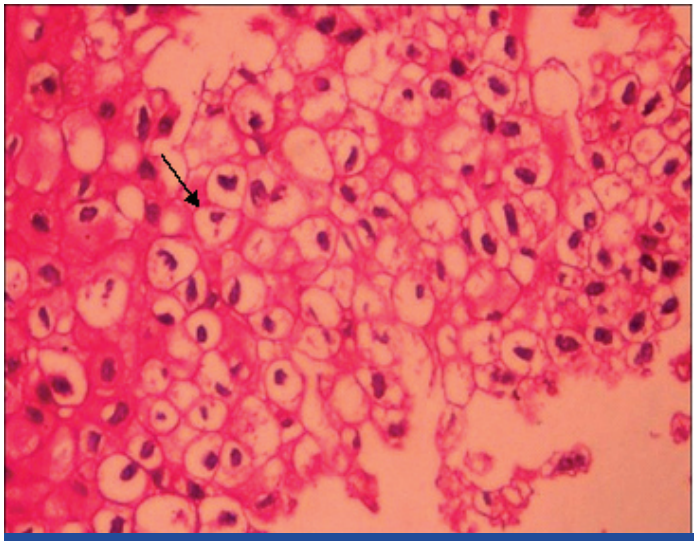
Presence of clear cells in odontogenic neoplasms are quite unusual and represent a diagnostic challenge. Originally thought of as benign tumours, these neoplasms have been referred to as clear cell odontogenic tumours or clear cell ameloblastomas. However, these tumours are now considered malignant because of their aggressive behavior, recurrence, evidence of distant metastasis, and histologically distinct features, Therefore these neoplasms have been subsequently classified as clear cell odontogenic carcinomas (CCOCs). Because numerous benign and malignant tumours may present in the mandible or maxilla with clear cell components, it is crucial to establish the correct diagnosis to develop appropriate treatment strategies. CCOC is associated with pain and enlargement of the jaw or loosening of the teeth. CCOC lesions are typically confined to the anterior or body regions of the mandible, and most lesions of the maxilla are also noted to be in the anterior portion. Radiographically, CCOC presents with nonspecific features, including a poorly defined radiolucency with alveolar bone loss. Overall, CCOCs of the maxilla or mandible are rare. Hansen et al., and Waldron et al., reported the first cases of clear cell odontogenic tumours of the mandible in 1985. Light microscopy and ultra structural features have been described to aid in the identification of CCOC. CCOC lesions are composed of islands of tumour cells surrounded by a fibrous stroma of collagen and fibroblasts with elements of epithelial differentiation. Ameloblastomas and CEOT are most similar to CCOC because of their epithelial differentiation but can be distinguished by their structural features. Ameloblastomas tend to have plexiform and follicular features, whereas calcifying epithelial odontogenic tumours typically display solid proliferations of large pleomorphic clear cells and spindle cells with concentric calcification and amyloid deposits. There seem to be three histologic patterns of CCOC: biphasic, monophasic and ameloblastomatous. Most tumours have a biphasic pattern with oval and linear nests of clear cells among small islands of hyperchromic polygonal cells with marked cytoplasmic eosinophilia. Occasionally these two cell-types co-exist in a tumour nest yielding a “glomeruloid appearance”. The monophasic pattern is described as containing islands entirely of clear cells whereas, the third and the least common variant is composed of clear cell with a tendency for ameloblastoid palisading around the cells arranged in periphery. In general, encapsulation of CCOC lesions are usually not seen, and they frequently invade into the medullary bone, muscle, and perineural tissues. The immunohistochemical profile of this tumour suggests that this is of odontogenic epithelial origin [17].

2. Clear Cell Calcifying Epithelial Odontogenic Tumour (CCCEOT)

The calcifying epithelial odontogenic tumour (CEOT) is a rare benign odontogenic neoplasm of the jaws, accounting for approximately 1% of all intraosseous odontogenic tumours. Some histologic variants have been described, including CEOT with Langerhans cells, with cementum-like and bone-like material, combined epithelial odontogenic tumour and adenomatoid odontogenic



[Table/Fig-4]: Islands of clear cells with foci of calcification. (H&E stain, 10x) [18].



[Table/Fig-5]: Islands of clear cells which are large polygonal in shape with distinct outline (black arrow) [19].

tumour, myoepithelial cells, and the clear cell variant of calcifying epithelial odontogenic tumour (CCCEOT) [Table/Fig-4]. The diagnosis of CCCEOT is very difficult and other clear cell lesions that affect the oral cavity should be excluded. These tumour variants demonstrate a rather consistent "biphasic" histologic pattern with areas diagnostic of the tumour entity in question and other areas with conspicuous clear-cell component. It is not yet known whether clear-cell variants of odontogenic tumours biologically behave differently from the "mother tumour" The clear cell variant of CEOT (CCEOT) was first described by Abrams and Howell. Only 11 cases of clear cell tumours variants have been reported so far, 7 being clear cell variant of calcifying epithelial odontogenic epithelium [18]. It is characterized by polyhedral epithelial cells alternating with huge epithelial cells with a clear, foamy cytoplasm; distinct cell borders; moderate variation in nuclear size; some vacuolated nuclei; and no extreme hyperchromatism or bizarre nuclei [19].

3. Clear cell ameloblastoma

Ameloblastoma is the most common odontogenic neoplasm. Churchill is credited with the first use of the term ameloblastoma in 1934. A thorough description of an ameloblastoma was given by Falkson in 1879. Robinson and Martinez in 1977 were the first to draw a clear distinction between unicystic ameloblastoma and clear cell ameloblastoma and to call for recognition of the entity [19].

Clear cell odontogenic tumour is an uncommon or unusual neoplasm of the jaw. According to Lewis et al., the first case of clear cell neoplasm of odontogenic origin was attributed to Hansen et al., Waldron et al., were the first to report the clear-cell variety of intraosseous ameloblastoma in 1995. An additional intraosseous case of clear-cell ameloblastoma has been reported by Muller and Slootweg. The occurrence of clear-cell ameloblastoma as an extraosseous lesion has been recently reported by NG and Siar [Table/Fig-5].

Presence of clear cells in the odontogenic tumours should not be considered surprising because of their origin from the dental lamina that has clear cell components. The odontogenic clear cell tumour should also be differentiated from the other clear cell tumours such as clear cell variant of mucoepidermoid carcinoma, clear cell squamous cell carcinoma, metastatic renal carcinoma, etc [19,20].

CYSTS

1. Clear Cell Variant of Lateral Periodontal Cyst

The lateral periodontal cyst is developmental in origin and occurs in a lateral periodontal location and arises from cystic degeneration of clear cells of the dental lamina. A botryoid odontogenic cyst is a rare multilocular variant of a lateral periodontal cyst. Botryoid odontogenic cyst (BOC) was originally described in 1973 by Weathers and Waldron as an intraosseous lesion characterized by a macroscopic and microscopic multilocular growth pattern, resembling a bunch of grapes (from the Greek word botrios). BOC is considered to be a variant of a lateral periodontal cyst [21].

The microscopic observation of multiple cystic cavities lined with non-keratinized stratified epithelium consisting of a few cell layers with focal entangled thickenings, the presence of voluminous clear cells in the epithelium, and a thin connective tissue capsule having a few inflammatory cells infiltration.

The fact that the clear cells present in the epithelium were not stained with PAS indicates that they did not contain glycogen or it may be just an example of the vagaries of histochemical staining procedures. Negative findings may well be due to tissue handling or other technical details. This finding is in contrast to the results of Greer and Johnson and Gurol et al., who observed staining of these cells with PAS. Greer and Johnson reported a similarity between these clear cells rich in glycogen, frequently observed in the epithelium of BOC, and in dental lamina cells, suggesting that the dental lamina is one of the possible origins of BOC [22]. However, these cells do not seem to exert any influence on the biologic behavior of the cyst. The diagnosis of BOC should not be discarded in cases of negative PAS staining when all other histologic features are present [22,23].

2. Clear Cell Variant of Glandular Cyst

The glandular odontogenic cyst (GOC) is a rare developmental cyst of the jaws that was described in 1988 by Gardner et al., as a distinct entity. The first two patients with features of GOC were reported by Padayachee and Van-wyk in 1987. It is also known as sialoodontogenic cyst, mucoepidermoid cyst (MEC) or polymorphous odontogenic cyst. Its name was changed to GOC by Gardner et al., because of the lack of evidence of salivary gland origin, and the term was later adopted by the World Health Organization (WHO) [21].

Microscopically, the specimen usually shows a nonkeratinized epithelial lining with areas of papillary growth enclosed with intraepithelial crypts that are either empty or filled with mucin. The cystic lining is thin and consists of cuboidal cells resembling reduced enamel epithelium. In certain areas, the cyst lining is continuous with the sinus lining. Many mucous cells, clear cells and few cells resembling epidermoid cells are also observed. Focal areas depicting epithelial thickening or plaque formation may be seen. Many cystic spaces filled with mucin are evident in the fibrous connective tissue capsule.

The presence of mucin can be confirmed by mucicarmine, PAS and alcian blue staining. Mucous cells and mucous pooling showed positivity to alcian blue and PAS, suggestive of acidic mucin. Clear cells were positive for PAS without diastase and negative for PAS with diastase, indicating their content of glycogen [21,23].

The GCA specimens displayed the following staining pattern: CKs 7 and 8 could be detected immuno-histochemically in the suprabasal layer (consisting of cuboidal cells) and in the focal epithelial thickenings (clear cells); CK 13 was present in a thin lining of clear cells intermingled with occasional cuboidal cells. This intermediate filament of CK 13 was not observed in the focal epithelial thickenings that consisted of clear cells. CK 14 was positive in clear cells, basal cells, and isolated intermediate cells that corresponded to the focal epithelial thickenings. CK 19 was positive in the thin lining of clear cells intermingled with occasional cuboidal cells, whereas CKs 10 and 16 were completely negative. Although the cystic epithelium showed weak, strong, and negative scores in equal amounts, all four types of staining scores were presented [24].

II). METASTATIC

1) Renal cell carcinoma

Metastatic tumours in the oral cavity are very uncommon and represent approximately 1% of all the cases of neoplasms in the oral cavity. In the majority of cases, the primary tumour is known; although in one-third of such cases, metastasis is the first clinical manifestation. The most common primary tumours metastasize in oral cavity are lung carcinoma in men and breast carcinoma in women [11]. Renal cell carcinoma (RCC) or renal cell adenocarcinoma is by far the most common kidney cancer [25]. It is the third most frequent neoplasm to metastasize to the head and neck region preceded only by breast and lung cancer. In the case of head and neck metastasis without lung involvement, several theories exist to address a route of dissemination that avoids pulmonary vascular filtration.

Histologically, it is characterized by the presence of a solid nest of epithelial cells with clear cytoplasm and small, round hyperchromatic nuclei. A rich vascular network was also noted. Differentiating among clear cell tumours with conventional light microscopy can be challenging. It can be especially difficult to distinguish between RCC metastasis and clear cell malignancies of salivary glands. Clear cell carcinomas of salivary gland origin usually have nest of clear cells which is divided by thin, fibrous connective septa and irregular vascular tissue Immunohistochemical staining helps in this distinction, with RCC metastasis exhibiting focal cytokeratin positivity (versus minor salivary gland cancers showing diffuse positivity) and a strong reaction for vimentin [11].

CONCLUSION

Clear cell changes may be virtually observed in any benign or malignant tumour of epithelial, mesenchymal, melanocytic and hematopoeitic derivation. The distinction between tumours having clear cell changes is perplexing due to their similar histological appearance. So as to differentiate between different clear cell tumours, we designed classification according to the cell of origin. The biological behavior of these neoplasms may range from indolent to aggressiveness. But in most of the cases the presence of clear cells in tumours of different origin may be a sign of increased tumour aggressiveness and malignancy. Thus their appropriate designation is crucial.

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