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Review Article

A Diagnostic Approach to Oral Clear Cell Lesions - A Comprehensive Review

T Muthukumar[1], N Malathi[2] and S Vijaya Nirmala[2]*

[1]*Department of Anatomy, Sri Ramachandra Institute of Higher Education and Research, India*

[2]*Department of Oral Pathology and Microbiology, Sri Ramachandra Institute of Higher Education and Research, India*

***Corresponding Author:** S Vijaya Nirmala, Senior Lecturer, Department of Oral Pathology and Microbiology, Sri Ramachandra Institute of Higher Education and Research, India.

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Abstract

Clear cells are found in many different tumors and also result from fixation artifacts in histopathological section. Clear cell neoplasms are rare which could result in misdiagnosis or difficulties and delays in establishing precise diagnosis. A Proper algorithmic approach of the lesions aids to arrive at accurate diagnosis and treatment plan. Few researchers had put forth classifications of clear cells in the literature, of varying degrees of complexity. An attempt has been made in the present article to provide comprehensive approach of clear cell lesions in oral and maxillofacial region and to assist the pathologist to render a precise and accurate diagnosis in such lesions.

Keywords: *Oral and Maxillofacial Lesion; Histopathological Clear Cell; Artifact and Unstained Cytoplasm*

Introduction

Clear cells can be encountered in a variety of physiological [1-6] and pathological states in the oral and maxillofacial region [7-10]. In 1938, Feyrter discovered the clear cells in several organs especially in the diffuse endocrine system. It is normally found in the parathyroid gland and also in specific type epidermal cell of neural origin. Clear cells are characterized by failure of the cytoplasm to stain with hematoxylin and eosin when examined via the light microscope. These cells appear clear because of intracellular accumulation of non staining compounds such as glycogen, lipids and mucin and also due to the sparsity of cell organelles [11].

Physiological clear cells

Major cell type of histologic section of oral epithelium is keratinocytes, rest of the 10% formed by clear cell population which includes Melanocytes, Langerhans cells, Merkel cell and lymphocytes. These cells are located in different level of oral epithelium, characterized by lack of large number of tonofilament and desmosomes and also none of these cells participates in the maturation process. During tissue processing, the cytoplasm of these cells shrinks around the nucleus to form the clear halo. Epithelial derivatives of glandular cells or secretory cells are also physiological clear cells which contains special substances i.e. mucins, mucoids and sebum. The important protein-carbohydrate complex present in these substances are glycosaminoglycans and based on the amount of glycosaminoglycans present in

those cells affects their staining reactions and also leads to poor fixation. In connective tissues, the cytoplasm of the adipocytes appears clear and empty, their nucleus is pushed to the periphery, as during histological preparation the formalin which is commonly employed as a fixative alters their relationship with the protein and also xylene which is used as a clearing agent clears the lipid content of these cells [1-6].

Pathological clear cells

The clear cell is one of important clues for histopathological reporting. Focal or extensive clear cell changes can be due to artifactual or degenerative changes or neoplastic and non neoplastic conditions. Most important clear cell lesions of oral and maxillofacial region are originated from odontogenic apparatus, salivary gland tissues, connective tissues and metastatic tumors. Based on the patterns of clear cell presentation of the lesion, tumor origin and the knowledge of the frequency may helpful in determining a diagnosis and to differentiate into benign and malignant clear cell tumors [7-16]. Establishing a diagnosis of primary and metastatic cancers is essential. As the management of metastasis of tumor is mainly palliative, but in case of primary tumors is surgical excision and prognosis vary between them [17]. This treatise aims at systematic approach towards appropriate diagnosis of the clear cell tumors and lesion.

Various approaches

1. BR Premalatha article described the various conditions associated with clear cells, causes, limitation and drawbacks observed in clear cell lesions. This article provided an algorithmic approach towards these tumors with immunohistochemistry markers to arrive at an appropriate diagnosis [18] (Figure 1). The above classification does not consider the Special stains and also artifactual changes (improper cellular preservation, Hydropic degeneration) which might lead to hindrances in electron microscopy procedures and to arrive at an accurate diagnosis.
2. Humaira Nazir highlighted clearing of cytoplasm or clear cell change can be seen in different tumors of various parts of the body due to diverse reasons. Nazir., *et al*. approach the clear cell entities from artifactual, a impersonate of clear cell tumors to a true clear cell tumor. A tumor has to be differentiated either primary tumor of clear cell origin or secondary changes. Based on histopathological patter, the tumor can be easily distinguished between benign or malignant in nature. In malignancy, primary tumors must be ruled out from the secondary or metastatic tumor i.e. Renal clear cell carcinoma, clear cell tumor from liver, prostate. It is mandatory to have a thorough knowledge of differential diagnoses of these tumors [19] (Figure 2). This system is limited to pathologic clear cell, however it does not allow the physiological clear cells and also after morphological evaluation, how to reach the final diagnosis is not mentioned.
3. Anshi Jain developed a classification system for Clear cell tumours on the basis of tissue of origin - These system enlists characteristic histomorphological features of glandular especially salivary gland clear cell lesions and non glandular-odontogenic clear cell entities and role of Special stains, immunohistochemistry and electron microscopy used for differential diagnosis [20] (Figure 3). This classification does not includes few epithelium derived tumors - clear cell variant of squamous cell carcinoma and basal cell carcinoma and normal variation i.e. Fordyce ‘s granules.

Physiological clear cell: 1. Epithelial: a. odontogenic – Rests of malasseez
--Rests of Serre
b. Non odontogenic – Lower level clear cell ie Melanocytes & Merkel cells
- Higher level clear cell ie Langerhans cells
- Salivary gland-Mucous acinar cells
- Cutaneous adnexa
2. Mesenchymal : Adipocytes

Clear Cell tumors: The pathological clear cells are present in odontogenic cyst & tumors, salivary gland tumor, Metastatic tumor, keratinocystic tumor, Melanocytic tumor, Cartilage ,Bone, Adipocytes ,Skin tumors and Miscellaneous.

I. Clear cell odontogenic lesion: 1. Odontogenic cyst :
   a. Gingival cyst of adults
   b. Lateral Periodontal cyst
   c. Clear cell calcifying odontogenic cyst
   2. Odontogenic tumors :
   a. Clear cell odontogenic tumors
   b. Clear cell odontogenic ghost cell tumor
   c. Clear cell calcifying odontogenic tumor

II. Clear cell Salivary gland tumor :
   a. Clear cell Myoepithelioma
   b. Clear cell oncocytoma
   c. Clear cell Mucoepidermoid carcinoma
   d. Clear cell Acinic cell carcinoma
   e. Clear cell Myoepithelial carcinoma
   f. Epithelial Myoepithelial carcinoma
   g. Hyalinizing Clear cell carcinoma

III. Clear cell metastatic tumors include carcinomas arising from
   a. Kidney
   b. Liver
   c. Thyroid
   d. Prostate
   e. Large bowel

IV. Clear cell keratinocytic tumors:
   a. Clear cell variant of Squamous cell carcinoma
   b. Clear cell variant of Basal cell carcinoma

V. Clear cell melanocytic tumors:
   a. Balloon cell nevus
   b. Balloon cell melanoma

VI. Clear cell bone & cartilaginous tumors:
   a. Clear cell chondrosarcoma
   b. Clear cell Osteosarcoma

VII. Adipocytic tumors:
   a. Lipoma
   b. Liposarcoma

VIII. Clear cell tumors arising from skin adnex :
   a. Trichilemmoma
   b. Clear cell acanthoma
   c. Sebaceous adenoma
   d. Sebaceous carcinoma
   e. Syringomas
   f. Eccrine spiradenoma
   g. Clear cell hidradenoma

IX . Miscellaneous clear cell conditions:
   a. Storage diseases- Hurler's syndrome
   b. Viral lesion- Koilocytes
   c. Alveolar soft part sarcoma
   d. Paraganglioma

Figure 1

Salivary gland tumors

- Benign
  - ✓ Clear cell myoepithelial carcinoma
  - ✓ Clear cell oncocytoma
- Malignant
  - ✓ Clear cell mucoepidermoid carcinoma
  - ✓ Clear cell acinic cell carcinoma
  - ✓ Clear cell epithelial-myoepithelial carcinoma
  - ✓ Hyalinising clear cell carcinoma

1) **Nonodontogenic non salivary gland tumors**

Benign

- Clear cell melanocytic tumor
- Leukoedema
- White sponge nevus
- Fordyces granules

Malignant

- Clear cell variant of squamous cell carcinoma
- Clear cell variant of basal cell carcinoma
- Clear cell variant of malignant melanoma

2) **Tumors and cysts of Odontogenic Epithelial origin**

- Clear cell variant of calcifying epithelial odontogenic tumor
- Clear cell odontogenic carcinoma
- Clear cell ameloblastoma

3) **Tumors of connective tissue origin**

Benign

- Lipoma
- Hibernoma
- Xanthoma
- Juvelinexanthogranuloma
- Verruciformxanthoma

Malignant

- liposarcoma
- Clear cell chrondrosarcoma
- Clear cell osteosarcoma
- Clear cell leiomyosarcoma
- Clear cell sarcoma

4) Metastatic tumors

- Renal cell carcinoma
- Liver
- Thyroid
- Prostrate

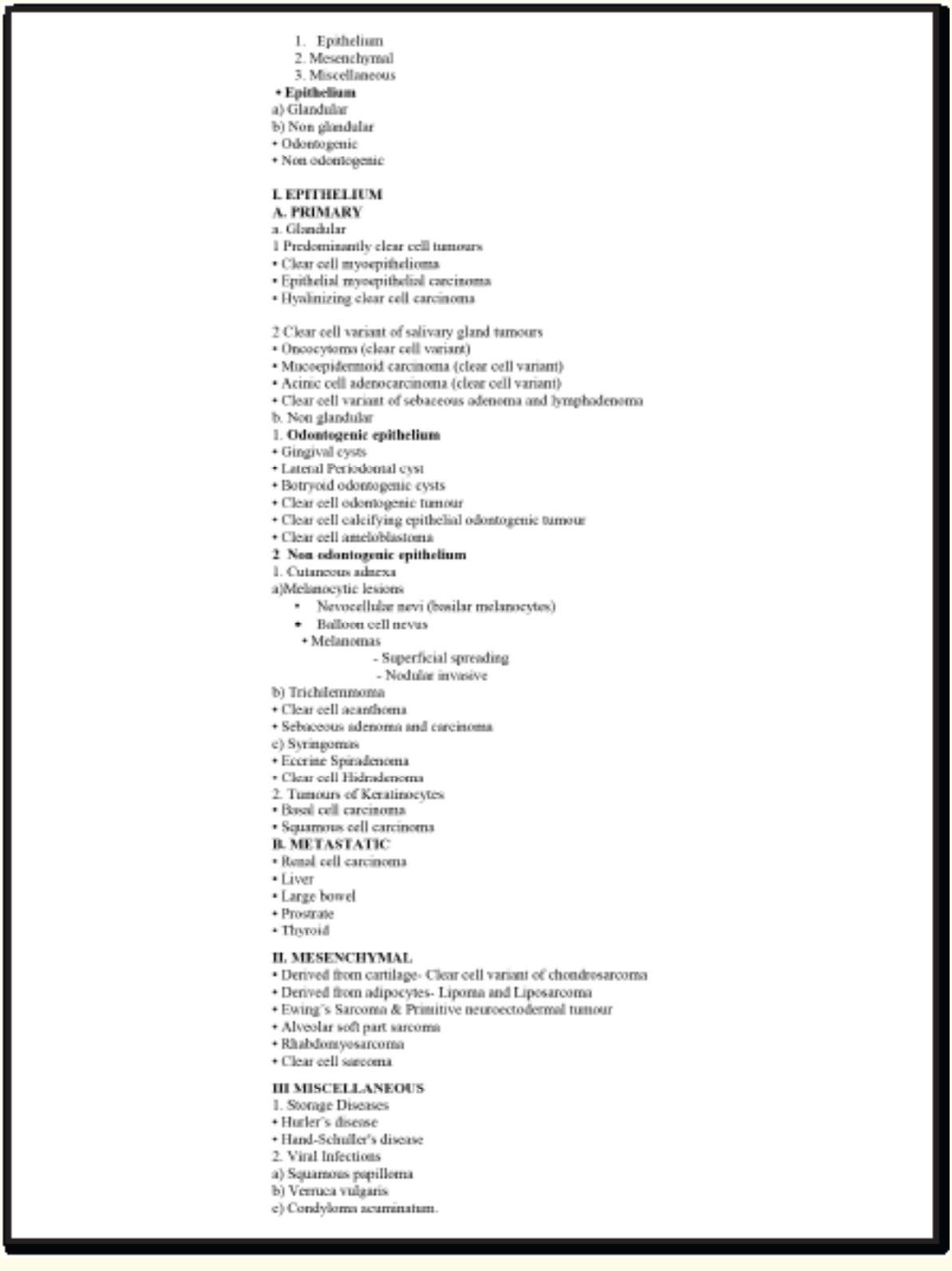
5) Infections

Herpes

Lesions Containing Clear Cells:

- ✓ Gingival cyst of adult
- ✓ Lateral periodontal cyst
- ✓ Clear cell calcifying odontogenic[22]

Figure 2



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**
• Gingival cysts
• Lateral Periodontal cyst
• Botryoid odontogenic cysts
• 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.

Figure 3

Discussion

Clear cell can be observed in histology and histopathological spectrum. Physiological clear cell is the accumulation of glycogen, mucopolysaccharides, lipid, mucin or phagocytosed foreign body material in the cytoplasm of cells. Artifact Clear cell - may be attributed to improper fixation and Hydropic degeneration of cellular organelles. Artifactual changes may limit the applicability of immunohisto-

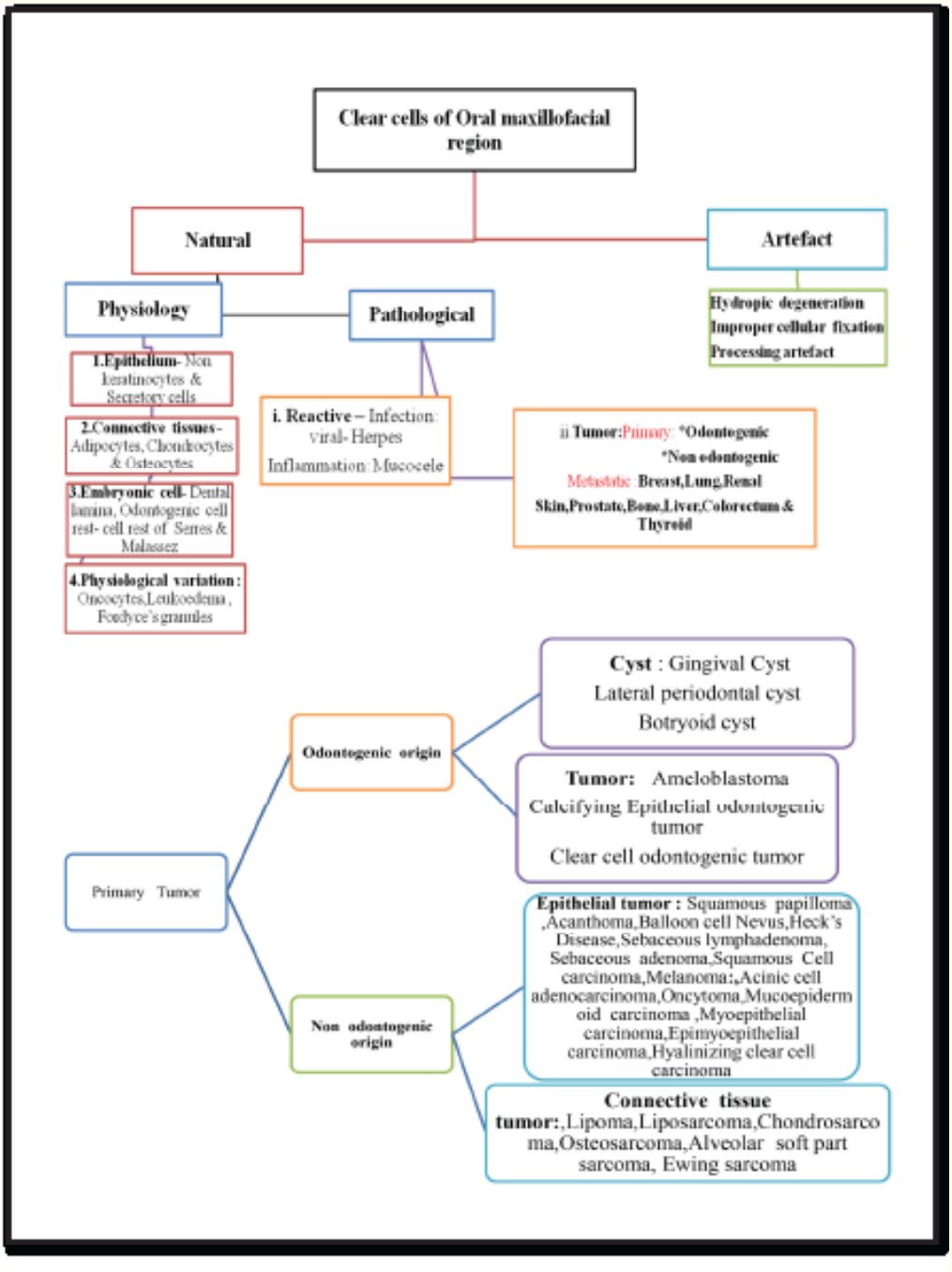


Figure 4

chemistry staining [11]. In maxillofacial region, clear cell tumors are schematically subdivided into two categories based on their origin (Figure 4). Primary clear cell tumors of the salivary gland, jaws and oral mucosa constitute 9 - 10%, and metastatic tumors represent approximately 1%. Clear cells constitute only a minor component of the salivary gland tumor [21]. Odontogenic neoplasms composed of predominantly clear cell are also found in the lining epithelium of odontogenic cyst [7]. In a differential diagnosis of an clear cell tumors, a histochemical stain for cytoplasmic vesicles may assist the pathologist in distinguishing a tumor of origin. Metastatic tumors are rare to the oral region and pose a diagnostic challenge for pathologist. The primary tumors of lung, kidney and skin which can metastases in the oral cavity. Clinical Features of metastatic lesions in the oral cavity mimics like reactive lesion, so appropriate designation of these tumors is very essential [17].

Salivary gland clear cell tumors

Clearcell tumors of salivary glands are habitually malignant excluding clear cell variant of oncocytoma and myoepithelioma. Primary salivary clear cell neoplasia contributed by the myoepithelial differentiation based on this can be divided into clear cell Myoepithelioma or myoepithelial carcinoma and epithelialmyoepithelial carcinoma. Non- myoepithelial differentiation, clear cell salivary gland tumors are acinic cell carcinoma, mucoepidermoid carcinoma and Oncocytoma. Based on distribution, pattern and number of clear cells, myoepithelioma can be differentiate benign or malignant [21]. Wang., *et al.* analyzed the entities with myoepithelial cells differentiation and reported hyalinizing clear cell variant of salivary gland tumor which contains hyaline stroma. Primary oral clear cell carcinoma present with high glycogen content and have indolent course in contrast to the other two aggressive tumors [22]. Milchgrub S., *et al.* reported that clusters of tumor cells are separated by broad bands of hyalinized stroma [23]. The distinctive growth pattern of epithelialmyoepithelial carcinoma is biphasic tumor that. In epithelialmyoepithelial carcinoma and clear cell myoepithelial tumors, clear cells are positive for glycogen stains. In this context, calponin and p63 immunohistochemistry marker can be used diagnostic tool for myoepithelial origin [22].

Presence of clear squamous, mucous, and intermediate cells are important histopathologic diagnostic clue for Clear cell mucoepidermoid carcinoma. The occurrence of clear cell variant of acinic cell carcinoma is unusual, characterized by foci of parent tumor growth pattern and presence of the vacuolated cells due to lack of glycogen. Clear cell variant of oncocytoma shows encapsulated tumor mass with organoid growth pattern, separated by thin vascular septa. An oncocytic tumor cells have abundant eosinophilic granular cytoplasm with small pyknotic nuclei. In oncocytosis, usually the clear cells lie haphazardly in the salivary gland a important clue [9]. With help of histochemical stains, each entities can be differentiated by positive stain. Oncocytic clear cells -phosphotungstic acid haematoxylin (PTAH) and periodic acid–Schiff (PAS) stain is positive with glycogen. clear cell variant of mucoepidermoid carcinoma is positive for mucin, clear cell variant of acinic cell carcinoma with focal mucicarmine positivity. PAS stain are used to express the non-sulfated and sulfated acidic mucins in epithelium, neutral and mucopolysaccharides, but not for mesenchymal and connective tissue acidic mucins. Acidic mucin can be demonstrated by Mucicarmine stains. To demonstrate sialomucin and sulfomucin neutral and acidic mucopolysaccharides, alcian blue can be used [11].

Odontogenic clear cell lesions

In odontogenic cysts and tumors, the clear cell change is unusual [25]. Clear cell found in the epithelium of odontogenic cysts i.e. gingival cyst of adults, dentigerous cyst, calcifying odontogenic cyst and lateral periodontal cyst [8]. Clear cell odontogenic tumors are clear cell ameloblastoma, clear cell odontogenic ghost cell tumor (CCOGCT), clear cell odontogenic carcinoma (CCOC) and calcifying epithelial odontogenic tumor (CCCEOT). Clear cells component in odontogenic tumors and cysts originate from the dental lamina [8] and ever sole proposed that the clear cells are epithelial in nature, ultrastructurally containing desmosomes, lacking secretory granules and also related

to the presecretory ameloblast. In addition to the characteristic features of the respective entity, clear cells of odontogenic lesions are arranged in the form of sheets, cords, or nests by which can be differentiated from one another [26]. Abrams and Howell described the first case of CCEOT, calcification is a distinctive feature of tumors that are usually scattered within it. In polarized light, amyloid-like materials Liesegang ring calcifications of CCEOT exhibits an apple-green birefringence, which stain positively for Congo red or thioflavin T [27]. The extraosseous CEOT clear cell variant is extremely rare, and shows hyaline materials are usually positive for Congo red, crystal violet, and Lugol's iodine, but negative for Coomassie blue. The aggressive tumor growth in vascular connective tissue usually indicated by presence of clear polyhedral cells in extraosseous CEOT [28,29]. The intraosseous CEOT noncalcifying variant is also believed to be aggressive [30]. The potential origins of clear tumor cells in CCCEOT can be found from histochemical, immunohistochemical, and electron microscopic findings [31]. In CCOC has large clear cells arranged in islands with delicate fibrous connective stroma in between and also presence of hyperchromatic basaloid cells with focal nuclear palisading. Ultrastructural features of CCOCs are organelle poor cells, containing few mitochondria, desmosomes, tonofilament bundles and lysosomes. Presence of granules, which are usually combination of mitochondria and lysosomes. Electron microscopic features of desmosomes and tonofilament bundles are important clue for squamous phenotype of CCOC. Lesional cells are positive for CK8 and CK19 but nonreactive for S100 and vimentin [32-34]. A CCOGCT variant showed clear epithelial cells arranged as sheets and islands separated by a thin fibrous connective tissue stroma. These cells are rich in glycogen [35]. These lesion can be derived as *de novo* from odontogenic epithelium or pre-existing GCOT clear cell change. The most prominent feature of CCOGCT were the clear cell component which were immunopositive for cytokeratin 19 and AE1/3 [36]. In 1995, "clear cell ameloblastoma" term coined by Waldren., *et al*. biphasic tumor consists of ameloblastoma pattern with clear cell component in the follicles. Clinically, it has an aggressive course and most of the time showed recurrence and metastasis. Presence of clear cell component is a clear indication of dedifferentiation of malignancy with or without metastasis [37].

Other epithelial clear cell tumors

Clear cell squamous cell carcinoma (CCSCC) is a rare variant, characterized by the presence of intracellular fluid and the extensive hydropic degeneration of neoplastic cells without glycogen, mucin and lipid [38]. Some authors suggested that incidence is related to ultraviolet radiation exposure. The growth pattern and nuclear features of these tumor is no different from conventional Squamous cell carcinoma [39]. These features distinguishes CCSCC from Clear Cell sebaceous carcinoma and also a negative fat stain using Oil Red O. The histopathologic features, special histochemical staining and immunoreactivity are the diagnostic criteria [40]. Clear cell basal cell carcinoma (CCBCC) was first described by Barr and Williamson in 1984, the large membrane bound intracellular vacuoles to be found in Electron microscopy. Clear cell BCC stain positive for glycogen [41] sebaceous carcinoma, clear cell squamous cell carcinoma, clear cell melanoma, and metastatic clear cell renal carcinoma should be considered as differential diagnosis of clear cell basal cell carcinoma. Sebaceous clear cells carcinoma and clear cells of metastatic renal cell carcinoma contains lipid which is positive for Oil Red O or Sudan IV. But it can be differentiated from Sebaceous cells characterized by "foamy-bubbly" cytoplasm [42]. Clear cells of metastatic renal cell carcinoma are negative for immunostains of CEA and S-100 protein. The histopathological and immunohistochemical features of Melanoma similar to those observed in clear cell variant of melanoma. cytogenetic hallmark of Clear Cell melanoma is characterized by translocation t(12,22)(q13;q12) or less commonly t(2;22)(q34;q12) translocation fusing EWSR1 and CREB1 [43].

Metastatic clear cell tumors

Metastatic clear cell carcinomas of oral cavity are rare, contributes 1% of all oral neoplasms; these can be from kidney, liver, prostate, large intestine, and thyroid. The attached gingiva followed by the tongue are most common oral sites for metastatic tumors [44]. Clinically,

the risk of bleeding after biopsy of metastasis of RCC lesions is documented [17]. However, the previous history of RCC, histomorphology and immunohistochemical findings are valuable diagnostic tool of an oral metastatic lesion with the primary entities. Renal Cell Carcinoma can be distinguish from other clear-cell-variant with help of CD10 marker [45].

Conclusion

The diagnosis of clear cell tumor in the oral and maxillofacial region shows various signs ranging from indolent to aggressive behavior due to different origin. As management and treatment strategies depends upon primary and metastatic lesions, a comprehensive assessment to distinguish between them is almost important. An attempt has been made to provide the concise knowledge of Approach to definitive diagnosis and also envisages therapeutic plan of clear cell lesions.

Conflict of Interest

No conflict of interest exists.

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