

# Clear Cell Tumors of the Head and Neck: An Overview

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## ABSTRACT

Clear cells are routinely encountered in the histopathological sections. They most frequently result from fixation artefacts; cytoplasmic accumulation of water, glycogen, lipids, mucins; hydropic degeneration of organelles, etc. When these clear cells predominate in a tumor, arriving at a definitive diagnosis becomes problematic. Thus, this review gives an idea of clear cells associated with various conditions, causes for clearing of these cells, clear cell tumors of the head and neck and a systematic approach towards arriving at an appropriate diagnosis of these tumors.

**Keywords:** Clear cells, Clear cell tumors, Mechanism of clearing, Physiological clear cells.

**How to cite this article:** Premalatha BR, Rao RS, Patil S, Neethi H. Clear Cell Tumors of the Head and Neck: An Overview. *World J Dent* 2012;3(4):344-349.

**Source of support:** Nil

**Conflict of interest:** None declared

## INTRODUCTION

Clear cells are either epithelial or mesenchymal cells composed of pale or clear cytoplasm with a distinct nucleus. Clear cells are associated with both physiological and pathological conditions. Physiological clear cells can sometimes give rise to pathologic conditions like, the remnants of dental lamina can give rise to odontogenic cysts, melanocytes give rise to melanomas, and adipocytes are associated with lipomas and liposarcomas. Other pathological clear cells include the koilocytes seen in human papilloma virus (HPV) infections.

Clear cells can be observed in any benign or malignant tumor of epithelial, mesenchymal melanocytic and hematopoietic derivation but are rare in the head and neck region.<sup>1</sup> When clear cells predominate, a definitive diagnosis is difficult as many of these tumors share histological features: Indeed, the segregation of benign from malignant neoplasia may be obfusatory.<sup>2</sup> Focal clear cell changes may become more extensive with tumor progression or may appear secondarily reflecting clonal evolution.<sup>1</sup> These changes may make the diagnosis of clear cell tumors challenging.

## MECHANISM OF CLEARING OF CELLS

Clear cells most frequently result from artifactual changes; cytoplasmic accumulation of water, glycogen, mucopolysaccharides, lipids, mucin, intermediate filaments and immature zymogen granules; phagocytized foreign body

material in the cytoplasm; hydropic degeneration of organelles and paucity of cellular organelles.<sup>1,3</sup>

## Causes for Physiologic Clearing of Cells

The rich glycogen content of the cytoplasm gives a clear cell appearance in remnants of dental lamina,<sup>4</sup> rests of malassez<sup>5</sup> and eccrine sweat glands.<sup>6</sup> Neutral polysaccharide-glycogen is negatively charged and does not take up the stain with eosin which is also negatively charged hence giving a clear appearance.<sup>7</sup>

The nonkeratinocytes which include the Langerhan's cells, melanocytes except Merkel cells lack desmosomal attachments to adjacent cells and during histologic processing the cytoplasm shrinks around the nucleus to produce a clear halo.<sup>8</sup>

In routine histologic sections, lipid is lost when it is subjected to organic solvents such as xylene during processing; consequently, adipose tissue appears clear.<sup>9</sup>

## Causes for Pathologic Clearing of Cells

The presence of clear cells in odontogenic cysts and tumors is due to their origin from the dental lamina.<sup>4,10</sup>

Most of the salivary gland tumors contain glycogen in their cytoplasm causing cytoplasmic clearing. Mucoepidermoid carcinoma contains mucins with glycogen which contributes to the clearing.<sup>11</sup> The clear cells in acinic cell adenocarcinoma represent fixation or tissue processing artifactual changes and alterations of cytoplasmic organelles.<sup>12</sup> Clear cells in metastatic renal cell carcinoma are due to the accumulation of glycogen and lipids.<sup>11</sup>

In clear cell variants of squamous cell carcinoma (CSCC) the hydropic degeneration of neoplastic cells and accumulation of intracellular fluid and in basal cell carcinoma (CBCC) accumulation of glycogen, sialomucin and degradation products of intracellular organelles result in clear cell appearance.<sup>13</sup>

The clearness of cytoplasm in balloon cell melanoma (BCM) or nevus (BCN) may be due to intracellular accumulation of glycogen. In the majority of ultrastructural studies the empty appearing vacuoles are thought to represent degenerating melanosomes. A case of metastatic BCM was shown to contain lipid.<sup>14</sup>

The clear cell changes in osteosarcoma and chondrosarcoma is due to cytoplasm containing exaggerated glycogen deposits accompanied by the formation of glycogen containing phagolysosomes or vacuolar

degeneration of the cells, large dilated endoplasmic reticulum and bundles of actin like filaments.<sup>15,16</sup>

Liposarcoma, lipomas show clearing because of the presence of lipids. The presence of lipids and glycogen causes clearing of cytoplasm in clear cell tumors of skin adnexa.<sup>13</sup>

## CLASSIFICATION

Clear cells can be broadly classified into physiological and pathological. The pathological clear cells are encountered in various tumors. The physiological clear cells can either be epithelial or mesenchymal in origin and include both odontogenic and nonodontogenic tissues (Table 1). Clear cell tumors constitute a heterogeneous group of lesions. Table 2 enumerates the various clear cell tumors of the head and neck.

## CLEAR CELL TUMORS OF THE HEAD AND NECK

### Clear Cell Odontogenic Lesions

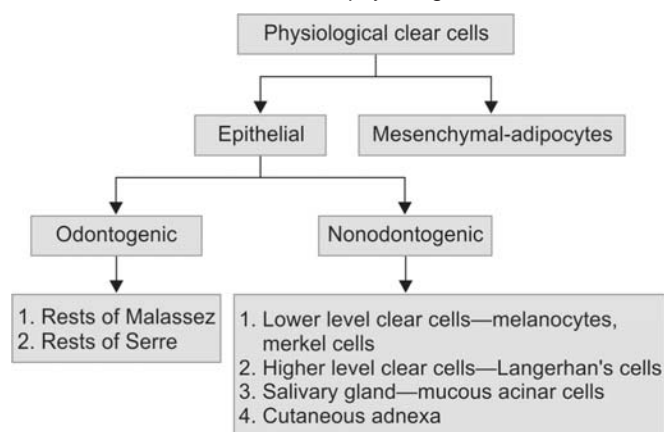
Odontogenic neoplasms with a significant clear cell component are exceedingly uncommon.<sup>17</sup> Clear cell odontogenic tumors are: Clear cell variant of calcifying epithelial odontogenic tumor (CCCEOT), clear cell odontogenic carcinoma (CCOCa)<sup>4</sup> and clear cell odontogenic ghost cell tumor (CCOGCT).<sup>18</sup> In these lesions, the clear cell components may be evident as glycogen rich plaques, rests, pseudoglandular clusters, or as large sheets.<sup>19</sup> Clear cell odontogenic cysts are: Calcifying odontogenic cyst (CCOC), gingival cyst of adults (GCA) and lateral periodontal cyst (LPC);<sup>19</sup> the former consists of ghost cells and dentinoid like material and the latter two consists of reduced enamel epithelium-like nonkeratinized epithelium.<sup>10</sup>

Except for the CCOCa which consists primarily of clear cells, all the other odontogenic lesions contain areas bearing histologic features characteristic of the respective entities which help in differentiation of one from another.<sup>19</sup> Numerous studies have shown that the occurrence of clear cells may prove to be a sign of increased tumor aggressiveness indicating a more radical surgical approach.<sup>20-22</sup>

### Clear Cell Salivary Gland Tumors

Clear cells constitute less than 1% of all primary salivary gland tumors.<sup>23</sup> Clear cell salivary gland tumors are almost invariably malignant in nature but they do include two benign lesions namely: Clear cell variant of oncocytoma (CCO) and myoepithelioma (CCM). Clear cells in acinic cell carcinoma (CACC) seldom comprise a significant portion of the tumor whereas clear cell mucoepidermoid

**Table 1:** Classification of physiological clear cells



**Table 2:** Clear cell tumors of the head and neck

- I. Clear cell odontogenic lesions
  1. Odontogenic cysts
    - a. Gingival cyst of adults
    - b. Lateral periodontal cyst
    - c. Clear cell calcifying odontogenic cyst
  2. Odontogenic tumors
    - a. Clear cell odontogenic carcinoma
    - b. Clear cell odontogenic ghost cell tumor
    - c. Clear cell calcifying epithelial odontogenic tumor
- II. Clear cell salivary gland tumors
  - 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 and cartilagenous 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 lesions—koilocytes
  - c. Alveolar soft part sarcoma
  - d. Paraganglioma

carcinoma (CMEC) can readily be identified by an admixture of clear-squamoid, mucous and intermediate cells.<sup>3</sup>

Some tumors may be composed exclusively of myoepithelial cells and are designated as myoepitheliomas. Both benign and malignant variants have been described to contain clear cells with latter being less common. Epithelial myoepithelial carcinoma (EMC) supposedly takes origin from intercalated ducts with biphasic duct like structures. Hyalinizing clear cell carcinoma (HCCC) show clusters of tumor cells separated by broad bands of hyalinized stroma that may undergo myxoid or hyaline degeneration.<sup>3</sup>

Primary salivary tumors should be distinguished from clear cell metastatic tumors since they have diagnostic and therapeutic consideration.<sup>1</sup> With respect to biological behavior, clear cell salivary gland tumors are considered low grade malignancies because in spite of their benign appearance they are capable of local infiltrative growth and destruction as well as metastasis with poor prognosis.<sup>23</sup>

### Clear Cell Metastatic Tumors

Metastatic tumors in the oral cavity are uncommon and represent approximately 1% of all oral neoplasms.<sup>24</sup> Carcinomas from the kidney, liver, large bowel, prostate and thyroid are known to have the potential for clear cell differentiation and are able to metastasize to the maxillofacial area with renal cell carcinoma (CRCC) doing so most frequently.<sup>2</sup> The latter may mimic salivary gland and odontogenic tumors but is characterized by prominent sinusoidal vascular component and hemorrhagic areas.<sup>3</sup> The prognosis of patients with metastatic carcinomas is poor. The average 5-year survival rate for surgically resected renal clear cell carcinoma is 50%.<sup>2</sup>

### Clear Cell Keratinocytic Tumors

Surface epidermal and cutaneous adnexal tumors are common on the facial skin. Both squamous and basal cell carcinomas have been reported to manifest clear cell variants and 90% of such neoplasms are located on the skin of the head and neck. Although individual islands in these neoplasms may be composed exclusively of clear cells, neighboring cells will exhibit the typical features of either basal or squamous cell carcinoma.<sup>25</sup> It is difficult to determine the prognosis of CSCC based on the six cases reported in the literature<sup>26</sup> and CBCC is a rare and unusual variant; the underlying clinical effect on treatment and prognosis of this subtype remains unclear.<sup>13</sup>

### Clear Cell Melanocytic Tumors

Malignant melanomas as well as melanocytic nevi are known to be composed of cells with varied morphological

phenotypes. Balloon cell melanoma is a rare form of vertical growth phase melanoma characterized by a nodular proliferation of neoplastic balloon cells. The tumor is characterized by nests and sheets of large cells that exhibit a clear or finely vacuolated cytoplasm. The prognosis is similar to other types of melanoma. In the largest series on record, 57.5% of patients died with metastatic disease 2 months to 12 years after initial surgery.<sup>14</sup>

Nevus cells can rarely demonstrate peculiarly large clear, foamy or finely vacuolated cytoplasm. Focal vacuolization is not rare, but nevi demonstrating a predominance of clear cells (over 50%) are distinctly uncommon and designated as balloon cell nevi (BCN). BCN can rarely transform into malignant melanoma. In these instances, separation from a benign BCN is made by the presence of nuclear pleomorphism, atypia and mitoses.<sup>27</sup>

### Clear Cell Bone and Cartilagenous Tumors

The clear cell variant of chondrosarcoma (CCC) is an extremely rare variant that accounts for about 2% of all chondrosarcoma. Only nine cases are reported in the head and neck area. The histological finding of head and neck cases are consistent with general features of this entity in the whole body and represent a component of conventional chondrosarcoma. CCC is a distinct low-grade sarcoma with potential for local recurrence or distant metastasis. Recurrence rate of 19% has been described in some case series.<sup>28</sup> Three cases of high-grade osteosarcoma with significant areas of clear cells have been reported.<sup>15,28</sup> Although extremely rare, this entity must also be considered.<sup>28</sup>

### Adipocytic Tumors

The overall incidence of lipoma in the oral cavity is about 1%<sup>29</sup> and liposarcoma accounts for 5.6 to 9% in the head and neck region.<sup>30</sup> Histologically, lipomas show mature adipose tissue without cytologic atypia<sup>29</sup> and liposarcoma show the presence of lipoblasts, cellular pleomorphism, vascular proliferation and mitotic activity. Several authors have commented that the prognosis of liposarcoma of the oral cavity is generally favorable because of the predominance of myxoid and well-differentiated types and the small size of these neoplasms.<sup>30</sup>

### Clear Cell Tumors of Skin Adnex

Cutaneous and adnexal clear cell tumors are distinct from clear cell salivary gland and jaw lesions since the former lesions are clinically defined as skin nodules. Some maintain their continuity with the epidermis while others are located in the dermis. Regardless, the overall growth pattern and

the presence of other cell populations that are indicative of cutaneous derivation are usually present. Even the rare malignant variants of the adnexal tumors that contain clear cells are slow to metastasize.<sup>25</sup>

### Miscellaneous Clear Cell Conditions

A long-recognized, pathognomonic feature of HPV infection is the appearance of koilocytotic cells. Koilocytes are epithelial cells containing a hyperchromatic nucleus that is eccentrically displaced by perinuclear vacuole(s), and these morphological alterations are used by pathologists to identify HPV-infected epithelial cells.<sup>31</sup>

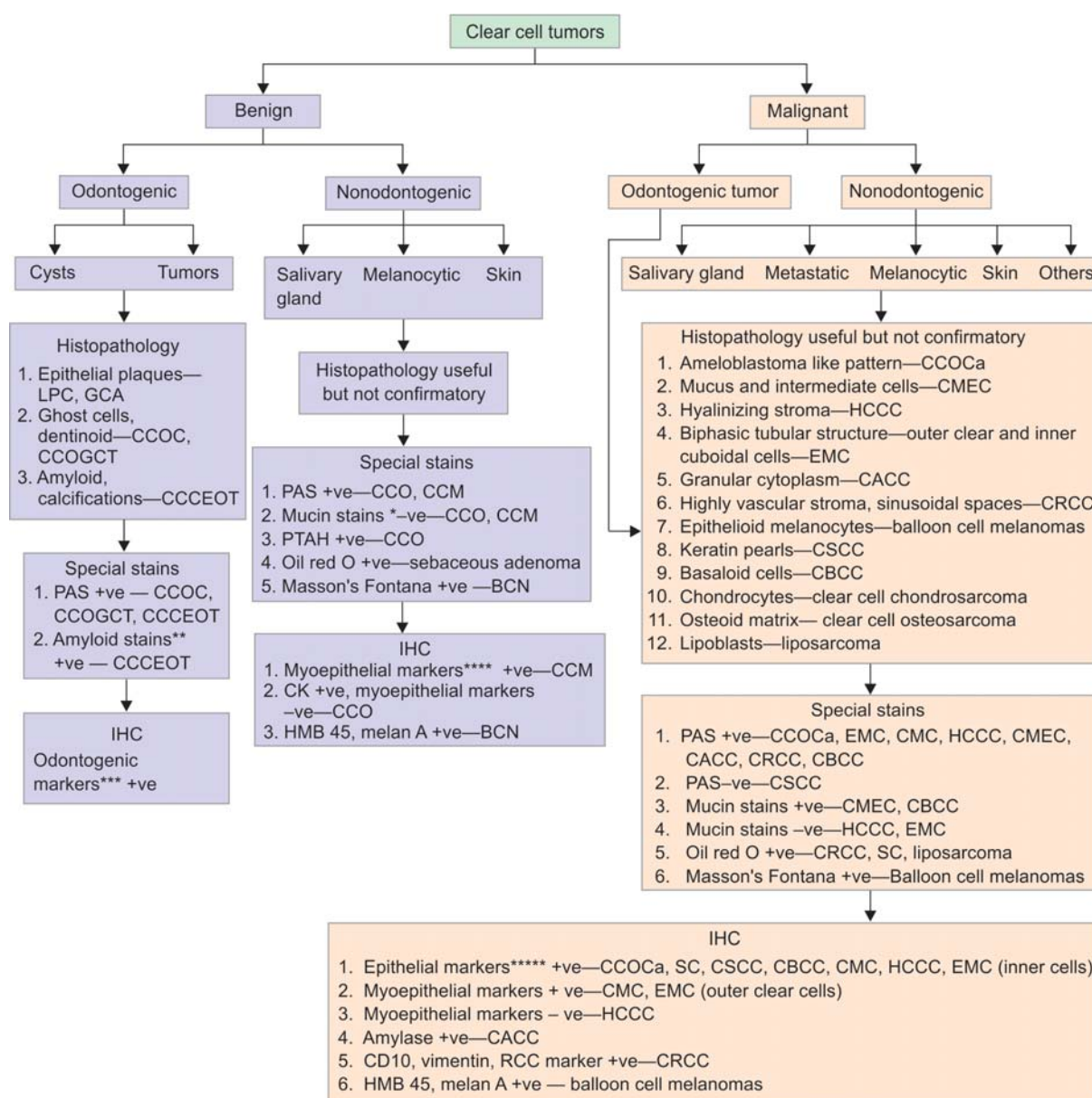
In disturbances of carbohydrate metabolism as in Hurler syndrome, there is excessive accumulation of intracellular mucopolysaccharide. Abnormal deposits are found in many sites with involved fibroblasts assuming the appearance of 'clear' or 'gargoyle' cells.<sup>32</sup>

In addition, alveolar soft part sarcoma and paraganglioma that occur in the head and neck region contain clear cells and should be included in the differential diagnosis of clear cell tumors of the head and neck.<sup>33</sup>

### DIAGNOSIS OF CLEAR CELL TUMORS

The features of clear cell tumors often impose a challenge and differentiating one from the other is enigmatic. Table 3

**Table 3:** Diagnostic work chart of clear cell tumors of the head and neck



\*Mucin stains—alcian blue, mucicarmine; \*\*Amyloid stains—congo red, crystal violet, thioflavine T; \*\*\*Odontogenic markers—CK 14, 19; \*\*\*\*Myoepithelial markers—SMA, S-100, CK, GFAP, vimentin, calponin; \*\*\*\*\*Epithelial markers—pancytokeratin and EMA

**Table 4:** IHC screening panel for clear cell tumors of the head and neck

Antibody to	Odontogenic tumors	Salivary gland tumors	Metastatic tumors	Keratinocytic tumors	Melanocytic tumors	Bone cartilagenous tumors	Adipocytic tumors
Pan cytokeratin	+	+/-	+/-	+	+/-	-	-
Vimentin	-	+/-	+	-	-	+	+
SMA	-	+/-	-	-	-	-	-
Calponin	-	+/-	-	-	-	-	-
Melan-A	-	-	-	-	+	-	-

**Table 5:** Diagnostic tumor markers for clear cell tumors of the head and neck

Tumors	Tumor markers	
Odontogenic tumors	Clear cell odontogenic carcinoma	CK 19, calretinin
Salivary gland tumors	Myoepithelioma	Calponin
	Epithelial myoepithelial carcinoma	Calponin
	Myoepithelial carcinoma	Calponin
	Acinic cell carcinoma	Amylase
Metastatic tumors	Renal cell carcinoma	CD10, RCC marker
	Prostate	PSA
	Lung	Villin
	Colon	Villin
Melanocytic tumors	Balloon cell melanoma	Melan-A, HMB-45
	Balloon cell nevus	Melan-A, HMB-45
Adipocytic tumors	Liposarcoma	MDM2

illustrates the diagnostic workup for clear cell tumors of the head and neck; Table 4 provides the IHC screening panel and Table 5 elaborates the diagnostic tumor markers.

## CONCLUSION

The clear cell tumors and conditions of the head and neck are a heterogenous group with a common entity—the ‘clear cells’. The distinction between these tumors is confounding due to their similar histological appearance. The biological behavior may range from indolent to aggressive. But in most cases the presence of clear cells may prove to be a sign of increased tumor aggressiveness. Thus, their appropriate designation is crucial.

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