

Clear Cell Entities of the Head and Neck: A Histopathological Review

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Abstract: Clear cell changes may be observed in virtually any benign or malignant tumor of epithelial, mesenchymal, melanocytic and hematopoietic derivation not be attributed to variable etiologies. 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. This review will selectively discuss the causes of clearing of cells and the pathological features of tumors with clear cell changes, which, at times, may pose a diagnostic challenge and dilemma.

Keywords: Clear cell tumors, Head and neck region.

I. Introduction

A clear cell is epithelial or mesenchymal cells composed of pale or clear cytoplasm with distinct nucleus. Clear cells are associated with both physiological and pathological conditions. Physiological clear cells like remnants of dental lamina sometimes give rise pathological conditions like odontogenic cyst, melanocytes gives rise to melanoma, adipocytes are associated with lipoma and liposarcoma. Any discussion regarding clear cell requires an understanding of what constitutes a clear cell in general, clear cell is defined as "A cell, especially a neoplastic, finely vacuolated with central dark nuclei, containing abundant glycogen or other material that is not stained by haematoxylin or eosin, so that the cytoplasm appears clear histologically"

Why Cells Appear "Clear"??

Following are the reasons responsible for optically clear appearance of cytoplasm (Batsakis 1979):³

The cytoplasm may contain a considerable amount of **glycogen** and a normal number of sub cellular organelles. Neutral polysaccharide glycogen is negatively charged and do not take up the stain of eosin which is negatively charged and hence give clear appearance. The microscopic changes are similar to acute cell swelling where clear vacuoles are present in the cells. This is because in routinely prepared sections, glycogen that is water-soluble is lost in the preparation. Special stains in frozen sections could show the abnormal accumulation of this substance in affected cells.²¹

Non keratinocytes which include Langerhans cells, melanocytes and merkel's cell, during histological processing cytoplasm shrinks around the nucleus to produce a clear halo.⁴

The **intracellular oedema** becomes more pronounced as the cells migrate into the stratum spinosum. eg leukoedema Intracellular oedema results from an alteration in the semipermeable membrane of the cell and subsequently allows the absorption of abnormal quantities of extracellular fluid.²²

Hydropic degeneration without significant amount of glycogen present and only a small number of organelles demonstrable. This Cellular swelling is first manifestation of almost all forms of injury to cell. It occurs because of marked mitochondrial damage, cessation of ATP production and failure of sodium pump leading to increased

osmotic pressure within cells. The alteration is on selective permeability of cellular membranes leading to influx of water molecules.²³ Acute cell swelling or hydropic degeneration occurs due to failure of the injured cells to maintain electrolyte balance through the "Sodium-Potassium pump". As this mechanism is energy dependent, a fall in ATP in injured cells causes the efflux of Potassium ions. With the influx of Sodium ions, the increasing osmotic pressure in the cytoplasm attracts water molecules. As a result, swelling of the cells occurs, and is evident grossly as enlarged pale, and heavy organ. Microscopically, affected cells show vacuoles in the cytoplasm with no distinct borders. The cytoplasm is diluted, and dispersed²³

Virus induced due to long-standing inflammation or infection which are involved in the occurrence of the clear cells and that the perinuclear vacuoles or halo represented degenerative changes. Koilocyte (from Greek, a hollow cell) the squamous cells with enlarged nuclei and sharply demarcated perinuclear clear zone, surrounded by a rim of cytoplasm.²⁴

Due to **scarcity** of organelles which results in clear appearance of cell as in clear salivary duct cell.³ Clear cell changes may be observed in virtually any benign or malignant tumour of epithelial, mesenchymal, melanotic and hematopoietic derivation not to be attributed to variable etiologies.³

An **artefact** during fixation may occur by which cellular material disappears from the cell and Improper Cellular Preservation. In routine histological sectioning, **lipid** is lost when subjected to organic solvents like xylene during processing, consequently cells appears clear.³

Classification Of Clear Cells:

Clear cells can be broadly classified as physiological and pathological. Pathological can be seen in various tumours while as physiological can be either epithelial or mesenchymal in origin and include both odontogenic and non odontogenic tumours.

Classification Of Physiological Clear Cells²⁰

1. Epithelial:

- a. Odontogenic:
 - Rests of malassez
 - Rests of serres
- b. Non odontogenic:

Lower level epithelial clear cells- melanocytes. Merckels cells.

Higher level epithelial clear cells- Langerhans cells.

Salivary gland- mucous acinar cells

2. Mesenchymal:

Adipocyte

Classification Of Pathological Clear Cells

i. Clear cell odontogenic lesions:

- 1) Odontogenic cyst
 - a) Gingival cyst of adult.
 - b) Lateral periodontal cyst
 - c) Clear cell calcifying odontogenic cyst.
- 2) Odontogenictumors
 - a) Clear cell odontogenic carcinoma
 - b) Clear cell odontogenic ghost cell tumor
 - c) Clear cell calcifying epithelial odontogenictumor.

ii. Clear cell salivary gland tumors

- a) Clear cell myoepithelial carcinoma
- b) Clear cell oncocytoma
- c) Clear cell mucoepidermoid carcinoma
- d) Clear cell acinic cell carcinoma
- e) Clear cell epithelial-myoepithelial carcinoma
- f) Hyalinizing clear cell carcinoma.

iii. Clear cell metastatic tumor include carcinoma arising from

- a) Kidney
- b) Liver
- c) Thyroid
- d) Prostate
- e) Large bowel

iv. Clear cell keratinocytictumors

- a) Clear cell variant of squamous cell carcinoma
- b) Clear cell variant of basal cell carcinoma

v. Clear cell melanocytic tumor

- a) Balloon cell nevus
- b) Balloon cell melanonoma

vi. Clear cell bone and cartilagenoustumors

- a) Clear cell chondrosarcoma
- b) Clear cell osteosarcoma

vii. Adipocytictumors

- a) Lipoma
- b) Liposarcoma

viii. Clear cell arising from skin adnexa

- a) Trichilemmoma
- b) Clear cell acanthoma
- c) Sebaceous adenoma carcinoma
- d) Syringomas
- e) Eccrinespiradenoma
- f) Clear cell hidradenoma

ix. Miscellaneous clear cell conditions

- a) Storage diseases--- Hurlers syndrome
- b) Viral lesions ----koilocytes
- c) Alveolar soft part sarcoma
- d) Paraganglioma
- e) Hybernoma(adipose tissue)

II) Functional Classification:

Lesions In Which Clear Cells Are The Predominant Histologic Finding And Form The Basis For Their Recognition

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

2) Nonodontogenic non salivary gland tumors

Benign

- ❖ Clear cell melanocytic tumor
- ❖ Leukoedema
- ❖ White sponge nevus
- ❖ Fordyce granules

Malignant

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

3) Tumors and cysts of Odontogenic Epithelial origin

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

4) Tumors of connective tissue origin

Benign

- ❖ Lipoma
- ❖ Hibernoma
- ❖ Xanthoma
- ❖ Juvelinexanthogranuloma
- ❖ Verruciform xanthoma

Malignant

- ❖ liposarcoma
- ❖ Clear cell chondrosarcoma
- ❖ Clear cell osteosarcoma
- ❖ Clear cell leiomyosarcoma
- ❖ Clear cell sarcoma

5) Metastatic tumors

- ❖ Renal cell carcinoma
- ❖ Liver
- ❖ Thyroid
- ❖ Prostate

6) Infections

- ❖ Herpes

Lesions Containing Clear Cells:

- ❖ Gingival cyst of adult
- ❖ Lateral periodontal cyst
- ❖ Clear cell calcifying odontogenic

Pathological Clear Cells:

I) Clear Cell Odontogenic Lesions: Odontogenic lesions with significant clear cell component are exceedingly uncommon. In these lesions clear cell component may be evident as glycogen rich plaques, pseudo glandular clusters and sheets.

Odontogenic Cyst:

1. The Gingival Cyst Of Adult:

Histopathologically, it consists of a thin, flattened epithelial lining with or without focal plaques that contain clear cells. Clear cells are rich in small nests of glycogen and are seen as small nests, seen in the surrounding connective tissue. (Fig 1)

2. Lateral Periodontal Cyst:

Histopathologically, it has a thin, generally non-inflamed, fibrous wall with an epithelial lining that is 1 to 3 cell thick in most areas. Foci of clear cells rich in glycogen may be interspersed among the lining epithelial cells. Also some cysts show focal nodular thickenings of the lining epithelium which chiefly consists of clear cells. (Fig 2)

Odontogenic Tumors:

Clear Cell Odontogenic Carcinoma: In the WHO classification of odontogenic tumors given in 1992, clear cell odontogenic tumor (CCOT) was classified as a benign but locally invasive tumor. However, high rate of recurrence, local and distant metastasis and tumor related deaths have led to its reclassification as clear cell odontogenic carcinoma (CCOC).

Histopathology: exhibit three histological patterns:

- ▶ **Monophasic**
- ▶ **Biphasic**
- ▶ **Ameloblastomatous.**

The **monophasic variant** is represented by islands that show only the clear cell phenotype.

Biphasic tumor is the most common characterized by oval and linear nests of large clear cells intermixed with smaller islands of smaller polygonal cells with eosinophilic cytoplasm.

The ameloblastomatous is the least common variant which is comprised of clear cell nests with a tendency for ameloblastoid palisading at the periphery. (Fig 3 & 4)

Calcifying Epithelial Odontogenic Tumour (Ceot)/ Pindborg Tumour:

It was first described in 1959 by Pindborg. It accounts for less than 1% of all odontogenic tumors. A clear cell variant of CEOT (CCCEOT) has been identified in limited number of cases.

Histopathology, (CCCEOT) shows sheets or strands of clear cells are present which are almost entirely composed of polyhedral epithelial cells with clear vacuolated cytoplasm in bland fibrous stroma. Frequent homogenous masses that sometimes called as Liesegang ring within tumor sheets are present. Amorphous eosinophilic areas of amyloid were noted in the connective tissue. (Fig 5)

ii) Clear Cell Salivary Gland Tumors:

In the instance of tumors of the salivary tissues, the "clear cell" is slowly emerging from its enigmatic status. This has been attributed to the results of histochemical and ultrastructural analysis. Studies have shown that the clear cell appearance is the light microscopic manifestation of the three basic factors, depending upon the particular salivary gland lesion being investigated.

- ✓ First, clear cells may contain large amount of intracellular non staining compounds (glycogen, mucin, lipid).
- ✓ Second, they may have a sparsity of cell organelles.
- ✓ Third, the cells may appear clear because of postremoval or fixation artifact.⁴⁵

Clear cells may predominate or be only a component of major and minor salivary gland tumor. The mucous cell component is basophilic and will stain positively with mucicarmine or alcian blue. The true clear cell tumors fail to stain positively for mucosubstance. These clear cell salivary tumors are differentiated from one another on variety of histopathological features that is discussed below^{46,47}

Clear cell oncocytoma is a variant of oncocytoma described for the first time by ELLIS G L in 1988. Till date more than ten cases of Clear cell oncocytoma have been reported.

Clear Cell Variant Of Oncocytoma

Histopathology: Most of the tumor cells are completely clear, where as others had variable amount of eosinophilic granular cytoplasm at the periphery of the cells. It has been shown that the clear cell change is due to combination of fixation artefact and intracytoplasmic glycogen accumulation. (Fig 6)

Epithelial Myoepithelial Carcinoma of salivary gland is an uncommon salivary gland neoplasm representing less than 1% of all salivary gland tumors and takes origin from intercalated duct. This tumor has been described in past by many names, including clear cell adenoma, glycogen rich adenoma and clear cell carcinoma. (Fig 7)

iii) Clear Cell Metastatic Tumors:

In oral cavity metastatic tumors are very rare and represent approximately 1% of all oral neoplasms. Carcinomas from kidney, liver, bowel, prostate and thyroid are known to have potential for clear cell differentiation and are able to metastasize to maxillofacial area. Renal cell carcinoma (RCC) is most frequently metastasizing tumor. The prognosis of patients with metastatic carcinoma is poor.

Renal Cell Carcinoma: Renal cell carcinoma (RCC), also known as renal cell cancer or renal cell adenocarcinoma, is by far the most common type of kidney cancer. About 9 out of 10 Kidney cancers are renal cell carcinomas. Although RCC usually grows as a single tumor within a kidney, sometimes there are 2 or more tumors in one kidney or even tumors in both kidneys at the same time.¹⁵ (Fig 8)

Iv) 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 head and neck. The tumor cells are arranged in islands and sheets with unmistakable origin from the surface. Although individual islands may be composed exclusively of clear cells, neighbouring cells will exhibit the typical features of either basal or squamous cell carcinoma.²⁰

Clear Cell Variant Of Basal Cell Carcinoma: is an unusual variant of BCC which is characterized by a variable component of large clear cells.

Histopathology: The tumor is composed of clear cells with faintly eosinophilic cytoplasm. Degenerative changes are present along with calcium deposition. Mucin is present within stroma and within degenerative areas of tumor(Fig 9)

Clear Cell Variant Of Squamous Cell Carcinoma: Also referred to as hydrophic squamous cell carcinoma (SCC).It was first described by Kuo in 1980 as a variant of SCC with extensive hydrophic change. The hydrophic generation of neoplastic cells and the accumulation of intracellular fluid, not accumulation of glycogen, lipid or mucin, results in clear cell appearance.(Fig 10)

V) Clear Cell Melanocytic Tumor: Malignant melanomas and melanocytic nevus are known composed of cells with varied morphological phenotypes.

Balloon Cell Nevus:

Histopathology: Balloon cells are comparatively large, pale, polyhedral cells with diameter varying from 15 to 40 um and containing small, round basophilic nuclei usually centrally located. Multinucleated balloon cells might be found. Usually cytoplasm is well demarcated and may be foamy, vacuolated slightly granular or clear in appearance. Pigment may be absent or sparse or abundant. (Fig 11)

Vii) Adipocytic Tumors:

The significance and multiple functions of fat are not always fully appreciated. Fat serves not only as one of the principal and most readily available sources of energy in the body. It functions as a barrier for the conservation of heat and as mechanical protection of the underlying tissues against physical injury.

The overall incidence of lipoma in oral cavity is 1% and liposarcoma accounts for 5.6 -9% of head and neck region. Histologically lipoma shows mature adipose tissue without cytological atypia while as liposarcomashows lipoblasts, cellular pleomorphism, vascular proliferation and mitotic activity. Several authors have commented that the prognosis of liposarcoma of oral cavity is favourable because of predominance of myxoid and well differentiated types and the small size of neoplasms.^{18, 20}

Liposarcoma:

Histopathology: They are mostly divided into three major categories:

Well differentiated liposarcoma / typical liposarcoma (Fig 12)

Myxoid / round cell liposarcoma(Fig 13)

Pleomorphic liposarcoma(Fig 14)

Viii) Tumors Of Epidermal Appendages:

Histopathology, tumors of the epidermal appendages have been classified into four groups that exhibit histologic features analogous to hair follicles, sebaceous glands, apocrine glands and eccrine glands. In general ,this type of diagnostic nosology based on the microscopic attributes of appendageal structures have been practical for classification of adnexal lesions .In general ,tumors are not derived directly from mature (differentiation, postmitotic) cells;rather ,tumor originate from multipotential undifferentiated cells present within the epidermis or its appendageal structures.¹⁹

Trichilemmoma is fairly common solitary tumor. Multiple facial trichilemmomas are specifically associated with Cowden's disease.

Histopathology: tumour cells have the appearance of clear cells because of their content of glycogen. The periphery of the tumor lobules usually shows palisading of columnar cells and a distinct, often thickened basement membrane zone resembling the vitreous layer surrounding the lower portion of normal hair follicles (Fig 15)

II. Conclusion

The clear cell tumors are derived from diverse group of cell types like odontogenic epithelium, salivary glands, keratinocytes, skin appendages, melanocytes, renal epithelium and even mesenchymally derived cells like adipose tissue. The clear cell lesions and conditions of head and neck are a heterogenous group with common entity – “clear cells”. The distinction between these tumors is perplexing due to similar histological appearance. So as to differentiate these clear cell tumors they have been classified according to the cell of origin. The biological behaviour may range from indolent to aggressiveness. But in most of the cases the presence of clear cells tumor may be a sign of increased tumor aggressiveness and malignancy. Thus their appropriate designation is crucial.

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Figures:

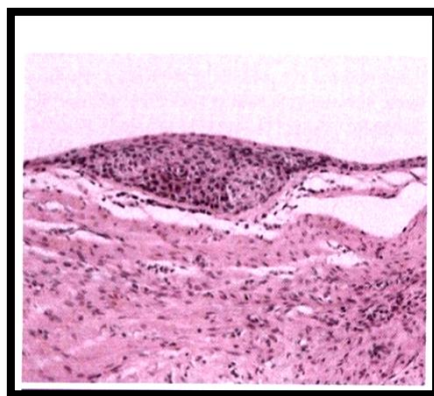


Fig 1: Gingival cyst of adult.

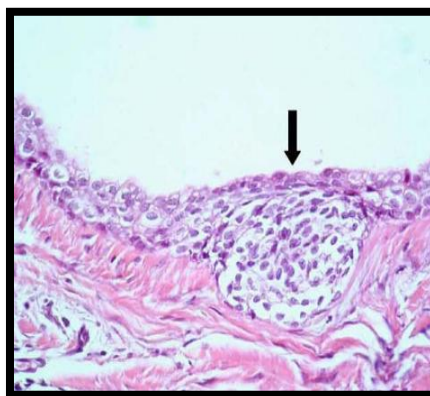


Fig 2: Lateral Periodontal cyst.

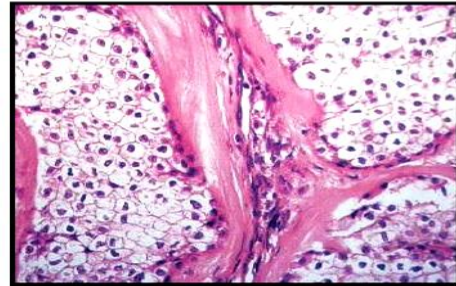
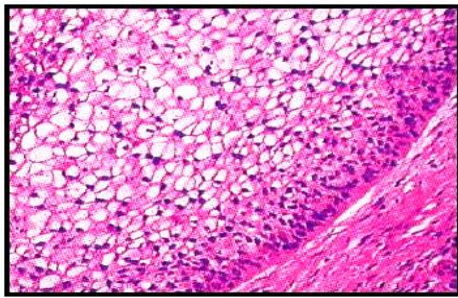


Fig 3: CCOC showing palisading of ameloblast like cells. **Fig4:** CCOC showing polygonal cells.

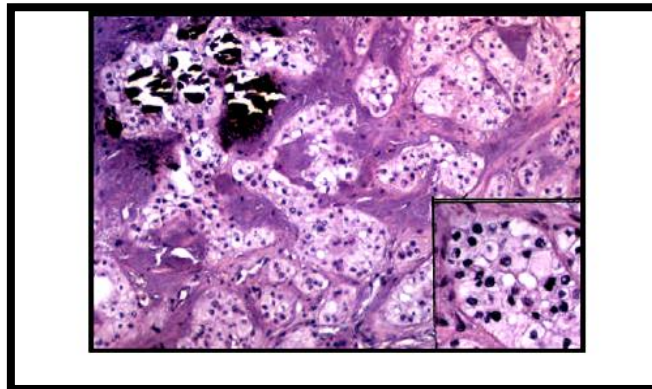


Fig 5: CCCEOT showing clear cells (clear cells with hyper chromatic, centrally placed nuclei).

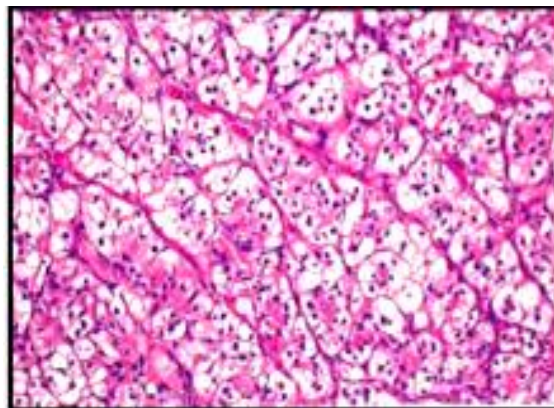


Fig 6: Clear cell variant of Oncocytoma

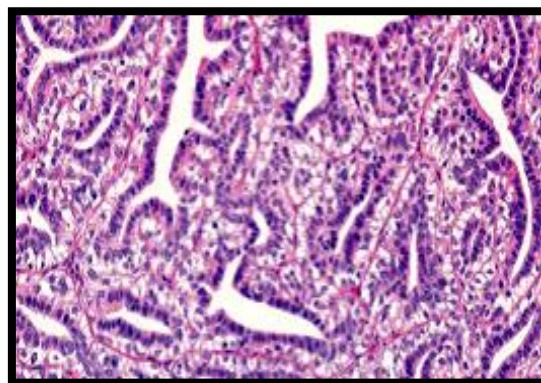


Fig 7: Epithelial myoepithelial carcinoma

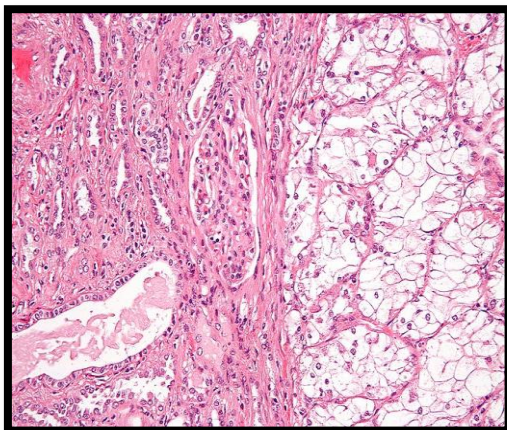


Fig 8: Renal Cell Carcinoma with cells having clear cytoplasm, typically arranged in nests and nuclear atypia.

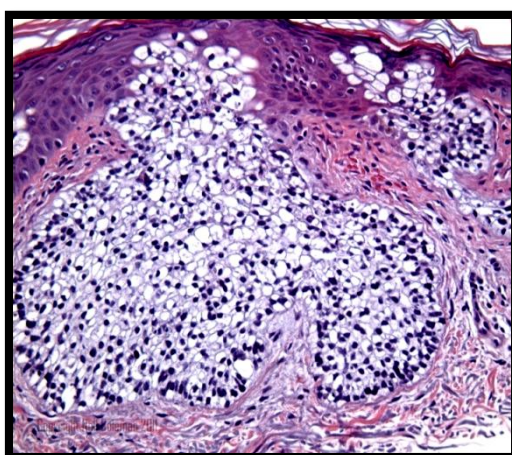


Fig 9: Clear cell variant of Basal cell carcinoma.

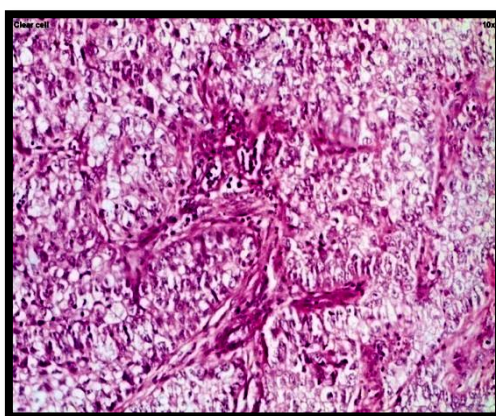


Fig 10: Clear cell variant of squamous cell carcinoma

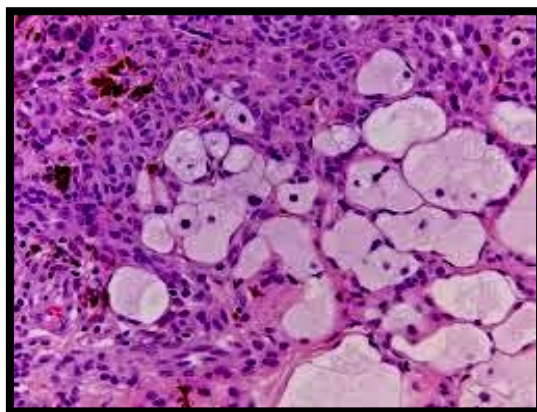


Fig 11: Balloon cell Nevus with clear cells.

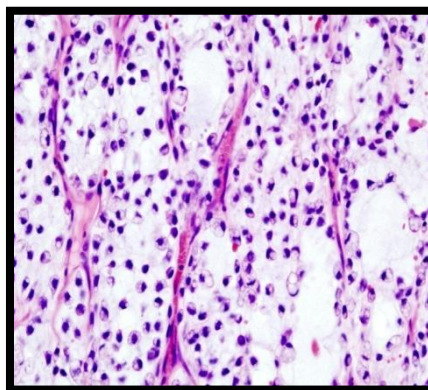
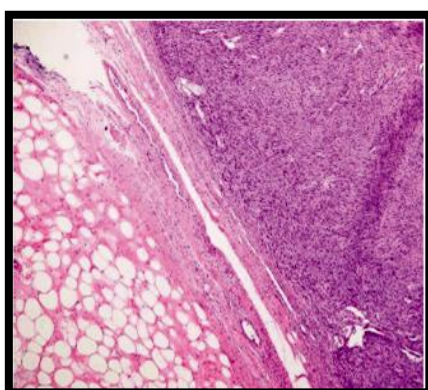


Fig 12: Well differentiated liposarcoma **Fig 13:** Myxoid / round cell liposarcoma

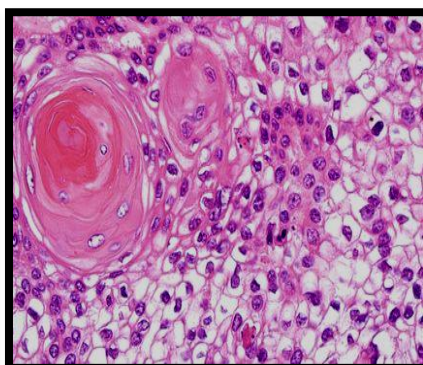
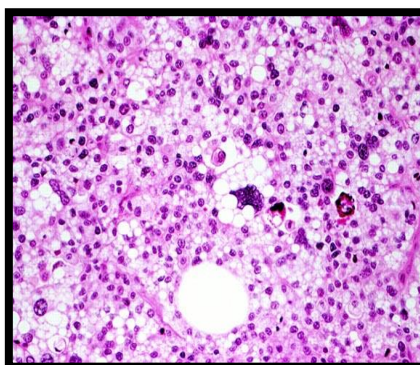


Fig 14: Pleomorphic liposarcoma **Fig 15:** Trichilemmoma with clear cells.