Introduction

- Clear cell changes may be virtually observed in any benign or malignant tumor of epithelial, mesenchymal, adnexal, and melanocytic and hematopoietic derivation.
- May be attributed to:
  - Artifactual changes
  - Improper cellular preservation
  - Hydropic degeneration of organelles
  - The accumulation of glycogen/ mucopolysaccharides/ lipid, mucin/or phagocytized foreign body material in the cytoplasm of tumor cells.
  - Others

- With few exceptions, most neoplasms show some original histomorphological characteristics.
- Changes can potentially lead to challenges and delays in establishing the diagnosis;
  - Artifactual changes may limit the applicability of immunohistochemistry staining;
  - Focal clear cell change may become more extensive with tumor progression or may appear secondarily, reflecting clonal evolution.
  - Electron microscopic examination of deparaffinized section can often have clear cell artifact as well.

Collectively may potentially make the diagnosis of clear cell tumors difficult and challenging.

Clear cell Tumors of the head and neck (Figure1)

- Primary, benign and malignant, clear cell tumors of the head and neck are rare.
- May involve various regions and may be also derived from various cell types.
- Only 1-2% of tumors of the salivary glands, jaws and oral mucosa are primarily or almost exclusively composed of clear cells.

Clear Cells and Clear Cell lesions of the Salivary Glands (Table1)

- Clear cells can be seen in various types of benign and malignant salivary gland tumors.
- In most cases, clear cells constitute only a minor component of the tumor.
- Malignant neoplasms comprise around 15%-35% of all parotid gland tumors
- 21 - 42% of those represent metastatic disease
The majority of metastatic tumors to the salivary glands originate in the head and neck area, especially from cutaneous squamous cell carcinomas and melanomas (45% & 37% respectively) > than metastases from the lung, breast, kidney, gastrointestinal tract, and prostate.

Distinguishing metastatic cancers with clear cell features has essential therapeutic and prognostic considerations.

Classification of Clear Cell Tumors of Salivary Glands

Myoepithelioma/ Myoepithelial carcinoma

- Modified Myoepithelial cells constitute a significant component of numerous salivary gland neoplasms.
- Both the benign myoepithelialiomas (and myoepithelial carcinoma) are made exclusively of myoepithelial cells, with histologic variation.
- All of the malignant myoepithelial cell types would be + for S-100 protein, vimentin, and high molecular weight cytokeratin (can help differentiate from other clear cell tumors).

Myoepitheliomas represent 1.5 % of all salivary gland tumors; M = F, develop at any site; parotid > hard and soft palates.

- Clear cell myoepithelial carcinoma comprises about 16% of all myoepithelial carcinomas.
- The infiltrative and destructive growth pattern unequivocally remains the most important diagnostic criteria.

Clear cell Oncocytoma

- Oncocytes are modified epithelial cells, may be seen in many organs including the parotid gland, the minor salivary glands, larynx, nasal mucous membranes, thyroid, and parathyroid glands.

- Benign and malignant oncocytic neoplasms are extremely rare in that region; Oncocytomas comprise approximately 1% of all salivary gland tumors.

- Clear-cell Oncocytoma of the salivary gland is a benign tumor with excellent prognosis as compared to other salivary tumors with exclusively or predominantly clear cell features which are at least low-grade malignant tumors.

- Clear cell features may predominate some lesions.

- The clear cell change could be attributed to intracytoplasmic glycogen deposition or to fixation artifact.

- Clear cell Oncocytoma also has the same morphological growth patterns as typical Oncocytoma.

- Typically demonstrates a localized, none infiltrative growth pattern. Occasionally, the tumor demonstrates a multifocal pattern [nodular oncocytic hyperplasia] with lack of the desmoplastic stromal reaction around those areas.

- Oncocytomas/ Clear cell variant;
  ✓ PTAH +, CK +.
  ✓ S-100 protein & MSA negative.

Oncocytic Carcinoma

- Oncocytic carcinoma is rare and represents less than 1% of salivary gland tumors.

- Primarily involves the parotid >> submandibular gland, palate and buccal mucosa.
• Characterized by cellular atypia, mitotic figures, pleomorphism, hyperchromatism, vascular and perineural invasion as well as lymph node metastasis.

**Mucoepidermoid Carcinoma**

- Mucoepidermoid carcinoma is the most common malignant salivary gland tumors with > 50% of cases involve the major salivary glands with the balance involving the minor salivary glands of the plate, buccal mucosa, retromolar trigone, and lips.

- Microscopically, three distinct cell types are recognized; the epidermoid, mucous and intermediate cells.

- The mucous cells are the neoplastic cells of mucoepidermoid carcinoma.

- The clear cells are common; comprise approximately 10% of tumor population but may occasionally form a large portion of the tumor cell population.

- The clear cells appear to be modified epidermoid and intermediate cells

- The transition between the epidermoid and clear cells is often seen.

- The clear cells in mucoepiermoid carcinoma stain positively with PAS with and without digestion with diastase confirming its glycogen content.

- Special staining for mucicarmine or Alcian blue can readily identify the mucous cell population; diagnostic since mucous cells are rarely encountered in other tumors with marked clear cell pollution.

**Acinic Cell Carcinoma**

- 83% of acinic cell carcinomas involve the parotid gland and only 4% involve the submandibular gland with the balance seen in the intraoral minor salivary glands.

- The tumors may be infiltrative or well circumscribed, may demonstrate variable growth patterns including the vacuolated and clear cell patterns.

- Clear cells are much more commonly encountered in mucoepiermoid carcinoma than acinic cell carcinoma/Similar to mucoepiermoid carcinoma, the % of clear cells in acinic cell carcinoma has no prognostic value.

- Clear cells are generally found in approximately 6% of acinic cell carcinomas but may comprise a major population of tumor cells in about 1% of neoplasms.

- The existence of pure clear cell variant of acinic cell carcinoma is doubted.

- The presence of acinar cells predominates in 40% of tumors.

- The identification of PAS positive diastase resistant; zymogen granules is diagnostic.

- The clear cells do not contain glycogen and the clearing is probably attributed to fixation artifact or reduction in the
number of organelles.

- Takahashi and colleagues *Takahashi, an owl, 1982* hypothesized that the clear cells transform from neoplastic acinar cells.
  - Acinic cell carcinoma is a low grade tumor with good prognosis with 5 year survival rate ranging from 80 to 85%.
  - An overall incidence of recurrence & distant metastasis/death reported to be around 35% and 16% respectively.
  - The identification of PAS positive diastase resistant; zymogen granules is diagnostic.
  - The clear cells do not contain glycogen and the clearing is probably attributed to fixation artifact or reduction in the number of organelles.

- Immunohistochemistry;
  ✓ + staining for anti-S-100 protein, cytokeratin, Vimentin, transferrin, alpha 1- antitrypsin, CEA (carcinoma embryonic antigen), GFAP (Glial fibrillary acidic protein) and amylase

  **Epithelial-Myoepithelial Carcinoma**

  - Epithelial - myoepithelial carcinoma is an uncommon salivary gland tumor which comprises about 1% of all salivary gland tumors.
  - Primarily involve the major salivary glands / parotid, only 10-15% involving the minor salivary glands.
  - Adults, average age is in the 7th decades of life.
  - Males and females are equally involved.
  - Duct like structures or solid, cystic, spindle, tubular, organoid nodular, papillary, or cribriform proliferation of cells, characteristically arranged in a *biphasic pattern*:
    ➢ Ductal, cuboidal intercalated duct like eosinophilic cells typically arranged around a lumen.
    ➢ Larger polygonal cells exhibiting clear cytoplasm/myoepithelial differentiation peripherally

  **Epithelial-Myoepithelial Carcinoma**

  - Immunohistochemical stains can further delineate the biphasic pattern:
    - The inner intercalated duct like cells stain positively with Cytokeratin and EMA (epithelial membrane antigen)
    - The outer clear myoepithelial cells stain positively with anti-S-100 protein (SMA +).
  - PAS special stain confirms the glycogen content within the clear cells.
  - The PAS stain can further highlight a well formed basement membrane that separates the cells, while mucicarmine stain is negative.
Clear cell Carcinoma

- Clear cell adenocarcinoma is an uncommon.
- The majority of cases are seen in the minor salivary glands of the palate, buccal mucosa, tongue, floor of mouth retromolar pad and tonsillar areas.
- Shows no sex predilection; involve adults in the 6th to 7th decades of life with rare exceptions.
- Made of a monotonous and monomorphic pure clear cell population that lacks the biphasic cellular pattern which characterizes epithelial - myoepithelial carcinoma.
- The clear cells may or may not demonstrate glycogen content by PAS staining.
- Cystic space may be occasionally present but ductal structures are generally absent.
- Immunohistochemistry staining; variable results; most tumors are focally immunoreactive for cytokeratin, but reactivity to S-100 protein, glial fibrillary acidic protein, actin, and vimentin may be seen.
- Ultrastructural studies favor ductal differentiation but do not demonstrate myoepithelial differentiation.

Clear cell Carcinoma

- Among all salivary tumors with clear cell features, clear cell carcinoma is probably the most difficult to differentiate from metastatic renal cell carcinoma.
- The 3rd most common metastatic lesion to the head and neck after breast and lungs.
- Approximately 15-16% of these tumors would ultimately metastasize to the H & N through hematogenous route via Batson’s plexus, bypassing the pulmonary circulation and capillary filtration mechanism.
- Metastasis represents the initial presenting symptoms of the tumor in 8% of these tumors.
- RCC most commonly metastasize to the nose/paranasal sinuses, larynx, parotid gland, temporal bone, thyroid gland and jaws (mandibular involvement 4-5 times more frequent than the maxilla).
- Metastasis to the oral soft tissues is also rarely seen.
- S & S of flank pain/ hematuria, accompanied by a clinically and radiographically detectable renal mass can help in early detection.
- The tumor is known for its slow growth rate and the potential for late metastasis.
- Patients with metastatic lesions may be initially asymptomatic and may present with non-specific radiographic evidence of bone destruction that may mimic primary bone lesions.

Clear cell carcinoma Vs metastatic renal cell carcinoma; points to consider:

- Glycogen positivity can be demonstrated in both tumors.
Positive immunohistochemistry staining for RCC antigen & others.

The identification of intracytoplasmic lipid on frozen sections favors a diagnosis of renal cell carcinoma.

The presence of heterogeneous highly vascularized tumor with lots of sinusoidal spaces favors a diagnosis of renal cell carcinoma.

The presence of hemorrhage and hemosiderin, coupled with pronounced pleomorphism and cytological atypia should favor metastatic renal cell carcinoma.

The identification of a clinically and radiographically detectable renal mass accompanied by hematuria and flank pain would further prompt confirmation of the presence of renal cell carcinoma.

**Odontogenic Tumors & Cysts with Clear Cell Features**

- Odontogenic neoplasms composed of predominately clear cells are quite unusual and represent a diagnostic challenge
- Clear cells are frequently observed in the epithelial lining of inflammatory odontogenic cysts

**Odontogenic Tumors & Cysts with Clear Cell Features**
**Calcifying Epithelial Odontogenic Tumor (CEOT)**

- Calcifying epithelial odontogenic tumor (CEOT) is a rare benign odontogenic tumor; constitutes less than 3% of odontogenic tumors.
- Males = Females, Wide age range, AV age = 4th /5th decades of life
- Intraosseous location >>> peripheral lesion.
- May also occur in pericoronal Location.
- Well known for its variable histomorphological presentation; the clear cell variant is well recognized in both central and peripheral locations.
- PAS positive granules are seen within the clear cells.
- All epithelial cells (including the clear cells) react positively with cytokeratin Cocktail (but not with other cytokeratins), fibronectin, and collagen IV.

**Odontogenic Tumors & Cysts with Clear Cell Features**
**Calcifying Odontogenic Cyst (COC)**

- A benign odontogenic cyst that represents approximately 2% of all benign odontogenic lesions.
- Occurs centrally or peripherally
- Wide age range; 2nd to the eight decades of life.
- No sex prevalence; maxilla = mandible.
- Known predilection for anterior jaw involvement.

**Odontogenic Tumors & Cysts with Clear Cell Features**
**Calcifying Odontogenic Cyst (COC).**

- Variations within the highly-differentiated epithelium have been described including spindle-cell change, epithelial pearl formation, ghost cell dominant type, and less commonly the presence of melanin pigmentation and clear cells.
- The clear cell change in COC is exceptionally rare and bears resemblance to clear cell changes in CEOT.
The clear cells form clusters and are arranged in an organoid pattern and surrounded by a collagenuous background.

The recognition of clear cell changes in both CEOT and COC is expediently important to exclude the possibility of metastatic clear cell carcinoma of renal origin & others.

**Ameloblastoma**

- Ameloblastoma is relatively rare odontogenic tumor, first recognized by Falkson in 1879
- Represents approximately 1% of all oral tumors
- The most common odontogenic tumor.
- Involves patients with a wide age range with no sex predilection approximately 85% arise in the posterior mandible > posterior maxilla & sinonasal area.
- Histologically, all Ameloblastomas display features that more or less recapitulate the process of odontogenesis prior to the epithelial mesenchymal interaction.

**Central clear cell odontogenic carcinoma**

- The description of clear/pale cells including mucous cells, in an otherwise typical Ameloblastoma, without features of malignancy or unusual aggressive behavior, is very rare but well documented in the literature

- Both peripheral and central cases are well documented.

- Clear cell odontogenic tumors with some features of Ameloblastoma demonstrating aggressive clinical behavior were initially and independently described by Hansen and colleagues and Waldron and co workers in 1985.

- Raised the suggestion that these tumors might represent odontogenic carcinomas.

- Many of the cases that were initially diagnosed as clear cell Ameloblastomas, atypical Ameloblastoma or clear cell odontogenic tumors were justifiably considered as and renamed to "clear cell odontogenic carcinomas".

**Central Clear Cell Odontogenic Carcinomas**

- Central Clear cell odontogenic carcinomas are uncommon but well documented neoplasms.
- Brandwein and co-workers in 2000 identified 30 cases in the English literature and reported one case in a 81 year old female which involved the mandible;
  - Female predilection; prevalence for mandibular involvement
  - A median age of 64.5 years
  - The tumor was indolent but locally aggressive and has a potential for multiple local recurrences
  - Initial complete resection with negative margins is the best management strategy
  - Adjuvant radiation therapy for tumors with positive soft tissue margins.

- Ebert and colleague in 2005 emphasized he findings by Brandwein and colleagues and reviewed 43 cases of CCCOC and reported;
  - An age range from 17-89 years old
  - Prevalence for mandibular involvement
  - 55% overall recurrence rate (local recurrence only in 32%; LN Mets only in 5%; both nodal involvement and local recurrence in 18% ; of patients experienced.
  - 43% recurrence rate with resection < 73% recurrence < 80% recurrence rate with curettage with soft tissue extension < with evidence of soft tissue extension while only 43% of patients treated with resection alone developed recurrence a s
compared to an 80% recurrence rate that was seen with curettage alone.

- Initial aggressive treatment is necessary

- Histologically, the tumors can show biphasic or monophasic patterns
- The clear cells stain positively with PAS and negatively with mucicarmine

- Electron microscopic studies; aggregates of cells with small desmosomes surrounded by a continuous basement membrane.

- Most cells did not contain organelles with the exception of few that demonstrated glycogen (which explains the PAS positivity)
- No zymogen granules or a concentration of intermediate microfilaments or dense bodies which favored an odontogenic rather than a salivary origin

- Clear cell odontogenic carcinoma must be differentiated from various odontogenic tumors and intraosseous salivary gland tumors, where the diagnosis is not usually entertained because of high resemblance of clinicopathological and radiographic characteristics to odontogenic tumors.

  **Salivary Gland Tumors in the Head and Neck/ Intraosseous Location**

- Salivary gland tumors account for less than 7% of cancers involving the head and neck. Reported in various organs including the skin, neck, thyroid gland, mastoid bone, middle ear, and jaw bones.

- Salivary gland tumors may also occasionally be seen in intraosseous location and these may be derived from
  - Ectopic salivary tissue,
  - Neoplastic transformation of the mucous cells found in the lining of dentigerous cysts.
  - From embryonic remnants of submandibular glands found within the mandible
  - From entrapped mucous cells of the retromolar pad within the bone during embryogenesis
  - May arise from salivary tissue within stafne mandibular defect
  - The most common intraosseous salivary gland tumors are mucoepiermoid carcinoma, then adenoid cystic carcinoma.

- Although central clear cell carcinoma of salivary origin is extremely rare, they must be distinguished from central clear cell odontogenic carcinoma & other clear cell tumors in that location.

  **Osteosarcoma with Clear Cell Features**

- Osteogenic sarcoma; considered to be the most common primary bone malignancy accounting for approximately 35% of skeletal malignancies.

- Only 6-10% of cases are seen in the head and neck area with involvement of the skull, craniofacial bones, sinonasal area, the jaws, cervical vertebra, and others.

- Jaw OS; Conventional > Periosteal and Parosteal subtypes.

- Variable histomorphologic patterns have been reported including the epithelioid and the rare clear cell variants.
• The clear cell variant of OS:

✔ Extremely rare, but should be theoretically included in the differential diagnosis of clear cell tumors of bone
✔ Does not appear to constitute a clinically distinct well defined entity or even exhibit a uniform histological pattern.
✔ The clear cell change is presumably due to scarcity of organelles, dilatation of rough endoplasmic reticulum, scattered phagolysosomes, the accumulation of glycogen;
✔ The clear cells show no difference from the conventional osteosarcoma by reacting negatively with anti-S-100 protein.

Chondrogenic Sarcoma

• Chondrosarcoma constitutes approximately 11% of all primary malignant tumors.

• The tumors most commonly involve the pelvis, followed by proximal femur, proximal humerus, distal femur, and ribs.

• Common in a fourth to sixth decades of life with exceptions.

• The head and neck region involvement ranges from 1-12% and can practically involve any site.

• Most common locations in the head and neck area, the maxilla and mandible, the skull, sinonasal area, and Larynx among others.

Clear Cell Chondrosarcoma

• Various histologic patterns have been recognized including a myxoid, mesenchymal, dedifferentiated and the uncommon clear cell variant.

• The myxoid and mesenchymal subtypes constitute a significant proportion of head and neck cases.

• The clear cell variant primarily involves the proximal femur and humerus and is rarely reported in the head and neck region.

• Clear cell Chondrosarcoma accounts for approximately 2% of all Chondrosarcoma.

• The tumor also shows marked predilection for males

• Commonly display a radiolucent lesion with well defined sclerotic margin that separates the neoplasm from the surrounding bone.

• The tumor shows characteristic histomorphological features;
  • Lobules of large cells with well distinct borders and clear to granular cytoplasm
  • Round centrally situated nuclei.
  • An admixture of osteoid matrix.
  (An important feature that distinguish the clear cell variant from conventional Chondrosarcoma).

• Osteoclasts type giant cells.
• (A feature that is not common for the conventional Chondrosarcoma.)

• The clearing of the cytoplasm may be attributed to accumulation of glycogen, decrease in the number of organelles or
dilatation or endoplasmic reticulum and or Golgi.

- Areas, reminiscent of the conventional Chondrosarcoma may be occasionally seen.

- Cystic changes are frequently seen but necrosis, hemorrhage and mitosis are uncommon.

- Immunohistochemistry staining of clear cells; uniformly positive for anti S-100 protein, Vimentin, collagens II and X as well as cartilage associated glycoproteins, in keeping with their cartilaginous derivation.

- Clear cell Chondrosarcoma is a low grade malignant tumor that exhibits an indolent growth and proliferative activity that is best treated with en-bloc resection with or without adjuvant therapy, yet local recurrence, distant metastasis and tumor related death are documented.

**Chordoma**

- Chordomas are rare slow growing bone tumors, representing less than 4% of all primary bone tumors.

- Thought to be derived from notochord remnants that present in the craniospinal axis.

- Classically seen in the craniospinal location.

- The involvement of the Sinonasal area is uncommon but well documented.

- Marked male predilection, with peak incidence is in the fifth and sixth decades of life.

- Histologically display various cell types (physaliferous, epithelioid, and Chondroid cells) (the latter is referred to Chondroid Chordomas).

- Can mimic other clear cell tumors.

- Regardless of the histological subtype, the tumor cells characteristically contain multiple vacuoles resulting in a bubbly pattern and referred to as physaliferous cells.

  - **Immunohistochemistry**

- Nearly all cell types (physaliferous, epithelial-like, and cells of Chondroid differentiation) of both recurrent and nonrecurring chordomas are + for EMA, and S-100 protein, and also co express cytokeratins (KL1, AE1/AE3) and vimentin.

- Stain negatively with HMB45 and desmin but may occasionally stain positively for NSE.

- The immunohistochemical properties are useful in differentiating the tumor from Chondrosarcoma (only express S-100 protein) & from metastatic renal cell carcinoma which otherwise share many immunohistochemical and immunophenotypic properties with chordomas.

- Chordoma are best managed with complete surgical resection, but this may not always be possible because of the invasive nature of the lesion.

- Radiotherapy is still controversial but often needed for incomplete excisions case or applied as palliative for recurrent disease.

**Alveolar soft-part sarcoma (ASPS)**

- Alveolar soft-part sarcoma (ASPS) rare, accounting for only 1% of all soft tissue sarcomas.
• The tumor primarily involves the extremities and has predilection for teenagers and young adults with documented female predilection.

• 27% of cases involve the head and neck area; orbital area >> the tongue (the tongue is the most common site recognized in infants and children).

• The tumor is often well circumscribed but infiltrates the surrounding tissues in areas.
• Histologically; well delineated nests of large uniform polygonal cells, separated by thin fibrous connective tissue septae. The cells exhibit well distinct borders, one or more vesicular nuclei with small nucleoli, and granular, eosinophilic to vacuolated cytoplasm.

• Typical eosinophilic crystalline or rod shaped inclusions are seen by routine microscopy in approximately 80% of cases, also the identification of PAS positive, diastase-resistant rhomboid or rod-shaped crystals is considered characteristic.

• Thin sinusoidal vascular spaces are interspersed between the individual cells and some vessels may display a hemangiopericytoma-like pattern in areas.

  • Immunohistochemistry

  • The tumor cells stain:
  ✓ + with vimentin, muscle-specific actin, and desmin.
  ✓ Neg for cytokeratin, epithelial membrane antigen, neurofilaments, glial fibrillary acidic protein, and serotonin
  ✓ Neg for synaptophysin and HMB45 which are two important stains to factor in distinguishing the lesion from paraganglioma and metastatic melanoma respectively.
  ✓ The PAS positive crystals can readily distinguish tumor from metastatic renal cell carcinoma.
  ✓ The PAS positive staining crystals also characteristically immunoreactive for CD147.
  ✓ Alveolar soft part sarcoma must be treated with adequate radical resection
  • The disease usually follows a slow course but the prognosis is generally poor since a large percentage of patients experience progression even in the absence of local recurrence and distant metastasis (most commonly to the lungs {via hematogenous route}).
  • The smaller the tumor size, the younger the age at presentation, the better the prognosis.
  • The presence of metastatic diseases at presentation is associated with unfavorable prognosis.

Certain neon neoplastic reactive conditions and storage diseases may manifest as bony lesions and may be included in the differential diagnosis of clear cell entities based on the histomorphological presentation.

Rosai Dorfman Disease (RDD)

• Rosai Dorfman disease (RDD) is a rare, non-neoplastic histiocytosis
• Commonly occur in adolescent young males with slight predilection for African Americans.

• Characterized by painless, generalized cervical lymphadenopathy.

• Extranodal involvement of the head and neck region is well documented; nose and paranasal sinuses, soft tissues, orbit, major salivary glands, larynx, pharynx, tonsils, thyroid gland, ear, and facial skeleton > craniofacial bones.

• Histologically demonstrate a diffuse proliferation of large, bland foamy Histiocytes that contains a vesicular nucleus, supported by eosinophilic cytoplasm.
• Mitoses are rarely seen.

• A diffuse acute and chronic inflammatory cell infiltrate and emperipolesis is observed in lesions of both nodal and extranodal sites.

• The foamy macrophages stain positively with S-100 protein and CD68, similar to Langerhans cell histiocytosis and keeping with their histiocytic derivation, however are constantly negative for CD1a; and Birbeck granules are not demonstrated on ultrastructural studies which can further help to differentiate between the Langerhans cell histiocytosis and Rosai- Dorfman disease.

Langerhans cell histiocytosis

• Benign but locally infiltrative process of bone of Langerhans cell origin.

• The process may be
  • Confined in either Polyostotic or Monostotic forms; eosinophilic granuloma.

• Disseminated.; may occur in infant and may be associated with eczematous cutaneous rashes, hepatomegally, splenomegally, anemia and lymphadenopathy (Letterer-Siwe disease) or may be also seen in young children older than the age of patients involved with Letterer-Siwe disease and is characterized by the triad of diabetes mellitus, exophthalmia, and the Langerhans histiocytosis bony lesions (Hand- Schuller- Christian disease).

• Patient classically exhibit noticeable welling in the jaw area.

• Radiographically, LCH typically display lytic lesions of the jaw and skull (punched out radiolucencies), accompanied by resorption around apices of teeth (teeth hanging in air phenomenon) and mobility of teeth.

Erdheim - Chester disease (ECD)

• Erdheim - Chester disease (ECD) is a rare focal or systemic infiltrative disorder resulting from xanthogranulomatous tissue deposition.

• Affects bone marrow, long bone metaphyses symmetrically and sparing epiphysis) > retroperitoneal space, periaortic area, skin, brain and lungs.

• Wide age range, males slightly more involved than females.

• Etiology unknown but may be related to lipid storage disorder.

• May also rarely involve jaw bones.

• Characterized by a diffuse infiltrate of foamy macrophages that stain positively with anti CD 68, rarely show foal positive staining with S-100 protein but consistently reacts negatively with CD1a.

Gaucher’s Disease

• Gaucher’s disease, the most common lysosomal storage disease occurring as a result of genetic defect in production of
the enzyme β-glucocerebrosidase, and the consequent accumulation of the glycolipid/glucocerebroside, in the cells of
the monocyte-macrophage system.

• The disease occur in 3 types,
• Type I, the non-neuronopathic form, a milder form of the disease with many patients relatively asymptomatic is the
most common.
• Type 2 which is more acute form characterized by visceral and bone involvement as well as seizures.

• Type 3 of the disease is also characterized with mild to moderately severe involvement of the visceral organs,
progressive calcification of aortic and mitral valves, bone involvement, CNS involvement and others.

• Involvement of the maxillofacial bones is well documented, therefore the disease should be also included in the
differential diagnosis of clear cell entities of the head and neck.

• Bone involvement is characteristically seen in 75–80% of cases of type I and Type III Gaucher’s disease.

Gaucher’s Disease

• Gaucher’s cells accumulate in the visceral organs and in bone marrow, leading to the so called “Erlenmeyer flask
deformity”.
• Jaw involvement demonstrates non specific lytic lesions without teeth devitalization or cortical resorption.
• Histologically, sheets of lipid laden macrophages with marked bluish cytoplasm are seen.

Thank You

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• Dr. Margaret Brandwein.


Seifert G (1996). Classification and differential diagnosis of clear and basal cell tumors


Figure 1

Clear Cell Entities of the Head and Neck

Clear Cell Tumors and Tumor like Conditions of Intraosseous location

Miscellaneous head and neck Tumors with Clear Cell Features

Clear cell tumors of the skin

Table 1

<table>
<thead>
<tr>
<th>Classification of Clear Cell Tumors of Salivary Glands</th>
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| Malignant primary |a) Carcinoma not usually characterized by clear cells but with clear cell predominant areas (e.g.; Mucoep. & acinic cell carcinoma |
|-------------------|b) Carcinoma usually characterized by clear cells |
|                   |i: Dimorphic: Epithelial – myoepithelial Carcinoma |
|                   |ii: Monomorphic: Clear cell carcinoma |
|                   |Myoepithelial carcinoma |

| Malignant metastatic Ca | Carcinoma especially kidney, thyroid and melanoma |
Clear Cell Entities of the Head & Neck

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- Only 1-2% of tumors of the salivary glands, jaws and oral mucosa are primarily or almost exclusively composed of clear cells.
Clear Cell Entities of the Head and Neck

- Clear Cell Tumors of Salivary Glands
- Clear Cell Tumors and Tumor like Conditions of Intraosseous location
- Miscellaneous head and neck Tumors with Clear Cell Features
- Clear cell tumors of the skin

Nasser Said-Al-Naief, USCAP, 2008
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## Classification of Clear Cell Tumors of Salivary Glands

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                               ii: Monomorphic: Clear cell carcinoma  
                               Myoepithelial carcinoma |
| Malignant metastatic Ca   | Carcinoma especially kidney, thyroid and melanoma                           |

*Cardina and Alos, WHO, 2005*
Myoepithelioma/ Myoepithelial carcinoma

- Modified Myoepithelial cells constitute a significant component of numerous salivary gland neoplasms.
- Both the benign myoepithelialiomas (and myoepithelial carcinoma) are made exclusively of myoepithelial cells, with histologic variation.
- All of the malignant myoepithelial cell types would be + for S-100 protein, vimentin, and high molecular weight cytokeratin (can help differentiate from other clear cell tumors).

- Myoepitheliomas represent 1.5% of all salivary gland tumors; M = F, develop at any site; parotid > hard and soft palates.
- Clear cell myoepithelial carcinoma comprise about 16% of all myoepithelial carcinomas.
- The infiltrative and destructive growth pattern unequivocally remains the most important diagnostic criteria.
Clear cell Oncocytoma

- Oncocytes are modified epithelial cells, may be seen in many organs including the parotid gland, the minor salivary glands, larynx, nasal mucous membranes, thyroid, and parathyroid glands.

- Benign and malignant oncocytic neoplasms are extremely rare in that region; Oncocytomas comprise approximately 1% of all salivary gland tumors.

- Clear-cell Oncocytoma of the salivary gland is a benign tumor with excellent prognosis as compared to other salivary tumors with exclusively or predominantly clear cell features which are at least low-grade malignant tumors.

- Clear cell features may predominate some lesions.

- The clear cell change could be attributed to intracytoplasmic glycogen deposition or to fixation artifact.

- Clear cell Oncocytoma also has the same morphological growth patterns as typical Oncocytoma.
Clear cell Oncocytoma

- Oncocytomas/ Clear cell variant;
  - PTAH +, CK +.
  - S-100 protein & MSA negative.
Oncocytic Carcinoma

- Oncocytic carcinoma is rare and represents less than 1% of salivary gland tumors.

- Primarily involves the parotid >> submandibular gland, palate and buccal mucosa.

- Characterized by cellular atypia, mitotic figures, pleomorphism, hyperchromatism, vascular and perineural invasion as well as lymph node metastasis.
Mucoepidermoid Carcinoma

• Mucoepidermoid carcinoma is the most common malignant salivary gland tumor with > 50% of cases involve the major salivary glands with the balance involving the minor salivary glands of the palate, buccal mucosa, retromolar trigone, and lips.

• Microscopically, three distinct cell types are recognized; the epidermoid, mucous and intermediate cells.

• The mucous cells are the neoplastic cells of mucoepidermoid carcinoma.

• The clear cells are common; comprising approximately 10% of tumor population but may occasionally form a large portion of the tumor cell population.

• The clear cells appear to be modified epidermoid and intermediate cells
• The transition between the epidermoid and clear cells is often seen.

• The clear cells in mucoepiermoid carcinoma stain positively with PAS with and without digestion with diastase confirming its glycogen content.

• Special staining for mucicarmine or Alcian blue can readily identify the mucous cell population; diagnostic since mucous cells are rarely encountered in other tumors with marked clear cell pollution.
Acinic Cell Carcinoma

- 83% of acinic cell carcinomas involve the parotid gland and only 4% involve the submandibular gland with the balance seen in the intraoral minor salivary glands.

- The tumors may be infiltrative or well circumscribed, may demonstrate variable growth patterns including the vacuolated and clear cell patterns.

- Clear cells are much more commonly encountered in mucoepidermoid carcinoma than acinic cell carcinoma. Similar to mucoepidermoid carcinoma, the % of clear cells in acinic cell carcinoma has no prognostic value.

- Clear cells are generally found in approximately 6% of acinic cell carcinomas but may comprise a major population of tumor cells in about 1% of neoplasms.

- The existence of pure clear cell variant of acinic cell carcinoma is doubted.

- The identification of PAS positive diastase resistant; zymogen granules is diagnostic.

- The clear cells do not contain glycogen and the clearing is probably attributed to fixation artifact or reduction in the number of organelles.

- Immunohistochemistry;
  - + staining for anti-S-100 protein, cytokeratin, Vimentin, transferrin, alpha 1- antitrypsin, CEA (carcinoma embryonic antigen), GFAP (Glial fibrillary acidic protein) and amylase.
Epithelial-Myoepithelial Carcinoma

- Epithelial - myoepithelial carcinoma is an uncommon salivary gland tumor which comprises about 1% of all salivary gland tumors.

- Primarily involve the major salivary glands / parotid, only 10-15% involving the minor salivary glands.

- Adults, average age is in the 7th decades of life.

- Males and females are equally involved.

- Duct like structures or solid, cystic, spindle, tubular, organoid nodular, papillary, or cribriform proliferation of cells, characteristically arranged in a biphasic pattern:
  - Ductal, cuboidal intercalated duct like eosinophilic cells typically arranged around a lumen.
  - Larger polygonal cells exhibiting clear cytoplasm/myoepithelial differentiation peripherally.
Epithelial-Myoepithelial Carcinoma

- Immunohistochemical stains can further delineate the biphasic pattern:
  - The inner intercalated duct like cells stain positively with Cytokeratin and EMA (epithelial membrane antigen)
  - The outer clear myoepithelial cells stain positively with anti-S-100 protein and GFAP/ (SMA +).

- PAS special stain confirms the glycogen content within the clear cells.
- The PAS stain can further highlight a well formed basement membrane that separates the cells, while mucicarmine stain is negative.
Clear cell Carcinoma

- Clear cell adenocarcinoma is an uncommon.
- The majority of cases are seen in the minor salivary glands of the palate, buccal mucosa, tongue, floor of mouth retromolar pad and tonsillar areas.
- Shows no sex predilection; involve adults in the 6th to 7th decades of life with rare exceptions.
- Made of a monotonous and monomorphic pure clear cell population that lacks the biphasic cellular patter which characterizes epithelial - myoepithelial carcinoma.
- The clear cells may or may not demonstrate glycogen content by PAS staining.
- Cystic space may be occasionally present but ductal structures are generally absent.
- Immunohistochemistry staining; variable results; most tumors are focally immunoreactive for cytokeratin, but reactivity to S-100 protein, glial fibrillary acidic protein, actin, and vimentin may be seen.
- Ultrastructural studies favor ductal differentiation but do not demonstrate myoepithelial differentiation.
Clear cell Carcinoma
Clear cell Carcinoma

- Among all salivary tumors with clear cell features, clear cell carcinoma is probably the most difficult to differentiate from metastatic renal cell carcinoma.

- The 3rd most common metastatic lesion to the head and neck after breast and lungs.

- Approximately 15-16% of these tumors would ultimately metastasize to the H & N through hematogenous route via Batson’s plexus, bypassing the pulmonary circulation and capillary filtration mechanism.

- Metastasis represents the initial presenting symptoms of the tumor in 8% of these tumors.

- RCC most commonly metastasizes to the nose/paranasal sinuses, larynx, parotid gland, temporal bone, thyroid gland and jaws (mandibular involvement 4-5 times more frequent than the maxilla).

- Metastasis to the oral soft tissues is also rarely seen.
• S & S of flank pain/ hematuria, accompanied by a clinically and radiographically detectable renal mass can help in early detection.

• The tumor is known for its slow growth rate and the potential for late metastasis.

• Patients with metastatic lesions may be initially asymptomatic and may present with non-specific radiographic evidence of bone destruction that may mimic primary bone lesions.
53 year old male with Generalized metastasis from renal cell carcinoma to the head and neck
Clear cell carcinoma Vs metastatic Renal cell carcinoma; points to consider:

- Glycogen positivity can be demonstrated in both tumors.
- Positive immunohistochemistry staining for RCC antigen & others.

<table>
<thead>
<tr>
<th>% Positive</th>
<th>Marker</th>
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<tbody>
<tr>
<td>100%</td>
<td>CK-LMW/8.18, Vimentin and RCC</td>
</tr>
<tr>
<td>90%</td>
<td>CD10</td>
</tr>
<tr>
<td>+</td>
<td>EMA (may be focal)</td>
</tr>
<tr>
<td>+</td>
<td>CK-AE1/AE3 (few cases may be neg)</td>
</tr>
<tr>
<td>+ or neg</td>
<td>S-100 *</td>
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- The identification of intracytoplasmic lipid on frozen sections favors a diagnosis of renal cell carcinoma.
- The presence of heterogeneous highly vascularized tumor with lots of sinusoidal spaces favors a diagnosis of renal cell carcinoma.
- The presence of hemorrhage and hemosiderin, coupled with pronounced pleomorphism and cytological atypia should favor metastatic renal cell carcinoma.
- The identification of a clinically and radiographically detectable renal mass accompanied by hematuria and flank pain would further prompt confirmation of the presence of renal cell carcinoma.
Odontogenic Tumors & Cysts with Clear Cell Features

- Odontogenic neoplasms composed of predominately clear cells are quite unusual and represent a diagnostic challenge.
- Clear cells are frequently observed in the epithelial lining of inflammatory odontogenic cysts.
Odontogenic Tumors & Cysts with Clear Cell Features
Calcifying Epithelial Odontogenic Tumor (CEOT)

- Calcifying epithelial odontogenic tumor (CEOT) is a rare benign odontogenic tumor; constitutes less than 3% of odontogenic tumors.

- Males = Females, Wide age range, AV age = 4th /5th decades of life.

- Intraosseous location >>>>> peripheral lesion.

- May also occur in pericoronal Location.

- Well known for its variable histomorphological presentation; the clear cell variant is well recognized in both central and peripheral locations.

- PAS positive granules are seen within the clear cells.

- All epithelial cells (including the clear cells) react positively with cytokeratin Cocktail (but not with other cytokeratins), fibronectin, and collagen IV.
Odontogenic Tumors & Cysts with Clear Cell Features
Calcifying Odontogenic Cyst (COC)

- A benign odontogenic cyst that represents approximately 2% of all benign odontogenic lesions.
- Occurs centrally or peripherally
- Wide age range; 2nd to the eight decades of life.
- No sex prevalence; maxilla = mandible.
- Known predilection for anterior jaw involvement.
Odontogenic Tumors & Cysts with Clear Cell Features
Calcifying Odontogenic Cyst (COC)

• Variations within the highly-differentiated epithelium have been described including spindle-cell change, epithelial pearl formation, ghost cell dominant type, and less commonly the presence of melanin pigmentation and clear cells.

• The clear cell change in COC is exceptionally rare and bears resemblance to clear cell changes in CEOT.

• The clear cells form clusters and are arranged in an organoid pattern and surrounded by a collagenous background.

• The recognition of clear cell changes in both CEOT and COC is expediently important to exclude the possibility of metastatic clear cell carcinoma of renal origin & others.
Ameloblastoma

- Ameloblastoma is relatively rare odontogenic tumor, first recognized by Falkson in 1879
- Represents approximately 1% of all oral tumors
- The most common odontogenic tumor.
- Involves patients with a wide age range with no sex predilection, approximately 85% arise in the posterior mandible > posterior maxilla & sinonasal area.
- Histologically, all Ameloblastomas display features that more or less recapitulate the process of odontogenesis prior to the epithelial mesenchymal interaction
Central clear cell odontogenic carcinoma

• The description of clear/pale cells including mucous cells, in an otherwise typical Ameloblastoma, without features of malignancy or unusual aggressive behavior, is very rare but well documented in the literature.

• Both peripheral and central cases are well documented.

• Clear cell odontogenic tumors with some features of Ameloblastoma demonstrating aggressive clinical behavior were initially and independently described by Hansen and colleagues and Waldron and co workers in 1985.

• Raised the suggestion that these tumors might represent odontogenic carcinomas.

• Many of the cases that were initially diagnosed as clear cell Ameloblastomas, atypical Ameloblastoma or clear cell odontogenic tumors were justifiably considered as and renamed to "clear cell odontogenic carcinomas".
Central Clear Cell Odontogenic Carcinomas

- Central Clear cell odontogenic carcinomas are uncommon but well documented neoplasms.
- Brandwein and co-workers in 2000 identified 30 cases in the English literature and reported one case in a 81 year old female which involved the mandible;
  ✓ Female predilection; prevalence for mandibular involvement.
  ✓ A median age of 64.5 years.
  ✓ The tumor was indolent but locally aggressive and has a potential for multiple local recurrences.
  ✓ Initial complete resection with negative margins is the best management strategy.
  ✓ Adjuvant radiation therapy for tumors with positive soft tissue margins.

- Ebert and colleague in 2005 emphasized the findings by Brandwein and colleagues and reviewed 43 cases of CCCOC and reported;
  ✓ An age range from 17-89 years old.
  ✓ Prevalence for mandibular involvement.
  ✓ 55% overall recurrence rate (local recurrence only in 32%; LN mets only in 5%; both nodal involvement and local recurrence in 18% ; of patients experienced.
  ✓ 43% recurrence rate with resection < 73% recurrence < 80% recurrence rate with curettage with soft tissue extension < with evidence of soft tissue extension while only 43% of patients treated with resection alone developed recurrence a s compared to an 80% recurrence rate that was seen with curettage alone.
  ✓ Initial aggressive treatment is necessary
• Histologically, the tumors can show biphasic or monophasic patterns
• The clear cells stain positively with PAS and negatively with mucicarmine

• Electron microscopic studies; aggregates of cells with small desmosomes surrounded by a continuous basement membrane.

• Most cells did not contain organelles with the exception of few that demonstrated glycogen (which explains the PAS positivity)
• No zymogen granules or a concentration of intermediate microfilaments or dense bodies which favored an odontogenic rather than a salivary origin

• Clear cell odontogenic carcinoma must be differentiated from various odontogenic tumors and intraosseous salivary gland tumors, where the diagnosis is not usually entertained because of high resemblance of clinicopathological and radiographic characteristics to odontogenic tumors.
Salivary Gland Tumors in the Head and Neck/
Intraosseous Location

- Salivary gland tumors account for less than 7% of cancers involving the head and neck. Reported in various organs including the skin, neck, thyroid gland, mastoid bone, middle ear, and jaw bones.

- Salivary gland tumors may also occasionally be seen in intraosseous location and these may be derived from:
  - Ectopic salivary tissue,
  - Neoplastic transformation of the mucous cells found in the lining of dentigerous cysts.
  - From embryonic remnants of submandibular glands found within the mandible.
  - From entrapped mucous cells of the retromolar pad within the bone during embryogenesis.
  - May arise from salivary tissue within stafne mandibular defect.
  - The most common intraosseous salivary gland tumors are mucoepiermoid carcinoma, then adenoid cystic carcinoma.

- Although central clear cell carcinoma of salivary origin is extremely rare, they must be distinguished from central clear cell odontogenic carcinoma & other clear cell tumors in that location.
Osteosarcoma with Clear Cell Features

- Osteogenic sarcoma; considered to be the most common primary bone malignancy accounting for approximately 35% of skeletal malignancies.

- Only 6-10% of cases are seen in the head and neck area with involvement of the skull, craniofacial bones, sinonasal area, the jaws, cervical vertebra, and others.

- Jaw OS; Conventional > Periosteal and Parosteal subtypes.

- Variable histomorphologic patterns have been reported including the epithelioid and the rare clear cell variants.
Osteosarcoma with Clear Cell Features

- The clear cell variant of OS:
  - Extremely rare, but should be theoretically included in the differential diagnosis of clear cell tumors of bone
  - Does not appear to constitute a clinically distinct well defined entity or even exhibit a uniform histological pattern.
  - The clear cell change is presumably due to scarcity of organelles, dilatation of rough endoplasmic reticulum, scattered phagolysosomes, the accumulation of glycogen;
  - The clear cells show no difference from the conventional osteosarcoma by reacting negatively with anti-S-100 protein.
Chondrogenic Sarcoma

- Chondrosarcoma constitutes approximately 11% of all primary malignant tumors.

- The tumors most commonly involve the pelvis, followed by proximal femur, proximal humerus, distal femur, and ribs.

- Common in a fourth to sixth decades of life with exceptions.

- The head and neck region involvement ranges from 1-12% and can practically involve any site.

- Most common locations in the head and neck area, the maxilla and mandible, the skull, sinonasal area, and Larynx among others.
Clear Cell Chondrosarcoma

- Various histologic patterns have been recognized including a myxoid, mesenchymal, dedifferentiated and the uncommon clear cell variant.

- The myxoid and mesenchymal subtypes constitute a significant proportion of head and neck cases.

- The clear cell variant primarily involves the proximal femur and humerus and is rarely reported in the head and neck region.

- Clear cell Chondrosarcoma accounts for approximately 2% of all Chondrosarcoma.

- The tumor also shows marked predilection for males.

- Commonly display a radiolucent lesion with well defined sclerotic margin that separates the neoplasm from the surrounding bone.
Clear cell Chondrosarcoma

- The tumor shows characteristic histomorphological features;
- Lobules of large cells with well distinct borders and clear to granular cytoplasm
- Round centrally situated nuclei.
- An admixture of osteoid matrix. (An important feature that distinguish the clear cell variant from conventional Chondrosarcoma).
- Osteoclasts type giant cells.
  (A feature that is not common for the conventional Chondrosarcoma.)
- The clearing of the cytoplasm may be attributed to accumulation of glycogen, decrease in the number of organelles or dilatation or endoplasmic reticulum and or Golgi.
- Areas, reminiscent of the conventional Chondrosarcoma may be occasionally seen.
- Cystic changes are frequently seen but necrosis, hemorrhage and mitosis are uncommon.
- Immunohistochemistry staining of clear cells; uniformly positive for anti S-100 protein, Vimentin, collagens II and X as well as cartilage associated glycoproteins, in keeping with their cartilaginous derivation.
- Clear cell Chondrosarcoma is a low grade malignant tumor that exhibit san indolent growth and proliferative activity that is best treated with en-bloc resection with or without adjuvant therapy, yet local recurrence, distant metastasis and tumor related death are documented.
Chordoma

- Chordomas are rare slow growing bone tumors, representing less than 4% of all primary bone tumors.
- Thought to be derived from notochord remnants that present in the craniospinal axis.
- Classically seen in the craniospinal location.
- The involvement of the Sinonasal area is uncommon but well documented.
- Marked male predilection, with peak incidence is in the fifth and sixth decades of life.
- Histologically display various cell types (physaliferous, epithelioid, and Chondroid cells) (the latter is referred to Chondroid Chordomas).
- Can mimic other clear cell tumors.
- Regardless of the histological subtype, the tumor cells characteristically contain multiple vacuoles resulting in a bubbly pattern and referred to as physaliferous cells.
16. Ratio: 6.0
Chordoma

- Immunohistochemically;
- Nearly all cell types (physaliferous, epithelial-like, and cells of Chondroid differentiation) of both recurrent and nonrecurring chondromas are + for EMA, and S-100 protein, and also co express cytokeratins (KL1, AE1/AE3) and vimentin.
- Stain negatively with HMB45 and desmin but may occasionally stain positively for NSE.

- The immunohistochemical properties are useful in differentiating the tumor from Chondrosarcoma (only express S-100 protein) & from metastatic renal cell carcinoma which otherwise share many immunohistochemical and immunophenotypic properties with chondromas.

- Chordoma are best managed with complete surgical resection, but this may not always be possible because of the invasive nature of the lesion.

- Radiotherapy is still controversial but often needed for incomplete excisions case or applied as palliative for recurrent disease.
Alveolar soft-part sarcoma (ASPS)

- Alveolar soft-part sarcoma (ASPS) rare, accounting for only 1% of all soft tissue sarcomas.
- The tumor primarily involves the extremities and has predilection for teenagers and young adults with documented female predilection.
- 27% of cases involve the head and neck area; orbital area >> the tongue (the tongue is the most common site recognized in infants and children).
Alveolar soft-part sarcoma (ASPS)

- The tumor is often well circumscribed but infiltrates the surrounding tissues in areas.
- Typical eosinophilic crystalline or rod-shaped inclusions are seen by routine microscopy in approximately 80% of cases.
- PAS positive, diastase-resistant rhomboid or rod-shaped crystals.
- The crystals also characteristically immunoreactive for CD147.
- Histologically; well delineated nests of large uniform polygonal cells, separated by thin fibrous connective tissue septae. The cells exhibit well distinct borders, one or more vesicular nuclei with small nucleoli, and granular, eosinophilic to vacuolated cytoplasm.
- Thin sinusoidal vascular spaces are interspersed between the individual cells and some vessels may display a hemangiopericytoma-like pattern in areas.
ASPS

- Immunohistochemistry; variable results reported.
- The tumor cells stain:
  - + with vimentin, muscle-specific actin, and desmin.
  - Neg for cytokeratin, epithelial membrane antigen, neurofilaments, glial fibrillary acidic protein, and serotonin.
  - Neg for synaptophysin and HMB45 which are two important stains to factor in distinguishing the lesion from paraganglioma and metastatic melanoma. respectively.
- The PAS positive crystals can readily distinguish tumor from metastatic renal cell carcinoma.

- Must be treated with adequate radical resection
- The disease usually follows a slow course but the prognosis is generally poor since a large percentage of patients experience progression even in the absence of local recurrence and distant metastasis (most commonly to the lungs {via hematogenous route}).
- The smaller the tumor size, the younger the age at presentation, the better the prognosis.
- The presence of metastatic diseases at presentation is associated with unfavorable prognosis.
Certain neon neoplastic reactive conditions and storage diseases may manifest as bony lesions and may be included in the differential diagnosis of clear cell entities based on the histomorphological presentation.
Rosai Dorfman Disease (RDD)

- Rosai Dorfman disease (RDD) is a rare, non-neoplastic histiocytosis.
- Commonly occur in adolescent young males with slight predilection for African Americans.

- Characterized by painless, generalized cervical lymphadenopathy.

- Extranodal involvement of the head and neck region is well documented; nose and paranasal sinuses, soft tissues, orbit, major salivary glands, larynx, pharynx, tonsils, thyroid gland, ear, and facial skeleton > craniofacial bones.

- Histologically demonstrate a diffuse proliferation of large, bland foamy Histiocytes that contains a vesicular nucleus, supported by eosinophilic cytoplasm.

- Mitoses are rare

- A diffuse acute and chronic inflammatory cell infiltrate and emperiploesis is observed in lesions of both nodal and extranodal sites.

- The foamy macrophages stain positively with S-100 protein and CD68, similar to Langerhans cell histiocytosis and keeping with their histiocytic derivation, however are constantly negative for CD1a; and Birbeck granules are not demonstrated on ultrastructural studies which can further help to differentiate between the Langerhans cell histiocytosis and Rosai- Dorfman disease.
Langerhans cell histiocytosis

• Benign but locally infiltrative process of bone of Langerhans cell origin.

• The process may be
  • Confined in either Polyostotic or Monostotic forms; eosinophilic granuloma.

• Disseminated.; may occur in infant and may be associated with eczematous cutaneous rashes, hepatomegally, spleenomegally, anemia and lymphadenopathy (Letterer-Siwe disease) or may be also seen in young children older than the age of patients involved with Letterer-Siwe disease and is characterized by the triad of diabetes mellitus, exophthalmia, and the Langerhans histiocytosis bony lesions (Hand- Schuller- Christian disease).

• Patient classically exhibit noticeable welling in the jaw area.

• Radiographically, LCH typically display lytic lesions of the jaw and skull (punched out radiolucencies), accompanied by resorption around apices of teeth (teeth hanging in air phenomenon) and mobility of teeth.
Erdheim - Chester disease (ECD)

- Erdheim - Chester disease (ECD) is a rare focal or systemic infiltrative disorder resulting from xanthogranulomatous tissue deposition.

- Affects bone marrow, long bone metaphyses symmetrically and sparing epiphysis) > retroperitoneal space, periaortic area, skin, brain and lungs.

- Wide age range, males slightly more involved than females.

- Etiology unknown but may be related to lipid storage disorder.

- May also rarely involve jaw bones.

- Characterized by a diffuse infiltrate of foamy macrophages that stain positively with anti CD 68, rarely show foal positive staining with S-100 protein but consistently reacts negatively with CD1a.
Gaucher’s Disease

- Gaucher’s disease, the most common lysosomal storage disease occurring as a result of genetic defect in production of the enzyme β-glucocerebrosidase, and the consequent accumulation of the glycolipid/glucocerebroside, in the cells of the monocyte-macrophage system.

- The disease occurs in 3 types,
  - Type I, the non-neuronopathic form, a milder form of the disease with many patients relatively asymptomatic is the most common.
  - Type 2 which is more acute form characterized by visceral and bone involvement as well as seizures.
  - Type 3 of the disease is also characterized with mild to moderately severe involvement of the visceral organs, progressive calcification of aortic and mitral valves, bone involvement, CNS involvement and others.

- Involvement of the maxillofacial bones is well documented, therefore the disease should be also included in the differential diagnosis of clear cell entities of the head and neck.

- Bone involvement is characteristically seen in 75–80% of cases of type I and Type III Gaucher’s disease.
Gaucher’s Disease

• Gaucher’s cells accumulate in the visceral organs and in bone marrow, leading to the so called “Erlenmeyer flask deformity “.

• Jaw involvement demonstrates non specific lytic lesions without teeth devitalization or cortical resorption.

• Histologically, sheets of lipid laden macrophages with marked bluish cytoplasm are seen.
Thank You

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