Understanding Oral Pathology Through Clinical-Pathologic Correlation

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Goals
1. Recognize and categorize diseases upon presentation
2. Make a differential diagnosis
3. Use of appropriate diagnostic tests to arrive at a final diagnosis
4. Appropriate treatment or referral

*The Diagnostic Sequence*
1. Detection of a deviation from the normal
2. History (first appearance and duration)
3. Methodical examination of the oral cavity
4. Reexamination of the change from the normal
5. Attempt to classify
6. Develop differential diagnosis
7. Definitive diagnosis

Initial Evaluation
(History and Clinical Examination)

Differential Diagnosis

Additional evaluation
Exposures, Diagnostic course of medication, Blood tests, Imaging, Biopsy

Definitive Diagnosis

Morphology of Oral Lesions
1. Configuration
2. Texture
3. Color
4. Consistency
5. Location
6. Size
7. Distribution

Classification Categories of Oral Lesions

- Etiopathogenic
  - “What's the cause?”
- Clinical classification
  - “What does it look like?”
  - Basis for differential diagnosis (“What could it be if it looks like that?”)
- Classification by tissue type involved
  - “What is it made of?”
  - Histopathologic classification
Clinical Classification

- Surface color change
  - White lesions
  - Red lesions – increased vascularity
  - Pigmented lesions
    - Blue/black – Pigment, foreign material, congested vessels
    - Brown - Melanin
- Loss of epithelium
  - Ulcerations and pseudomembranes
  - Can be from trauma, infectious, autoimmune, or neoplastic
- Vesiculobullous lesions
- Masses

Etiopathology

- Developmental
- Inflammatory
- Infectious
- Reactive
- Hereditary
- Neoplastic
- Metabolic

Initial Evaluation
(History and Clinical Examination)

Differential Diagnosis

Additional evaluation
Exposures, Diagnostic course of medication, Blood tests, Imaging, Biopsy

Definitive Diagnosis

White Sponge Nevus

- Definition
  Condition inherited in an autosomal dominant manner causing benign white lesions of mucosa
- Etiology & Pathogenesis
  Mutation of genes coding for keratin 4 and 13 proteins

WHITE SPONGE NEVUS
Features

- Asymptomatic
- Deeply folded white lesions most often of BM but other sites also
- Symmetrical, appear early in life
- Do not disappear by stretching
- Other sites: esophageal, vaginal, vulval and anal mucosa
- Spongiosis, acanthosis, parakeratosis, clear cells in prickle layer
- Perinuclear condensation of keratin
- Treatment: none, no malignant potential

Medical History

- Mild asthma; history of pneumonia in 1999
- Meds: Albuterol (PRN)
- NKDA
- Patient has not seen a dentist for a long time
- Patient brushes 1x/day, flosses 0x/week
- Patient snacks 3-4x/day
Examination

- EOE: WNL
- IOE: Hyperpigmentation in area of #22-24
- Generalized moderate-heavy plaque and calculus b/u
- All permanent teeth present except third molars and #22, 23, 24
- Anterior open bite
- Posterior cross bite

Initial Evaluation
(History and Clinical Examination)

Differential Diagnosis

Additional evaluation
Exposures, Diagnostic course of medication, Blood tests, Imaging, Biopsy

Definitive Diagnosis

Regional Odontodysplasia
“Ghost Teeth”

- Localized, non-hereditary, idiopathic
- Proposed causes: Malnutrition, Abnormal migration of neural crest cells, local circulatory deficiency, radiation, etc....
- Abnormal deciduous teeth typically followed by affected permanent
- Delayed or failure of eruption, early exfoliation
- Retention of altered teeth to allow for proper development of ridge
- Tooth preparation is contraindicated

14-year-old female presented with painless swelling of anterior palate

Differential diagnosis of a blue fluctuant lesion of hard palate

- Salivary gland lesions
  - Mucocele
  - Cystadenoma
  - Mucoepidermoid carcinoma
- Benign cyst
  - Nasopalatine duct cyst

Nasopalatine Duct Cyst

- Proliferation of epithelial remnants of the nasopalatine canal, which closes off early in embryologic development
- Slow growth; must be excised
15 y/o male with 9 month h/o expansion with slight pain of left anterior maxilla which was tender to palpation and no paresthesia. There was no history of trauma.

Differential Diagnosis of a Unilocular Radiolucency of the Anterior Maxilla
- Odontogenic keratocyst
- Ameloblastoma
- Nasopalatine duct cyst
- Radicular cyst

14 y/o female with raised nodular lesions of lips and tips of tongue. Clinician reports these to be sexually transmitted.

Differential Diagnosis
Multiple Nodules of Oral Mucosa
- Multiple oral papillomas/verrucae
- Condylomata
- Focal epithelial hyperplasia
- Multiple hamartoma syndrome
- MEN type 3 (2b)
- Neurofibromatosis

Multifocal Epithelial Hyperplasia
- Heck’s disease
- 1st described in native Americans
- Numerous nodules over oral mucosa
- HPV 13 and 32 implicates
- Spontaneous regression
  - Viral recognition and cell mediated immunity
- No malignant potential

HPV in Oral Cancer: Mainstream Press
- USA Today – “Oral infections with HPV...more common than doctors expected” “...traced more than 70% of new cases of oral cancers to HPV”
- NYTimes – “HPV...has fueled a rise in oropharyngeal cancers”
- AP – “White mouth cancers are on the rise - probably from oral sex – most people with oral HPV never develop cancer”
- ABC News – “Men were at 3 times greater risk than women” researchers speculated that virus may have an easier time transmitting orally in men than in women”
- Bloomberg News – “Besides sex, other demographics associated with oral HPV infection include age, lifetime number of sex partners, and the number of cigarettes smoked each day”
- Washington Times – “the most prevalent HPV strain is HPV16, a type particularly likely to cause cancers”
HPV in Oral Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>HPV Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous papilloma</td>
<td>2, 6, 11</td>
</tr>
<tr>
<td>Condylomata</td>
<td>6, 11</td>
</tr>
<tr>
<td>Verruca vulgaris</td>
<td>2, 4</td>
</tr>
<tr>
<td>Focal epithelial hyperplasia</td>
<td>13, 32</td>
</tr>
<tr>
<td>Dysplastic wart (HIV)</td>
<td>7, 32</td>
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</tbody>
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Squamous Papilloma

- HPV subtypes 2, 6, 11
  - Similar to condyloma accuminatum (a term used to denote oro-genital warts. In oral cavity, lesions >1cm)
- Papillary, cauliflower-like proliferations
- Very low infectivity
- Surgical excision

Verruca Vulgaris

- “Common wart” of skin
- Auto-inoculation
- HPV subtypes 2, 4
- Similar to, if not indistinguishable from, papilloma
- Histology slightly different
- Surgical excision

Dysplastic Oral Warts in HIV+

- Dome shaped nodular lesions
- Incidence in HIV + is ~1-3%
- Studies suggest incidence in HAART
  - Restoration of CD4 cells may allow for improved HPV antigen recognition
- Most common HPV subtypes 7, 32
  - Non-oncogenic and low malignant potential
- Surgical excision when necessary

HPV in Head and Neck Squamous Cell Carcinoma

- HPV is a causative agent for some HNSCC
  - Overwhelmingly HPV 16
  - Nasopharyngeal HPV 33
- HPV-associated HNSCC
  - Location: Palatine and lingual tonsils, oropharynx
  - Poorly differentiated histopathology
  - Younger and non-smoking patients

So what carcinomas of the head and neck are caused by HPV subtypes???
**HPV in Head and Neck Squamous Cell Carcinoma**

- Oropharyngeal Ca was 18% of HNSCC in 1973
  - Increased to 31% in 2005
- Significantly reduced risk of dying
  - Lack of field cancerization effect
  - Enhanced radiation sensitivity (negated by 10+ years of smoking
  - 3 year survival 82.4% if HPV+
    * 57.1% in patients whose tumors are HPV-

**Oropharyngeal Squamous Cell Carcinoma**

- May present as metastatic neck masses
- Typically basaloid phenotype
- **p16** – A cell cycle protein overexpressed in HPV 16 infected cells
  - HPV infection causes inactivation of the tumor suppressor genes p53 and pRB
  - Viral oncoproteins E6 and E7 encoded by HPV genome
  - Some oral cavity cancers (~5%) are p16+ but HPV 16-

**HPV16 + Oropharyngeal Squamous Cell Carcinoma**

- 3.6/100,000 2003-2004 but expected to be ~12,000 by 2020
- HPV16 prevalence is 6.9%
- BUT most people who are HPV16+ WILL NOT develop oropharyngeal cancer
- Testing for HPV not beneficial
- HPV-16 – positive HNSCC was independently associated with several measures of sexual behavior and exposure to marijuana but not with cumulative measures of tobacco smoking, alcohol drinking, or poor oral hygiene

**Connection Between Human Papilloma Virus and Oropharyngeal SCC in the US**

- Molecular and epidemiologic evidence for strong etiologic association of HPV with oropharyngeal cancers
- Incidence of oropharyngeal cancers have increased while other head and neck sites have decreased
- HPV + cancers:
  - Associated with certain sexual behaviors
  - Occur more often among white men and those who do not use tobacco or alcohol
  - Occur in a younger population (~4 years)
  - Lower risk of dying or recurrence
- Effectiveness of HPV vaccine unknown

**CDC Facts**

- HPV causes cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancer
- HPV spread through skin to skin contact
- 15,000 cases of HPV associated cancers/year in women
- 7,000 cases of HPV associated cancers/year in men
- CDC recommends vaccination for females age 11-26 and males age 11-21
  - Gardasil (Merck) also protects against genital warts (HPV 6, 11) and is approved for males
NIH scientists find promising biomarker for predicting HPV-related OPCa
- Antibodies against HPV may help identify those at increased risk of HPV-related cancer
  - Abs are to the E6 gene in HPV that contributes to tumor formation
- Detected many years prior to onset of disease
- 1 in 3 with OPCa have antibodies compared to 1 in 100 without cancer

Six Questions: Clinical Assessment of Oral Mucosal Ulcers
1. **Onset history?** gradual v. acute
2. **Preceded by vesicle?**
3. **Mucosal lesion distribution or sites?**
   - symmetrical v. asymmetrical
   - keratinized v. non-keratinized mucosa
4. **Associated skin/ocular lesions?**
5. **Outcome history?** self-limiting v. chronic
6. **Current drug use contributing?**

Recurrent Aphthous Stomatitis
- Most common ulcerative lesion of the oral cavity
- Recurrent, painful ulcers
- Typically confined to moveable mucosa
- 10-20%; Genetic predisposition
- 3 types
  - Minor
  - Major
  - Herpetiform

8 year old daughter of an endodontist
- **History of aphthous ulcers over the last few years**
- Very painful, enlarging and a new one on the other side is forming

Initial Evaluation
(History and Clinical Examination)

Differential Diagnosis
Aphthous ulceration
Recurrent aphthous ulceration
Primary HSV1
Traumatic ulceration
Langerhans cell disease

Definitive Diagnosis
Exposures, Diagnostic course of medication, Blood tests, Imaging, Biopsy

RAU - Management
1. History and diagnosis
2. Identification and elimination of local factors
3. Investigate deficiencies
4. Investigate hormonal imbalance
5. Investigate dietary factors and allergies
6. Investigate for gastrointestinal association
7. Investigate psychological factors
8. Treatment
**RAU - Treatment**

- Palliative
- Chemical cautery (Debacterol)
- Fluocinonide (Lidex) gel .05%
- Clobetasol (Temovate) gel .05%
- Dexamethasone (Decadron) elixir .5mg/5ml
- Intraliesional steroid injection
- Oral prednisone

**What other conditions would you advise the parents to consider?**

- Behçet’s syndrome – ocular and genital lesions
- PFAPA syndrome – periodic fever, aphthae, pharyngitis, lymphadenopathy
- Nutritional deficiency
- Celiac disease

**A 58 year old male presented with 2 month history of ulceration on anterior palate**

**Initial Evaluation**

- (History and Clinical Examination)

**Differential Diagnosis**

- Additional evaluation
  - Exposures, Diagnostic course of medication, Blood tests, Imaging, Biopsy

**Definitive Diagnosis**

- Inflammatory
- Infectious
- Reactive
- Neoplastic
- Aphthous ulcer
- Syphilis, TB
- Idiopathic
- Squamous cell carcinoma, Lymphoma

- Diffuse Large B-Cell Lymphoma

- High-grade lymphoma
- Oral lymphoma is often extranodal and may represent extent of disease
- Must be staged
- Radiation and chemotherapy
  - 60% mortality rate at 5 years
  - Targeted therapy with Rituximab, an antibody to B-cell antigens, shows promise

**A 3 y/o female was evaluated by her pediatric dentist for a labial ulceration and painful red and bleeding gums for ~3 months. Diagnosed by pediatrician as having eczema and UTI’s.**
Initial Evaluation
(History and Clinical Examination)

Differential Diagnosis

Additional evaluation
Exposures, Diagnostic course of medication, Blood tests, Imaging, Biopsy

Definitive Diagnosis

Differential Diagnosis

Prepubertal Periodontitis

• Disturbances in leukocyte numbers
  – Agranulocytosis
  – Congenital/cyclic neutropenia

• Defects in leukocyte function
  – Lazy leukocyte syndrome
  – Job’s syndrome
  – Chronic granulomatous disease of childhood
  – Myeloperoxidase deficiency
  – Leukocyte adhesion deficiency

Work up

• Biopsy showed ulceration with few neutrophils in ulcer bed
• Circulating neutrophil count may be normal or high
  – WBC 30,220/μL (n=5000-13,500)
  – Neutrophil count 24,630 (n=60-70% of WBC)
• Flow cytometry necessary for diagnosis
  – Antibodies against leukocyte integrins
  – Mild to severe deficiencies found

Diagnosis

• Leukocyte Adhesion Deficiency
  – Rare
  – Autosomal recessive defects in the CD18 gene which encodes leukocyte integrins
  – Life threatening bacterial infections
  – Rapidly progressing juvenile periodontitis is prevalent
  – Treatment:
    • Allogenic bone marrow transplantation
    • Allogenic granulocyte transfusions

Defects in leukocyte function

Chemotaxis
  Lazy leukocyte syndrome
  Chediak-Higashi syndrome

Phagocytosis
  LAD-I
  Job’s syndrome

Degranulation
  Specific granule deficiency
  Chediak-Higashi syndrome

Oxidative burst
  Chronic granulomatous disease of childhood

Hypochlorous acid production
  Myeloperoxidase deficiency

* LAD-I, leukocyte adhesion deficiency type 1

8½ year old daughter of an endodontist

History of aphthous ulcers over the last few years

Very painful, enlarging and a new one on the other side is forming
Six Questions: Clinical Assessment of Oral Mucosal Ulcers

1. **Onset history?** gradual v. acute
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Primary Herpetic Gingivostomatitis

- ~12% of children infected
- May present as pharyngitis
- 6 mos – 5 years
- Cervical lymphadenopathy, high fever, chills, nausea, and irritability
- Acyclovir suspension (children 15mg/kg) in first 3 days, rinse and swallow 5 times/day for 5 days
- Valacyclovir 1gm/day x 7 days

This 64 year old woman complains of tenderness in her gums. This symptom has gradually increased during the last several weeks. Her medical history is non-contributory.

Lichen Planus

- Chronic disease of skin and mucous membranes
- 1-2% of population
- Unknown etiology
- Destruction of basal cell layer by activated lymphocytes
- Reticular, papular, plaque-like, atrophic, ulcerative, bullous
- Malignant transformation potential?

Lichen Planus - Treatment

- Rule out drug eruption
- Histopathologic diagnosis
- Immunofluorescence
- Treatment
  - Doxycycline 100mg x 30 days
  - Fluocinonide (Lidex), 0.05% gel
  - Clobetasol (Temovate), 0.05% gel
  - Dexamethasone (Decadron) elixir, 5mg/5ml
*Antifungal treatment may be necessary
Oral Lichenoid Lesions
Associated Drugs

- NSAIDs
  - Many
- Anti-diabetic
  - Chlorpropamide
- Diuretic
  - Furosemide (Lasix)
- Anti-hypertensive
  - methyldopa (Aldomet)
  - ACE inhibitor Captopril (Capoten)
  - Beta blocker Altenolol (Tenormin)

Traumatic Ulcer in Infancy

- Site of trauma
- Riga-Fede disease, natal teeth
- Appears between 1 week and 1 year of age
- Remove source of irritation
- Biopsy if persistent

The patient is a 9 year-old girl with a rapidly growing maxillary mass.

Differential Diagnosis of Maxillary Jaw Lesion

- Odontogenic keratocyst
- Calcifying odontogenic cyst
- Adenomatoid odontogenic tumor
- Ameloblastoma
- Myxoma
- Central Giant Cell Granuloma
- Desmoplastic fibroma

Central Giant Cell Granuloma

- Young
- Female
- Radiolucent uni/multilocular
- Recurrence unpredictable (~10-50%)
- Excision
- Calcitonin
- Interferon alfa
- Intralungal steroids
- Hyperparathyroidism, cherubism, ABC

9 year-old Hispanic female with solitary erythematous mass of attached gingiva
Observed over 6 weeks with no change
Differential Diagnosis
Gingival Bumps

• Peripheral Fibroma
• Pyogenic granuloma
• Peripheral ossifying fibroma
• Peripheral giant cell granuloma

Localized Juvenile Spongiotic
Gingival Hyperplasia

• Unique form of gingival hyperplasia in young patients (Avg age ~11 years)
• 2:1 female: male
• 77% seen in Caucasians
• Anterior gingiva with most on the maxilla
• Generally asymptomatic, pedunculated, papillary, red and bleed easily
• May be hormonally stimulated growth

Localized Juvenile Spongiotic
Gingival Hyperplasia

• Treatment:
  – Unresponsive to periodontal treatment and OH
  – Surgical excision is treatment of choice
  – Recurrence may occur

Localized Spongiotic
Gingival Hyperplasia

“Juvenile” is not used in the name any more because adults are commonly affected. UNC files from 2006-2012 contain over 100 cases in adults dxed as pyogenic granuloma

16 year old female with a fluctuant and painless mass of the left retromolar trigone

Initial Evaluation
(History and Clinical Examination)

Differential Diagnosis

• Developmental
• Neoplastic

Additional evaluation
Exposures, Diagnostic course of medication, Blood tests, Imaging, Biopsy

Definitive Diagnosis
Diagnosis

Mucoepidermoid carcinoma, low-grade (AFIP)

The patient is a 19 year old girl with an expanding mandibular mass.

Ameloblastoma

- Most common true odontogenic tumor
- Benign, slow-growing, locally invasive neoplasm
- Clinically three types:
  1) conventional solid/multicystic (86%)
  2) unicystic (13%)
  3) peripheral (extraosseous) (1%)

Ameloblastoma

Clinical features
- 3rd-7th decades (μ = 30 years), M=F
  - Rare in children
- Asymptomatic or painless swelling
- Majority (85 %) mandible, especially molar-ramus area, 15 % maxilla, mostly posterior regions

Ameloblastic fibroma

- Mixed epithelial and mesenchymal tumor
- Younger patients, first two decades of life
- Small lesions asymptomatic, larger lesions swelling
- Posterior mandible most common site
- Unilocular or multilocular radiolucency with well-defined borders, may be associated with unerupted tooth
- Histopathology: may be encapsulated, composed of cellular mesenchymal stroma resembling dental papilla containing cords or small islands of odontogenic epithelium
- Treatment: enucleation

Ameloblastic fibro-odontoma

- Ameloblastic fibroma + enamel or dentin
- Usually children > 10 years, M = F
- Often asymptomatic; failure of tooth to erupt
- Well-circumscribed unilocular or multilocular radiolucent lesion containing variable amount of calcified material
- Histopathology: soft tissue component identical to ameloblastic fibroma with enamel & dentin matrix
- Treatment: conservative curettage, recurrence unusual
The patient is a 12 year old girl with a slowly expanding mandibular lesion.

Myxoma

- Wide age range; young adults
- Asymptomatic or painless swelling of jaw
- Radiograph: unilocular or multilocular radiolucency “soap bubble appearance”
- Loosely arranged stellate, round and spindle-shaped cells in myxoid stroma with few collagen fibrils; ground substance acid mucopolysaccharide; small odontogenic rests
- May be infiltrative, incomplete removal may lead to recurrences

The patient is a 15 year-old woman with a floor of mouth mass that has been slowly enlarging.

MIDLINE NECK MASSES

- Thyroglossal Duct Cyst – moves with swallowing
- Dermoid or Epidermoid tumors – firm, rubbery
- Ranulas
- Lipomas
- Lymphangiomas (in children)
- Lymphoid: HL, NHL, *Bartonella henselae*

An infant with a palatal lesion

An 11-year old girl with an ulcerative oral lesion and bilateral lymphadenopathy
Differential Diagnosis

- Unilateral palatal ulcerations
  - Primary herpes
  - Zoster - rare in children
- Palatal ulcerations + cervical lymphadenopathy
  - Cat scratch disease, lymphoma, tuberculosis

Additional stains

- FITE stain - negative for acid-fast bacilli
- Gram stain - negative for fungal organisms
- Warthin-Starry stain - negative for *Bartonella henselae*

The patient is a 17-year-old girl with a two month history of a maxillary anterior swelling. She has no other associated symptoms.

Adenomatoid Odontogenic Tumor

**Clinical**
- "two-thirds tumor"

**Treatment**
- Simple enucleation

**Prognosis**
- does not recur

13 year old female presents with expansion of right maxilla and stuffiness

Fibro-Osseous Lesions of the Jaws

- Generic microscopic term
- Benign fibrous stroma with immature bone
- Includes reactive, dysplastic, neoplastic lesions
- Histologic overlap
- Diagnosis based upon clinical-pathologic correlation
  - Need x-ray to often make diagnosis
Fibrous Dysplasia

- 1st & 2nd decades (stabilizes at puberty & very slow growth thereafter)
- Maxilla > mandible
- Ribs, femur, tibia also affected
- Unilateral diffuse opacity
- Asymptomatic, self limiting
- Serum lab values normal
- New fibrillar bone trabeculae; few osteoblasts, no osteoclasts, homogeneous pattern; vascular matrix, no inflammation
- Surgical recontouring for cosmetics
- Regrowth in 25% of treated cases

McCune-Albright Syndrome

*Polyostotic fibrous dysplasia*

- Multiple ossifying fibromas
- Café au lait pigmentation
- Endocrinopathies

Ossifying Fibroma

- 3rd & 4 decades
- Mandible>maxilla
- Well circumscribed
- Lucent or lucent/opaque pattern
- Continuous growth; often expansile and may be destructive
- Cellular fibrous matrix, islands/trabeculae of new bone, osteoblasts, no osteoclasts, relatively homogeneous pattern, no inflammatory cells
- Curettage/excision

Fibrous Dysplasia vs Ossifying Fibroma

- 1st & 2nd decades
- Max>mandible
- Diffuse opacity
- Self limited
- One or more bones
- Vascular matrix
- Woven bone trabeculae
- Stabilizes at puberty
- Recontour for cosmetics

- 3rd & 4 decades
- Mandible>max
- Circumscribed
- Continuous growth
- One bone
- Cellular fibrous matrix
- Bony islands & trabeculae
- Not hormone related
- Excise

Differential Diagnosis of a Multilocular Jaw Radiolucency

- Ameloblastoma
- Odontogenic keratocyst
- Myxoma

15 year old male with left facial swelling of several years
3 year old female presents with a swelling in the right mandible that has been present for five weeks

- Parents report rapid growth of lesion after a traumatic fall
- PMH – No significant findings

Differential

- Aneurysmal bone cyst
- Central Giant cell granuloma
- Langerhans cell disease
- Desmoplastic fibroma
- Sarcoma

Langerhans Cell Disease

- A proliferation of Langerhans cells
  - Cells are S-100, CD1a & Langerin positive
  - Cells contain Birbeck granules (ultrastructure)
  - Few macrophages are present
- Cause unknown
- Any age, 3 variants
- Radiograph shows “punched out” non-corticated lesions or “floating teeth”
- Several treatment options
- Prognosis, good to excellent
  - Depends on form

Langerhans Cell Disease

- Eosinophilic granuloma (chronic localized)
  - Solitary or multiple bone lesions
- Hand-Schuller-Christian (chronic disseminated)
  - Bone lesions, exophthalmous, diabetes insipidus
- Letterer-Siwe (acute disseminated)
  - Bone, skin, internal organs

Follow Up

- Patient referred HEME-ONC
- No other foci of disease identified
- Patient received low dose chemotherapy