Disclosure

Patricia Wills Bagnato has no industry relationships to disclose.
Objectives

- The learner will be able to identify common symptoms of LCH.
- The learner will be able to distinguish features of an LCH rash in infants.
- The learner will be able to determine indications for referral of suspected LCH to oncology.
Case Study

- 7 month male. Brought to the pediatrician for a “bump” on his top palate which interfered with feeds and a chronic diaper rash.
- Thought to be possible "fungus" inside his mouth, unresolved with nystatin.
- Rash present since birth per mom. Waxed and waned; unresponsive to multiple treatment failures (topical antibiotics, steroids, antifungals).
- Mom also mentioned that child recently had "pus in his ears", which PCP thought was related to chronic groin rash.
- This was an otherwise healthy child, growing normally.
History, Review of Systems

- ROS: as noted in HPI
- Medications: clotrimazole, triamcinolone, nystatin, bactroban, zinc oxide
- Allergies: no medication or food allergies
- PHx: as described in history. Multiple clinic visits, no hospitalizations, surgeries or trauma.
- Social/family: mother primary caregiver. Father is construction worker. Only child.
Physical Exam

- **Constitutional**: He is alert, well-developed, well-nourished, and in no distress.
- **HENT**: Bilateral ear drainage. Oral lesions present at hard palate
- **Cardiovascular**: Normal
- **Pulmonary/Chest**: Normal.
- **Abdominal**: No hepatosplenomegaly.
- **Musculoskeletal**: Normal range of motion.
- **Neurological**: Normal cranial nerves, balance and coordination.
- **Skin**: Extensive, bright red, weeping rash on folds of groin, extending to perineal area and gluteal cleft.
Oral lesion
Diaper dermatitis
Course

- Referred to Dermatology
  - Biopsy - chronic idiopathic dermatitis
  - Prescribed triamcinolone .025% mixed with nystatin twice a day covered with a diaper rash paste

- 1 week: Presented to ED with fever and diarrhea (10-15 stools/day). Rash unchanged.
  - Prescribed amoxicillin, clotrimazole and probiotic

- 2 weeks: Clinic follow-up: diarrhea resolved. Persistent inguinal rash. s/p hydrocortisone, triamcinolone, clotrimazole, nystatin, clobetasol.
- Differential: psoriasis, intertrigo.
Course

- **Derm follow-up.** Oral lesions improved. **Rash persists.** Oral zinc supplements started.
- Seen by **ENT** for ear drainage: ears debrided and prescribed **ciprofloxacin and dexamethasone ear drops.**
- 1 month: Improvement in ear drainage. Continued **topical creams** for persistent diaper rash.
- 2 months: **Follow-up dermatology** visit. Skin **biopsy** repeated.
- 3 months from initial ED presentation: outside biopsy of rash consistent with **Langerhans Cell Histiocytosis.**
- **Referred to Oncology** for further evaluation and treatment.
Laboratory studies

- CBC DIFF, PLATELETS
- CHEM10, LIVER PANEL, SED RATE
- URINE AND SERUM OSMOLALITY
Oncology work up  PET scan

Lytic lesions:
- Right first rib
- R mastoid
- R iliac bone
- Oral cavity
Case Study

- Diagnosed with multisystem (multifocal bone, CNS Risk+) LCH.
- Sites of disease - skin, hard palate, 1st rib with destructive soft tissue lesion involving T1 vertebral body with pedicle, right mastoid lesion, external auditory canals, right iliac bone.
- No evidence of liver, spleen or bone marrow involvement.
WHAT IS LANGERHANS CELL HISTIOCYTOSIS?
Langerhans Cells

- Derived from dendritic cells (antigen-presenting cells) found in the skin and mucosa and myeloid progenitor cells from the bone marrow
- LC role in immunosurveillance: Migrate to nearby lymph nodes for antigen-presentation
- Overproduction leads to tumor formation
  - Histiocytes, lymphocytes, macrophages and eosinophils infiltrate organs
    - Skin, lymph nodes, lungs, thymus, liver, spleen, bone, bone marrow, or CNS

(McClain, 2021a)
Etiologies

- Male predominance
- No genetic susceptibility
  - Rare in twins or singleton siblings
- Possible etiologies:
  - Solvent exposure
  - Perinatal infections
  - Pulmonary LCH in smokers

(McClain, 2021a)
## Incidence

<table>
<thead>
<tr>
<th>Age</th>
<th>Langerhans</th>
<th>Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 years</td>
<td>4-5 / million</td>
<td>140-160/million</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>1-2 / million</td>
<td></td>
</tr>
</tbody>
</table>

Namayandeh et al., 2020; Ozer, et. Al., 2019)
Prognosis

- Overall survival with high risk disease (+ liver, spleen or bone marrow) = 80%
- 40% patients with low risk have disease will have recurrence

- Study of infants
  - Skin-only disease usually < 1 year age: 89% progression free survival
  - Multisystem disease > 18mos age: 23% progression free survival

(Simko, et al., 2014)
## Presentations / Signs & Symptoms

<table>
<thead>
<tr>
<th>Pain</th>
<th>Swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rashes</td>
<td>Otorrhea (ear drainage)</td>
</tr>
<tr>
<td>Fever</td>
<td>Oral lesions</td>
</tr>
<tr>
<td>Hepatomegaly, splenomegaly</td>
<td>Appetite loss, poor weight gain</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>Polyuria</td>
</tr>
<tr>
<td>Irritability</td>
<td>Neurological changes-ataxia</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>Behavioral changes, learning difficulties</td>
</tr>
</tbody>
</table>

(Haupt, et.al., 2013)
Differential Diagnoses

- Lymphoma
- Solid tumors
- Primary CNS tumors (germinoma, meningioma)
- Vasculitis
- Cutaneous lymphoma
- Interstitial lung disease
- Other histiocytic disorders

(McClain, 2021a)
LCH Sites of Occurrence

(McClain, 2021)
LCH Sites of Occurrence in Bone / Symptoms and CNS Risk

Skull (40%), maxillofacial bones, hypothalamic pituitary axis
- Scalp and/or facial swelling
- Seizures
- Hearing loss, otitis media
- Gingival bleeding
- Tooth loss or early tooth eruption in infants
- Proptosis
- Diabetes insipidus
- Cranial nerve palsies

(McClain, 2021a)
Other common LCH Sites of Occurrence in Bone

Femur
Rib
Vertebra, vertebra plana
Humerus

(McClain, 2021a)
LCH Occurrence in the Skin
LCH Occurrence in the Skin
LCH - Skin rash at birth
LCH Skin rash in neonate
LCH Diaper rash
LCH - Oral lesions

Intraoral mass
Gingivitis
Mucosal ulcers
Loose teeth
Abnormal early tooth eruption in infants
Classification

- **Single-system** (uni-focal or multi-focal):
  - Bone, skin, lymph nodes, lungs, CNS, (rare-thyroid, thymus)

- **Multi-system**: two or more different organs w/wo involvement of “risk” organs
  - **High “risk” organs**: bone marrow, spleen, liver
  - **BRAFV600E gene mutation** – in 50% cases

- **CNS-risk**: sphenoid, orbital, ethmoid, temporal bones
  - Three-fold increased risk for diabetes insipidus and other CNS disease

(McClain, 2021a)
LCH – CNS Risk

- Facial bones, bones of the anterior or middle cranial fossae – 25% incidence of CNS involvement
  - Neurodegeneration can occur years after the initial diagnosis of LCH

- Endocrinopathies / Hypothalamic-pituitary involvement
  - Diabetes insipidus
  - Hypogonadism
  - Growth failure
  - Abnormal glucose metabolism
  - Thyroid abnormalities
  - Ataxia
  - Cognitive dysfunction

(McClain, 2021a, Wnorowski, 2008)
CNS – risk: Pituitary bright spot

Permission from Dr. Arjit Argarwal 4.28.2021. https://www.researchgate.net/figure/Sagittal-T1W-image-showing-absent-posterior-pituitary-bright-spot-C-Department-of_fig1_328860494
Diagnostic Evaluations

- Skeletal survey or plain x-ray
- CT scan or MRI
- PET scan
- Bone marrow aspirate and biopsy – indicated with liver, spleen involvement, cytopenias and age less than 2 years
  - Stain for anti-CD1a, anti-CD207, anti-CD163, BRAFV600E
- Lower GI endoscopy if have malabsorption or decreased albumin

(McClain, 2021b)
Treatment Options

Based on site of involvement and # of lesions

- Single – system
  - Observation
  - Curettage of bone lesions
  - Intra-lesional steroid for solitary bone lesions
  - Topical therapy for skin lesions
  - Oral mercaptopurine, oral methotrexate, oral hydroxyurea
  - Vinblastine IV, prednisone PO
  - Cytarabine IV
Treatment Options

- Multi-system, multi-focal and CNS risk – 1 year / + (based on response or relapse)
  - Vinblastine IV, prednisone PO
  - Cytarabine IV or SQ
  - Clofarabine IV
  - MEK pathway inhibitors PO
  - + Mercaptopurine, methotrexate, or hydroxyurea PO
Case – Treatment course

- 1/2019 – vinblastine 6mg/m² IV, prednisone 20mg/m² po BID x 5 days – weekly
- Scans after 6 weeks – persistent disease
- 3/2019 – cytarabine 100mg/m² IV qd x 5 days every 28 days
- 5/2020 – end of therapy scans with resolution
Pre – and post-PET scan
Outcome – Case 1
Take-away notes for the primary care provider

- Dermatology referral for the unrelenting rash - skin biopsy
- Plain x-rays for bone lesions
- Referral to oncology for additional evaluation
Resources

- https://www.histiocytessociety.org/
References


References

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  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7541866/#!po=28.7879
