Case Presentation
Multidisciplinary Approaches to Cancer Symposium

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Hematology/Oncology Fellow
11/10/16
Disclosures

I do not have anything to disclose.
Chief Complaint

34 yo Armenian male with jaw pain of several months
HPI

- Bilateral jaw pain over past 6 months, exacerbated with chewing

- PMH: Schizophrenia, intellectual disability
- SH: Denies T/E/D, sister is conservator
- FH: Noncontributory
- Meds: Trihexyphenidyl, fluoxetine, quetiapine, clozapine, clonazepam
- Allergies: NKDA
- PSH: None
Physical Exam

- T 97.0° F, BP 107/74, HR 94, RR 14, 96% RA, BMI 30.2 (109 kg)
- GEN: NAD
- HEENT: NC/AT, EOMI, PERRL, poor dentition, bilateral multiple carious teeth
- NECK: No JVD, thyromegaly, or LAD
- CV: RRR, S1 and S2 normal intensity
- PULM: CTABL
- ABD: Soft, NT/ND, BS normoactive
- EXT/SKIN: No C/C/E, no abnormal skin findings
- NEURO: Limited exam but no focal deficits
Laboratory

- WBC 4.4, Hgb 14.6, Hct 44.3, PLT 201K
  - MCV 87.7, MCH 29.0, RDW 15.5%, MPV 8.4
  - N 55.9%, L 37.2%, Mono 6.8%, Eos 0%, Basos 0.1%

- Na 143, K 3.9, Cl 109, CO2 26, BUN 5, Cr 1.05, Glu 81, Ca 9.6
- Alb 4.5, T. bili 0.5, AST 21, ALT 26, Alk phosph 90, T. protein 7.2
CT maxillofacial: Multiple lucent lesions in the mandible and maxilla. The differential diagnosis includes eosinophilic granuloma, metastatic disease, and multiple myeloma.
Laboratory

- Serum kappa/lambda 731/450 = 1.62
- Urine kappa/lambda 4 mg/dL/3 mg/dL
- SPEP: T. prot 5.9, alb 2.69, alpha 1 0.35, alpha 2 0.87, beta globulin 1.12 H, gamma globulin 0.87 g/dL (MILD DECREASE IN ALBUMIN AND INCREASE IN BETA FRACTION ARE NOTED. THE SERUM PROTEIN ELECTROPHORESIS PATTERN IS UNSPECIFIC AND CAN BE SEEN IN INFLAMMATIONS OR INFECTIONS, AUTOIMMUNE DISORDERS, DIABETES MELLITUS, AND ANEMIA)

- Urinalysis negative
- IgA 209, IgE, 36.6, IgG 941, IgM 114
- LDH 190, Uric acid 4.6, Ferritin 54.0, ESR 26 H
Laboratory

- UPEP: Urine prot 23 mg/dL, alb 10.06 (no paraprotein, trace proteinuria)
- Beta-2 microglobulin: 1.6 μg/mL
- HIV negative, Hep B/C serologies negative
Left mandibular mass (incisional biopsy):

- 1. LANGERHANS CELL HISTIOCYTOSIS, mandible and maxillar, biopsy (See note)
- 2. TWO TEETH (GROSS DIAGNOSIS ONLY)

Note: IHC stains of Langerhan cells are positive for CD1a, Langerin, S100, supporting the above diagnosis. Recommend correlation with clinical and imaging findings.

Biopsy

Langerin (CD207, a transmembrane receptor) is localized in organelles found solely in Langerhans cells, the Birbeck granules.
CT chest:
Multiple bilateral subcentimeter pulmonary nodules, several of which are described as follows:
* 6 mm right upper lobe
* 3 mm right upper lobe
* 3 mm left upper lobe
* 7 mm left lower lobe
Lucent region the posterior T11 vertebral body near midline.
CT abdomen/pelvis:
Spleen: The spleen is at the upper limit of normal in size, measuring 14 cm in the craniocaudal dimension.
Lymph nodes: No pathologically enlarged abdominal or pelvic lymph nodes by CT size criteria.
Bones: The L3 vertebral body has a mottled appearance.
11 mm lucency in the right iliac bone.
12 mm lucency in the L5 vertebral body with sclerotic margins.
Soft tissues: Normal.
SPECT:
Comparison is made to the prior nuclear medicine bone scan and maxillofacial CT. There is intense, abnormal FDG uptake in the left maxilla, right mandibular angle, and body of the mandible. Areas of increased FDG uptake on the current exam correlate well with lytic regions seen on the CT.
There is no abnormal FDG uptake in the thorax.
There is faint uptake in the L1, L2, and L4 vertebral bodies which are not as intense as in the jaw.

IMPRESSION:
1. FDG uptake corresponding to lytic lesions seen on the comparison maxillofacial CT, favored to represent areas of active disease. 2. Faint FDG uptake in the L1, L2, and L4 vertebral bodies
Question 1

Langerhans cell histiocytosis is becoming more increasingly recognized as a clonal neoplastic disorder?
A.) True
B.) False
Nikolas Symposium

- For >30 years, annual “think-tank” symposia on Langerhans cell histiocytosis (LCH)

- Discuss 2 longstanding questions over the past century:
  1.) The origin of LCH cells?
  2.) LCH is primarily an immune dysregulatory disorder or neoplasm?

1.) Langerhans Cell

Bone marrow/hematopoietic stem cell

↓

Histiocyte (Greek for tissue + cell)

Histiocytoses

Macrophages
- Phagocytosis
  ↓
  Haemophagocytic lymphohistiocytosis (HLH)
  - 1:1,000,000 cases/year

Dendritic cell
- Antigen-presenting cell
  ↓
  - Lymphoid and myeloid lineage
  Langerhans cell histiocytosis
  - 1:200,000 children/year
  - 1:560,000 adults/year


Clinical Presentation

Organ involvement (RS 1741 pts)
- Bone (77%) → lytic
- Skin (39%)
- Lymph nodes (19%)
- Liver (16%)
- Spleen (13%)
- Oral mucosa (13%)
- Hematologic (13%)
- Lung (10%) → pneumothorax
- CNS (6%) → diabetes insipidus

Single system or unifocal LCH
- Eosinophilic granuloma
- Involvement of one organ/system (bone, skin, or lymph nodes)
- High rate of both spontaneous remission and favorable outcome

Multisystem or multifocal LCH
- Letterer-Siwe disease (<2 yo), Hand-Schüller-Christian syndrome
- Involvement of ≥ two organs/systems
- “High risk” organs: hematopoietic system, liver, spleen = poor prognosis

### Diagnosis

**Biopsy is critical**

*(excisional preferred)*

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**Table 1. Baseline Evaluation at Diagnosis of Adult LCH**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>Abdominal ultrasound</td>
</tr>
<tr>
<td>Hemoglobin, white blood cell and</td>
<td>(size and structure of liver and spleen)</td>
</tr>
<tr>
<td>differential count, platelet count</td>
<td></td>
</tr>
<tr>
<td>Blood chemistry</td>
<td>Chest radiograph</td>
</tr>
<tr>
<td>Total protein, albumin, bilirubin,</td>
<td>(cystic lung lesions, pneumothorax)</td>
</tr>
<tr>
<td>ALT, AST, alkaline phosphatase,</td>
<td>Skeletal radiograph survey</td>
</tr>
<tr>
<td>gamma GT</td>
<td>(lytic bone lesions)</td>
</tr>
<tr>
<td>BUN, creatinine, electrolytes</td>
<td>PET scan</td>
</tr>
<tr>
<td>Ferritin</td>
<td>(PET scan has proven to be the most sensitive functional test to determine LCH staging, disease activity and response to treatment)</td>
</tr>
<tr>
<td>ESR, CRP</td>
<td></td>
</tr>
</tbody>
</table>

**Coagulation studies**

| PT/PTT/fibrinogen/D-dimer           |                                              |
|                                     |                                              |

**Early morning urine sample**

**Specific gravity and osmolality**

**Specific clinical scenarios**

<table>
<thead>
<tr>
<th>Bicytopenia</th>
<th>Bone marrow biopsy to rule out causes other than LCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver dysfunction</td>
<td>Liver biopsy* to confirm sclerosing cholangitis</td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>High-resolution chest CT, pulmonary function test, lung biopsy*</td>
</tr>
<tr>
<td>Craniofacial bone lesions</td>
<td>MRI head with gadolinium</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>MRI pituitary axis with gadolinium</td>
</tr>
<tr>
<td>Aural discharge</td>
<td>High resolution CT of temporal bone</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>Endoscopy and biopsy*</td>
</tr>
</tbody>
</table>

Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; CT, computed tomography; ESR, sedimentation rate; LCH, Langerhans cell histiocytosis; MRI, magnetic resonance imaging; PET, positron emission tomography; PT, prothrombin time; PTT, partial thromboplastin time.

*Immunohistochemistry for CD1a, Langerin, S100, and CD68.

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2.) Inflammatory vs. Neoplasm

LANGERHANS’-CELL HISTIOCYTOSIS (HISTIOCYTOSIS X) — A CLONAL PROLIFERATIVE DISEASE

Cheryl L. Willman, M.D., Lambert Busque, M.D., Barbara B. Griffith, M.S., Blaise E. Favara, M.D., Kenneth L. McClain, M.D., Ph.D., Marilyn H. Duncan, M.D., and D. Gary Gilliland, M.D., Ph.D.

Abstract: Background. The lesions of Langerhans’-cell histiocytosis (histiocytosis X), a proliferative histiocytic disorder of unknown cause, contain histiocytes similar in phenotype to dendritic Langerhans’ cells. The disease ranges in severity from a fatal leukemia-like disorder to an isolated lytic lesion of bone. Intermediate forms of the disease are usually characterized by multisystem involvement, diabetes insipidus, and a chronic course.

Methods. To determine whether Langerhans’ histiocytosis is a polyclonal reactive disease or a clonal disorder, we used X-linked polymorphic DNA probes (HUMARA, PGK, M27[DXS255], and HPRT) to assess clonality in lesional tissues and control leukocytes from 10 female patients with various forms of the disease. Lymphoid clonality was also assessed by analysis of rearrangements at immunoglobulin and T-cell–receptor gene loci.

Results. The HUMARA assay detected clonal cells in the lesions of 9 of the 10 patients: 3 patients had acute disseminated disease, 3 had unifocal disease, and 3 had intermediate forms. The percentage of clonal cells closely approximated the percentage of CD1a-positive histiocytes in each lesion. Clonality was also confirmed in two of nine cases with the PGK or M27β probe. Exceptional constitutional lyonization precluded assessment of clonality in the 10th case. Lymphoid clonality was ruled out in all cases.

Conclusions. The detection of clonal histiocytes in all forms of Langerhans’-cell histiocytosis indicates that this disorder is probably a clonal neoplastic disorder with highly variable biologic behavior. Thus, genetic mutations that promote clonal expansion of Langerhans’ cells or their precursors may now be identified. (N Engl J Med 1994; 331:154-60.)

LCH is a clonal disorder
- Some cases of LCH and T-cell ALL may even occur as clonally related diseases with a common pathogenetic background


2.) Inflammatory vs. Neoplasm

Detection of driver mutations
- 50% activating BRAF mutations
- 25% activating MAP2K1 mutations
- 25% RAS-RAF-MEK-ERK pathway mutations


**Treatment**

**Skin-limited LCH**
- Topical steroids, nitrogen mustard, or imiquimod
- Surgical resection of isolated lesions
- Phototherapy
- Systemic methotrexate (20 mg/m² weekly) and 6-mercaptopurine (50 mg/m² per day) → adjusted for myelosuppression

**Single bone lesions**
- Radiation therapy (pelvis and vertebrae) → 90% achieve control of disease
- Intralesional corticosteroids or limited curettage (smaller lesions)

Treatment

Age < 18 years

**Multifocal LCH (low risk)**
- Vinblastine/prednisone for 1 year

**Multifocal LCH (high risk)**
- Vinblastine/prednisone/mercaptopurine for 1 year

LCH-III

Question 2

Borrowing from the pediatric data, evidence appears to support that a similar regimen of vinblastine/prednisone is the most optimal and best tolerated regimen in adult multisystem LCH:

A.) True
B.) False
Treatment

Adults

Multifocal LCH (low or high risk)
- Cytarabine 100 mg/m² daily × 5 days per month × 12 months

## LCH- Adults

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>No. Pts.</th>
<th>No. / Type Bones</th>
<th>Therapy</th>
<th>Remission</th>
<th>Relapse</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6)</td>
<td>19</td>
<td>16</td>
<td>RT 7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surg. 11</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemo 6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2 (7)</td>
<td>84</td>
<td>60</td>
<td>RT Surg</td>
<td>78% of all pts.</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>3 (8)</td>
<td>30</td>
<td>30 40% skull, legs 20%, ribs 13%, spine 10%, pelvis 7% Multiple 10%</td>
<td>Surg, Surg + RT RT RT + Chemo</td>
<td>CR 70% PR 13% Stable 7% Progr. 7%</td>
<td>30% Lower rec. rate with surgery + RT</td>
<td></td>
</tr>
<tr>
<td>4 (9)</td>
<td>47</td>
<td>8</td>
<td>Chemo RT</td>
<td>Not given</td>
<td>Not given</td>
<td></td>
</tr>
<tr>
<td>6 (11)</td>
<td>2</td>
<td>Multifocal</td>
<td>Vlb/pred</td>
<td>1</td>
<td>1</td>
<td>Neurop</td>
</tr>
<tr>
<td>7 (12)</td>
<td>25</td>
<td>25 mandible &amp; maxilla</td>
<td>Surg. &amp; RT</td>
<td>93%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>8 (13)</td>
<td>30</td>
<td>22 spine 8 mfb</td>
<td>Surg. Plus Chemo 12 RT 5</td>
<td>87%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>9 (14)</td>
<td>7</td>
<td>MS 3 MFB 4</td>
<td>MACOP-B</td>
<td>CR 71% PR 29%</td>
<td>43%</td>
<td></td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0043257.t001

LCH- Adults

Retrospective study (Baylor)
- 58 adult patients w/biopsy-proven bone lesions either as solitary site or component of multisystem disease

- Goal to determine optimal chemotherapy:
  - Primary objective: Overall response to
    1.) Vinblastine 6 mg/m2 weekly X6 weeks + prednisone 40 mg/m2 daily X4 weeks then tapered over 2 weeks, if good response → vinblastine every 3 weeks + prednisone X5 days every 3 weeks for 1 year
    2.) 2-CdA (cladribine) 5 mg/m2 daily X5 days every month X6 months
    3.) Ara-C 100 mg/m2 infusion daily X5 days every month X6 months

- Median age 32 (18-72), male 51.7% vs. female 48.3%
- 78% had 1 or 2 bone lesions, 43% had other sites of disease: skin (35%), lung (28%), pituitary (20%), oral (10%), CNS lesions (6%)

LCH- Adults

Median length of follow-up 8.5 years
- 62% had 0 recurrences
- 38% had 1 or more recurrences

Table 6. Response by Type of Chemotherapy.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Number (%) Fail to Respond Or Relapse in 1 yr.</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
<th>Number (%) Grade 3–4 Toxicity</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinblastine/Prednisone</td>
<td>19</td>
<td>16 (94%)</td>
<td>20.3 (4.2–98.2)</td>
<td>&lt;0.001</td>
<td>14 (75%)</td>
<td>6.0 (1.1–32.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>2-CdA 5 mg/m2/d X5 Monthly X 6</td>
<td>22</td>
<td>13 (59%)</td>
<td>5.5 (1.5–20.2)</td>
<td>0.01</td>
<td>8 (37%)</td>
<td>1.2 (0.3–4.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>ARA-C 100 mg/m2/d X5 Monthly X 6</td>
<td>24</td>
<td>5 (21%)</td>
<td>1.0 (ref)</td>
<td></td>
<td>5 (20%)</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
</tbody>
</table>

The following have been shown to be molecular drivers in LCH?
A.) BRAF mutations  
B.) MAP2K1 mutations  
C.) Other RAF-MEK-ERK pathway mutations  
D.) All of the above
- \(BRAF^{V600E}\) + LCH has a higher rate of relapse
- \(BRAF^{V600E}\) in active multisystem LCH, but not in single-system or quiescent disease
- \(BRAF\) and \(MAP2K1\) appear mutually exclusive
- \(ARAF\), \(ALK\), and \(NTRK1\) alterations/fusions

Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation

References