What is a histiocytic disorder?

Histiocytic Disorders

Histiocytoses: a group of disorders due to abnormal accumulation of cells of the mononuclear-phagocytic system

Antigen presenting cells: Effector cells
- Dendritic cells: Monocyte/macrophage

Langerhans Cells

Critical role in immune surveillance
- epidermis (1-2% of epidermal cells)
- orobuccal mucosa
- vaginal mucosa
- respiratory epithelium
- rectal mucosa (small numbers)
Langerhans Cell

CCR7

Reduction of expression of adhesion molecules
Upregulation of MMP - passage across BM

CCl19/CCR7

cytokines

T Cell Area of Nodes/Spleen

LCH skin CD1a x 40
Do LCH cells arise from skin LCs?

- LCH cells likely arise from langerin positive circulating precursor cell

Disorder due to accumulation of cells with immunohistochemical characteristics of Langerhans cells (LCs)

Clinical Langerhans Cell Histiocytosis

Langerhans Cell Histiocytosis

↓

Single system

↓

Multisystem

↓

unifocal

multifocal

↓

low risk

high risk

risk of death

Letterer-Siwe

High risk multisystem infant
Clinical LCH

• Single system — spontaneous regression or good response to Rx

Chronic low grade disease — multiple reactivations
  high incidence of late effects
Multisystem risk organ disease
  life threatening

SS LCH

DAL-HX 83/90 studies n=170
Tiggesmeyer et al, 2001

- unifocal bone  68%
- multifocal bone  19%
- isolated skin  11%
- isolated lymph node  2%
Bone LCH

• Can spontaneously regress
• Can reactivate – once to many times
• Can progress to involve pituitary stalk (diabetes insipidus)

Bone LCH - natural history

Stuurman et al, 2004 
Sickkids study 
n=180 bone LCH

• Single bone – most disappear – healing is slow
  12% reactivated, only 1 Diabetes Insipidus
• SS Multifocal bone – 25% reactivated, some many times
• Bone as part of MS disease – 50% reactivated
  DI > 25%

Bone LCH – teaching points

• Do all first bone lesions need biopsy?
  Yes
  —except if too risky
• Vertebra plana without soft tissue mass?
  Observe carefully without biopsy
  —risk outweighs benefit
• Vertebral body LCH with soft tissue mass?
  *Paraplegia from LCH does occur due to soft tissue compression of cord – do MRI scan!
  *Misdiagnosis of malignancy

Unifocal bone LCH

• No surgical excision!!
• Majority heal after curettage
Bone -LCH

Why treat bone LCH?

• Treat acute problem
• Prevent late effects

DEFINITION OF REACTIV ATION

Reappearance of disease activity after resolution of signs and symptoms

Reappearance of old lesions
Appearance of new lesions

RISK AND TIMING OF FIRST REACTIV ATION

Multisystem LCH--According to Risk Organ involvement at diagnosis

Permanent Consequences after Reactivation

n=18/68, 5-yrs. cumulative incidence=0.32±0.07

Grois et al, 2007

Permanent Consequences after Reactivation

124/134 evaluable

Minkov et al, 2006- LCH data base

How Common is DI in LCH?

<table>
<thead>
<tr>
<th>Series</th>
<th>all pts (n)</th>
<th>DI in all pts (%)</th>
<th>MS-LCH (n)</th>
<th>DI in MS-LCH (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Great Ormond St (Randuri, 2006)</td>
<td>159</td>
<td>22%</td>
<td>108</td>
<td>34%</td>
<td>1/3 had DI @ LCH dx; Cum. risk 26% @ 14 yrs</td>
</tr>
<tr>
<td>Histiocyte Society (Haupt, 2004)</td>
<td>589</td>
<td>24%</td>
<td>108</td>
<td>40%</td>
<td>1/3 had DI @ LCH dx</td>
</tr>
<tr>
<td>French LCH SG (Donadieu, 2004)</td>
<td>1,741</td>
<td>15%</td>
<td>520</td>
<td>25%</td>
<td>1/3 had DI @ LCH dx; 20% risk @ 15 yrs</td>
</tr>
</tbody>
</table>

* Clin Endo 53:509; † PBC 42:438; ‡ J Pediatr 144:344; § PBC 46:228

| Series | all pts (n) | DI in all pts (%) | MS-LCH (n) | DI in MS-LCH (%) | Comments |

11 (9%) Endocrinopathies
17 (19%) Growth failure* 
24 (2%) CNS
115 10 (9%) 3.8 y
112 15 (13%) 2.8 y
114 7 (6%) 6.7 y
120 1 (1%) 1.9 y
119 4 (3%) 2.3 y
122 5 (4%) 1.5 y
119 2 (2%) 37d, 9mo
119 1 (1%) 1.2 y
124 1 (1%) 3.1 y
122 3 (2%) 2.5 y
121 0 (0%) -

median observation time 3 years (4mo-18y)

*growth hormone deficiency **median time from first reactivation
Risk of neurodegenerative LCH among the 589 patients, according to pituitary involvement.

**CNS Mass Lesions in LCH**

- Hypothalamus
- Meninges
- Choroid plexus
- Pineal Gland

**Neurologic and Cognitive Symptoms in LCH - neurodegeneration**

- Tremor
- Headaches
- Gait disturbances, ataxia
- Dysarthria, dysmetria
- Visual disturbances
- Cognitive problems
- Behavioral disturbances, psychosis


**T2-weighted axial image demonstrating a hyperintense of the dentate nucleus (black arrow) and the surrounding white matter (white arrow).**

**Bone LCH**

Can we prevent reactivations? Are they an inevitable part of the natural history and nothing we can do will prevent them?

LCH data base:
- MS LCH –53% LCH and 61% LCH-II (6 months)
- DAL-Hx studies—12 mo and 5 drugs  RR 27%
- LCH-II MFB:
  - local Rx MonoRx 2 drug DAL
  - React Rate 52% 45% 20% 10%
- LCH-III Low risk MS 6 mo vs 12 mo React Rate 44% 34%
- LCH-III high risk all 12 mo react rate 30% vs historical 50%

**If we decrease reactivations will that decrease late effects?**

- Can we prevent progression to DI and CNS-LCH?

Historically DI 25-50% more recent 7-20% (Gross N, 2006)
- DAL-Hx studies DI 10% when therapy promptly instituted

Historical comparisons – data from prospective trials are needed
- LCH-III
- LCH-IV
LCH teaching points

• Reactivations in risk bones need therapy

• Recent onset of DI should be treated as a reactivation
  -path = active LCH
  -warning sign of potentially disabling late CNS effects

• Chronic low toxicity therapy for chronic low grade disease?

Skin LCH

1/3 to 1/2 of patients with LCH
10% - skin is only affected site
Any area of skin including nails
Scalp>skin flexures>other
Any age, newborn to 70 years
70% <17 years of age

Langerhans Cell Histiocytosis - skin

Skin LCH - teaching points

• Seborrheic dermatitis that does not respond or keeps recurring

• Diaper dermatitis that does not respond or keeps recurring

Think LCH
**Natural history skin-only LCH**

Skin-only LCH in the young child may:

- Spontaneously disappear
- Progress to multisystem even fatal disease

_Lau et al, 2006_ Sickkids study n=13 infants <12mo

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**Skin-only LCH-teaching point**

All patients with skin-only LCH need careful observation

Some will come and go and then spontaneously disappear

Some will progress in weeks to months to life-threatening disease

Some, usually <2 years old will die from disease

_Self Healing LC Histiocytosis should only be diagnosed after a few years of observation_
Multisystem LCH

Skin, Bone, Lymph nodes
Lung
Liver*, spleen*
Hematopoetic*
GI
CNS
Endocrine

May be associated with secondary HLH which may need to be treated separately

Survival (RO+)

Reduction of mortality in MS

40% LCH I
20% LCH III

Possible reasons:
► second course initial tx
► earlier + effective salvage tx
► better supportive care

MS-LCH—better survival

- Early introduction of salvage therapy for poor responders
- Better salvage therapy

2-CdA/Ara-C combination LCH-S-2005
Clofarabine
Rodriguez-Galindo 2011
LCH-salvage

• If fail salvage protocol – mortality is very high

• Only survivors in LCH-S-98 study underwent allogeneic SCT

Risk of Treatment-related Mortality by day +100 after Myeloablative Preparative Regimen

Hypotheses for LCH-SCT

1. Allogeneic hematopoietic stem cell transplant (SCT) can salvage high risk LCH patients refractory to available chemotherapy approaches

2. Reduced intensity conditioning (RIC) regimen will allow SCT in heavily pretreated patients with acceptable transplant related mortality

Non-myeloablative/Reduced Intensity Conditioning Transplant in LCH

• Nine patients
  • 2/9 (22%) treatment-related mortality by day +100
  • 7/9 (78%) alive without LCH
    • One patient with recipient cells

Conclusions: Single system LCH

• Single system unifocal disease should not be overtreated

• Multifocal bone and low risk MS LCH--treat to try to prevent late effects

• 12 months therapy reduces reactivations by 10% but still >30% reactivate --? 24 months will be better?

Conclusions: “Risk” LCH

• Prolong induction therapy for partial responders

• Early switch of poor responders to salvage Rx

• Then treat to try to prevent late effects (12 or 24 months?)
We have learned a lot

We have a lot more to learn!!

References LCH I, LCH II, DAL-HX

- LCH-III -in press