Erdheim Chester Disease 2017

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Erdheim-Chester Disease

- Described as “Lipid Granulomatosis” by Jakob Erdheim and William Chester in 1930
  - Lipid-laden macrophages and Touton giant cells
  - CD 68+, FXIII+, CD1a-, S-100-
Erdheim-Chester Disease

- Xanthogranulomas with bony lesions
  - "Radio-pathologic" diagnosis
ECD Epidemiology

- Median age of onset: 53 yo
  - Range 7-84 years
- Equal male:female incidence
- Fewer than 1000 cases to date
- No known familial incidence
- No known infectious or exposure association
Common ECD Symptoms

- Bone pain
- Fatigue
- Neurologic
  - Loss of balance
  - Change in personality
  - Decreased alertness
- Shortness of breath
- Increased thirst and urination
- Abdominal pain
- Rash
- Bulging eyes

Estrada-Veras et al Blood Adv 1:357, 2017
Organ Systems Affected by ECD

- Large arteries
- Bones
- Kidneys
- Heart and Heart Lining
- Skin
- Brain
- Lungs
- Endocrine

ECD Clinical Challenges

• ECD can affect one system or many
  – Patients may go to a specialist who does not recognize that symptoms outside their interest are part of the ECD constellation

• By the time symptoms arise, the disease is often advanced

• There is no simple diagnostic test

• Since it is a rare disease, it is not an early diagnostic consideration
What is ECD?

• Previously considered an inflammatory or possibly autoimmune disease

• Now known that ECD is caused by acquired mutations in cells that become “histiocytes.”
  – Blood cell cancers
    • Myeloproliferative neoplasm
What is a “histiocyte?”
What is a “histiocyte?”

- Normal histiocytes help people to develop an immune response to infection.
What goes wrong in ECD?

Hematopoietic Cascade

Mutation
The mutation causes the histiocytes to grow without the normal controls. The mutated histiocytes retain some normal characteristics and attract other immune cells.

Paul Milne et al. Blood 2017;130:167-175
ECD Mutations

BRAF  
NRAS  
MAP2K
ECD Mutations

MAPK Pathway: normal activation of MAPK via extracellular factors.

Mutations in MAPK cause ECD

RAS-GTP (activated MAPK)

BRAF V600

MEK

ERK

BRAF V600E inhibitors, such as Dabrafenib and Vemurafenib, selectively bind to mutated BRAF V600 decreasing cell proliferation and survival.

MEK inhibitors such as Trametinib inhibit downstream MEK decreasing cell proliferation and survival.

Normal Cell Proliferation and Survival.
Significance of ECD Mutations

• BRAF mutations had been previously seen in other cancers (e.g. melanoma, thyroid, lung, Langerhans cell histiocytosis etc.)
  – BRAF inhibitory drugs had been previously tested

• Confirmed that ECD belonged in the “cancer family

• Allowed the biology of the disease to be better understood.
ECD Classification

- Association between ECD and Langerhans cell histiocytosis
  - Patients with both rare histiocytoses
  - LCH usually preceded ECD

- ECD also seen in patients with other “monocytic” cancers

Jean-François Emile et al. Blood 2016;127:2672-2681
Histiocytic diseases are more commonly associated with other blood cancers

Matthias Papo et al. Blood 2017;130:1007-1013
ECD Treatment-Interferon

- CNS involvement is associated with worse prognosis

Arnaud et al Blood 117:2778, 2011
ECD-Vemurafenib

8 patients with interferon-refractory ECD
  – 100% response by 6 months
  – Durable up to 16 months

Response of ECD and LCH to Vemurafenib

<table>
<thead>
<tr>
<th>Variable</th>
<th>NSCLC (N=20)</th>
<th>Colorectal Cancer</th>
<th>Cholangiocarcinoma (N=27)</th>
<th>ECD or LCH (N=18)</th>
<th>Anaplastic Thyroid Cancer (N=7)</th>
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<tr>
<td></td>
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<tr>
<td>Patients with ≥1 postbaseline assessment — no.</td>
<td>19</td>
<td>10</td>
<td>26</td>
<td>8</td>
<td>14</td>
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<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
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<tr>
<td>Partial response — no. (%)</td>
<td>8 (42)</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (12)</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Stable disease — no. (%)</td>
<td>8 (42)</td>
<td>5 (50)</td>
<td>18 (69)</td>
<td>4 (50)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>2 (11)</td>
<td>5 (50)</td>
<td>7 (27)</td>
<td>3 (38)</td>
<td>0</td>
</tr>
<tr>
<td>Missing data — no. (%) †</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall response — no. (%) [95% CI]</td>
<td>8 (42) [20–67]</td>
<td>0</td>
<td>1 (4) [1–20]</td>
<td>1 (12) [1–53]</td>
<td>6 (43) [18–71]</td>
</tr>
</tbody>
</table>

Other Therapies in ECD

“Conventional” Chemotherapies

– Cladribine (Goyal et al. JAMA Oncol. 3:1253, 2017)
– Cytarabine (Cao et al. Ann Hematol epub ahead of print)
– Zoledronate (Poiroux et al. Joint Bone Spine 83: 573, 2016)
Other Therapies in ECD

“Anti-Inflammatory” Agents


Other Therapies in ECD

“Targeted” Agents (beyond BRAF inhibitors)


Proposed Therapeutic Approach to ECD

[Diagram showing the proposed therapeutic approach to ECD.

1. Diagnosis of ECD
   - BRAF mutation testing*
     - BRAF V600E
       - Mild disease severity
         - IFN-α or other conventional therapy
           - Response
             - Continue treatment
           - Refractory
             - Consider vemurafenib
         - Refractory
           - Continue treatment
     - Moderate/severe disease
       - Vemurafenib
         - Response
           - Continue treatment
         - Refractory
           - Consider other therapies (e.g., cobimetinib, mTOR inhibitors, anticytokine therapies)
   - BRAF wild-type/not available
     - IFN-α or other conventional therapy
       - Response
         - Continue treatment
       - Refractory
         - Consider other therapies (e.g., cobimetinib, mTOR inhibitors, anticytokine therapies)

* BRAF mutation testing is the first step in the proposed therapeutic approach.

Augusto Vaglio, and Eli L. Diamond Blood 2017;130:1282-1284

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# Proposed Therapeutic Approach to ECD

## Table 2: Treatment recommendations for patients with Erdheim-Chester disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td>Interferon alfa or pegylated interferon alfa</td>
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<td>Best choice as front-line treatment of Erdheim-Chester disease; tolerance issues observed (fatigue, depression); pegylated form is better tolerated; this treatment is a major independent predictor of survival in Erdheim-Chester disease; higher doses (9 million units given three times per week) recommended in cases with meningeal infiltration, subcortical and retrostellar masses, and pericardial and pseudo-atrial infiltration</td>
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<td><strong>Second-line therapy</strong></td>
<td>Vemurafenib and other BRAF inhibitors</td>
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<td>(or first-line therapy for life-threatening manifestations)</td>
<td>Most impressive treatment responses seen if BRAF&lt;sup&gt;exon2&lt;/sup&gt; mutation is present (in 57-70% of patients) in multisystemic and refractory Erdheim-Chester disease despite interferon alfa therapy (eg, CNS and cardiovascular complications of Erdheim-Chester disease); safety issues (in particular, development of squamous-cell carcinoma); informed and signed consent mandatory; optimal length of treatment to be determined in future studies; and in particular with the LOVE trial (NCT02089724); less effective in neurodegenerative Erdheim-Chester disease; vemurafenib accessible through the basket trial (NCT01524978) in the USA and the AcSé trial in France (NCT02304809)</td>
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<td>Cobimetinib and other MEK inhibitors alone or in combination</td>
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<td>(or first-line therapy for life-threatening manifestations)</td>
<td>MEK inhibitors seem promising (perhaps even more so than BRAF inhibitors) in patients with wild-type BRAF; combination therapy (anti-BRAF plus anti-MEK) seems efficacious, a trial of combination therapy with trametinib plus dabrafenib (NCT02281760) is ongoing in the USA; the cobimetinib trial (NCT02649972) initiated for patients with wild-type BRAF or BRAF&lt;sup&gt;del&lt;/sup&gt; who are unable to take a BRAF inhibitor or have previously received treatment with a BRAF inhibitor that was discontinued because of intolerable side-effects or toxicity before disease progression is ongoing</td>
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<td>Steroids</td>
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<td>Usually not effective in Erdheim-Chester disease, except in severe exophthalmos or macrophage activation syndrome</td>
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<td>Anakinra</td>
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<td>Effective in mild Erdheim-Chester disease (bone pain, high concentrations of C-reactive protein); disappointing responses in severe cases with CNS and heart complications (eg, cardiac tamponade occurring with therapy)</td>
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<td>Double autologous stem cell transplantation</td>
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<td>Anecdotal efficacy was reported in 3 of 3 patients with Erdheim-Chester disease, but no improvement was seen in 2 of 3 patients&lt;sup&gt;77&lt;/sup&gt;</td>
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<td>Gadbirubine</td>
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<td>Potential benefit observed in treatment of Erdheim-Chester disease with CNS involvement refractory to interferon alfa,&lt;sup&gt;78&lt;/sup&gt; but unfavourable outcomes observed in unpublished small-scale studies at Pitie-Salpetriere Hospital</td>
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<td>Infliximab</td>
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<td>Beneficial after 12-18 months in 2 of 2 patients with Erdheim-Chester disease with cardiac involvement; efficacy needs to be studied further&lt;sup&gt;79&lt;/sup&gt;</td>
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<tr>
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<td>Imatinib</td>
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<td>Effective in three histiocytosis cases, but discouraging results seen in 6 of 6 patients with Erdheim-Chester disease in another study&lt;sup&gt;80&lt;/sup&gt;</td>
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<td>Sirolimus</td>
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<td>Objective responses or disease stabilisation seen when combined with prednisone&lt;sup&gt;81&lt;/sup&gt;</td>
</tr>
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*Haroche et al. Lancet Oncol 2017;18:e113-e125*
Challenges in ECD for 2018

• Nomenclature and classification
  – Underlying biology
• Treatment
  – Paucity of patients prevents the establishment of standard treatments

• Need for participation in the registry!!!
  – Heterogeneity of diseases hinders the development and recognition of effective therapy
The Promise of the Future

ECD Publications by Year
Mechanisms of accumulation of LCH pathogenic DCs through proliferation and prolonged survival.

Christine Delprat, and Maurizio Aricò Blood 2014;124:867-872
Major cell, cytokine, and protease players in LCH lesion.
Histioctyosis response to other targeted agents

Diamond et al Cancer Discov 6:154, 2015