RIDDLE WRAPPED UP IN A MYSTERY:
MAPing the Future of Erdheim-Chester Disease

Tejaswini Dhawale, M.D., Senior Fellow, Hematology & Oncology
Paul C. Hendrie, M.D., Ph.D., Clinical Associate Professor, Hematology

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NO DISCLOSURES

Image: https://openclipart.org/user-detail/centroacademico
OBJECTIVES

- Describe the approach to a diagnostically challenging case
- Review recent insights into the pathophysiology of this case
- Discuss treatment options
- What the future holds for ECD
"The world is full of obvious things which nobody by any chance ever observes."

Sherlock Holmes
-The Hound of the Baskervilles
Chapter 3: "The Problem"
CASE PRESENTATION:

- **Winter 2014**
  - Onset of edema and dyspnea.

- **January 2015**
  - Develops pleural and pericardial effusion.
  - Bone marrow biopsy and retroperitoneal biopsy.
  - Rapid symptomatic relief on **prednisone 80 mg** daily.

- **February 2015**
  - Diagnosed with idiopathic retroperitoneal fibrosis.
  - Starts **cellcept** and a steroid taper.

- **April 2015**
  - Off of oxygen. Feeling well.

- **May 2015**
  - **Warfarin** initiated for thrombosed IVC.

- **August 2015**
  - Suffers GI bleed.
  - Develops atrial fibrillation.
  - Gets progressively worse.

- **September 2015**
  - Intubated for respiratory failure, transferred to Harborview.

Notice anything unusual?
HISTORY CONTINUED

- PMH:
  - Coronary Artery Disease
  - HTN
  - Diabetes Mellitus
  - Atrial Fibrillation* recent diagnosis
  - Diverticulosis

- Family History:
  - Mother – colon cancer
  - Father alive, age 92
  - Sisters – healthy, alive
  - Brothers – deceased, accidental

- Social History
  - Prior exposure to pesticides. Runs a trucking company.

- Medications:
  - Atorvastatin 40 daily
  - Clopidogrel 75 mg daily
  - Diltiazem 360 mg daily
  - Lasix 20 mg daily
  - Metformin 500 daily
  - Metoprolol 25 mg daily
  - MMF 500 mg po BID
  - Prednisone 25 mg po daily
  - Ranitidine 150 mg po BID
  - Bactrim 1 tab Q MWF
  - Warfarin 5 mg po daily

Image: http://630thefan.com; classic.als.net
PHYSICAL EXAM

- VITAL SIGNS: His temperature is 36.5, blood pressure 129/72, heart rate is 88, weight 81.9.8 kg, respiratory rate is 18. Oxygen saturation 92%

- Decreased breath sounds bilaterally up to ~T10

- Dry scaly 1.2 cm scalp lesion
- Moon facies
- Irregularly irregular heart sounds, no rub
- Skin: multiple patchy areas of ecchymoses
- No HSM
- Compression stockings

**ROS**: no fever, no neuropathy, + edema + DOE + right hip pain
INITIAL DIAGNOSTIC WORKUP

- Infectious workup: negative for bacterial, viral, fungal, TB infection
  
- Immune:
  - Ferritin 58
  - ESR 23
  - CRP 79.9
  - C3 normal 103
  - IgG subclasses normal

- Hematologic
  - Absolute retic 67
  - Reticulocyte percentage 1.6%
  - TIBC 277
  - Transferrin 13
  - SPEP negative

- Rheumatologic
  - ANA negative
  - Anti cardiolipin antibodies negative
  - Anti beta 2 neg

Peripheral blood rare atypical monocyte, 100x

Image courtesy of Yi Zhou and Emily Glynn
- **Peripheral blood:**
  - Leukocytosis with mature neutrophils, rare hypogranular neutrophils with hypolobated nuclei
  - Persistent Monocytosis

- **Bone Marrow Biopsy**
  - Cytogenetics: normal
  - Molecular: BCR-Abl FISH negative, JAK2, MPL, CALR mutation negative
  - Summary: Suggestive of *chronic myelomonocytic leukemia*

- **Retroperitoneal Fine Needle Aspiration**
  - Fibrolastic proliferation with fibrosis and scattered lymphocyte infiltrate.
NM Bone Scan

- Focal uptake in the proximal humeri bilaterally
- Focal uptake in the left femoral head
- Increased bilateral knee uptake (R>L)
- Heterogenous uptake within the right mid and distal femur
SUMMARY OF CLUES:

- Recurrent pericardial effusions
- Recurrent pleural effusions
- Retroperitoneal fibrosis
- Monocytosis (CMML ?!)
- Elevated CRP
- Abnormal bone scan – uptake in bilateral humeri, lower extremities

DIFFERENTIAL DIAGNOSIS

- Erdheim Chester Disease
- Idiopathic retroperitoneal fibrosis
- IgG4 related disease
- Tuberculosis
- Whipple’s disease
- Coccidiomycosis

Image: http://cityofpasadena.net
'How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?'

Sherlock Holmes Quote
-The Sign of Four
ERDHEIM CHESTER DISEASE
NON-LANGERHANS HISTIOCYTOSIS

History
- First described in 1930 as “lipoid granulomatosis”
- Inflammatory vs neoplastic process

Epidemiology
- Extremely rare ~ 650 cases reported in the literature
- M>F predominance
- Mean age of onset 55 (40-70 yrs)

Image: http://static-content.springer.com

Jakob Erdheim M.D
ERDHEIM CHESTER DISEASE
NON-LANGERHANS HISTIOCYTOSIS

www.histio.org
CLINICAL FEATURES

A multisystem disorder with prognosis dependent on disease severity.

A Clinical Findings

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<th>Condition</th>
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<td>Diabetes insipidus</td>
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B Radiographic Abnormalities

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<th>Abnormality</th>
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<tbody>
<tr>
<td>Osteosclerosis in femurs and tibia</td>
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<td>Perinephric stranding (&quot;hairy kidney&quot;)</td>
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<td>Lung parenchyma</td>
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<td>Pericardial thickening or effusion</td>
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<td>Retroperitoneal fibrosis-like infiltrate</td>
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<td>Infiltration of entire thoracoabdominal aorta (&quot;coated aorta&quot;)</td>
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DIAGNOSTIC PEARLS:

Symmetric diaphyseal and metaphysial osteoclerosis
- 96% of patients

“Hairy Kidney”
- Iconic radiographic finding

Tissue Biopsy *key*
- Foamy or lipid-laden histiocytes
- Surrounding fibrosis
- IHC:
  - Positive: CD68+, CD163+, FXIIIa+, and fascin+
  - Negative for S100, CD1a, Langerin and Birbeck granules
  - Ki-67 usually very low/undetectable

LANDMARK DISCOVERY

- 2002: **BRAF** V600E discovered in melanoma
- 2010 – **BRAF** V600E found in 57% of archived LCH lesions (Badalian-Very)
- Recurrent **BRAF** V600E mutation >50% of ECD patients (Haroche)
- ECD is a clonal disorder

CASE PRESENTATION CONTINUED

Clues to a diagnosis:

- Recurrent pericardial effusions
- Recurrent pleural effusions
- Retroperitoneal fibrosis
- Monocytosis (CMML *)
- Elevated CRP
- Abnormal bone scan – uptake in bilateral humeri, lower extremities

NEXT STEPS:

1. Obtain tissue diagnosis
2. Pursue molecular testing

Image: http://cityofpasadena.net
Image courtesy of Yi Zhou and Emily Glynn
**MOLECULAR FINDINGS**

- **Oncoplex**
  - **Identical results**: Peripheral blood & pleural tissue
    - *BRAF* V600E
  - *TET2* x 2 (p.L957Yfs*50 and an insertion in exon 3)
  - *SRSF2*
  - The pericardial tissue did not have the *SRSF2* mutation
    - Only 5 reads in this position, could be false negative

Image courtesy of David Wu
URINE CELL-FREE DNA CONFIRMS BRAFV600E

Prospective Blinded Study of BRAFV600E Mutation Detection in Cell-Free DNA of Patients with Systemic Histiocytic Disorders

Hyman et al, Cancer Discovery 2015
BRAF IN CMML

- Commonly mutated genes in CMML include
  - genes encoding epigenetic modifiers (eg, ASXL1, TET2, EZH2)
  - regulators of alternative mRNA splicing (eg, SRSF2, ZRSF2)
  - transcription factors (eg, RUNX1)
  - cytokine signaling (eg, NRAS, JAK2, CBL)

- BRAF mutations found in 12% of CMML patients with wild-type RAS

ECD + CMML: A COMMON MYEOID PRECURSOR?

Shahlaee et al Histiocyte Disorders, Pediatric Hematology 2006
OBJECTIVES

- Describe the approach to a diagnostically challenging case
- Review recent insights into the pathophysiology of ECD
- Discuss treatment options for ECD
- Explore future considerations for research in this rare disease
'It is a capital mistake to theorize before one has data. Insensibility one begins to twist facts to suit theories, instead of theories to suit facts.'

Sherlock Holmes Quote
-A Scandal in Bohemia
ECD: AN INFLAMMATORY CONDITION

- Inflammatory milieu

- Proinflammatory Cytokines
  - TNF-α, INFγ, IL-12, IL-6, RANKL, Monocyte chemotactic protein-1
  - Decreased IL-4 and IL-7

- Elevated IL-6 → osteoclast differentiation and bone resorption

- Clinical response to INF-α, anakinra, etc

Cavalli et al (2014) Frontiers in Immunology, 5, 1-6
ECD: A CLONAL DISORDER

Recurrent somatic mutations of the MAP kinase and AKT pathways

- **BRAFV600E** 38%-100% of ECD
- **NRAS** 4% of ECD (WT BRAF)
- **PI3KCA** mutations in 11% of ECD patients (WT BRAF)
- Additional mutations by WES
  - **MAP2K1**
  - **ARAF**

'Come, Watson, come!' he cried. 'The game is afoot. Not a word! Into your clothes and come!'  

Sherlock Holmes Quote  

- The Adventure of the The Abbey Grange
OBJECTIVES

- Describe the approach to a diagnostically challenging case
- Review recent insights into the pathophysiology of ECD
- Discuss treatment options for ECD
- Explore future considerations for research in this rare disease
TREATMENT : A NEW ERA

- Paucity of prospective studies, limited data
- First line: Interferon $\alpha$-2a or pegylated interferon-$\alpha$
- 2015
  - Vemurafenib (Phase 2, NEJM, August 2015)
  - Sirolimus and Prednisone (Blood, September 2015)

Hyman et al. NEJM, August 2015
TREATMENT

1. MEK1 mutations
2. NRAS mutations
3. COT overexpression
4. BRAF amplification/splicing
5. RTKs overexpression/splicing (PDGFRβ, IGR1F)


## CLINICAL TRIALS

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<th>Recruiting</th>
<th>Study Title</th>
<th>Condition</th>
<th>Intervention</th>
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<td>1</td>
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<td>Long-term Outcome After Vemurafenib / BRAF Inhibitors Interruption in Erdheim-chester Disease</td>
<td>Erdheim-Chester Disease</td>
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<td>Clinical and Basic Investigations Into Erdheim Chester Disease</td>
<td>Myelofibrosis; Gaucher Disease; Pulmonary Fibrosis; Hermansky-Pudlak Syndrome (HPS); Cancer</td>
<td>Intervention:</td>
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<td>3</td>
<td>Recruiting</td>
<td>Dabrafenib and Trametinib in People With BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease</td>
<td>BRAF V600E Mutation</td>
<td>Drug: Dabrafenib Mesylate; Drug: Trametinib Dimethyl Sulfoxide</td>
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<td>4</td>
<td>Recruiting</td>
<td>A Study of Lenalidomide for Adult Histiocyte Disorders</td>
<td>Langerhans Cell Histiocytosis (LCH); Histiocytoses Erdheim-chester Disease; Histiocytic Sarcoma (HS)</td>
<td>Drug: Lenalidomide</td>
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Clinicaltrials.gov
CASE PRESENTATION

- Day 1: Admit to Harborview
- Day 2: MICU → Anakinra
- Day 4: s/p VATs pericardial window
- Day 4: post-op remains intubated
- Day 11: Tocilizumab 8 mg/kg x 1
- Day 14: Vemurafenib po BID
- Day 16: Extubated
- Day 20: Code Blue
“Education never ends, Watson. It is a series of lessons, with the greatest for the last.”

— Arthur Conan Doyle, His Last Bow: 8 Stories
MAPPING THE FUTURE OF ECD

- Increased research funding (LLS)
- Increased diagnostic accuracy
- Increased therapeutic options and efficacy
  - MAP kinase pathway inhibitors
  - Checkpoint blockade
  - Clinical trials
ECD GLOBAL ALLIANCE
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- Dr. Isabel Rostain
- Dr. Jonathan Sham
- Dr. Mark Wurfel
- Dr. Alison Bays
- Dr. Gordon Starkebaum
- Countless others

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- Kathleen Brewer
- ECD Global Alliance
- Dr. Eli Diamond
- Dr. Juvianee Estrada-Veras
- Dr. Paul Hendrie
- My patients
- My patients’ families
- Meera