Increasing Abdominal Distension and Ascites in a 29-year-old female

LASOP Annual Resident/Fellow Symposium

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Clinical History

- **Pt:** 29-year-old Caucasian female
- **CC:** Abdominal enlargement
- **PSH:** Umbilical hernia repair (2012)
  Hiatal hernia repair (2011)
  Cholecystectomy (2011)
  Cesarean section (2010)
<table>
<thead>
<tr>
<th>Laboratory Studies</th>
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<tbody>
<tr>
<td><strong>CBC</strong></td>
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<tr>
<td>• WBC: 18.2 H</td>
</tr>
<tr>
<td>• Hb: 10.1 L</td>
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<tr>
<td>• HCT: 31.1 L</td>
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<td>• PLT: 174</td>
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<tr>
<td><strong>COAG</strong></td>
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<td>• INR: 1.1</td>
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<td>• PT: 12.7 H</td>
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Physical Examination

- Decreased/altered mental status
- Marked abdominal distension & ascites
- Progressive abdominal pain
Exploratory Laparotomy

- Surgery operative note described:
  
  “an extensive process resembling severe fibromatosis versus carcinomatosis”

- Marked inflammation surrounding the appendix and right ovary; therefore the patient underwent appendectomy and right oophorectomy.

- Multiple biopsies were taken of the peritoneum, omentum, and hernia sac.
Peritoneum
CD163
Peritoneum
IHC Summary

Positive for:
• CD68
• CD163

Negative for:
• CD3
• CD20
• CD21
• CD23
• CD35
• CD34
• CD117
• CD138
• CD1a
• S100
• Langerin
• ALK
• β-catenin
• IgG4
• Ki-67
Final Diagnoses

• Appendix
  – Luminal obliteration with non-specific fibrohistiocytic inflammation

• Omentum
  – Non-specific fibrohistiocytic inflammation

• Peritoneum
  – Suspicious for “Juvenile” Xanthogranuloma
Postoperative Course

- **Bilateral hydronephrosis**
  - bilateral ureteral stent placement (failed)
  - bilateral nephrostomy tube placement

- **Renal failure**
  - started on hemodialysis

- **Large bowel obstruction**
  - partial colectomy and colostomy
Clinical History, cont.

• PMH: Hypothyroidism (2010)
  Central diabetes insipidus (2010)
  Esophageal strictures (2006)
  - “required multiple dilations”

• MEDS: Synthroid
  DDAVP
Abdominal CT: view of IVC and right atrium
Transthoracic Echocardiogram (TTE)

Cardiac CT
Cardiac Mass

FXIIIa
Final Clinicopathologic Diagnosis

Non-Langerhans cell histiocytosis, most consistent with disseminated juvenile xanthogranulomatosis/Erdheim-Chester disease
Erdheim and Chester

Jakob Erdheim
- Austrian pathologist
- Lived 1874-1937

William Chester
- American pathologist
- Erdheim’s pupil

Described “Über Lipoidgranulomatose” (1930)
The term “ECD” first used by Elaine Jaffe (1972)
Histiocytic & Dendritic Cell Neoplasms (2008 WHO Classification):

- Histiocytic sarcoma
- Tumours derived from Langerhans cells
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Other rare dendritic cell tumours
- Disseminated juvenile xanthogranuloma
Histiocytic/Dendritic Cells

- S100 +
  - CD1a+
    - Langerhans cells
    - Birbeck granules
    - Langerin+
  - CD1a-
    - IDC
      - Complex cytoplasmic processes
      - T-cell areas

- S100 -
  - CD21/23/35+
    - Mesenchymal stem cell
    - FDC
      - Desmosomes
      - B-cell areas
  - CD21/23/35-
    - Myeloid stem cell
    - Histiocytes
      - CD68+
      - CD163+
Histiocytic/Dendritic Cells

- S100 +
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- S100 -
  - Mesenchymal stem cell
  - Myeloid stem cell

- CD21/23/35+
  - FDC
  - Desmosomes
  - B-cell areas
  - CD68+
  - CD163+
  - CD123+
  - Histiocytes
  - PDC

- CD21/23/35-
  - Histiocytes
Disseminated Juvenile Xanthogranulomatosis

**DEFINITION**

- Characterized by a proliferation of histiocytes similar to those of the dermal JXG
- Commonly have a foamy (xanthomatous) component with Touton-type giant cells (xanthogranulomatous)
Disseminated Juvenile Xanthogranulomatosis

MORPHOLOGY

• The JXG cell = small, oval, slightly spindled with a bland, round to oval nucleus (without grooves) and pink cytoplasm

• Touton cells less common at non-dermal sites

• The cells become progressively lipidized (xanthomatous)

• EM = Histiocytic, w/o distinguishing features
Disseminated Juvenile Xanthogranulomatosis

IMMUNOPHENOTYPE

- Vimentin
- CD14
- CD68 (coarse granularity)
- CD163 (surface, cytoplasmic)
- Stabilin-1
- Factor XIIla
- Fascin (cytoplasm)
- S100
Disseminated Juvenile Xanthogranulomatosis

Adult Variant: Erdheim-Chester disease

- Later onset
- Retroperitoneal and periaortic involvement is common
- Concomitant macrophage activation syndrome can lead to:
  - cytopenias, liver damage and death

- Cumulative cohort of 259 cases (10 new cases)
- Most common signs & symptoms
- Noted differences in different age groups
Clinical presentation

Bone pain (26%)

Neurological symptoms (23%)
(exophtalmos; gaze disturbances; gait ataxia)

Diabetes Insipidus (22%)

 Constitutional symptoms (20%)

Retroperitoneal involvement (14%)
(renal failure; nephrovascular hypertension; hydronephrosis)

Pulmonary symptoms (12%)
(dyspnea)

Cutaneous involvement (11%)
(xanthoma; xanthelasma)

Cardiovascular involvement (6%)
(pericardial effusion)

Palpable mass (5%)

Hypogonadism, panhypopituitarism (3%)

Bilateral and symmetric cortical sclerosis
Bone Scintigraphy
• Most overlooked and misdiagnosed presentation
• Median diagnostic delay of 5 years.
Note:
- In 30% overall
- In 14% at presentation
- Frequently misdiagnosed as idiopathic retroperitoneal fibrosis.
Renal Involvement
Note:
- Independent predictors of poor prognosis and death
Cardiovascular Involvement

- Analyzed 127 cases of histiocytoses:
  - LCH, ECD, JXG, Rosai-Dorfman, HS, IDCS

- Positive in ECD (54%) and LCH (38%)

- The high frequency of BRAF V600E mutations in ECD and LCH suggests a common origin
BRAF V600E mutation

Described in various malignancies:

- Melanoma
- Colorectal cancer
- Thyroid carcinoma
- Hairy cell leukemia
- Histiocytoses (50%)
  - ECD
  - LCH

B-Raf is a member of the Raf kinase family of growth signal transduction protein kinases.

This protein plays a role in regulating the MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.
Missense substitution of valine by glutamic acid.

High Resolution Melt (HRM) Analysis

Wild-type control

Patient

V600E positive control

BRAF exon 15 c.1799T>A, V600E
Missense substitution of valine by glutamic acid.
A mouse monoclonal antibody specific for the BRAF V600E mutant

Cytoplasmic stain
Vemurafenib

• aka: Zelboraf, PLX4032

• Stands for “V600E mutated BRAF inhibition”

• Inhibitor of mutated BRAF

• Vemurafenib interrupts the B-Raf/MEK step on the B-Raf/MEK/ERK pathway

• FDA-approved for treatment of late-stage melanoma
Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation

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• 3 patients with multisystemic & refractory ECD
  – One patient had both ECD and LCH

• All patients had BRAF V600E mutation

• Treatment induced dramatic response
Erdheim-Chester Disease Therapy

BRAF +
- Vemurafenib

BRAF -
- Steroids
- Cladribine
- IFN-α
- Tyrosine kinase inhibitors
- Anakinra
Rationale and efficacy of interleukin-1 targeting in Erdheim–Chester disease

Achille Aouba,1,2 Sophie Georigin-Lavialle,2 Christian Pagnoux,1 Nicolas Martin Silva,3 Amédée Renand,2 Françoise Galateau-Salle,4 Sophie Le Toquin,3 Henri Bensadoun,5 Frederique Larousserie,6 Stéphane Silvera,7 Nicole Provost,8 Sophie Candon,9 Raphaèle Seror,1 Mathilde de Menthon,1 Olivier Hermine,2 Loïc Guillemin,1 and Boris Bienvenu3


- IL-1 network appears over-stimulated in ECD.
- IL-1 receptor antagonist synthesis is naturally induced after stimulation of IFN-α
- Recombinant IL-1 receptor antagonist
Clinical Follow-up

- Excellent response to Anakinra (Kineret)
- Regressed retroperitoneal fibrosis with resolution of ureteral obstruction, hydronephrosis and renal failure
- Regressed omental/peritoneal fibrosis with resolution of bowel obstruction
Unique Features of Present Case

• How is this case unusual?
  – Adult onset in absence of bony lesions
  – Cardiac and retroperitoneal involvement (<40 yo)
  – Aggressive dissemination within abdominal cavity
Summary

- ECD is a rare, systemic inflammatory disease of unknown etiology
- Characterized by multi-organ infiltration by CD68+ (CD1a-/S100-) lipid laden macrophages
- Extraordinarily heterogeneous clinical presentation and often overlooked diagnosis
- BRAF mutations identified in ~50% of cases
  - Therapeutic option: Vemurafenib
  - VE1 antibody
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References


Any Questions?

Thank You