Case Presentation

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History

- **Pt:** 22 month-old Hispanic male
- **CC:** Pallor, fatigue and “swellings” since 8 months of age
- **PMH:** “Leukemia and lymphoma”
- **PE:** Bilateral cervical, axillary and inguinal lymphadenopathy; Splenomegaly
# Laboratory Results

<table>
<thead>
<tr>
<th>CBC</th>
<th>Differential</th>
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<tbody>
<tr>
<td><strong>WBC</strong></td>
<td><strong>Segs</strong></td>
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<tr>
<td>14.8</td>
<td>46</td>
</tr>
<tr>
<td><strong>Hb</strong></td>
<td><strong>Lymphs</strong></td>
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<tr>
<td>11.1</td>
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<tr>
<td><strong>MCV</strong></td>
<td><strong>Monos</strong></td>
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<td>17</td>
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<tr>
<td><strong>MCH</strong></td>
<td><strong>Eos</strong></td>
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<tr>
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<td>2</td>
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<tr>
<td><strong>MCHC</strong></td>
<td><strong>Basos</strong></td>
</tr>
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<td>1</td>
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<tr>
<td><strong>Plts.</strong></td>
<td></td>
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<tr>
<td>246</td>
<td></td>
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</tbody>
</table>
Lab Results (cont.)

- HSV, EBV, CMV, and TORCH titers normal
- Total complement: 24 (60-90 U/mL)
- ESR: 50 mm/h
- Hypergammaglobulinemia:
  - IgG 2300 (400-1000 mg/dL)
  - IgA 158 (14-122 mg/dL)
  - IgM 213 (47-160 mg/dL)
Flow Cytometry - PB

(17%) CD8

CD3

T Cells

B Cells

CD4

(6):x0028074.lmd FL1 LOG/FL2 LOG t cells

(4):x0028071.lmd FL3 LOG/SS UnGated
Flow Cytometry - PB

(3): x0028070.lmd FL1 LOG/FL2 LOG UnGated

(4): x0028071.lmd FL1 LOG/FL2 LOG B Cells'

- CD19
- CD20
- CD10
- CD5

(11%)
PB Flow Cytometry - Results

• A population of CD19+ events immunophenotyped as follows:
  – Positive for: CD20
  – Subpopulation co-expressed CD5

• A population of CD3+ events immunophenotyped as follows:
  – Positive for CD2, CD4, CD5, CD7, CD8
  – Negative (17%) for: CD4, CD8, CD7
Medical records from Mexico reviewed

Two prior lymph node biopsies:
- #1: “Consistent with AML”
- #2: “Diffuse lymphoma of small cells”

At LAC+USC, underwent (third) biopsy of an enlarged cervical lymph node
Lymph Node Immunohistology

- CD3+
- CD43+
- **CD45RA+**
- **CD45RO-**
- "Virgin" T-cell immunophenotype
- CD4-
- CD8-
- TIA-1+
- Granzyme B+
Flow Cytometry - LN

![Flow Cytometry Graphs](image)

- **CD3**
  - B Cells: 24.3%
  - T Cells: 72.2%

- **CD8**
  - T Cells: 43.6%

- **CD4**
  - (44%)

- **CD8**
  - B Cells: 8.8%
  - T Cells: 1.0%
PCR for TCR-γ

• SPECIMEN:
  Lymph node

• Expected size: 242 bp

• RESULT:
  Negative for TCR-γ rearrangement

N = negative control
P = positive control
78 = patient
Additional Work-up

- **BONE MARROW BIOPSY:**
  - Normal findings

- **CYTOGENETICS:**
  - Normal male karyotype
Additional Work-up (cont.)

FLOW CYTOMETRY OF BLOOD

- **SIBLINGS:**
  - Normal findings

- **MOTHER:**
  - Normal findings

- **FATHER:**
  - Increased (10%) double negative T-cells
Putting it all together...
• Generalized LAD
• Splenomegaly
• Cytopenia (anemia)
• ↑ Immunoglobulins (IgG)
• CD5+ B-cells
• DNT > 5%
• Generalized LAD
• Splenomegaly
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• CD5+ B-cells
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↑ DNTs (17%)
- Generalized LAD
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• DNT > 5%

↑ DNTs (17%)
Final Diagnosis

- Autoimmune Lymphoproliferative Syndrome (ALPS)
ALPS: History

• First recognized in 1967

• New York Hospital Pediatricians:
  – Virginia C. Canale, M.D.
  – Carl H. Smith, M.D.

• A.K.A. “Canale-Smith syndrome”

• Described 5 patients over 13 yrs:
  – Generalized lymphadenopathy
  – Hepatosplenomegaly
  – Autoimmune phenomena
  – 3 diagnosed with “lymphosarcoma”
  – Stable clinical course over 13 years
ALPS: History (cont.)

SPONTANEOUS MURINE LUPUS-LIKE SYNDROMES
Clinical and Immunopathological Manifestations in Several Strains*

BY BRIAN S. ANDREWS, ROBERT A. EISENBERG,‡ ARGYRIOS N.
THEOFILOPOULOS,§ SHOZO IZUI, CURTIS B. WILSON, PATRICIA J.
McCONAHEY, EDWIN D. MURPHY, JOHN B. ROTH, AND FRANK J. DIXON

From the Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California
92037, and The Jackson Laboratory, Bar Harbor, Maine 04653

• 1978: Andrews, et al
• Massive lymphadenopathy
• Lupus-like autoimmunity:
  – Hypergammaglobulinemia
  – Autoantibody production
  – Glomerulonephritis
• Increased CD3+CD4-CD8-

• Mouse model for autoimmunity
• Autosomal recessive
  – lpr and gld
ALPS: History (cont.)

- Journal of Clinical Investigation
- Confirmed \[^{\uparrow\uparrow\uparrow}\] DNTs in patients with ALPS

- Nature
- Lpr mice lacked cell surface expression of Fas
ALPS: History (cont.)


• *Cell, Science, Lancet*

• Identified Fas mutations in patients with ALPS


• *New England Journal of Medicine*

• Confirmed Fas mutations in 2 of the original patients described by Canale and Smith
Fas Gene

- Located on chromosome 10q24.1
- Heterozygous mutations cause defective apoptosis suggesting autosomal dominance
- Familial studies suggest variable penetrance
- Our patient’s mutation likely paternal in origin
Fas Protein (Receptor)

- A.K.A. CD95, TNFRSF6
- Operates as a homotrimeric complex
- Functionally “poisoned” by even a single defective subunit
- Dominant mutations cause impaired binding of the intracellular “Death Domain” with FADD (linker molecule)
- FADD links Death Domain with procaspases = initiating cascade
Fas Apoptotic Pathway

Fas (CD95) → Fas Ligand → DISC → "Death-inducing signalling complex" → FADD → Procaspase-8 or 10 → Caspase 8, Caspase 10 → Caspase-3 → Cell Death → Substrates → Caspase-3
Defective Pathway in ALPS - IA

- Fas (CD95)
- Fas Ligand
- FADD
- Procaspase-8 or 10
- Caspase 8, Caspase 10
- Procaspase-3
- Caspase-3

Cell Death
Substrates
Defective Pathway in ALPS - IB

Fas (CD95) → FADD → Procaspase-8 or 10 → Caspase 8, Caspase 10 → Procaspase-3 → Caspase-3 → Substrates → Cell Death
Defective Pathway in ALPS - II

- Fas (CD95)
- Fas Ligand
- FADD
- Procaspase-8 or 10
- Caspase-8
- Caspase-10
- Procaspase-3
- Caspase-3

Cell Death
Substrates
ALPS Classification

- **Type I** – Canale-Smith syndrome
  - IA – Fas receptor (most common)
  - IB – Fas Ligand

- **Type II** – Caspase 10

- **Type III** – Unknown (20-30%)
Clinical Features

- Lymphoproliferation
- Autoimmunity
Clinical Features

Lymphoproliferation
- Secondary to predominant expansion of DNT cells
- Most pronounced in infancy (onset: 1-24 mo)
- Decreases with age:
  - After thymus involutes

Autoimmunity
- Secondary to B-cells and plasma cells
- Less prominent in infancy
- Increases with age:
  - AIHA, ITP; any organ
Prognosis

Susceptibility to Hematologic Malignancy
ALPS and Hematologic Malignancy

The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis


- 223 members of 39 families
- 130 pts heterozygous germline Fas mutations
- 10 pts from 8 families developed 11 diverse B- and T-cell lymphomas up to 48 yrs later
- Rel. risk: 51-fold ↑ in HL & 14-fold ↑ in NHL
ALPS and Lymphoma Types

- Hodgkin lymphoma, nodular sclerosing type
- Hodgkin lymphoma, nodular lymphocyte predominant
- 3 Hodgkin lymphoma, mixed cellularity type (1 EBV+)
  - 1 later developed Marginal Zone Lymphoma
- 2 Burkitt lymphoma (1 EBV+)
- B-cell lymphoma, unclassifiable
- T-cell rich large B-cell lymphoma
- EBV+ T-cell lymphoma
ALPS—Ten Lessons from an International Workshop on a Genetic Disease of Apoptosis

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National Institutes of Health, Bethesda, MD, 20892, USA
*Correspondence: mlenardo@niaid.nih.gov
DOI 10.1016/j.immunl.2010.03.013

September 21-22, 2009 in Bethesda, Maryland

• **Lesson #5:** The FAS pathway plays a general role in preventing B-cell lymphomas
  – Defective T-cell surveillance
  – Epstein Barr virus (EBV) infection
  – Defective B-cell apoptosis
ALPS and Evans syndrome: A Causal Link?

Identifying autoimmune lymphoproliferative syndrome in children with Evans syndrome: a multi-institutional study

Alix E. Seif,1 Catherine S. Manno,2 Cecilia Sheen,1 Stephan A. Grupp,1 and David T. Teachey1

1Divisions of Hematology and Oncology, Department of Pediatrics, Children’s Hospital of Philadelphia, PA; and 2Department of Pediatrics, New York University School of Medicine, New York

2010: Seif, et al (Blood)

• Screened 45 children with Evans syndrome from 22 institutions
• 21 children (47%) had increased DNTs (>5%)
• Children with cytopenias should be screened for ALPS (since treated differently than Evans)
• Suggests ALPS is more common than thought
Summary

- ALPS is characterized by lymphoproliferation, autoimmunity and increased DNTs (>5%)

- Mimics lymphoma

- Newly-recognized risk factor for lymphoma

- Lifelong risk of autoimmunity increasing with age (e.g. AIHA, ITP)
  - Recent studies highlight association with Evan’s syndrome in children
References


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Thank You