Case Presentations in Primary Immune Deficiency Diseases

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COPD and recurrent infections

• 42 WF non-smoker with diagnosis of COPD
• Chronic sinusitusus, recurrent bacterial pneumonia requiring treatment with IV antibiotics
• FEV1- 64% predicted with little reversibility
• History of thrombocytopenia and splenomegaly
Bilateral, diffusely distributed nodules in lung and liver, mediastinal lymphadenopathy, bronchiectasis biopsies shows non-caseating granuloma
The Specialists

• What does this patient have?
  – Her Rheumatologist said sarcoidosis.
  – Her oncologist suspected cancer.
  – Her pulmonologist said COPD.
  – She said “to H#$&!* with you guys!”
Immunology Evaluation

– After nearly ten years of persistent symptoms and progressive bronchiectasis an immune evaluation was performed.
– Immunoglobulins Levels
  • IgG 154 (613-1295 mg/dl)
  • IgA < 5 (69-309 mg/dl)
  • IgM 10 (53-334 mg-dl)
– Low T cell numbers, inverted CD4/CD8 ratio
– No functional antibody titers to tetanus, diphtheria, or pneumococcal polysaccharide
– HIV antibody testing was negative
– B cell enumeration was normal at 15%

– **DIAGNOSIS**: Common Variable Immunodeficiency
Pseudomonas Sepsis

• 15 mo male in good health until age 12 mo
• 3 episodes of OM
• Initial hospitalization for fever, pneumonia, meningitis, and illustrated rash
• Cultures positive for *Pseudomonas aeruginosa*
• Leukocytosis with PMN predominance
X-linked Agammaglobulinemia

- Maturation arrest in Pre-B cell development
- No Circulating CD19 or CD20 B lymphocytes
- All Immunoglobulins decreased
- T cell Development is Normal
- Mutation in B cell specific Src associated tyrosine kinase (BTK)
Infant with Neutropenia, Fever, and Spenomegaly

- The 14 mo with thrombocytopenia, neutropenia, autoimmune hemolytic anemia with fever, enlarged liver and spleen, “silver” hair, and abnormally light skin.
- Serum ferritin level 10,000
Griscelli Syndrome with Hemophagocytic Lymphohistiocytosis

Diagnostic Criteria for HLH

- Fever, splenomegaly,
- Cytopenia (Hb, plts, neutrophils)
- Hypertriglyceridemia or hypofibrinogenemia
- Hemophagocytosis (BM, Liver, LN, or CSF)
- Low NK activity
- Elevated ferritin (>500 mg/L)
- Abnormal sIL-2R in plasma
18 mo male with eczema, chronic OM, polyarticular arthritis with this immunoglobulin profile:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normal levels for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>383-1030 mg/DL</td>
</tr>
<tr>
<td>IgA</td>
<td>27-169 mg/DL</td>
</tr>
<tr>
<td>IgM</td>
<td>28-113 mg/DL</td>
</tr>
<tr>
<td>IgE</td>
<td>0-180 IU/ml</td>
</tr>
</tbody>
</table>

You would expect which of the following laboratory findings in this child?

a) elevated serum creatinine
b) abnormal serum aldolase level (>15 mg/DL)
c) positive HIV ELISA
d) platelet count of <20,000/ul
Wiskott Aldrich Syndrome

Clinical phenotypes correlate with genotype in WAS:

Four Clinical Phenotypes resulting from mutations of WAS:
- Wiskott Aldrich Syndrome
- X-Linked Thrombocytopenia
- Intermittent XLT
- X-Linked Neutropenia

Mutations mostly exonic and distributed across gene

Effect on protein expression generally correlates with phenotype severity
  - Milder: some protein expressed
  - Severe: no protein expressed
Staph aureus Lymphadenitis
Analysis of Granulocyte Respiratory Burst Using Dihydrorhodamine (DHR)

Granulocytes

Lymphocytes

Unstimulated cells

Stimulated with PMA
SI = 376
(Normal ≥ 100)

Stimulation Index (SI) = non-stimulated GMC ÷ stimulated GMC

GMC: 9.9

GMC: 372
ABNORMAL DHR RESULTS

$gp^{91-}$
(X-linked)

$gp^{91-}$
(female carrier)

$p^{47-/-}$

Non-
Stimulated

PMA
Stimulated

SI = 1.1
peak #1 SI = 1.5
peak #2 SI = 248

SI = 9.1
Severe Combined Immune Deficiency

- PCP
- Failure to thrive
- Rash and Hepatitis following transfusion
- Normal total WBC
- Severe Lymphopenenia
SCID: ADA Deficiency
(Defective Purine Salvage Pathway)

NORMAL:

(toxic metabolite)
deoxyAdenosine
+
Normal ADA
↓
Deoxyinosine
NON-toxic

Adenosine deaminase deficiency:

(toxic metabolite)
deoxyAdenosine
+
ADA deficiency
↓
accumulation of deoxyadenosine
lymphocyte death

Absent T, B, or NK Cells
Rash in a 4 mo old

- Failure to thrive
- Skin Biopsy shows perivascular lymphocytic infiltrate
- What are these cells telling you?
SCID with nonfunctional B cells: X-linked ($\gamma_c$) and Jak3

- Receptors for IL-2, 4, 7, 9, 15, 21 share common $\gamma$ chain ($\gamma_c$)
- Jak 3 is involved in intracellular signaling through $\gamma_c$
- Mutations in common $\gamma$ chain cause X linked SCID (44%)
- Mutations in Jak 3 cause an autosomal recessive SCID (6%)
- Intracellular signaling through $\gamma_c$ and Jak 3 important in T cell and NK cell development
- Phenotype is T-,NK-,B+ SCID for both of these forms

Adapted from: R. Buckley, Primary Cellular Immunodeficiencies. JACI May 2002.
# T/B/NK Phenotypes in SCID

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Defect</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>T⁻/ B⁻/ NK⁻</td>
<td>ADA Deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>T⁻/ B⁻/ NK⁺</td>
<td>RAG Deficiency</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Artemis</td>
<td>AR</td>
</tr>
<tr>
<td>T⁻/ B⁺/ NK⁻</td>
<td>γc IL-2R</td>
<td>X-linked</td>
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<tr>
<td></td>
<td>Jak3</td>
<td>AR</td>
</tr>
<tr>
<td>T⁻/ B⁺/ NK⁺</td>
<td>IL-7αR</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>CD3 δεζζ TCR</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Complete Di George</td>
<td>AD</td>
</tr>
</tbody>
</table>
TREC
TREC Assay for NBS

Screening all infants

DNA extraction

RT-qPCR
δRecψJαTREC primers
β actin control

40 cycle Amplification

Median TREC copies 827
Cutoff for SCID <25 copies
T cell Deficiencies with abnormal TREC levels

• SCID subtypes: ADA, RAG1, Artemis, Jak3, γcIL-2R (x-linked SCID), IL-7Rα, ζTCR, Zap70, reticular dysgenesis, CHH

• Non-SCID subtypes with low TREC: 22q Deletion Syndrome (DiGeorge), other thymic defects (CHARGE), Idiopathic T cell lymphopenia, extravascular T cells (chylothorax)