Non-Infectious Presentations and Complications of Immunodeficiency: A New Era of Immune Defects

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Disclosures

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- CSL-Behring – Speaker and Consultant
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- USF – grant support
Learning Objectives

• 1. Identify new rare defects of the immune system that cause immunodeficiency.
• 2. Understand non-infectious presentations and manifestations of primary immunodeficiency.
• 3. Describe the evaluation of patients with immunodysregulatory diseases.

The Immune System

• What does it do?

  • Recognizes pathogens (non-self)
  • Organizes a defense response
  • Facilitates pathogen destruction and elimination
The Immune System

1. Innate
   • Present from birth
   • Specificity is “pre-programmed”
   • Includes non-immunological cells (e.g. skin and cilia)

2. Adaptive
   • Develops during life with exposure to infection (memory)
   • Increases affinity with experience (specificity)
   • Two compartments:
     ▪ Cellular- Mediated by cells
     ▪ Humoral-Mediated by soluble factors
   ▪ Memory and Specificity are key features

Lymphocytes

T cells
• Develop in the thymus
• Mediate specific cellular immunity, kill infected cells
• Provide help to B cells for antibody production
• Regulate immune responses through cytokine secretion

B cells
• Develop in the Bone marrow
• Mediate humoral specific immunity by producing antibodies

Neutrophils
• Average count is 5000/ul
• Make approximately $10^{11}$ per day
• Most are in the bone marrow
• Can go up 10 fold in emergencies
• Circulating half life is about 7 hours
Molecular biology of PIDD

- Over 300 genetic abnormalities described for primary immune deficiencies

Primary Immunodeficiencies

Epidemiology

- Incidence: 1/1,200-20,000 (2:1, ♂:♀)

- Distribution:
10 Warning Signs of Immunodeficiency*

1. Eight or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or elsewhere on skin, after age 1.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections.
10. A family history of Primary Immunodeficiency.

*The Jeffrey Modell Foundation, Inc.*
Infections in PIDD

• Unusual
  • Opportunisitic, fungal, viral

• Severe
  • Deep, blood borne

• Chronic
  • Poor response to therapy, recurring

Antibody Deficiency

• Still by far the most common
• Recurrent sinopulmonary infections
• Susceptibility to GI infections
• Often managed with immunoglobulin supplementation
The Concept of Immune Dysregulation

- The immune system – Not just to fight infections
  - Prevention of autoimmunity
  - Cancer surveillance
  - Host – microbial interactions / symbiosis
- Quality matters more than quantity
- Too much of anything is bad

Case 1

- 12m male with
  - Chronic diarrhea
  - Chronic cough
  - Failure to thrive
  - Elevated liver enzymes

- Differential
  - PMN 88%
  - Eos 2%
  - Lymphs 2%
  - Monos 8%
- ALC = 165

PJP on micrograph of liver biopsy
SCID – Molecular Causes and Phenotypes

### Common Clinical Phenotype, Variable Genotype

- Failure to thrive, diarrhea
- Recurrent Opportunistic Infections
  - Fungi – Candida
  - Viruses – parainfluenza virus, CMV, adenovirus
- Absence of T cells
- Specific gene defect defines impact on B and NK cell development

### Table II. Molecular causes of SCID and characteristic lymphocyte phenotypes

<table>
<thead>
<tr>
<th>Molecular Cause</th>
<th>Lymphocyte Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked SCID</td>
<td>T(-),B(+),NK(-)</td>
</tr>
<tr>
<td>1° c gene mutations</td>
<td>T(-),B(+),NK(-)</td>
</tr>
<tr>
<td>Autosomal Recessive SCID</td>
<td>T(-),B(+),NK(-)</td>
</tr>
<tr>
<td>2° ADA gene mutations</td>
<td>T(-),B(-),NK(-)</td>
</tr>
<tr>
<td>2° Jak3 gene mutations</td>
<td>T(-),B(-),NK(-)</td>
</tr>
<tr>
<td>3° IL7Rα chain gene mutations</td>
<td>T(-),B(+),NK(+),NK(+)</td>
</tr>
<tr>
<td>4° RAG1 or RAG2 mutations</td>
<td>T(-),B(-),NK(+),NK(+)</td>
</tr>
<tr>
<td>5° Artemis mutations</td>
<td>T(-),B(-),NK(+),NK(+)</td>
</tr>
<tr>
<td>6° CD45 gene mutations</td>
<td>T(-),B(+),NK(-),NK(-)</td>
</tr>
</tbody>
</table>
Treatment of SCID: Immunologic Emergency

Curative:
- Stem cell transplantation

Adjuvant:
- Enzyme replacement (PEG-ADA)
- Gene therapy (ADA, XL-SCID)
- IVIG
- Avoidance live viral vaccines
- Irradiation of blood products
- CMV negative blood products only
- Prophylactic antibiotics (Bactrim for PJP)
- Protective isolation

Effect of Age at Transplant on Survival of 166 SCIDs Transplanted at Duke University Medical Center Since 1982
Case 2

- 2m male presents with 1 day of fever and erythema, discharge, and swelling at site of heelstick.
- Culture + *Serratia marcesens*
- 1 month later develops bilateral cervical lymphadenitis
- Cultures + *Klebsiella oxytoca*
- He is growing well and has no other positive family history.

The NBT Fallen out of Favor

![CGD Patient](image1.jpg)

![Normal](image2.jpg)

![X-CGD Carrier (Lyonization)](image3.jpg)
Flow Cytometry Analysis of Granulocyte Respiratory Burst Using Dihydrorhodamine

Granulocytes

Lymphocytes

Unstimulated cells

Stimulated with PMA
SI = 376
(Normal ≥ 100)

DHR Assay to Diagnose CGD

Normal

Phox<sup>91</sup> deficient CGD (X-linked)

AR deficient CGD

X-linked CGD carrier
NADPH → e⁻ → NADP⁺ → O₂⁻

Cytoplasmic

NADPH

p47phox

p40phox

p67phox

p22phox

gp91phox

Rac

NADP⁺

Cytoplasmic

Other Problems in PIDD

- Failure to Thrive
- Enteropathy
- Colitis
- Autoimmunity
- Hematologic Disorders
  - Neutropenia, anemia, thrombocytopenia
  - Lymphoproliferative disease
  - Splenomegaly
- Atopy
  - Severe eczema, food allergies, environmental allergies
- Endocrinopathies
- Dysmorphic features

What this gives you

Unusual Presentations of Common PIDDs

Brand New Diseases
Case 3

- 10yo female with oxygen dependent lung disease
  - Bronchiectasis secondary to chronic asthma
  - Recurrent pulmonary infections
  - Digital clubbing
  - Recurrent ear infections
  - Failure to thrive


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Table 1: Immunologic evaluation of patient

<table>
<thead>
<tr>
<th>Test</th>
<th>Control</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (mg/dL) (608–1,572)</td>
<td>783</td>
<td>363</td>
</tr>
<tr>
<td>IgA (mg/dL) (45–235)</td>
<td>896</td>
<td>70</td>
</tr>
<tr>
<td>IgM (mg/dL) (52–242)</td>
<td>183</td>
<td>70</td>
</tr>
<tr>
<td>IgE (IU/mL) (&lt;25)</td>
<td>&gt;2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Tetanus titer (IU/mL) (&lt;0.1)</td>
<td>0.59</td>
<td>0.59</td>
</tr>
<tr>
<td>Diphtheria titer (IU/mL) (&gt;0.1)</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Post-pneumococcal titer (IU/mL) (&gt;1.3)</td>
<td>&gt;50% serotypes protective</td>
<td>62</td>
</tr>
<tr>
<td>Absolute lymphocyte count cells/µL (1,900–3,700)</td>
<td>363</td>
<td>363</td>
</tr>
<tr>
<td>Absolute CD3⁺ cells/µL (1,200–2,600)</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Absolute CD4⁺ cells/µL (650–1,500)</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Absolute CD8⁺ cells/µL (370–1,100)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Absolute CD19⁺ cells/µL (270–860)</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Absolute CD56⁺ cells/µL (100–480)</td>
<td>224</td>
<td>224</td>
</tr>
<tr>
<td>CD4⁺/CD8⁺ ratio (51%–67%)</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>CD4⁺/CD56⁺ ratio (33%–48%)</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Lymphocyte stimulation to mitogens (counts/min)</td>
<td>4,904</td>
<td>4,904</td>
</tr>
<tr>
<td>Phytohemagglutinin (&gt;99,000)</td>
<td>101,27</td>
<td>101,27</td>
</tr>
<tr>
<td>Concanavalin A (&gt;70,000)</td>
<td>31,207</td>
<td>31,207</td>
</tr>
<tr>
<td>Pokeweed (&gt;85,000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte stimulation to antigens (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus (&gt;3)</td>
<td>13.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Candida (&gt;3)</td>
<td>1.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>

SCID – Molecular Causes and Phenotypes

**TABLE II. Molecular causes of SCID and characteristic lymphocyte phenotypes**

<table>
<thead>
<tr>
<th>Genetic Cause</th>
<th>Lymphocyte phenotype</th>
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<tbody>
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<td><strong>X-linked SCID</strong></td>
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<tr>
<td>(1) γc gene mutations</td>
<td>T(−),B(+)NK(−)</td>
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<td>(6) CD45 gene mutations</td>
<td>T(−),B+</td>
</tr>
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</table>

Buckley et al. Primary Cellular Immunodeficiencies JACI 2002

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**T cell Receptor Excision circle (TREC)**

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[Diagram of T cell Receptor Excision circle (TREC)]
New Classification of SCID

**Classic SCID**
CD3 <300 cells/mm³ and PHA <10% control

**Leaky SCID**
CD3 300-1500 cells/mm³, PHA 10-30% control, no maternal T cell engraftment

**Variant SCID**
CD3 300-1500 cells/mm³ with impaired function, no maternal T cells found, no genotype found.

**Idiopathic Lymphopenia**
CD3 300-1500 cells/mm³, Normal PHA, no maternal T cell engraftment, no known genetic cause of SCID

Case 4

- 2 y.o. Caucasian male presents to the pediatrician for several weeks of diarrhea
  - Possible fever the first week
  - Intermittent abdominal pain
  - Loose stools, 3-4 per day
  - No frank blood
  - Decreased appetite, but drinking well
- **PMH:** wheezes with viral URIs, left
- **Family Hx:** maternal cousin with inflammatory bowel disease

CBC with differential-normal
CMP- albumin 2.9
ESR 12, CRP 2.6
Stool culture: negative
Ova & parasites: negative
DHR Assay to Diagnose CGD

Types of CGD

**XL** – CYBB, gp91phox 70%
Female carriers
AR – NCF1, p47phox 20%
1/250 are carrier
NCF2, p67phox 6%
CYBA, p22phox 6%
CGD Infections

- **Staph aureus**: liver, lymph nodes, osteo
- **Serratia marsescens**: skin, lung, lymph nodes
- **Burkholderia spp.**: pneumonia, bacteremia
- **Nocardia spp.**: pneumonia, brain, liver
- **Aspergillus spp.**: lung, esp. miliary, spine
- **Salmonella spp.**: sepsis, diarrhea, osteo
- **BCG**: lymph node, rarely disseminates

Others more rare:
- *Chromobacterium violaceum* (*brackish water, e.g. Disney World*)
- *Francisella philomiragia* (*brackish water, Chesapeake Bay*)
- *Granulibacter bethesdensis* (*widespread*)
- *Methylobacter extorquens*

Granulomatous Complications

- Esophageal Strictures
- Gastric Outlet obstruction
- Vesicoureteral Reflux
Inflammatory Bowel Disease in CGD

Frequency of symptoms in the preceding 3 years

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>37</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>33</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>23</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>22</td>
</tr>
<tr>
<td>Distension</td>
<td>21</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>10</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>8</td>
</tr>
</tbody>
</table>

16 (64.0 %) were documented as experiencing at least one symptom relating to the gastrointestinal tract in the preceding 3 years


Inflammatory Bowel Disease in CGD

- a. Colonic inflammation and ulceration
- b. Colonic mucosa with active inflammation and withered crypts
- c. Active chronic colitis with architecture distortion
- d. e. epitheliod granuloma with Langerhan’s type giant cells
- f. Pigment laden macrophages in noninflamed regions****

Diagnosis of CGD-colitis

• Subjective complaints
• Weight loss, microcytic anemia, hypoalbuminemia
• Antimicrobial panels: ASCA IgG, ASCA IgA, anti-OMPC, anti-I2, and anti-CBir1 present at high levels and not predictive of colitis.
• Routine screening of CGD in patients with colitis is not high yield.

Management of CGD-colitis

• Steroids
• Metronidazole, 6-MP, salicylic acid derivatives, mesalamine.
• Surgery
Complications of Tumor Necrosis Factor-α Blockade in Chronic Granulomatous Disease–Related Colitis

Gulbu Uzel,† Jordan S. Orange,² Nina Polian,² Beatriz E. Marciano,¹ Theo Heller,² and Steven M. Holland¹

5 Patients
Severe infections after 3 to 12 infusions
2 Deaths despite prophylaxis

Case 4

• 3m male with severe failure to thrive, profound diarrhea and weight loss.
• Eczematous dermatitis
• Developed type 1 diabetes with +anti-insulin antibodies
• Developed hypothyroidism with +anti-TPO antibodies
• Developed Coomb’s postive hemolytic anemia
• No infections
• Immune evaluation is normal with the exception of low Treg cells
**IPEX: Immunodeficiency Polyendocrinopathy Enteropathy X linked**

**Synopsis:**

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>X linked recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Diarrhea, secretory</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>Ileus</td>
</tr>
<tr>
<td>Villous atrophy</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Skin</td>
<td>Eczema/Atopy</td>
</tr>
<tr>
<td>Hematology</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Immunology</td>
<td>Immune dysregulation</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Variable autoimmune disorders</td>
</tr>
<tr>
<td>autoantibodies</td>
<td></td>
</tr>
<tr>
<td>Molecular basis</td>
<td>Mutation in FOXP3</td>
</tr>
<tr>
<td>Endocrine</td>
<td>DM, thyroid</td>
</tr>
</tbody>
</table>

**Mutation in FOXP3**

↓

**Lack of CD4+ CD25+ FOXP3+ Regulatory T cells**

CD4+CD25+ Tregs are critical for the maintenance of peripheral immunological tolerance

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**FOXP3 Protein**

**FOXP3: Transcription factor responsible for development of Treg**

Mutations can occur throughout the gene, more reported in the “forkhead” domain

Treatment

- Immunosuppression
  - Steroids, sirolimus, tacrolimus
- Bone Marrow Transplant

Enteropathy in PIDD

- Chronic diarrhea and weight loss
- Failure to thrive
- Celiac like
- Autoimmune enteropathy
- Granulomas
- Lymphocytic infiltrate

Endocrinopathy in PIDD

- Type 1 diabetes mellitus
- Thyroid disease
- Addison’s disease
- Hyperparathyroidism
- Gonadal failure
- Growth hormone deficiency
Case 5 Hyper IgE at its worst

- 3yo male with
  - severe allergic rhinitis
  - asthma
  - severe eczema
  - food allergies – milk, egg, tree nuts, sesame
  - Recurrent URI’s
  - Recurrent otitis media
  - 2 pneumonias
- Total IgE >3000

Hyper-IgE Syndromes

- Autosomal Dominant Hyper IgE Syndrome
  - AD-HIES
  - Job’s Syndrome
  - STAT3 deficiency
  - Loss of Function in STAT3 (LOF-STAT3)
- Autosomal Recessive Hyper IgE Syndrome
  - AR-HIES
  - DOCK8 deficiency
Autosomal Recessive HIES – Combined Immunodeficiency with DOCK8 Mutations

- Dedicator of cytokinesis 8 protein
- Recurrent sinopulmonary tract infections
- Recurrent cutaneous viral infections
- Severe atopy with elevated serum IgE levels and hyper-eosinophilia

Immunology
- Low numbers of T-cell and B-cells
- Low serum IgM, variable IgG antibody responses
- Decreased numbers and function of Th17 cells

Dermatitis and Viral Infections of the Skin in DOCK8 PIDD

AD  Herpes simplex  Molluscum  warts

Zhang et al NEJM 2009
High IgE without Atopy

• 18 yo female admitted for Herpes zoster involving V1 and V2 of the trigeminal nerve.

• History of:
  • Pneumonia as a child associated with pneumatocele development
  • Retained primary teeth
  • Mother died of *Aspergillus* pneumonia
  • IgE as high as 13,000 IU/ml

AD-HIES / Job’s Syndrome

• Recurrent pneumonia
• Recurrent boils
• eosinophilia
• markedly increased serum IgE (>10,000 IU/ml)
• eczema
• Distinct abnormalities of connective tissue

Schimke et al JACI 2010
Woellner et al JACI 2010
AD-HIES / Job’s Syndrome

What is all the STAT about?

Grimbacher et al NEJM 1999
Sowenwize KJ Ann NY Acad Sci 2012
11 year old female with autoimmune hepatitis

- Autoimmune hepatitis
  - Treated with tacrolimus, cellcept, remicaide, rapamycin, rituximab, cytoxan
  - Cadaveric liver transplantation 2013.
  - New liver is failing with chronic ascites, portal hypertension, and severe electrolyte abnormalities
- Celiac disease, ulcerative colitis
- Growth failure
- Also had history of T and B cell lymphopenia and profound hypogammaglobulinemia.
- Thrombocytopenia post liver transplant
- Mom- looks very small. No real medical history.

Labs

- Bone marrow biopsy – myelodysplasia
- Intermittently neutropenic and intermittently thrombocytopenic.

IgG 497
IgA 107
IgM 71 mg/dl

CD3+ 645
CD4+ 74
CD8+ 494
CD19+ 2
CD56+ 22 cells/mm³
DNT’s (CD4-CD8-) 77 (12%)
Double Negative T cells

• CD4+CD8+ $\rightarrow$ CD4+CD8- or CD4-CD8+ $\rightarrow$ CD4-CD8-
Mother becomes a patient

- Fatigue and unintentional weight loss
- Growth failure, on growth hormone as a child
- Enteropathy as a child
- Colitis as a child
- Enlarged spleen, cervical and axillary adenopathy

- WBC 3.4 ANC 2489 ALC 731
- IgG 350, IgA 80, IgM 106, IgE <2, albumin 2.8
- S. pneumoniae titers 20/23
- VZV IgG 4.79
- Diptheria IgG 0.19 tetanus IgG 1.80
- Rubella <0.9, mumps 0.9, measles 0.9
- CD3+ 383 CD4+ 216 CD8+ 153
  CD19 +238 CD56+ 20 cells/mm³
- DNT’s (CD4-CD8-) 52 (14%)

Lymphoproliferative Disease

- Splenomegaly
- CD4-CD8- γδ T cell population
- Cervical and inguinal lymphadenopathy
Age 44y – weight 39.4kg, height 139.5cm (4.5 feet)

At age 13y – 17.9kg, 97cm (a little over 3 feet)

GOF-STAT3 mutations

Autoimmunity
Enteropathy
Growth Failure
Infections
Lymphoproliferation

Cooper Lab, Washington University
LOF-STAT3 vs GOF-STAT3
Same gene, Different Phenotype

**LOF-STAT3**
- Autosomal dominant HyperIgE syndrome
- Eczema
- Pneumonias with pneumatoceles
- Abscesses
- Characteristic face
- Mucocutaneous fungi
- Retained primary teeth

**GOF-STAT3**
- Enteropathy
- Growth failure
- Autoimmunity
- Lymphoproliferation
- Malignancy
- Combined immune defect – lymphopenia, hypogammaglobulinemia

Both LOF and GOF STAT3 mutations have significant clinical consequences.

Elie Haddad Blood 2015;125:583-584
Case – 21yo female with Mucocutaneous Candidiasis and fungating hand granuloma

• Initially presented at age 3 yrs with recurrent mucocutaneous candidiasis
• Intermittent leukopenia and neutropenia
STAT1 mutations

- Amorphic
  - Autosomal recessive
  - Severe viral and bacterial infections
  - Typically fatal
- Hypomorphic
  - Autosomal recessive
  - Non tuberculous mycobacteria
- Hypermorphic
  - Autosomal Dominant
  - CMC
  - Coccidoides
  - Histoplasma

Clinical Presentation
STAT1 GOF

- Expanded GOF Phenotype
  - IPEX-like phenotype
    - Autoimmunity
    - Enteropathy
  - Combined Immunodeficiency
    - Antibody Deficiency
    - T cell defects
  - Broader infection susceptibility
    - Histoplasmosis
    - Cryptococcus
    - Coccidioidomycosis
    - HSV
    - VZV
    - EBV

References:
- Boisson-Dupuis S. Current Opinion in Immunology, 2012
- Liu L, JEM, 2011
- Sampaio EP. J Allergy Clinical Immunology, 2013.
- Uzel G. J Allergy Clinical Immunology, 2013.
Hematologic Cytopenias and Lymphoproliferative Disease
Case 6
• 5yo male with 1 year history of profound thrombocytopenia
• + anti-platelet antibodies
• + Coomb’s
• +anti-granulocyte antibody
• Splenomegaly
• Enlarged axillary and cervical lymphadenopathy
• Mild lymphopenia
• Mild hypogammaglobulinemia (IgG 500)

CTLA-4 deficiency
(Cytotoxic T Lymphocyte Associated Protein 4)
• Brain, GI, lung, lymphocytic infiltrates.
• Autoimmune thrombocytopenia and other cytopenias,
• Hypogammaglobulinemia
• Clonally expanded gd-CD8+ T cells
• CD4 T cell lymphopenia.
• Low circulating mature B cells
• Reduced expression of FOXP3 Treg cells

CTLA-4

- Inhibitory receptor expressed on activated T cells

Treatment of this patient

- Steroids
- Rituximab

Lee et al. JACI. 2016
LPS-responsive beige-like anchor protein (LRBA) deficiency

- Chronic Diarrhea
- Autoimmunity – Cytopenias, arthritis
- Organomegaly
- Respiratory Infections – frequent bronchiectasis
- Hypogammaglobulinemia
- Growth Retardation
- Neurologic Disease – cerebral lesions

**Immune Phenotype**

- Very low number of peripheral Treg cells
- Decreased immunoglobulins
- Decreased B cells
- Absent class switched B cells
- ALPS like phenotype

**Extended Spectrum**

<table>
<thead>
<tr>
<th>TABLE III. Current treatment of living and symptomatic patients with the diagnosis of definitive LRBA deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current treatment</strong></td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
</tr>
<tr>
<td>Immunoglobulin replacement</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Abatacept</td>
</tr>
<tr>
<td>HSCT</td>
</tr>
<tr>
<td>Tacrolimus + sirolimus</td>
</tr>
<tr>
<td>Budesonide</td>
</tr>
<tr>
<td>Cyclosporine</td>
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<tr>
<td>Azathioprine</td>
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<tr>
<td>Rituximab</td>
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<tr>
<td>Infliximab</td>
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<tr>
<td>Hydroxychloroquine</td>
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<tr>
<td>Remicilim</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
</tr>
</tbody>
</table>

Charbonnier et al. JACI. 2015.
Alkhairy et al. JACI. 2016.
Gamez-Diaz L. JACI. 2016.
12yo male with lymphadenopathy and bronchiectasis

- Recurrent pneumonia
- Recurrent sinusitis and otitis media
- Lymphopenia
- Cervical and occipital lymphadenopathy – benign hyperplasia
- Cobblestoning of the mucosal layer of the respiratory and gastrointestinal tract.

Gain of Function PI3 Kinase

**T cell development markers**
- Naïve: CD45RA+ CD62L+ CCR7+
- Central Memory: CD45RA-CD62L-CCR7+
- Effector Memory: CD45RA-CD62L-CCR7-
- TEMRA: CD45RA+ CD62L- CCR7-

**B cell development markers**
- Naïve: CD27- CD10-
- Transitional: CD27 – CD10+
- Memory: CD27+ CD10-

Gain of Function PI3 Kinase

**Phenotype**
- Sinopulmonary Infections
- Lymphoproliferation
- Chronic EBV or CMV
- Nodular lymphoid hyperplasia
- Autoimmune cytopenias

**Immunology**
- Low IgG, high IgM, low IgA
- Low memory B cells
- High/normal CD8 T cells
- Low CD4 T cells
- Low naïve T cells
  - CD45RA+CD62L+
  - High effector memory and TEMRA T cells

Summary

• Immune dysregulatory diseases are newly recognized and an expanding field.
• Infections still are key, but PIDD patients present and develop a variety of other symptoms.