Very Early Onset Inflammatory Bowel Disease: A Model for Personalized Medicine in IBD

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Objectives

• Review unique features of VEO-IBD
• Review the underlying drivers of disease
• Review the individualized evaluation for patients with VEO-IBD
• Discuss approach to personalized medicine for patients with VEO-IBD and application to select older patients with IBD
VEO-IBD: A Different Disease

• Presentation ≤ 5 years of age
  – Neonatal/infantile onset
  – Toddler and early childhood onset

• Heterogeneous phenotype

• Significant subset
  – Distinct, more severe and refractory disease
Distinct Phenotype
Phenotypic Differences

• Growth Failure
  – Stunting
  – Persists beyond diagnosis
Phenotypic Differences

• Growth Failure
  – Stunting
  – Persists beyond diagnosis
• Endoscopic findings
Histologic Clues

Colon: abundant apoptosis, eosinophilic granules, “sheets of Eos”

Duodenum: severe villous atrophy and blunting
Phenotypic Differences

• Growth Failure
• Endoscopic findings
• Histology
• Response to Therapy
Therapeutic Response Compared to Older Patients

![Graph showing failure rates of Infliximab and all Anti-TNF Therapies for VEO and Older Onset patients.](#)
Phenotypic Differences

- Growth Failure
- Endoscopic findings
- Histology
- Refractory Disease
- Surgical intervention
Surgical Differences

Kelsen, Conrad, Patel et al, IBD 2019
Different Drivers of Disease

- **Approach**
  - Whole Exome
  - GWAS

- **Genes**
  - Monogenic
  - Polygenic

- **Variants**
  - Penetrance
  - Frequency
Genomics Changed the Game

IL-10R Mutation

VEO-IBD Networks

Epithelial Barrier: ADAM17, IKBKG, COL7A1, FEMT1, TTC7A, GUCY2

Phagocyte Defects: NADPH Complex SLC37A4 G6PC3 ITGB2

Immuno-regulation: IL10, IL10RA, IL10RB, FOXP3, IL2RA, STAT1, STAT3

T & B Cell Defects: RAG1/2, IL7R, PTEN, WAS, LRBA, ICOS, CTLA4, BTK, PIK3R1, DKC1

Hyper/Auto-Inflammatory: XIAP, STXBP2, LYST, RAGB27a, MKV, PLCG2, NLRC4, MEFV, HSP1, 4, 6, SH2D1A, TRIM22

VEO-IBD
Evaluation
Goal of VEO-IBD Evaluation

- **Recognize Monogenic Disease**
  - PMH, FHx
  - Exam

- **Identify those who will benefit from targeted therapy**
  - Monogenic
  - Specific Phenotypes

- **Identify those at risk of non-GI complications**
  - HLH/Malignancy
  - Sepsis/Septic Shock
Integration of genomics and immunophenotyping
**Endoscopy, Histology, Labs, Imaging**

**Immunoglobulins, vaccine titers, lymphocyte subsets**

**DHR**

**Cytokine Panel**

**Specific Screens**

**Hyperinflammatory Defects**
- XIAP, STXBP2, LYST, RAGB27a, MVK, PLCG2, NLCR4, MEFV, HSP1,4,6, SH2D1A, TRIM22

**Oxidative Stress/Neutrophil Function**
- NADPH Complex genes SLC37A4, G6PC3, ITGB2

**Antibody or Combined B/T Defects**
- RAG1/2, IL7R, PTEN, WAS, LRBA, ICOS, CTLA4, BTK, DKC1, PIK3R1

**Immune Dysregulation**
- IL-10, IL-10RA/RB, FOXP3, IL2RA, STAT1, STAT3
Genetic Evaluation

- Targeted sequencing panels
  - High suspicion for monogenic disease, consistent with previously identified genes

- WES
  - Targeted panel is negative, or driving pathway is unclear

- WGS
  - Negative WES, but high likelihood of monogenic disease
Case 1: Neonatal Onset

- Full term newborn baby boy with persistent hypoglycemia: NICU admission
- DOL 2: developed petechial rash, fevers, severe thrombocytopenia, cholestasis, leukocytosis, markedly elevated inflammatory markers
- Over next few days: transfusion dependent hematochezia, persistent fevers
- Hemodynamic instability
- Transferred to CHOP for further work up
- Elevated ferritin, cytokine panel abnormal and IL-18 markedly elevated
de novo p.V341L in *NLRC4*

Frachi et al, Nature Immunology 2012
Targeted Therapy

• Canakinumab and tadekinig: IL-18 blockade
• Currently well, growing and meeting developmental milestones
Case 2: Systemic Autoimmunity

• 17 yo male presented at age 2 with polyarthritis, growth failure, and diarrhea
• 3 yo: diagnosed with JIA
• Course progressed: psoriasis, uveitis, autoimmune diabetes
  – Arthritis worsened: cervical spine, temporomandibular, chronic dislocation of left patella with left knee contracture
• IBD: pancolitis and profound growth failure
  – Progressed despite aggressive immunosuppressive therapy
Severe Growth Failure
VEO-IBD Evaluation

- T-cell lymphopenia
  - naïve-skewed CD8 T cells
  - NK cell and CTL functional analysis: reduced
- Low pneumococcal vaccine titers
- Decreased overall B cells
  - low switched-memory B cells
  - relatively increased naïve B cells
Monogenic Autoinflammatory Disease

- WES performed: compound het *ITCH* (E3 ubiquitin ligase)
  - c.337+2T>C (splice donor) and c.772C>T, p.Arg258* (stop gain)
Itch Expression
Deep Immunophenotyping

HC

ITCH deficient

ICH deficient
Follow Up

- Hematopoietic Stem Cell Transplant
  - Dramatic improvement in arthritis, diarrhea and HbA1c
  - Weaned off steroids first time in > 1 decade
  - Off all immunosuppressive therapy
Therapeutic Approach
Therapeutic Strategies

- **Neutrophilic infiltrate**
  - IFX
  - Anakinra/canakinumab (CGD)

- **Regulatory defect, adaptive immunity, Lymphocytic predominance**
  - Rapamycin (sirolimus)
  - Tacrolimus
  - Abatacept
  - Vedolizumab

- **B cell directed therapy**
  - Rituximab
  - IVIG

- **Hyper-/auto-inflammatory**
  - IL-1 blockade
  - IL-18 blockade
  - JAK inhibitors
  - IL-6 blockade

- HSCT
Disease Assessment

Individualized Immunophenotyping

Genetic Testing

Functional Studies and Targeted Therapies

PRECISION MEDICINE
Conclusions

- VEO-IBD is a different disease
  - Each patient has their own disease drivers
  - Lessons can be applied to older onset IBD

- Sequencing (Targeted panel/WES/WGS): powerful tool to identify disease causing mutations

- Multidisciplinary approach is needed to evaluate and treat this population

- Goal: **targeted individualized** therapy to identified pathways can be life-saving!
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