A Case of Monogenic Immune Deficiency and Autoimmunity

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Initial Presentation

A 40 year old F was referred for investigation of possible immunodeficiency

Background history:

• Recurrent infections
  • 18/12 recurrent sinopulmonary infections
  • Oral herpes simplex, shingles, oral and vaginal candidiasis
  • Previous history of peripartum Listeria sepsis
• ITP – requiring splenectomy 6 years prior, penicillin prophylaxis
• Chronic hepatitis B – on lamivudine

Social History:

• Migrated from Burma, married with 2 well children
• Youngest of 9 children
• Short stature, no other dysmorphic features
Initial Investigations

- Total WCC $12.2 \times 10^9$, LC $6.34 \times 10^9$
- IgG 5.73g/L, IgA 0.43g/L, IgM 0.67g/L
- Suboptimal antibody responses
  - Tetanus IgG <0.10IU/mL
  - Pneumococcus – undetectable for most serotypes
CVID panel

- Consistent with Freiburg Ia classification

Diagnosis of CVID made and commenced on IVIg replacement

Responded well to therapy with appropriate trough levels
2 Years Later

- Recurrent LRTI and exacerbations of bronchiectasis
- Recurrent herpes zoster infections
- Reactivation of HBV, started tenofovir
- Psoriatic arthritis, commenced on sulfasalazine
- Recurrent groin and skin abscesses
  - *Mycobacterium haemophilum* isolated, ?likely indolent therefore not treated
  - In retrospect, TB therapy in 1989

A Further 2 Years Later

- Recurrent thrombocytopenia
  - Sulfazalazine stopped as possibly implicated
  - No recovery of platelets
  - Romiplostim administered
ANZADA
Australia and New Zealand Antibody Deficiency Allele Study

WES = 80,000 base calls

**SNV**

Homozygous: 0 novel

Heterozygous:

- 60 Nonsense
- 9152 Missense
- 220 Novel missense
- 271 PID genes

-> 1 Heterozygous novel missense mutation

**STAT3 Exon 13 M394>T**

Filters – prevalence, in silico measures of damage (PolyPhen2, Sift, MutationTasker), gene ontogeny, mouse phenotypes, OMIM
Mogensen, Int Rev Immunol 2015

O'Shea J. NEJM 2013 368; 162.
Activating Mutations of STAT3


4 different de novo germline mutations identified in highly conserved STAT3 domains

5 patients with early-onset autoimmune disease
- Early onset diabetes
- Autoimmune enteropathy
- Autoimmune interstitial lung disease
- Juvenile arthritis
- Primary hypothyroidism
- Short stature & eczema

Reduced Treg numbers
13 individuals, 10 families with early onset autoimmunity + LPD
- WES $\rightarrow$ 9 germline mutations in STAT3 causing gain of function
- Lymphadenopathy, autoimmune cytopaenias, multiorgan autoimmunity, infections and short stature
- Hypogammaglobulinaemia, T cell lymphopaenia & $\geq$CD3+CD4-CD8-

*Milner. Blood 2015;125(4):591-599*
3 patients with activating mutations in STAT3

- Immunodeficiency phenotype
  - Hypogammaglobulinaemia with deficiency of switched memory B cells
  - High proportions of CD3+CD4-CD8-
  - Reduced Treg
  - Reduction in Th17
  - Reduced NK cells
  - Peripheral eosinopaenia
- Multisystem autoimmunity

1st described case of M394T described

- Mild autoimmunity - lymphocytic colitis, ITP, eczema
- Recurrent LRTIS
- <LC, <IgG, <memory + swM B cells, >CD21lo B cells
- <NK cells, <DCs, <Tregs
- Disseminated mycobacterial disease
  - IL-12-IFNγ signaling not impaired

Summary

- Germline activating mutations in STAT3 cause dysregulated cytokine signaling, reduction in Treg and altered Th17
- This results in autoimmunity and immunodeficiency
- M394T mutation -> recurrent mycobacterial infections
- Phenotype is not the opposite of HIES (loss of function)
- These findings have important implications for the understanding of lymphocyte tolerance and pathogenesis of systemic autoimmunity
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Mogesen T. Primary immunodeficiencies with elevated IgE. Int Rev Immunol 2015;1-18.