Normal IgG Antibody Deficiency

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A diagnostic problem

- 32 year old male
- Recurrent bacterial pneumonia
  - 5 hospital admissions 1993-94

- Underlying Immunodeficiency?
  - Low IgA during childhood and recurrent pneumonia <5 years
  - No family history of infection
  - IgA 0.1 (0.8-3.5g/L), IgM 0.3 (0.5-2g/L), IgG 8.3 (7.0-14g/L)
Immunology investigations 1995

Peripheral lymphocyte subsets:
- very few CD19+ and/or CD20+ B cells (less than 1% of lymphocytes)
- normal T cell and NK cell populations

Poor vaccination response to Pneumovax 23, conjugated Haemophilus and Tetanus toxoid
- Normal full blood count and ESR
- Normal IgG subclasses
- Normal complement
- Normal serum protein electrophoresis
What we know

• Treated as **antibody deficiency** with IV immunoglobulin

• No further serious infection or hospital admissions

• No autoimmune/ lymphoproliferative sequelae
What we don’t know

Diagnosis?
- Immunodeficiency phenotype
- Poor antibody response
- Clinical improvement after immunoglobulin

Normal IgG without CD19+ B cells?

Normal IgG with absent/ low IgM?
Possible theories

B cell development problem?
• Reservoir of restricted IgG secreted from plasma cells
• Abnormality arising in heavy chain isotype-switching mechanism?
Possible theories

Presence of an inhibitor?

• Blocking/Inhibiting agent
  • autoantibodies
  • cytokine milieu
Possible theories

Detection
  • Measurement error
Bone marrow examination 1995

- Trephine: no evidence of a lymphoproliferative disorder
- Aspirate: normal active marrow, no abnormal lymphocytes
- Flow: CD19 cells 4.4%

“majority of CD19+ cells display early B cell phenotype and less than 12% of CD19+ cells expressed mature B cell markers CD21 and CD22”
A defect of B cell maturation arising in the bone marrow

Atypical presentation of CVID?

Pre B-cell check-point defect?


### Table 3: Clinical data and Btk mutations of 16 patients reported in the world literature with atypical XLA.

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<th>Patient no.</th>
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<th>IgG</th>
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Source of immunoglobulin production?

• “Leaky B cells”
  • Pre-B cells in bone marrow may be source of limited immunoglobulin production

• Restricted IgG from plasma cells or memory B cells
A real problem

- Moved to UK in 2017
  - last SC immunoglobulin in Oct 2017

- Clinically well in Feb 2018
  - IgG 10.02g/L (6-16), IgA <0.05g/L (0.8-4) and IgM 0.09g/L (0.5-2)

- Admitted to ICU with sepsis in June 2018

- Re-commenced on immunoglobulin therapy July 2018
Investigations in UK

• Repeat immunoglobulin in July 2018: IgG 7g/L (6-16g/L)

• Lymphocyte markers:
  • Absent CD19 cells (<1%)
  • normal T cell and NK cell populations

• Poor response to Pneumovax and Haemophilus vaccination

• No paraprotein band on serum electrophoresis
Where to from here?

- Life long immunoglobulin +/- antibiotics when required
- Molecular genetic testing