Relapsing-remitting granulomatous disease in 22q11 deletion syndrome

Dr Paxton Loke
Department of Allergy and Immunology, Royal Children’s Hospital, Melbourne, Victoria.
Background

13 year old girl
- 22q11 deletion (a.k.a. DiGeorge syndrome)
  - Diagnosed by FISH at age 3 ½ years in context of developmental delay in Tasmania
  - Confirmed on microarray 2014
- Referred to Immunology in 2011 (age 8)
  - Long history of recurrent sino-pulmonary infections (Pneumonias/Suppurative Otitis Media/Chronic Moist cough)
- Immune investigations
  - Mild CD8 T cell lymphopenia.
  - Markedly reduced naïve T cells.
  - Reduced lymphocyte proliferation to PHA and anti-CD3.
  - Pan-hypogammaglobulinaemia (IgG 2.33/IgA 0.12/IgM 0.33)
- Reduced memory B cells
- Poor response to vaccines (Pneumovax, tetanus & Hib)
- Diagnosed with antibody deficiency (“CVID-like”)
  - Started on IVIG replacement, now on SCIG.
- CT chest 2011
  - Bronchiectasis
  - Generalised extensive lymphadenopathy with bilateral scattered discrete lung nodules.
1st episode - Oct 2013

- Presented with cough, lethargy & fever
  - BAL – CMV +ve. Treated with IV ganciclovir.
- Anaemic, thrombocytopenic with hepatosplenomegaly
  - Workup over the next few months
  - Bone Marrow biopsy – no marrow infiltrate
  - Lymph node biopsy – granulomatous changes
  - CT chest/abdo/pelvis
    - Multiple lung nodules. Multiple enlarged mediastinal lymph nodes
    - Bronchiectasis.
    - Retroperitoneal lymphadenopathy and splenomegaly 23cm.

- Started on 2mg/kg Prednisolone in Jan 2014 for:
  - Granulomas in lung and abdomen
  - Cytopaenias (presumed autoimmune).
  - Gradual wean over 6 months, ceased 1/7/2014.
  - Cytopaenias resolved.
2\textsuperscript{nd} episode - October 2014

- Relapse of granulomatous disease
  - Presented to local hospital with 3/52 fatigue, fevers and transferred to RCH.
  - Mediastinal mass on CT chest at local hospital, with airway compression.
  - Malignancy (i.e. lymphoma) ruled out.
    - Bone marrow biopsy – normal
    - PET scan – no malignancy.
    - CT chest/abdomen/pelvis
      - Thoracic and abdominal (retroperitoneal) lymphadenopathy
      - Splenomegaly 24cm
    - Cervical Lymph node biopsy – non-necrotising granulomatous changes
- Treated with 2 doses of Rituximab
- Commenced on MMF 750mg BD.
- No steroids this admission.
3rd episode – September 2015

- Presented to local hospital with fevers and lethargy.
- Background – 2/12 of issues with her bone-anchored hearing aid (BAHA) – infected/treated/re-infected
- Cytopaenias recurred and increased splenomegaly at local hospital.
- IV methypred 1mg/kg prior to transfer to RCH.
- At RCH
  - BAHA replaced by ENT.
  - Treated for infections (started at local hospital).
  - Bone marrow biopsy – no evidence of malignancy.
  - B cells have returned – Treated with 2 doses of Rituximab.
  - MMF increased to 1g/750mg.
  - On weaning regimen of oral Pred.
- CT chest/abdo/pelvis
  - Near-complete resolution of previous numerous small lung nodules. Reduced splenomegaly persist.
4th admission – March 2016

- Presented to local Hospital with 1/52 history of headache, photophobia & lethargy
  - LP: 117 WCC (predominantly lymphocytes), 99 RBCs.
  - CSF infection screen negative (viral, bacterial, mycobacterial, fungal)
  - Developed 1x GTC and 2x ?Temporal lobe seizures (aggression/strange smell).
  - Initial MRI - 2 focal deep white matter lesions
  - MRI - multifocal areas of cortical abnormality/leptomeningeal disease/associated ischaemia.
  - No clinical improvement on ceftriaxone, azithromycin, amphotericin and acyclovir.
    - Developed short periods of confusion & subtle right facial droop
    - Commenced on IV Dexamethasone 10mg/m² and sirolimus (load 4mg/m²), with clinical improvement.
- Progress 3 months post discharge
  - Weaning of steroids and ongoing sirolimus (target 5-10).
  - MRI/Neurology opinion – areas of ischaemia likely secondary to focal inflammation/cerebral vasculitis.
- Final diagnosis – likely inflammatory meningitis with vasculitis
soluble CD25 (sIL-2R)
Surrogate marker of T cell dysregulation
Introduction & pathogenesis of 22q11.2 deletion

- Hemizygous deletion at 22q11.2 and autosomal dominant inheritance
- *De novo* (93%, range 90-95%) vs inherited from a parent (7%, range 5-10%)
- Incidence: 1:3000 – 1:4000 live births
- Loss of 1.5-3.0Mb (30-40 genes) with role of many genes still unclear.
- Deletion affects the pharyngeal arches and pouches
  - Forms the embryonic precursor for thymus, parathyroid glands and conotruncal heart regions.
- *TBX1* gene (T-box, a transcription factor) implicated in:
  - Heart defects, cleft palate, facial features, hearing loss, thymic aplasia, hypocalcaemia
  - Regulates expression of other transcription factors
  - Important for the development of the branchial arches
- *COMT*
  - Increased behavioural problems & mental/psychiatric illness
- *CRKL*
  - Abnormal growth factor signalling & aberrant thymic development.

http://www.ncbi.nlm.nih.gov/books/NBK1523/
Immunological features of DGS

• Complete DGS (cDGS)
  • Complete absence of the thymus (athymia)
  • Absolute T Lymphopenia
  • SCID-like phenotype (T-B-NK+) with other variable features of DGS
  • Absent mitogen (proliferation) responses
  • Suffer from opportunistic infections
  • Rare and affects < 1% of patients with 22q11 deletion
  • Treatment of choice is thymic transplant
  • Using donor thymus from infants undergoing cardiac surgery (CMV positive excluded)
  • Donor thymus cultured (12-21 days) and implanted in the quadriceps muscle.

• Atypical cDGS
  • Presence of some mature T cells via maternal engraftment or oligoclonal expansion of memory T cells (no thymic processing).
  • Erythrodermic rashes, enteropathy and lymphadenopathy (Omenn’s-like)
  • Treatment is thymic transplant (pre-conditioning ATG, and cyclosporine)
Immunological features of DGS

- Partial DGS (pDGS or incomplete DGS)
  - Most common clinical scenario with small, often atopic, thymus development
  - Variable number of T cells (low to normal) and naïve T cells (reduced or normal)
  - Generally normal mitogen responses
  - Most pDGS do not suffer opportunistic infections
  - Infections are more towards sino-pulmonary (humoral) types
  - Humoral deficiency with functional B cell deficit & hypogammaglobinaemia associated with more severe infections (2.7% on Ig replacement in 2012 study of 1023 DGS cohort).

- Partial DGS with autoimmunity
  - Immune dysregulation → autoimmunity
  - Between 8.5% to 33% and likelihood increases with lower T-cell numbers.
  - Cytopenias, juvenile RA, autoimmune haemolytic disease (ITP, anaemia), hypo/hyperthyroidism.
  - Disturbance of central or peripheral tolerance as a consequence of thymic abnormality.
  - Reduced numbers of natural T regulatory cells (CD4+ FOXP3+)
  - Higher numbers of naïve T cells in early childhood may be protective.
Partial DGS with granulomatous lymphoproliferation - Case Reports

- 11 yr girl with mutation in TNFRSF13B with granulomatous lymphoproliferation.
  - CVID with heterozygous mutation in TACI (encoded by TNFRSF13B - 10% of patients with CVID)
  - Developed GLILD and widespread granulomatous-lymphocytic disease
  - Treated with steroids, IVIG, hydroxychloroquine and azathioprine
  - Deceased following early haemorrhagic post-operative complications following splenectomy.
- 15 yr girl with pulmonary/extranodal marginal zone lymphoma (MALT) & granulomatous inflammation
  - Lung biopsy: inflammation & granulomatous disease & extranodal marginal zone lymphoma of MALT
  - Bone marrow: granuloma but no lymphoma
  - PET: extensive hypermetabolic pulmonary nodules & lymphadenopathy
    - 6 cycles of rituximab/cyclophosphamide/hydroxydaunorubicin/vincristine/prednisolone (R-CHOP) - achieved remission
  - Later new lymphadenopathy - all granuloma and follicular hyperplasia
    - 4 doses of weekly rituximab & azathioprine
- 4 other case reports of DGS with LPD has also been reported:
  - 23 month girl with widespread EBV+ Diffuse large B-cell lymphoma
    - Refused treatment for malignancy, deceased
  - 7 month boy with EBV+ Diffuse large B-cell lymphoma
    - Treatment not reported, deceased
  - 14 yr girl with EBV+ Diffuse large B-cell lymphoma and generalized lymphoadenopathy
    - Chemotherapy, thymus transplantation, EBV CTLs
  - 25 yr male with EBV+ peripheral T cell lymphoma
    - Nil treatment, decreased
Treatment options

• Treatment of granulomatous disease in CVID
  • Steroids
  • Azathioprine
  • Cyclosporine
  • Mycophenolate mofetil (MMF)
  • Cyclophosphamide
  • Infliximab
  • Others – thalidomide, hydroxychloroquine, methotrexate

• Treatment of GLILD in CVID
  • 10–15 % of patients with CVID develop GLILD (granulomatous lymphocytic interstitial lung disease)
  • Combination therapy - rituximab and azathioprine

• Treatment of autoimmune lymphoproliferative disease
  • Steroids
  • MMF
  • Sirolimus
  • Rituximab

Rao & Oliveira, Blood. 2011;118(22): 5741-5751
Back to the patient

• Aetiology of underlying condition
  • 22q11 deletion
  • Whole exome sequencing—nothing identified at this stage (i.e. unable to find 2nd mutation)
• Probable cerebral vasculitis on MRI brain
  • No evidence of vasculitis elsewhere at this stage.
• Granulomas, bronchiectasis and cytopaenias appear stable.
• Poor quality of life
  • Significantly cushingoid.
  • Complications of OSA – snoring, poor sleep.
• Elective admission this week at RCH for further mx
Acknowledgements

- Patient and family
- Medical Team
  - Consultants Dr Joanne Smart, Dr Sharon Choo & Dr Theresa Cole
  - Past/Present Immunology Fellows and Nurses
  - Prof Graham Davies