APID2016 CASE SUMMARY: CTLA-4 DEFICIENCY PRESENTING AS A PID

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Case summary

19yo male who was transferred to our care from the local Children’s Hospital. He was initially referred to the Immunology Department at the children’s hospital at the age of 16yo with a chronic moist cough, persistent lymphopenia and panhypogammaglobulinemia. (IgG 1.43g/L, IgA <0.05g/L, IgM 0.24 g/L). He had no other symptoms and was noted to have some mild splenomegaly on examination. Both parents are alive, he has one well brother with no significant past medical history and there is no family history of immunodeficiency. Our patient had a significant history of autoimmune haemolytic anaemia that was not responsive to steroids or IVIG, so he was treated with Rituximab with good response.

On testing organised by the Immunology department at the children's hospital, our patient was found to have normal numbers of T cells, B cells and NK cells but reduced switched and marginal zone memory B cells with reduced naïve CD4 and CD8 T cells. He had evidence of poor specific antibody production to polysaccharide vaccines, with seroconversion to 0/15 Pneumovax serotypes. He was promptly started on immunoglobulin replacement.

On further investigation of his cough, he was found to have innumerable solid and ground glass nodules in both lungs on CT Chest, with a restrictive pattern on RFTs. Lung biopsy of one of these nodules revealed changes consistent with Lymphocytic Interstitial Pneumonitis (LIP), with focal infiltration of mostly CD3+ Lymphocytes. He was started on Sirolimus as management of the LIP.

He then went on to have Genetic testing, and on SNP microarray was found to have a deletion in chromosome region 2q33.2-2q33.3 in the region of the ICOS and CTLA4 genes. Further sequencing of his second ICOS gene was found to be normal, which means his presentation and genetic findings were consistent with a CTLA4 Haploinsufficiency. In January of 2016, he was admitted to our hospital with a right lower quadrant visual field defect in his right eye with normal visual acuity and evidence of papilloedema. MRI showed changed consistent with an inflammatory pseudotumour involving his right medical rectus and optic nerve. He was pulsed with IV Methylprednisolone and his Sirolimus dose was uptitrated.

CTLA4 Haploinsufficiency

Cytotoxic T-lymphocyte Antigen 4 (CTLA-4) is the high affinity receptor for CD80/86 ligand and acts as a ‘costimulator’ with a critical inhibitory function. It is constitutively expressed by CD4+FOXP3+ Regulatory T cells (TReg), but becomes dramatically upregulated following activation. CTLA-4 is also expressed on regular CD4+ T cells following activation.

There have been 2 major papers published on patients presenting with primary immunodeficiency (PID) in which CTLA4 Haploinsufficiency is the underlying genetic defect leading to their phenotype. Kuehn et al 2014 described 4 unrelated families with unique mutations and 6 affected individuals between them, whilst Shubert et al 2014 described 6 families with unique mutations and 14 affected individuals between them. There was evidence of incomplete penetrance with unaffected members of the family carrying the same mutation. The clinical phenotype amongst the affected individuals were similar, with hypogammaglobulinemia and autoimmune manifestations like enteropathy, autoimmune haemolytic anaemia, splenomegaly and lymphocytic tissue infiltration (Lung, Bone Marrow, Liver, Brain). The immune phenotype of these individuals were also similar between the
two papers, with reduced naïve T cells, reduced switched memory B cells, evidence of increased lymphocyte exhaustion and persistent immune activation. Kuehn et al was able to demonstrate reduced CTLA-4 expression and mRNA production in affected patients compared to healthy controls.

Treatment options
The treatment of patients with CTLA4 haploinsufficiency to date has been replacement of immunoglobulin to mitigate their infection risk, as well as the use of systemic immunosuppression to manage their autoimmune manifestations. As a lack of CTLA-4 is the underlying pathological cause of disease in patients with CTLA4 haploinsufficiency, it was postulated that replacement of CTLA4 in these patients would reverse the effects of their underlying mutation. Kuehn et al showed that in vitro addition of CTLA4-Ig to CD4+ and CD8+ T cells lead to reduced activation.

Abatacept is a commercially produced CTLA4-Ig that has historically been used for the treatment of rheumatoid arthritis. Unfortunately, there have been no trials examining the utility of Abatacept in the treating individuals with CTLA4 Haploinsufficiency. There has been a paper published, however, on the use of Abatacept in vivo in patients with LRBA deficiency, a disease that presents like CTLA4 Haploinsufficiency as LRBA is a critical control point for lysosomal turnover of CTLA-4. In a paper by Lo et al 2015, they described the treatment of 3 individuals with LRBA Deficiency with Abatacept. They were revealed to have prompt resolution of their autoimmune and tissue infiltration manifestations of their disease after the introduction of Abatacept, as well as an improvement in their FEV1 and DLCO.

Summary:
- CTLA-4 has a critical inhibitory function in the immune system
- Patients with CTLA4 Haploinsufficiency display features of severe immune dysregulation, with a combination of immunodeficiency and autoimmune tissue infiltration and destruction
- This is consistent with their immunophenotype with reduced naïve T cells, switched memory B cells and features of immune hyperproliferation
- Treatment options include systemic immunosuppression, directed therapy with CTLA4-Ig (Abatacept)

References