

a mixture of CD20+ B and CD3+ T cells, abundant CD138+, IgG+ plasma cells (PCs), with some IgG+ PCs (CT of the neck and chest was completed for possible staging and revealed cervical lymphadenopathy, nasal polyposis, a soft tissue mass vs. enlarged lateral rectus muscle (left orbit), and mediastinal lymphadenopathy. A diagnosis of Autoimmune Lymphoproliferative Syndrome (ALPS) was presumed by the hematologic/oncologic team given his elevated IgG (6.682 mg/dL) and elevated vitamin B12 (>2000) with multiorgan involvement. ALPS panel revealed a mutation in FASLG (Allele 1, c.-2C>T) which is a variant of uncertain clinical significance. ALPS Criteria/Score was + for 1/4 criteria (CD3+CD25+/HLA DR Ratio < 1.0). He had been referred to the NIH for further management of ALPS before initial presentation to our office. Immunologic work up revealed immunoglobulins of IgG: 6,600 mg/dL, IgA: 83 mg/dL, IgM: 71 mg/dL; 13/23 protective streptococcal titers (> 1.3 mcg/mL); HIB: 0.46 mg/L; negative Quantiferon gold, and HIV-serology. At that point IgG4RD vs. Castleman disease was suspected instead of ALPS. Further work up showed a normal IL-6 level, and Human Herpes Virus 6 was also negative. IgG subsets showed an elevated IgG1 (2670 mg/dL), IgG2 (1450 mg/dL), IgG3 (355 mg/dL) and normal IgG4 (20.9 mg/dL). Excisional lymph node biopsy was recommended to rule out Castleman syndrome or IgG4RD. A left salivary gland was removed and showed mainly IgG4 positive PCs with no multicentric lymphocytic infiltrates. Dilution of the patients serum to determine if there was a prozone affect that minimized the IgG4 level showed an elevated IgG4 level of 2700.9 mg/dL. This is in the 1st percentile of all cases of IgG4RD in terms of serum IgG4 concentration. He was diagnosed with IgG4RD, a form previously called Mikulicz disease, which is comprised of lacrimal and parotid gland enlargement. Rituximab was given initially because of the severity of his disease. After two cycles he showed decreased lymphadenopathy, notable weight gain and marked decrease in fatigue. Conclusions: IgG4RD is a rare and complex immunologically based disease process rarely seen in children or adolescents. Patients with IgG4RD often undiagnosed at initial evaluation. Normal serum IgG4 levels are seen in 40% of patients with IgG4RD and thus a normal IgG4 level should not be used as a biomarker to make the diagnosis of IgG4RD or in treating this disease. Furthermore, the possibility of having a prozone affect in measuring IgG4 needs to be considered and evaluated. Meticulous correlation of clinical, pathologic, and imaging findings is required to make the diagnosis.

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Modelling human immune deficiency from novel missense mutations with orthologous heterozygous mutations engineered in mice by CRISPR/Cas9

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Introduction/Background: Next generation sequencing has resulted in substantial progress in identification of Mendelian immune deficiency syndromes. In some cases, however, putative causal mutations occur in single kindreds, or even individual patients. Under these circumstances, functional analysis of patient derived cells combined with

in vitro analysis of genetically manipulated cell lines can provide additional evidence in support of genetic causation, but this might not be conclusive.

Objectives: Understanding how genetic defects result in complex syndromes of immune deficiency and immune dysregulation can be impossible to achieve in vitro. One method for overcoming these obstacles is to generate accurate mouse models of human immune deficiency

Methods: Mouse models of human immune deficiency are a valuable tool in which the murine genome is engineered to introduce a mutation orthologous to that discovered in the patient. We have applied this strategy to elucidate causation and mechanism of immunological defect in several mutations affecting the NF- κ B pathway.

Results: So far, defects in both canonical and non-canonical pathways of NF- κ B activation have been shown to cause immune deficiency, often associated with immune dysregulation. We describe a known defects and novel putative defect identified in the canonical NF- κ B pathway

Conclusions: CRISPR-cas9 mouse models can be used to elucidate mechanism of disease and provide compelling evidence that mutations are causative.

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Novel Epigenetic Immune Cell Quantification Suitable For Primary Immune Deficiencies And Immundysregulatory Disorders

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Introduction/Background: Primary immune deficiencies (PID) with or without immunodysregulation are rare diseases resulting from monogenetic aberrations leading to either infections or autoimmune manifestations or both. Early diagnosis and treatment are crucial for reducing morbidity and mortality. Beside genetic diagnosis not commonly yet performed, current standard methods for early diagnosis are dependent on either fresh samples or limited to certain cell types. To overcome those limitations, especially in newborn screening, a novel technology of methylation-based qPCR can be applied. Among the known epigenetic modifications, DNA demethylation is the most stable and genomic loci with highly cell type specific demethylation sites can be identified. Differential methylation can be measured from blood samples of limited availability, or with suboptimal storage. We previously showed that thymic-derived T