Auto Anti-E in a 2 Month Old Male: A Case of IPEX

UC DAVIS HEALTH

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Background:
A 2 month old boy presented to our institution after a 1 month hospitalization in Japan. He was admitted there, several weeks after his unremarkable term birth to an AB Rh positive woman, with lethargy, failure to thrive, bloody mucoid stools with eosinophilia, and an elevated serum white count. He was found to be anemic and thrombocytopenic and required multiple transfusions. Additionally, he had a diffuse, scaling, erythematous rash over his inner thighs and abdomen (**Figure 1a**).

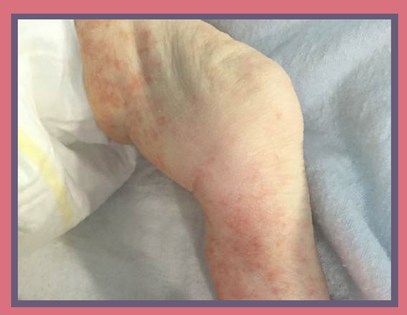

Figure 1a: *At presentation, the patient had a scaling erythematous rash on his bilateral thighs and abdomen.*

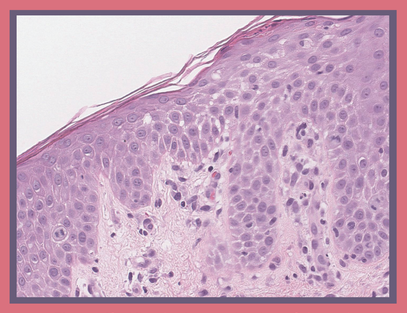

Figure 1b: *Histologic examination of the rash showed spongiotic dermatitis with focal parakeratosis, a nonspecific finding in inflammatory dermatitides.*

Methods:
Records received with the patient included English- and Japanese-language reports, and the suspected diagnosis at the outside institution was not known. Initial workup was suspicious for an allergic / necrotizing enterocolitis. The patient had an elevated LDH and potassium, and concern was raised for leukemia with possible tumor lysis syndrome. Standard panels of flow cytometric studies performed at our institution showed no increase in blasts, and a nonspecific finding of increased CD4:CD8 T-cell ratio (**Figure 2**). The baby's antibody screen performed at our institution was positive and anti-E was identified. In addition, AHG testing was positive using polyspecific (anti-IgG; -C3d), anti-IgG and anti-complement (anti-C3b; -C3d) reagents. His RBC antigen phenotype was positive for E, e, and C antigens.

Concern for hemolytic disease of the newborn due to maternal anti-E was raised as was the possibility of passive transfer of anti-E from administered blood products. However, records review confirmed the maternal antibody screen was negative, and confirmed he had been transfused with antibody-negative units. Further workup revealed no infection or hematologic proliferation. Biopsy of his rash showed spongiotic dermatitis (**Figure 1b**). His clinical course deteriorated, and he developed hepatomegaly and jaundice. A concern for Wiskott-Aldrich syndrome was raised, and workup showed normal immunoglobulin levels, but with elevated IgE (15270 kU/L; RR: 0-2.9). Anti-platelet antibodies were identified. Three days after admission, testing was sent for genetic alterations of *FOXP3*, while simultaneously a Japanese-speaking physician at our institution was located and asked to interpret a prior flow cytometry study which showed a deficiency of CD4+ / CD25+ / FOXP3+ lymphocytes.

Findings:
First reported in 1982, there are now over 70 mutations of the Forkhead Box Protein 3 (*FOXP3*) gene implicated in a syndrome called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked; **Figure 3**). The FOXP3 protein is a transcription factor regulatory protein constitutively expressed in CD4+ regulatory thymus-derived T cells (tT_{reg}), and is the "master regulator" of tT_{reg} development and function. Mutations in this gene, located at Xp11.23, result in decreased tolerance to self antigens and resultant autoimmune disease. Patients, all male, present prenatally or within months of birth, often with profuse watery and bloody diarrhea. This results from auto-antibody production. Similarly, they can develop a variety of autoimmune conditions (e.g. DMI, dermatitis, thyroid disease, renal failure, cytopenias), some of which were present in this case (i.e. dermatitis; RBC and platelet antibodies). While infections are not characteristic of the disease process, breakdown of mucosal barriers from autoimmunity can result in opportunistic infections.

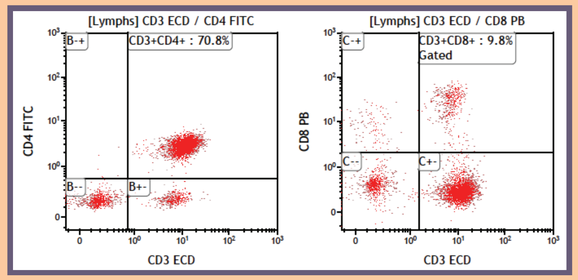

Figure 2: *Flow cytometry findings show an increased CD4:CD8 ratio in the lymphocyte-gated population consistent with IPEX syndrome.*

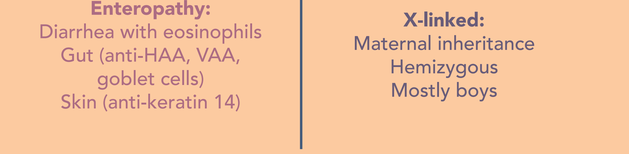

Figure 3: *IPEX syndrome has a number of effects, including immune dysregulation with a tolerance for auto-reactive B-cells and disturbances in interleukins that have multiple downstream effects, including eosinophilia. This leads to polyendocrinopathy, with antibodies to glutamic acid decarboxylase (GAD), islet cell antibodies (ICA), insulin autoantibodies (IAA), islet antigen 2 (IA2), and zinc transporter 8 (ZNT8) leading to type I diabetes mellitus; and, antibodies to thyroperoxidase (TPO) and anti-thyroglobulin (TGB), leading to thyroiditis. Auto-antibodies also lead to epithelial damage, including anti-harmonin antibodies (HAA), anti-villin antibodies (VAA), and antibodies to goblet cells in the gut; also, anti-keratin antibodies lead to dermatitis. The disorder is X-linked and most patients are hemizygous for the mutant allele.*

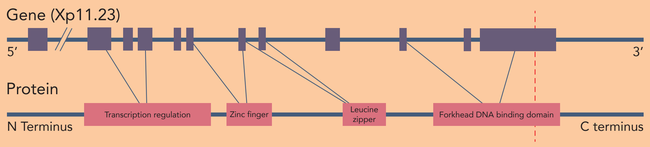

Figure 4: *Schematic representation of the Forkhead Box Protein 3 (FOXP3) gene and protein. The red dashed line indicates the mutation in our patient (c.1189C>T [p.Arg397Trp]) in the forkhead DNA binding domain. This mutation inhibits the function of the protein; there is moderate physiochemical difference between Arg and Trp (Grantham dist: 101). Our patient was hemizygous for this mutation.*

Our patient had a mutation (c.1189C>T [p.Arg397Trp]) located within the protein's DNA-binding domain (**Figure 4**), associated with high mortality in reported cases. The mutation results in a nonfunctional FOXP3 protein and loss of the inhibitory action of tT_{regs} on B cells (leading to auto-antibody proliferation) and on T effector cells (leading to Th2 proliferation, IL-5 over-expression, and eosinophilia), in addition to the over-expression of IL-17 producing T-cells. Not all patients with this mutation have a similar clinical course, suggesting other genetic interactions, epigenetic diversity, and environmental cofactors in disease progression. Standard of care includes immunosuppression and stem cell transplantation.

Conclusion:
While rare, the presentation of a neonatal patient with a positive antibody screen and DAT with a negative maternal workup is cause to consider possible autoimmune processes, including IPEX. The neonate was transferred to an outside institution as a stem cell transplantation candidate and the subsequent clinical outcome is unknown.

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