TNFAIP3: Evolving clinical picture from Autoinflammatory syndrome to Autoimmune lymphoproliferative syndrome

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By Sosa Adah

Background: Autoimmune lymphoproliferative syndrome (ALPS) is a rare genetic disorder of the immune system that can affect children and adults. The most frequent presentation is benign lymphoproliferation limited to lymphoid organs such as the lymph nodes, liver, and spleen which result in splenomegaly and lymphadenopathy, two prominent features in ALPS patients. ALPS can lead to anemia, thrombocytopenia, and neutropenia which increase risks of infection and hemorrhage. Most cases are caused by either a germline or somatic mutation in the FAS, FASLG, or CASP10 genes that are involved in cell apoptosis. Tumor Necrosis Factor Alpha, Induced Protein 3 (*TNFAIP3*) is a protein coding gene associated with Haploinsufficiency of A20 (HA20). Hallmark features of HA20 include recurrent oral, genital and/or gastrointestinal ulcers, arthralgia/arthritis, and early-onset systemic inflammation.

Case: A 3-year-old female presented at 4-months old to the intensive care unit in shock with a vesiculopustular skin rash & indurated plaques on her extremities. Upon presentation, she was febrile and in respiratory failure requiring intubation. Infectious workup was unrevealing. Following discharge, genetic evaluation revealed heterozygous *TNFAIP3* c.475del, p.Tyr159Metfs*57. Brain MRI/MRA/MRV were normal, EGD/colonoscopy showed chronic gastritis with normal biopsy, and eye exam showed no ocular inflammation. Immunology evaluation revealed T cell lymphopenia: CD3 1576 mm^3, CD4 1182 mm^3, CD8 368 $mm^{3,}$ $CD4^{-}CD8^{-}$ $TCR\alpha\beta^{+}$ T cells(1.6 % of T cells) with normal CD 19, NK cells, immunoglobulins, hib/tetanus titers, oxidative burst test and lymphocyte proliferation to mitogen. At the age of 2, patient developed elevated AST/ALT (~300s-700 units/L) with associated pancytopenia 8 months later in addition to physical findings of recurrent oral ulcers Abdominal ultrasound remarkable for splenomegaly. Liver biopsy showed acute & chronic hepatitis with lymphocyte predominance, bile duct injury and bridging fibrosis. Bone marrow biopsy was negative for malignancy. Flow cytometry on peripheral blood had elevated $CD4^{-}CD8^{-}$ $TCR\alpha\beta^{+}$ (4.7% of T cells), suggestive of ALPS. Fas mediated assay, sFASL, IL-10, IL-18 were obtained & pending.

Discussion: *TNFAIP3* is known to present with autoinflammatory symptoms. Our case shows that patients with *TNFAIP3* variants can have an evolving clinical picture that can include a spectrum of autoimmune lymphoproliferative syndrome -like disease. A hallmark finding of ALPS is a high proportion of $CD4^{-}CD8^{-}$ $TCR\alpha\beta^{+}$ T cells, called double-negative T cells. A 2017 case report revealed a 1 year old male with findings of bilateral cervical lymphadenopathy and hepatosplenomegaly. *TNFAIP3, A20* was identified in this patient showing the ALPS-like phenotype with elevated double-negative T cells (5.1% of T cells).