Pediatric Recurrent Rosai-Dorfman Disease with germline heterozygous SLC29A3 and somatic MAP2K1 mutations

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Abbreviations Table

RDD	Rosai Dorfman Disease
LCH	Langerhans cell histiocytosis
HHV6	Human herpes virus 6
TCR	T-cell receptor
T-LGL	T-cell large granular lymphocyte
ALPS	Autoimmune lymphoproliferative syndrome

This case has been submitted for presentation at the Histiocyte Society meeting in 2020.

To the Editor:

Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytosis (LCH), disorder listed under the 'R group' of histiocytosis including familial and sporadic forms by the Histiocyte Society.[1-3] Patients with RDD classically present with cervical lymphadenopathy and some have extranodal disease. Somatic *KRAS* and *MAP2K1* mutations were reported in RDD patients.[4] We report a patient with recurrent RDD with underlying germline and somatic mutations.

A currently 7-year-old African-American male patient presented with cervical lymphadenopathy at 19 months of age. He had dysgammaglobulinemia with increased IgG, IgA, and IgE levels and elevated C-reactive protein and erythrocyte sedimentation rate. He tested positive for human herpesvirus 6 (HHV6). Lymph node biopsy findings were consistent with RDD and negative for HHV6 staining. Due to the progression, he was treated on oral steroids with improvement. He presented 2 1/2 years later with recurrent lymphadenopathy and also had been diagnosed with autism spectrum disorder. Repeat scans and biopsy confirmed the recurrence of RDD (Figure1 A-C). A sizeable population of CD5-dim lymphocytes and clonal T-cell receptor (TCR) rearrangement pattern suggested T-cell large granular lymphocyte (T-LGL) expansion correlating with B-cell population (Figure1-D). He failed intravenous steroids and has had two debulking surgeries so far. Vitamin B12 levels were very high and methylmalonic acid within normal levels. He has decreased lymphocyte responses to phytohemagglutinin, concanavalin A, tetanus and candida antigens with currently normal immunoglobulin levels and small lymphadenopathy. Tumor tissue 596 gene mutational analysis on the most recent sampling, but not on previous ones revealed a known pathologic somatic *MAP2K1* gain of function mutation (c.159T>A p.F53L), along with overexpression of*MAP2K1* , *NFBK1,* and *NFBK2* mRNA level; whole-exome sequencing showed likely pathogenic germline heterozygous mutations in SLC29A3 (c.45delC) and ACSF3 (c.1075G>A) genes.

This patient has dysgammaglobulinemia, and increased inflammatory markers, which has correlated with disease burden and shown improvements following debulking surgeries. Increased T-LGL (18-41%) with clonal TCR rearrangement pattern likely reflect persistent immune dysfunction.[5] Despite very high vitamin B12 levels, a known feature of autoimmune lymphoproliferative syndrome (ALPS) and known link between ALPS and RDD, he neither has increased double-negative TCR alpha/beta T-cells, another hallmark of ALPS nor any known ALPS-related mutations.[6-7]

Homozygous germline *SLC29A3* mutations are described in Faisalabad histiocytosis and familial, but not sporadic RDD.[8]Cases of Faisalabad histiocytosis may mimic RDD.[9]Mutations in *ACSF3* are associated with combined malonic and methylmalonic aciduria and 40% of the patients develop symptoms in adulthood.[10]

Reactive nature of RDD and possible association with viruses have been suggested.[11,12] Discovery of BRAFV600E mutations in LCH and Erdheim-Chester disease supported the neoplastic nature of histiocytic disorders.[13] Mutations in *MAP2K1*have been associated with LCH and RDD and mutually exclusive somatic mutations in *KRAS* and *MAP2K1* with RDD.[14,4] Though somatic *MAP2K1* mutation might have been crucial in RDD pathogenesis in this patient, likely pathogenic and heterozygous SLC29A3 mutation might have been contributory as well. Similarly, dysgammaglobulinemia and inflammation process could be related to *SLC29A3* mutation.[15,16] Therefore, this case raises the possibility of cooperating germline and somatic mutations in the development of RDD.

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Figure Legend

Figure1. Clinical, imaging and flow cytometric findings in the case. (A) Large right cervical lymphadenopathy; (B) Magnetic resonance imaging showing multiple enlarged lymph nodes forming a conglomerate in right cervical region; (C) Several lymph nodes removed by surgery; (D) While increased peripheral blood CD5-dim T cells (24.9%) express predominantly CD8 (61%), some are CD4/CD8-negative (double negative).