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Letter to the Editor

Probable Autoimmune Lymphoproliferative Syndrome with Monogenic Lupus Due to KRAS Mutation

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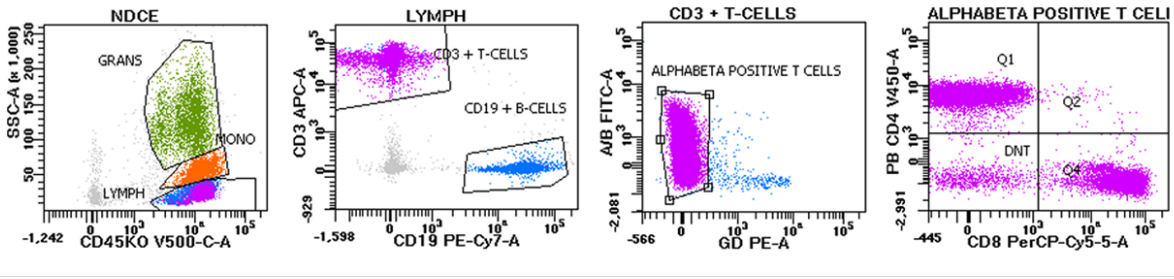
To the editor.

Autoimmune lymphoproliferative syndrome (ALPS) is a rare hereditary disease due to a defect in immune regulation defined by disrupted lymphocyte homeostasis. This condition is characterized by the accumulation of abnormally active lymphocytes in lymphoid organs due to an alteration of the extrinsic apoptotic pathway mediated by the protein receptor FAS which results in the autoimmune lymphoproliferative syndrome and more recently in defects affecting the intrinsic apoptotic pathway mediated by RAS proteins.[1,2] This apoptotic defect induces the persistence of autoreactive cells, with an increase (>1.5 % of total Lymphocytes or 2.5% of CD3+ lymphocytes in the setting of normal or elevated lymphocyte counts) in TCRαβ+CD4-CD8- double negative T (DNT) lymphocytes. These cells are a hallmark of ALPS and other ALPS-like disorders. The abnormal accumulation of lymphocytes DNT lymphocytes produces a myriad of clinical manifestations including lymphadenopathy, splenomegaly, autoimmune cytopenias and propensity for lymphoid malignancies. The most common defect responsible for ALPS is germline heterozygous mutation in FAS, which shows an autosomal dominant pattern of inheritance. Somatic FAS mutations turn out to be the 2nd most common cause. Other pathogenic genes include FASL, CASP10, CASP8 and NRAS.[3,4]

Germline KRAS pathway mutations have been described in association with cardio facio-cutaneous or Noonan syndrome.[5] Some rare cases of ALPS-like disease caused by somatic KRAS mutation have been published.[6,7]

Monogenic lupus is a kind of SLE that commonly manifests in childhood, usually before the age of five, with severe disease symptoms. This type of lupus is caused by a genetic variation in a specific gene. KRAS mutation is an uncommon cause of the aforementioned phenomenon.[8] We describe a case of probable ALPS with systemic lupus erythematosus in a child, who was found to have a KRAS G13C mutation.

Case. A one-and-a-half-year-old boy of Indian origin was brought by his parents with a 1-year history of fever on and off and gradually progressive abdominal distension for 10 months. Fever was mild to moderate grade and intermittent in nature. Parents have consulted multiple centers for the same and the child has been prescribed multiple antibiotics including anti-tubercular therapy during the last 1 year. He had also received 1 aliquot of packed red blood cells at 6 months of age and multiple random donor platelets in the last 2 months. Family history was insignificant. General physical examination revealed pallor and multiple petechial spots over both the lower limbs. On per abdomen examination, the spleen was palpable 7 cm below the left costal margin and the liver was palpable 5 cm below the right costal margin. Complete blood count showed hemoglobin of 3.4 mmol/L (5.5 g/dl), WBC counts of 17×10^9/L, and platelet count of 3×10^9/L. Peripheral smear showed spherocytes and numerous nucleated RBCs. Serum LDH level was 441 mg/dL and direct Coomb's test was significantly positive (4+). A provisional diagnosis of Evan's syndrome was made, and he was started on steroids. Because of a prolonged history starting from infancy and organomegaly, the possibility of autoimmune disorders including ALPS was considered. Peripheral blood immunophenotyping determined 4.8% double negative $\alpha\beta$+ T cells out of total CD3+ cells (**Figure 1**). The autoimmune panel was positive for antinuclear antibody (>1:40) and high anti-dsDNA antibody (ELISA) (200 IU/ml). 2D echo didn't show any evidence of valvular defect but showed mild pericardial effusion. Based on SLICC criteria, he was diagnosed with SLE. Clinical exome sequencing was sent. Even after one week of steroid therapy, there was



Tube: DNT

Population	#Events	%Parent	%Total
All Events	1,221,486	####	100.0
SINGLETS	486,237	39.8	39.8
NDCE	125,015	25.7	10.2
LYMPH	53,314	42.6	4.4
CD3 + T-CELLS	18,792	35.2	1.5
ALPHABETA POSITIVE T (	18,380	97.8	1.5
Q1	9,131	49.7	0.7
Q2	80	0.4	0.0
DNT	889	4.8	0.1
Q4	8,280	45.0	0.7
CD19 + B-CELLS	23,999	45.0	2.0
MONO	31,482	25.2	2.6
GRANS	32,432	25.9	2.7

Figure 1. Flow Cytometry plots showing sequential gating to determine the percentage of double negative T cells among CD3 positive T cells.

inadequate response, for which IVIG (2 g/kg) was given over 2 days. There's gradual improvement in hemoglobin and platelet count and he became transfusion independent. During the fever workup, his blood culture grew *Escherichia coli* and it was treated with sensitive antibiotics. Clinical exome sequencing by next-generation sequencing detected a pathogenic variant of KRAS (Gly13Cys) at exon 2. The patient has been following up with us and doing well with low-dose steroids.

Discussion. Our patient showed severe autoimmunity in the form of immunological cytopenia and hepatosplenomegaly, which was identical to ALPS in certain ways. The patient also fulfilled SLE categorization criteria, including the presence of anti-ds-DNA, which is thought to be reasonably specific for SLE. Considering childhood onset of disease, simultaneous occurrence of two immune dysregulated disorders, and a genetically proven pathogenic mutation, a monogenic cause is the most likely explanation for the described phenotype.

There are around 16 case reports in the literature describing RALD (RAS Associated Leukoproliferative Disorder) secondary to KRAS mutation.[6,7] This entity has partial similarity to ALPS but usually doesn't match the requisite double negative T cell criterion. For the same reason, NRAS-associated ALPS, which was formerly classified as Type IV ALPS, is now considered under this entity. However, our patient did have increased TCR$\alpha\beta^{+}$-DNT cells. Hence, the diagnosis of 'probable ALPS' is more apt here.[2-4]

Monogenic lupus is a group of unique genetic defects that cause similar clinical symptoms and culminate in autoantibody production. It is characterized by childhood onset SLE with predominant renal, neurological, and hematological manifestations. It is reasonable to believe that in childhood-onset disease, genetic factors may be more relevant than hormonal and environmental influences.[8,9] With the development of sequencing techniques in recent years, multiple pathogenic genes have been identified including genes involved in the complement pathways, genes responsible for ALPS, interferonopathies, and many more.[10]

Mutations in KRAS at amino acid position G13 have been linked to cancer, RALD, and Noonan syndrome. Noonan syndrome is characterized by distinctive facies, cardiovascular disease, and various skeletal anomalies - none of which our present possessed. Position G13 is found within the KRAS protein's p-loop and participates in GTP-hydrolysis. When Glycine is replaced with another amino acid (e.g Cysteine as in our case), it reduces the enzymatic activity of KRAS GTPase. This causes growth factor-independent activation of downstream pathways, which helps in increasing cellular development and suppressing T-cell death.[11]

The literature search revealed around 9 previously reported cases of RALD related to p.G13C KRAS mutations. Among these, 5 patients did have evidence of pericardial effusion, similar to our case.[7] One patient also had associated SLE and massive lymphadenopathy with sinus histiocytosis.[11] However, enlarged lymph nodes were absent in our patient.

As autoimmunity is the primary mechanism behind the clinical spectrum, immunosuppressive therapy remains the cornerstone of treatment. Various combinations of steroids, IVIG, Rituximab, and calcineurin inhibitors have been tried in the past with good results.[3,4] Recently, progress has been achieved in the development of drugs that can target KRAS mutations seen in cancer. We believe that further clinical trials of these medications will be highly effective for patients with KRAS-mediated immune defects.[10]

To the best of our knowledge, this is the first case in India with SLE with probable ALPS caused by a KRAS mutation. This case highlights the necessity of constantly evaluating a monogenic origin for autoimmunity, especially when disease signs begin early in childhood and do not follow a conventional clinical course.

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Competing interests: The authors declare no conflict of Interest.

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