Congenital, Developmental, and Inflammatory Findings in a Patient with a Newly Described RASopathy (RRAS2)

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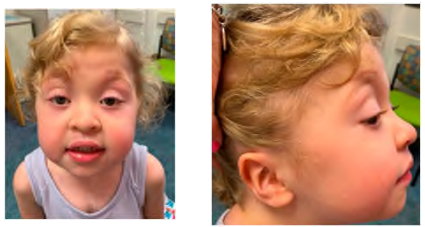
BACKGROUND/PURPOSE

Germline pathogenic variants in the RAS-MAPK pathway are implicated in a spectrum of developmental disorders characterized by short stature, distinct dysmorphology, and congenital heart disease collectively known as **"RASopathies."**

Patients with **RASopathies** appear at increased risk for also developing immune disorders, which may be secondary to **aberrant thymic selection**. Recently, activating germline mutations in RRAS2 were described as a novel RASopathy.

We report a patient with a *de novo* RRAS2 variant and immune dysregulation.

PHYSICAL EXAM



CLINICAL PRESENTATION

Birth – Infancy
Multiple Cardiac Complications Requiring Surgical Intervention

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15 - 35 Months
Post-Op Chylothorax, Pulmonary Embolism, Left Middle Cerebral Artery Stroke, Seizures, Chronic Lung Disease

→

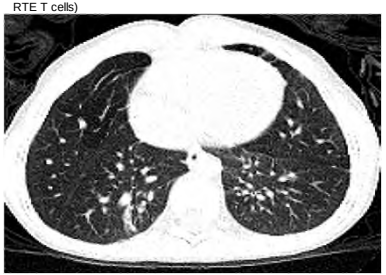
36 Months – 60 Months
Episodes of Ketotic Hypoglycemia of Unknown Etiology, Systemic Juvenile Arthritis (Fevers, Serositis, Polyarthritis and Rash), Macrophage Activation Syndrome, Hepatic Fibrosis

RESULTS

Lab	Patient*	Reference Range
CBC		
WBC	**3.14** - **15.6**	4.86 - 13.38 x 10^3 cells/uL
Hgb	**7.7** - **14.5**	10.2 - 14 g/dL
Platelet	237 - **1208**	189-403 x 10^3 cells/uL
ANC	**1110** - **13,330**	1500 – 6000 cells/uL
ALC	**690** - **6770**	1,250 - 10,500 cells/uL
Immunophenotyping#		
CD3+T Cell	**494** -1182	900 - 4500 cells/uL
CD4+T Cell	**359** - 918	500 - 2,400 cells/uL
CD8+T Cell	**154** - **236**	300 - 1,600 cells/uL
CD19+B Cell	**137** - **587**	200 - 2,100 cells/uL
CD4:CD8	2.9 - **3.9**	0.92 - 3.72
CD3+CD56+CD16	112 - 355	100 - 1,000 cells/uL
Lymphocyte proliferation		
Phytohemagglutinin 10 µg/mL	143,160	≥83,736 CPM
Pokeweed mitogen 100 ng/mL	91,469	≥47,775 CPM
Tetanus antigen	12,477	≥2000 CPM
Immunoglobulins		
IgA	36-86	22 - 140 mg/dL
IgG	**307** - 589	390 - 1,360 mg/dL
IgM	63- 107	26 - 150 mg/dL
Immunizations		
Pneumovax	**2**/23 serotypes	>1ug/mL
Serum cytokines#		
Sol IL-2R	304	144-1329 U/mL
CXCL-9	**1386**	<=647 pg/mL
S100A8/S100A9	1,151	716-3004 ng/mL
S100A12	116	32-385 ng/mL

Acute phase reactants		
C-Reactive Protein	<0.35 - **18**	0.10-1.0 mg/dL
D- Dimer	**0.97** - **10.6**	<0.50 mcg/mL FEU
Ferritin	16-**733.15**	5-100 ng/mL
Liver enzymes		
AST	27 - **135**	20 – 39 IU/L
ALT	14 - **185**	8 – 24 IU/L
GGT	16 - **488**	0 - 60 U/L

#Drawn after immune modulation initiated
*Further subsets of T and B cells were also quantitated and revealed no abnormalities for age (including naive, memory, switched memory, transitional, and plasma blast B cells and naive, Tcm, Tem, Temra and RTE T cells)



CT demonstrates prominent vasculature, ground glass opacities, and interstitial thickening.

METHODS

Exome Sequencing revealed a pathogenic, *de novo* duplication (p.Gly24_Gly26dup) in *RRAS2*.

CONCLUSIONS

Immune modulation controlled the patient's hyperinflammation, but she had persistent arthritis despite intraarticular and oral corticosteroids, meloxicam, hydroxychloroquine, leflunomide, and anakinra; she is now improved on tofacitinib.

This case underscores the association of RAS-MAPK activation with immune dysregulation, and highlights the importance of deep phenotyping in complex patients with rare and novel disorders.