The Young and the HOIP-less: Two siblings with autoinflammation and combined immunodeficiency due to autosomal recessive RNF31-loss of function

Estefanía Vásquez-Echeverri1, Armando Partida Gaytán1, Selma C Scheffler Mendoza1, Juan Carlos Bustamante Ogando1, Francisco Rivas Larrauri2, Alonso Gutiérrez Hernández1, Marco Antonio Yamazaki-Nakashimada2, Sara Elva Espinosa-Padilla1, and Saul O Lugo Reyes1
1 (1) Immune Deficiencies Laboratory and (2) Clinical Immunology Service, at the National Institute of Pediatrics, Mexico City

Introduction

• The linear ubiquitin chain assembly complex (LUBAC) plays crucial roles in immune NFκB signaling and cell death regulation.
• In the last five years, few patients have been described from consanguineous families.
• Phenotypes that include: myopathy, combined immune deficiency and autoinflammation.

Family History

Brother presented:
• HLH, regional BCG-itis
• Recurrent fever
• Hepatosplenomegaly
• Diarrhea
• High serum acute reactants
• Hyperleucocytosis
• Hypergamaglobulinemia

Whole Exome Sequencing Analysis

1 month
• Suspected milk protein allergy
• Recurrent fever
• Diarrhea
• Eczema

Recurrent infections:
• Gastrointestinal tract
• Respiratory tract
• Chronic hepatitis

Isolates:
• CMV
• Klebsiella sp
• E. coli
• Giardia lamblia
• S. haemolyticus
• Aspergillus

Blood tests
• Anemia
• Leukocytosis
• Neutrophilia
• Eosinophilia
• Monocytosis
• Thrombocytosis
• ↑ Serum acute reactants

Immunological tests
• IgG
• IgM
• IgA
• IgE
• IgD
• LTCD3+
• LTCD8+
• LB
• NK
• LTCD4+

Others: Lymphoproliferation assays, perforin expression, DHR, serum complement, and extended metabolic screening were all normal.

Case Presentation

1 month
• Suspected milk protein allergy
• Recurrent fever
• Diarrhea
• Eczema

Physical examination:
• Low weight
• Pallor
• Oral candidiasis
• Lymphadenopathies
• Hepatomegaly
• Diaper rash

Blood tests
• Anemia
• Leukocytosis
• Neutrophilia
• Eosinophilia
• Monocytosis
• Thrombocytosis
• ↑ Serum acute reactants

Immunological tests
• IgG
• IgM
• IgA
• IgE
• IgD
• LTCD3+
• LTCD8+
• LB
• NK
• LTCD4+

Others: Lymphoproliferation assays, perforin expression, DHR, serum complement, and extended metabolic screening were all normal.

Discussion

• Part of the LUBAC complex, involved in NFκB signaling, inflammation and cell death regulation, HOIP deficiency has been described to cause a Combined/Autoinflammatory syndrome.
• Our patient and her dead brother are, to our knowledge, the third and fourth patients identified with HOIP-LOF, expanding the clinical phenotype.

Other comorbidities: Epilepsy, failure to thrive, renal tubular acidosis, exogenous Cushing syndrome, osteoporosis, and truncal obesity.

Treatment: Ig, colchicine, prednisolone, valganciclovir, trimethoprim/sulfamethoxazole and itraconazole, and levetiracetam. HSCT was declined by her parents.