



ORAL PRESENTATION

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A de novo nonsense mutation in the tyrosine kinase lyn in a patient with an early onset autoinflammatory phenotype

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Introduction

Lyn kinase is a Src-family tyrosine kinase expressed by hematopoietic and non-hematopoietic cell types. It functions as an activator and an inhibitor of signaling pathways. Phosphorylation of a tyrosine residue at position 508 keeps the molecule in an inactive form. Lyn^{up/up} mice have a gain-of-function mutation generated at the tyrosine position 508 (Y508F) and present with severe anemia, autoimmune glomerulonephritis and positive ANA. Using whole exome sequencing (WES), we identified a pediatric patient with a nonsense de novo mutation in lyn kinase presenting with an early-onset autoinflammatory phenotype.

Objectives

To describe the successful characterization by WES of a patient with a de novo mutation in LYN, a gene not previously associated with human disease.

Methods

Genomic DNA was extracted from total blood of the patient and his parents and WES was performed using human exome capture Agilent V4 enrichment kit and Illumina HiSeq2000 platform.

Results

A 3 year-old Caucasian male born at 31 weeks' gestation presented with hydrops fetalis, requiring intra-uterine blood transfusion. Post partum he developed

hepatosplenomegaly, purpuric skin rash, periorbital erythema and testicular swelling. Laboratory exams showed increased C-reactive protein (CRP) anemia, severe thrombocytopenia and increased liver enzymes. At 9 months of age a splenectomy was performed for refractory thrombocytopenia. Post splenectomy, he developed leukocytosis, thrombocytosis and anemia persisted. A liver biopsy showed periportal lymphocytic infiltrate and vanishing bile duct disease. He had vasculitis on a skin biopsy and circulating autoantibodies (positive ANA, anti-Sm, anti-SSA, anti-phospholipids and anti-mitochondrial antibodies). Despite some improvement after initiation of prednisone and IVIG infusions, prednisone doses could not be weaned. We identified a *de novo* mutation in a candidate gene (*LYN*) by WES. The mutation was confirmed as *de novo* by Sanger sequencing. The change from cytosine to guanine (c.1524C>G) leads to a premature stop-codon at the tyrosine position (Y508*) with loss of the phosphorylation site. B lymphocytes showed a constitutive phosphorylation of lyn and B cell phenotyping showed a significantly diminished frequency of immature B cell populations in peripheral blood and in bone marrow. B cell activation was reduced upon IgM stimulation in comparison with healthy controls. The genetic defect identified in this patient led us to initiate treatment with a tyrosine kinase inhibitor (dasatinib). After 6 months of treatment, clinical improvement was observed with lower frequency of disease flares, resolution of anemia, improvement of leukocytosis, thrombocytosis and liver enzymes. A decrease of prednisone dose to physiologic levels and discontinuation of IVIG infusions were also achieved.

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Conclusion

A lyn kinase nonsense mutation was detected in a patient with a severe early-onset autoinflammatory phenotype. Treatment with dasatinib was shown to be promising in the patient described.

Disclosure of interest

None declared.

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