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Hematologic manifestations associated with deficiency of adenosine deaminase 2 and a novel ada2 variant

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Objective: Deficiency of Adenosine-deaminase 2 (DADA2) is an autoinflammatory, autosomal recessive disorder due to mutations in CECR1 gene. DADA2 is phenotypically extending beyond its classical features (fever, early-onset stroke, livedo reticularis and polyarteritis nodosa) to include various hematologic presentations and rarely manifests as pure red cell aplasia (PRCA). We report a novel mutation in CECR1 gene (ADA2), that results in DADA2 and presented with PRCA as a unique manifestation.

Case report: A 5-year-old female who presented with severe pallor, with no family or medical history of concern. Autoimmune hemolytic anemia (AIHA) was suspected due to positive DAT, so the child started intravenous immunoglobulin and steroids but with no response. Bone marrow aspirate/biopsy showed markedly reduced erythropoiesis consistent with PRCA. The child almost required blood transfusion on weekly basis. She has an HLA-matched sibling donor and started hematopoietic stem cell transplant (HSCT) process. Meanwhile, a whole exome sequencing (WES) was requested for final diagnosis.

Methodology: We obtained a sequence analysis of all protein coding genes in the patient's genome, coupled with Whole Exome Deletion/Duplication (CNV) Analysis. Also, we reviewed the literature for hematologic manifestations of DADA2.

Results: Whole Exome Plus identified a homozygous frameshift variant CECR1 c.714_738dup, p. (Ala247Glnfs*16). It duplicates 25 base-pairs and generates a frameshift, leading to a premature stop codon in exon 5 (of 10 total exons), at position 16 in a new reading frame that is predicted to cause a loss of normal protein function. To the best of our knowledge, this variant was not described in the medical literature or reported in disease-related variation databases. Interestingly, our patient did not show any features suggesting DADA2 nor congenital form of aplastic anemia as she presented solely with PRCA. We reviewed a total of 151 patients from 27 published reports for patients with DADA2 in which hematologic manifestations were part of their presentations. One hundred patients, (66%, Female $n=52$), median age 5 years, presented with hematologic manifestations. Different anemias (AIHA, Evans syndrome, PRCA, DBA like features) were the most frequent occurring in 51% of patients, followed by lymphopenia and organomegaly, (32% each). Of concern, PRCA was the main manifestation in 12 patients without typical features of DBA nor vasculitis. Four patients were successful on HSCT, 1 on anti-tumor necrosis factor (TNF), 2 failed on steroids and 2 failed on anti-TNF, while others are either maintained on blood transfusion, steroids, or monthly intravenous immunoglobulins. The treatment for DADA2 previously included steroids, thalidomide and tocilizumab that showed success but associated with severe adverse events. Recently, treatment with anti-TNF-agents is believed to be effective especially in cases of vasculitis due to a subtotal loss of ADA2 function. However, complete loss of function seen in hematologic disorders is not favoring TNF inhibitors. HSCT is the most definitive treatment, particularly, when reversal of cytopenias and immunodeficiency is aimed.

Conclusion: We report a novel ADA2 variant in child presented with PRCA. We emphasis on genetic testing for hematologic disorders that lacks a definitive etiology, as it might result in the best pharmacogenomic-based therapeutic strategies without the need of unnecessary interventions.

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Pyruvate kinase deficiency misdiagnosed as congenital dyserythropoietic anemia type i

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Objective: Objective: Pyruvate kinase (PK) deficiency is the most common enzyme abnormality in the glycolytic pathway, which leads to an anemia secondary to decreased ATP synthesis. The disease exhibits autosomal recessive inheritance and is caused by mutations in the PKLR gene. The diagnosis of PK deficiency is based on the presence of clinical signs and symptoms of hemolytic anemia, evidence of extravascular hemolysis on laboratory findings, measurement of the PK activity or antigen levels and detection of mutations in the PKLR gene.

Methodology: Here, we describe two siblings with PK deficiency that was misdiagnosed as congenital dyserythropoietic anemia (CDA) type I.

Results: Cases: The siblings were referred to our hospital for the evaluation of the anemia when they were newborn. On physical examination, they both had an icteric appearance. Their PK, glucose-6-phosphate dehydrogenase and 5' nucleotidase enzyme activities, hemoglobin electrophoresis and osmotic fragility test were normal. Erythroid hyperactivity with many bi-multilobed erythroblasts, which raised the concern of CDA, was seen in bone marrow aspiration. Spongy appearance (Swiss cheese appearance) of heterochromatin in all normoblasts and expansion of the perinuclear areas and the extension of the cytoplasm towards the nucleus in some, were observed with electron microscopy. CDA panel by next generation sequencing showed no mutation. Though their PK enzyme levels were normal, the molecular study of PKLR gene, a homozygote variant c.1623G>C (p.Lys541Asn) in exon 12 was found in our patients.

Conclusion: Discussion: Pyruvate kinase deficiency is a rare cause of hemolytic anemia and given to the rarity and the clinical heterogeneity, the diagnosis of PK deficiency can be difficult, mostly in atypical forms. PK deficiency should be considered in the differential diagnosis of CDA. Instead of the enzyme activity, comprehensive genetic analysis is warranted