PP 72

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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PP 73

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

more effective diagnosis of patients with suspected CDA and congenital hemolytic anemia.

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SICKLE CELL DISEASE

PP 74

How to treat and manage covid19 in SCD patients

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Objective: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan, China, and has resulted in an ongoing pandemic.

Case report: A 24-year-old man with a history of SCD (HbS/β0-thalassemia) on maintenance hydroxyurea therapy presented to our hospital, with a complaint of pain in the extremities and chest over two days. The patient with mild cough and high fever was hospitalized. Blood tests and lung CT were performed. Result of blood test show evidence of systemic hemolysis with a decrease in hemoglobin from 8.9 g/dL to 6.7 g/dL. His white blood cell count was $25.2 \times 10^3/\mu L$, CRP 243.21 mg/L. CT scans of the lungs showed a consolidated area where air bronchograms were observed in and around the medial segment of the middle part of the right lung and the posteriobasal segment of the lower part of both lungs, and an icy glass landscape was observed. Lung damage is 1–5% (grade I). His oxygen saturation SpO2 was normal (98%). The SARS-CoV-2 PCR nasopharyngeal swab testing was sent and returned negative on hospital day one after which the patient was started on antiviral and antibiotic for severe COVID-19 pneumonia. An improvement in blood counts was observed 4 days after starting treatment (WBC $16.93 \times 10^3/\mu L$, CRP 100.31 mg/L). On day ten, after normalization of all symptoms and blood values the patient was discharged home.

Methodology: In this study we selected 1 patient with SCD followed in Thalassemia Center of Azerbaijan.

Results: Given the higher likelihood of ACS it is possible that SCD patients are also at higher risk of such complications from COVID-19, particularly those with a history of pulmonary comorbidities. However, it is unclear if the SARS-CoV-2 pandemic will lead to increased rates of ACS for sickle cell patients. Still, hospitalized sickle cell patients should be monitored closely for development of ACS and if this occurs, exchange transfusion should be promptly initiated.

Conclusion: COVID-19 pneumonia as a cause of acute chest syndrome in an adult sickle cell patient. Patients with sickle cell disease (SCD) who are infected with COVID-19 may have a significant risk of developing acute chest syndrome (ACS), a potentially life-threatening complication. In this case we will present how manage COVID 19 in patient with SCD.

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STEM CELL TRANSPLANTATION

PP 75

High-dose methyl prednisolone in veno-occlusive disease

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Objective: Veno-occlusive disease (VOD) is a serious complication of hematopoietic stem cell transplantation (HSCT). If it is not identified and treated earlier, mortality is high. Combination usage of high-dose methyl prednisolone (MPZ) and defibrotide in VOD treatment have been described in some studies. Here, we present a patient with VOD who responded well to high-dose MPZ.

Case report: 14-month-old girl, diagnosed with thalassemia major, received HSCT from her sibling donor with busulfan and cyclo-phosphamide conditioning. On day +11, the patient experienced painful hepatomegaly and elevated total bilirubin (2.25 mg/dL) with 7% weight gain from baseline and respiratory distress while under defibrotide prophylaxis. VOD was diagnosed according to the modified Seattle criteria. Fluid and salt restriction were performed, spironolactone was started, and defibrotide was continued. Due to lack of significant improvement in the patient condition after 4 days of defibrotide, HDM was started at dose of 250 mg/m^2 per dose every 12 h on day +15.

Methodology: A day after MPZ, the patient's condition started to improve. After six doses of methylprednisolone, the dose was reduced to 2 mg/kg. Then, the dose was reduced by decreasing to half-dose in three-day periods. The defibrotide was discontinued on day +36, and the patient was discharged on day +45. The patient is currently being followed problem-free after 2 years of transplantation with 100% donor chimerism.

Results: VOD treatment response with high-dose MPZ and defibrotide combination can be better than treatment response with defibrotide alone. The easier and cheaper supply of steroids also prevents the treatment delay. In a study, it was shown that receiving high-dose MPZ without defibrotide was also found to be effective in the VOD treatment. The mortality rate in patients with multiple organ failure symptoms in VOD is between 50% and 100%. However, mortality rate can be decreased by early detection of VOD symptoms such as of painful hepatomegaly, weight gain and ascites. This findings may develop before hyperbilirubinemia especially in pediatric patients. Knowing this is important for early diagnosis and treatment of VOD.

Conclusion: As a conclusion; high-dose MPZ was found to be an effective treatment in VOD even at a dose of 250 mg/m^2 per dose every 12 h in aour patient. High-dose MPZ might be an alternative treatment to defibrotide in early phase VOD. Further studies are needed on the efficacy and dosage of MPZ in VOD.

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