**Novel mutation in CECR1 gene associated with deficiency of adenosine deaminase -2 presenting as severe congenital neutropenia**

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| Abbreviations | |
| DADA | Deficiency of adenosine deaminase |
| TNF | Tumor necrosis factor |

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**Abstract**

Children with congenital neutropenia frequently require hospitalization due to febrile neutropenia. Deficiency of Adenosine DeAminase -2(DADA-2) an autosomal recessive disorder caused by a mutation in CECR1 gene. It is an autoinflammatory disease presenting with autoimmunity and features of immunodeficiency. It usually presents in early childhood with recurrent stroke and vasculitis features.

Here, we report a young male with CECR1 mutation presenting predominantly with neutropenia.

**Introduction**

Children with congenital neutropenia frequently require hospitalization due to febrile neutropenia which can be life-threatening. Deficiency of Adenosine DeAminase -2(DADA-2) an autosomal recessive disorder caused by a mutation in CECR1 gene. It is an autoinflammatory disease presenting with autoimmunity and features of immunodeficiency [1, 2]. It usually presents in early childhood with recurrent stroke and vasculitis features. It involves multiple organs and can present as arthralgia, fever, stroke, hepatosplenomegaly and cytopenias. Here, we report a young male with CECR1 mutation presenting predominantly with neutropenia.

**Case Report**

A 19 years old male from Iraq presented to us with a 3-year history of recurrent fever with multiple nodular swellings in the body. These swellings evolved into ulcers and healed with depressing scars. He also had recurrent oral ulcers and lymph node swellings. Family history was insignificant of any medical history. There was no history of consanguinity. There was no history of neutropenia or vasculitis in any of the siblings or parents. He was evaluated at his home country and was noted to have neutropenia and referred to us for further evaluation. Complete blood counts showed a hemoglobin 12.5 g/dl, total leukocyte count of 1.8. with absolute neutrophil count of 170/ cmm and and platelet count 174/cmm. Peripheral smear revealed a no abnormality apart from neutropenia. Reticulocyte count was 1.28%. Renal and liver function tests were normal. Vitamin B12 and folate levels were normal. Vasculitis work up came as negative for antinuclear antibody. He had high IgG levels and IgA levels with normal IgM level (IgG 2671 mg/dL, IgA 862 mg/dL, IgM 120mg/dL) Bone marrow examination revealed 35% cellularity, megaloblastoid erythropoiesis and marked myeloid suppression. Patient had a normal karyotype, 46XY. Positron emission tomography study was done as part of work up of lymphadenopathy showed consolidation in right lower lobe of lung with SUV 12.5. Liver and spleen were enlarged (17cm and 13 cm below costal margin respectively). No lymph node uptake was seen. Next generation sequencing for congenital neutropenia was performed. Patient had homozygous CECR1 (cat eye syndrome chromosome region, candidate 1) mutation [907G>T] in exon 6, which is known to be associated with DADA-2 and childhood onset vasculitis. Thereafter, he was lost to follow up and came to us again after 8 months. During this time, he required multiple hospitalizations for febrile neutropenia. He presented to us with perforation of hard palate (Fig 1) and a large non healing ulcer in the right leg (Fig.2). Swab culture from palate perforation grew candida albicans was treated with fluconazole. However, the perforation in hard palate persisted. His absolute neutrophil count at admission was 0.01/L. He did not respond to granulocyte colony stimulating factor (G-CSF). Patient did not have any history of stroke or headache suggestive of CNS vasculitis. Rheumatology consult was taken and therapy with TNF inhibitors (Etanercept) was contemplated. However, in view of severe neutropenia he was advised for allogeneic stem cell transplant. Patient was not willing for the same and defaulted therapy.

**Discussion**

The clinical presentation of DADA-2 varies widely and as a result coming to an early diagnosis is difficult. It is predominantly a pediatric disorder and is rarely seen in adults [4]. It carries a mortality rate with up to 8% of patients succumbing before reaching 30 years of age [3]. Most of the deaths are due to complications of recurrent stroke or infection. Skin and central nervous system are the most commonly affected organs. Cutaneous manifestation is the most common presentation with 75% of patients presenting with skin related complaints. Patients may also present with gastrointestinal, liver, renal, coronary vessels involvement [5,6]. Pancytopenia has been reported in few patients. In some patients, cytopenia was the only presenting symptom and can present as autoimmune hemolytic anemia, thrombocytopenia and pure red cell aplasia [7-9]. Bone marrow biopsy can show reticulin fibrosis and characteristic lymphoid aggregates [[1](https://link.springer.com/article/10.1007/s10875-018-0525-8#CR1)0]. Hence, DADA2 should be considered in cases presenting with bone marrow failure and idiopathic aplastic anemia in the absence of an inflammatory etiology.

ADA2 is predominantly expressed in myeloid cells and is produced by activated monocytes, macrophages, and dendritic cells [11]. They are released during inflammatory responses and is detected in high levels in infectious diseases, autoimmune diseases, chronic liver disorders, AIDS, tuberculosis, Crohn’s disease and are detected in high levels in plasma in these conditions. [12, 13].

Sixty one disease-causing mutations have been identified to be associated with DADA-2.The most common disease variants are p.Gly47Arg (p.G47R), p.Gly47Ala (p.G47A), p.Arg169Gln (p.R169Q), and p.Tyr453Cys (p.Y453C) [[1](https://link.springer.com/article/10.1007/s10875-018-0525-8?shared-article-renderer#ref-CR1), [2](https://link.springer.com/article/10.1007/s10875-018-0525-8?shared-article-renderer#ref-CR2)].Our patient showed c907G>T (p.Glu303Ter) which has not been reported. The pathophysiology of the immunodeficiency in DADA2 is unclear and is speculated to be due to inhibition of B cell differentiation and function due to inflammation. The mainstay of treatment is TNF alpha-inhibition. Bone marrow transplantation or genetic manipulation of bone marrow cells has a role in the treatment of these patients. Allogeneic stem cell transplant can be offered in patients not responding to TNF-inhibitors [14].

**Conclusion**

In patients with congenital neutropenia DADA -2 is an important emerging differential diagnosis to consider especially in patients with features of autoimmunity. Timely recognition and initiation of therapy with TNF alpha inhibitor can help in amelioration of symptoms. Allogeneic stem cell transplant can be reserved for patients not responding to TNF inhibitor therapy or in whom TNF inhibitor therapy is contraindicated.

**References**

Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014;370(10):911–20.

Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370(10):921–31.

Ben-Ami T, Revel-Vilk S, Brooks R, Shaag A, Hershfield MS, Kelly SJ, et al. Extending the clinical phenotype of adenosine deaminase 2 deficiency. J Pediatr. 2016; 177:316–20.

Zavialov AV, Gracia E, Glaichenhaus N, Franco R, Zavialov AV, Lauvau G. Human adenosine deaminase 2 induces differentiation of monocytes into macrophages and stimulates proliferation of T helper cells and macrophages. J Leukoc Biol. 2010;88(2):279–90.

1. Fernandez E, Rodrigo L, Riestra S, Carcia S, Gutierrez F, Ocio G. Adenosine deaminase isoenzymes and neopterin in liver cirrhosis. J Clin Gastroenterol. 2000;30(2):181–6.

Sari RA, Taysi S, Yilmaz O, Bakan N. Correlation of serum levels of adenosine deaminase activity and its isoenzymes with disease activity in rheumatoid arthritis. Clin Exp Rheumatol. 2003;21(1): 87–90.

1. Hashem H, Egler R, Dalal J. Refractory pure red cell aplasia manifesting as deficiency of adenosine deaminase 2. J Pediatr Hematol Oncol. 2017;39(5): e293–e6.

Sundin M, Marits P, Nierkens S, Kolios AGA, Nilsson J. “Immune” thrombocytopenia as key feature of a novel ADA2 deficiency variant: implication on differential diagnostics of ITP in children. J Pediatr Hematol Oncol 2019 Mar;41(2):155-157.

Hsu AP, West RR, Calvo KR, Cuellar-Rodriguez J, Parta M, Kelly SJ, et al. Adenosine deaminase type 2 deficiency masquerading as GATA2 deficiency: successful hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2016;138(2):628–630.e2.

Trotta L, Martelius T, Siitonen T, Hautala T, Hamalainen S, Juntti H, et al. ADA2 deficiency: clonal lymphoproliferation in a subset of patients. J Allergy Clin Immunol. 2018; 141:1534–1537.e8.

Iwaki-Egawa S, Yamamoto T, Watanabe Y. Human plasma adenosine deaminase 2 is secreted by activated monocytes. Biol Chem. 2006;387(3):319–21.

Bae MJ, Ryu S, Kim HJ, Cha SI, Kim CH, Lee J. Mycobacterium tuberculosis ESAT6 and CPF10 induce adenosine deaminase 2 mRNA expression in monocyte-derived macrophages. Tuberc Respir Dis (Seoul). 2017;80(1):77–82.

Niedzwicki JG, Kouttab NM, Mayer KH, Carpenter CC, Parks RE Jr, Abushanab E, et al. Plasma adenosine deaminase2: a marker for human immunodeficiency virus infection. J Acquir Immune Defic Syndr. 1991;4(2):178–82.

Van Eyck L Jr, Hershfield MS, Pombal D, Kelly SJ, Ganson NJ, Moens L, et al. Hematopoietic stem cell transplantation rescues the immunologic phenotype and prevents vasculopathy in patients with adenosine deaminase 2 deficiency. J Allergy Clin Immunol. 2015;135(1):283–7 e5.

Legend to Figure 1: Palatal Perforation

Legend to Figure 2: Large non-healing skin ulcer

A close up of a person with the mouth open

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