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Allogenic Stem Cell Transplant for A Rare Case of Cerc1 Mutation Presenting as Congenital Neutropenia

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Abstract

CERC1 mutation is inherited as an autosomal recessive disorder. A loss of function mutation causes ADA2 deficiency and is characterized by vasculopathy, immunodefi- ciency, and neutropenia. It is also associated with variable immunodeficiency pheno- types such as low or high Immunoglobulin levels, in particular, selective IgM defi- ciency, high IgG levels, pan-hypogammaglobulinemia-like CVID (common variable immunodeficiency), and low memory B cells, red cell aplasia, and pure antibody defi- ciency [1,2]. Here we describe a young man with biallelic loss of function mutation in CECR1 presenting with recurrent infections since childhood with severe neutropenia and stroke.

Keywords: Immune Deficiency; Neutropenia; Allogenic Stem Cell Transplant; Rare Mutation; CERC1 gene

Case Report

A 34-year-old man, born out of second-degree consanguineous marriage had a history of recurrent infections since 11 years of age. He was evaluated and found to have a low total leucocyte count with decreased neutrophils. Bone marrow evaluation showed normocellular to hypercellular with relative lymphocytosis. He was treated with intermittent filgrastim injections; however, there was a lack of adequate re- sponse. At the age of 19, he had left upper lobe pneumonia with a robust positive Mantoux test, hence he was started on antitubercular therapy, which he took for 10 months. But his cytopenia continued to worsen after antitubercular treatment. At the age of 30, he had sudden onset right-hand weakness and, on imaging, he was diagnosed to have acute infarct of the left parietal region and was treated for the same.

The prothrombotic assessment was negative.

Subsequently, in March 2019, he had recurrent fever with aphthous ulcers. Investiga- tions again showed low total leucocyte counts with severe neutropenia (absolute neu- trophil count of 150 cells/cumm). At this time, he presented to our haematology out- patient department for further evaluation. Bone marrow examination evaluation was repeated and showed normocellular marrow with myeloid maturation arrest at the metamyelocyte stage and absence of dysplasia. Bone marrow karyotyping was nor- mal. In the absence of an apparent cause for severe neutropenia, whole-exome se- quencing (WES) showed homozygous missense mutation in the CECR1 gene. He wasplanned for an allogeneic hematopoietic stem cell transplantation (aHSCT) given his severe disease. He had a matched sibling donor, WES on the donor was done, which showed that the donor was heterozygous for the same mutation. Donor workup was essentially normal and the patient underwent aHSCT.

Post-transplant, he had neutrophil and platelet engraftment on days +14 and +16, re- spectively. Unfortunately, he developed acute gut and skin graft versus host disease (GVHD) on day +35. GVHD responded to steroids, Etanercept and Ruxolitinib. From day + 60, he developed gradual onset of hypertension with increasing creatinine. Pe- ripheral smear showed thrombocytopenia and schistocytes; the possibility of TA- TMA was kept. A renal biopsy was done, which showed thrombosis of glomeruli and renal microvasculature. ADAMTS 13 level was within normal limits. Exome se- quencing to detect Complement factor mutation was also negative. He underwent 7 sessions of plasma exchange with steroids and two doses of Rituximab. However, he did not have any improvement in renal parameters, and LDH continued to increase.

He was initiated on dialysis for worsening renal functions.

At this point, the option of C5b inhibitor, Eculizumab, was considered. He was started on 900 mg Eculizumab from day 70 post transplant, weekly for 6 doses and then 1200 mg once in two weeks; he received a total of 9 doses of Eculizumab. After four doses of Eculizumab, his creatinine began to show a decreasing trend, and platelet counts improved. Gradually he could be weaned off dialysis support. At present, he is off Eculizumab therapy, and the last dose was received in April 2020. He has completed 20 months post allogeneic stem cell transplant and has been off immunosuppression over the previous 10 months. He has completed his routine vaccination and is cur- rently doing well.

Discussion & Conclusion:

CERC1 mutation is characterized by ADA2 deficiency. It is a monogenic form of sys- temic vasculopathy that presents in early childhood. Biallelic mutations are character- ized by vasculopathy, immune deficiency, neutropenia, and bone marrow failure syn- drome. Vasculopathy can range from livedo reticularis to polyarteritis nodosa (PAN) to life-threatening ischaemic stroke [3,4]. In this case, the patient had a stroke ex- plained by the vasculopathy caused by the above mutation.

Belot, et al. proposed that ADA2 may act as a regulator of neutrophil activation. The deficiency of ADA2 (DADA2) results in endothelial damage via a neutrophil-driven process [5], which explains the mechanism of vasculopathy in these patients. ADA2 seemed to be involved in the balance between pro-inflammatory and anti-inflamma- tory monocytes; in the case of its absence, ADA2 was associated with a defect in dif- ferentiation of anti-inflammatory macrophages, upregulation of neutrophils expressed genes, and an increased secretion of pro-inflammatory cytokines leading to a pro-in- flammatory state.[6] Aberrant ADA2 proteins (due to missense mutations) cause more vascular complications; whereas, the complete absence of ADA2 causes more pro- found cytopenias than vascular complications[7].

There was a history of repeated infections in our patient since 11 years of age; pri- mary immunodeficiency workup

showed only a mild reduction in serum IgM levels with normal levels of other immunoglobulins. Serology was non-reactive.

As he had repeated episodes of fever with neutropenia, secondary causes of cytope- nias, including drugs, connective tissue diseases, bone marrow evaluation for evi- dence of leukemia, malignancy, or myelodysplasia, were excluded.

This case demonstrates the importance of whole-exome sequencing (WES) in diag- nosing the cause of idiopathic cytopenias. The common gene mutations causing con- genital neutropenia are ELANE, HAX1, G6PC3, JAGN1, and WAS. In our patient, none of the mutations were detected in these genes. However, an extremely rare muta- tion was detected involving the exon 2 of CERC1 gene,(c278T>C) resulting in a ho- mozygous mutation, characterized bysubstitution of threonine for isoleucine at codon 93.This variation lies in the adenosine /AMP deaminase N terminal domain . The af- fected individuals present with anemia , leucopenia , immunodeficiency, vasculitis and neurological manifestations .The compound heterozygous mutation presents with early onset stroke and vasculopathy.

CECR1/ADA mutations underlie a complex autoinflammatory syndrome, and sys- temic immunosuppressants, including steroids and anti-TNF agents, have been tried without clear effectiveness. Hematopoietic stem cell transplantation is an effective treatment in severe phenotypes.[6] Hence, in a patient with unexplained cytopenias, WES can aid in accurate diagnosis, classification, and treatment of these disorders.

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Conflicts of interest

All authors declare that there is no conflict-of-interest.

Ethics statement

An informed patient consent was obtained for the academic publication.

Consent for publication

All authors provided consent for publication.

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