CASE REPORT
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Diverse Phenotypic Expressions of ADA2 Deficiency: Two Case Studies

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ABSTRACT

Adenosine deaminase 2 (ADA2) deficiency is an autosomal recessive disease with varying degrees of clinical phenotypes and disease severity. The phenotypic spectrum of the disorder has expanded from vasculitis with stroke to include pure red cell aplasia, bone marrow failure, autoimmune cytopenia, lymphoproliferation, and variable degrees of immunodeficiency.

Here, we describe two cases of ADA2 deficiency: one presented with an early-onset stroke that resembled an early-onset polyarteritis nodosa (PAN), and the other as an adult-onset vasculitis that progressed to severe neutropenia with recurrent infection and lymphoproliferation. Patient 1, a 10-year-old male, had a reported pathogenic *ADA2* homozygote variant; c.139G>C (p.Gly47Arg), and patient 2, a 34-year-old male, had a reported likely pathogenic homozygous *ADA2* variant; c.578C>T (p.Pro193Lys).

Our second patient was the first DADA2 patient who showed that DADA2 is not a static disease and can progress from vasculitis to bone marrow failure in the course of the disease. Therefore, the previous recommendation introducing anti–TNF-α as a preferred treatment for vasculitis manifestations and hematopoietic stem cell transplantation as the preferred treatment for bone marrow failure can no longer apply. We should consider HSCT for DADA2 patients from the very beginning.

The Physician has to be aware of this monogenic disorder's varied presentation and multi-organ involvement. Early recognition and proper treatment are crucial for this potentially fatal disease.

Keywords: Adenosine deaminase 2; Autoinflammation; Bone marrow aplasia; Deficiency of adenosine deaminase 2; Hematopoietic stem cell transplant

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INTRODUCTION

Deficiency of adenosine deaminase 2 (DADA2) (OMIM#615688) is a monogenic autoinflammatory disorder that affects multiple organ systems.[1] Biallelic loss-of-function mutations in the *ADA2* gene are causative of the disease and result in reduced adenosine deaminase2 (ADA2) enzyme activity in the peripheral blood. DADA2 comprises an extended phenotype ranging from fever, livedo racemosa, PAN-like systemic vasculopathy, early onset stroke, to pure red cell aplasia, bone marrow failure, immunodeficiency with hypogammaglobulinemia, sinopulmonary infections, and lymphoproliferation.[2,3]

Even within the same family and among individuals with the same mutations, the disease might manifest at various ages, with varying disease severity and organ involvement.[4,5] How diverse phenotypes result from mutations in the same gene is unknown. The pathogenesis of the illness is not fully understood; however, early reports have highlighted a skewed polarization of DADA2 macrophages towards the proinflammatory M1, leading to the overproduction of inflammatory cytokines like tumor necrosis factor alpha (TNF-α) and Interlukine (IL)-6. Subsequently, a dysregulation of NETosis brought on by excess extracellular adenosine is implicated in the pathogenesis. Furthermore, DADA2 B cells exhibit a block in terminal B cell differentiation. Additionally, impaired differentiation of $CD4^+$ and $CD8^+$ memory T cells accelerated exhaustion and senescence and compromised survival and granzyme production in ADA2-deficient $CD8^+$ T cells.[4,6]

Inhibitors of the tumor necrosis factor are often efficient at reducing inflammation and preventing strokes. However, hematological manifestations are mostly unresponsive to this intervention. Hematopoietic stem cell transplantation is recommended for severe hematologic and immunologic illnesses and for vascular symptoms that don't respond to anti-TNF medications.[3,7,8]

Herein, we present two DADA2 patients with different clinical presentations.

Case 1:

Patient 1 (P1) was an 11-year-old child born to non-consanguineous parents from a local village. He presented with recurrent febrile episodes, and weight loss since he was 1.5 years old, which were initially attributed to infectious diseases.

At four years old, he experienced an episode of sudden left trochlear nerve (cranial nerve IV) palsy. Both magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) results were normal. His echocardiography and electrocardiography also showed normal findings. Thrombotic investigations, including C protein, S protein, factor V Leiden, anti-thrombin III, and antiphospholipid antibodies, were all within normal limits. The patient was treated with low-dose aspirin. At age 7, he experienced fatigue, myalgia, and livedo racemosa rash. By the age of 10, he presented with acute ataxia and sudden onset left-sided hemiparesis. Brain MRI revealed acute ischemia in the anterior aspect of the right thalamus, while cranial MRV appeared normal. Intracranial and carotid MR angiography findings were unremarkable. Additionally, both primary and advanced immunologic tests were performed, all resulting within normal limits (Table 1) except variable specific antibody response to vaccines, even after a booster dose of the dT vaccine. Autoantibodies were evaluated for autoimmune diseases, and none were found positive. He received 25 mg (1 mg/kg) of Etanercept once a week for 4 months and is currently receiving 25 mg every 2 weeks. He did not experience recurrent fever or any further neurologic events, such as new strokes, and was doing well at the one-year follow-up. To identify a potential genetic defect, whole-exome sequencing (WES) was performed, revealing a reported pathogenic homozygous mutation in *ADA2*; c.139G>C (p.Gly47Arg). This deficiency was proven by recurrent fever, early-onset strokes, and elevated acute-phase reactants. Moreover, direct sequencing showed that his parents are heterozygous for the detected variant. His family history was negative for DADA2 in first, second, and third-degree relatives.

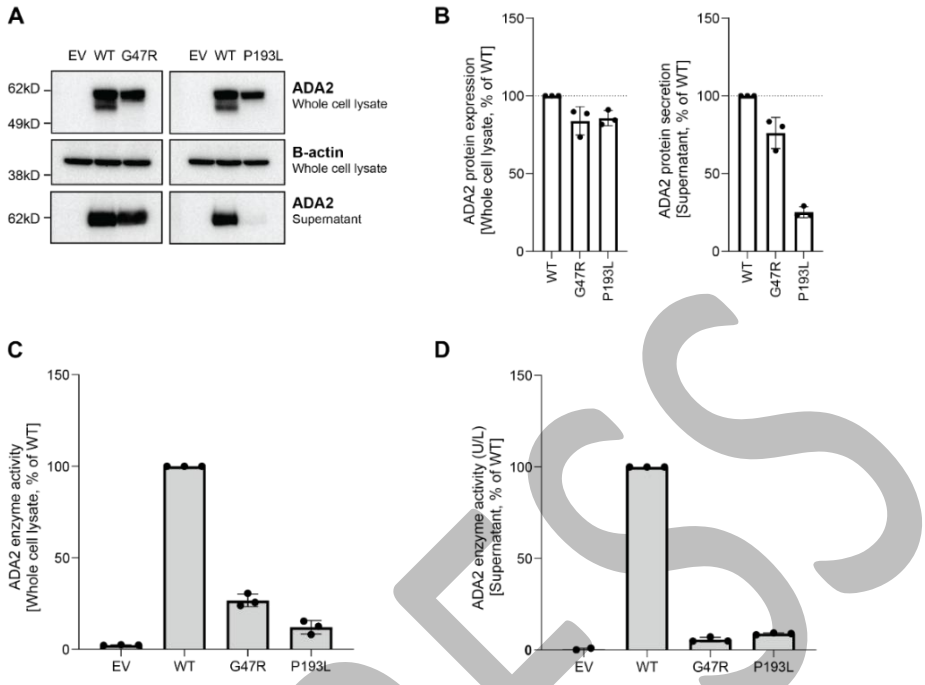

Figure 1. In vitro analysis of adenosine deaminase 2 (ADA2) variants in the HEK293T overexpression system. A. Western blot of whole cell lysate and supernatant of HEK293T cells transiently transfected with wild type (WT) ADA2 and different ADA2 variants. Cells and supernatant were collected 48h after transfection. The image represents 3 independent experiments. B. Quantification of ADA2 protein expression and secretion in whole cell lysate and supernatant of transfected HEK293T cells with WT ADA2 or different ADA2 variants. The bar graph represents the percentage of ADA2 protein expression/secretion relative to WT ADA2. C. Adenosine deaminase activity in the whole cell lysate of HEK293T transfected with WT and ADA2. Bar graphs represent the percentage of enzymatic activity relative to WT ADA2. D) Adenosine deaminase activity in the supernatant of HEK293T transfected with WT and ADA2. Bar graphs represent the percentage of enzymatic activity relative to WT ADA2. In B and C, data represent mean ± SD from 3 independent experiments.

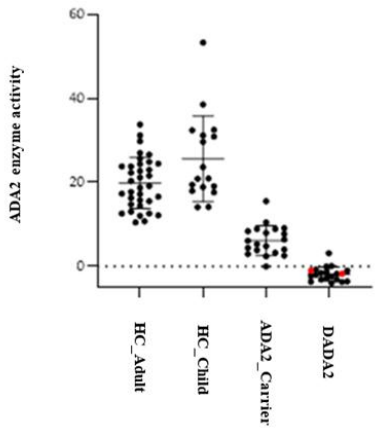

Figure 2. Results of adenosine deaminase 2 (ADA2) enzyme activity assay (U/L) in healthy control (HC) adults (n=35), HC children (n=17), ADA2 carriers (n=20), and deficiency of adenosine deaminase 2 (DADA2) patients (n=18). The data for the 2 patients described in this study are highlighted in red. ADA2, adenosine deaminase 2; DADA2, deficiency of adenosine deaminase 2; HC, healthy control; U/L, units per liter.

Case 2:

Patient 2 (P2) was a 34-year-old male born to first-degree consanguineous parents with no family history of inborn error of immunity in the first and second degrees relevant. Sinopulmonary infections, mouth ulcers, abdominal pain, and erythema nodosum first appeared when he was 18 years old. At age 25 years, he had oral ulcers, aphthous with sinusitis that caused hospital admission, severe neutropenia was identified at that time, despite previously having normal CBCs, and G-CSF was recommended. Initially, the patient declined to receive G-CSF regularly and discontinued G-CSF injections at age 30. Subsequently, he developed a recurring anal abscess, ischiorectal cellulitis, a trans-sphincteric fistula, ileitis, and localized ileal necrosis at the age of 31, which caused hospitalization twice for an extended period, including ICU admissions, and undergoing multiple surgeries while being treated with various broad-spectrum antibiotics and G-CSF. After being discharged from the hospital, he began injecting G-CSF as instructed by his physician. Despite having normal neutrophil counts at age 32 to 33, he experienced 3 to 4 episodes of acne, upper respiratory tract infections, and sometimes gastroenteritis within a year. At age 32, he was admitted to the hospital due to fever, chills, fatigue, and oral ulcers. He had developed lymphoproliferation, characterized by bilateral cervical lymphadenopathy in various nodal regions, right inguinal lymphadenopathy, and significant splenomegaly, along with elevated levels of acute-phase reactants. He was treated with antifungal, antiviral, and antibiotic medications. Following treatment, he underwent extensive testing for infections [including Epstein-Barr Virus (EBV) Polymerase Chain Reaction (PCR), Cytomegalovirus (CMV) PCR, Coronavirus Disease 2019 (COVID-19) PCR, Human T-cell Lymphotropic Virus types 1 and 2 (HTLV1 & 2) antigen and antibody tests, Human Immunodeficiency Virus types 1 and 2 (HIV1 & 2) antigen and antibody tests, Herpes Simplex Virus types 1 and 2 (HSV1 & 2), Hepatitis B Surface (HBs) Ag & Ab, Hepatitis C Virus (HCV) Ab, Varicella Zoster Virus Immunoglobulin G (VZV IgG), Venereal Disease Research Laboratory (VDRL) test, and toxoplasma Ab], autoimmune conditions, and bone marrow examinations. All tests were within normal limits, except for the antinuclear antibody test (FANA), which showed weak positivity. Serial immunologic panel testing revealed severe neutropenia; flow cytometry indicated low NK cell numbers. The double negative T cell population ($CD3^{+}TCR\alpha\beta^{+}CD4^{-}CD8^{-}$ T) and T cell receptor (TCR) panel results were normal. Repeated lymphocyte flow cytometry confirmed low B cell numbers. Complement levels, classic pathway activity (CH50, C3, and C4), specific antibodies, and immunoglobulin levels were all within the normal range. (Supplementary Tables 1, 2 and 3) An examination of the bone marrow before G-CSF use showed myeloid maturation arrest; however, repeated bone marrow aspirations and biopsies conducted at ages 28, 31, and 32 years old, after receiving G-CSF, returned normal results. Immunohistochemistry staining showed no evidence of myelodysplastic disorder. The karyotype analysis of the bone marrow aspiration sample indicated no cytogenetic abnormalities. He regularly used G-CSF and prophylactic cotrimoxazole and underwent close follow-up at the age of 32. At this time, he was referred to our center for genetic evaluation. The requested genetic analysis verified a reported homozygous *ADA2* mutation: c.578C>T (p. P193L), which is classified as likely pathogenic. This variant was confirmed in the patient and his parents through direct sequencing. Later on, at age 34, the patient developed leukopenia and thrombocytopenia, mild epistaxis, along with recurrent upper respiratory tract infections that did not respond to extensive antibiotic treatment, necessitating parenteral antibiotics and recurrent hospital admissions. First, his neutrophil counts were raised by G-CSF, but now his neutrophils do not rise during infections.

These recurrent infections are attributed to lymphopenia of B and NK cells, as well as severe neutropenia. Nevertheless, his immunoglobulin levels remained within normal limits. Variable responses were observed in specific antibody production, even after a booster dose of the dT vaccine. Despite having a low NK cell count, our patient didn't experience severe or persistent viral infections. In fact, he had three COVID-19 infections without any complications and did not require antiviral medication. He is currently a candidate for a hematopoietic stem cell transplant.

Moreover, the ADA2 enzyme activity of both patients was low using in vitro analysis of adenosine deaminase 2 (ADA2) variants in the HEK293T overexpression system (Figure 1A, B, C, D). Further study showed that ADA2 enzyme activity (U/L) assay in our patients is at the levels of genetically proven DADA2 patients (Figure 2).

DISCUSSION

In this report, we describe two patients suffering from the same rare IEI, DADA2, yet with entirely different clinical manifestations: P1 presented with early-onset polyarteritis nodosa-like syndrome, while P2 experienced severe neutropenia, recurrent infections, lymphoproliferation, erythema nodosum, and mouth ulcers.

DADA2 was first described as a cause of polyarteritis nodosa in 2014, with subsequent reports identifying a spectrum of clinical manifestations including cellular immunodeficiency, hypo-gammaglobulinemia, variable cytopenia, vasculopathy, lymphoproliferation, and autoimmune disease.[3,8-11] Asymptomatic cases have also been documented, which highlights the variability in disease expression.[12] Small to medium-sized vasculitis is the most common clinical manifestation of DADA2, occurring in 50 and 75 percent of patients.[8] The spectrum of vasculitis varies from fever and mild cutaneous involvement to stroke. Both of our patients exhibited vasculitis characterized by periodic low-grade fever, cutaneous rash, and abdominal pain. Notably, P1, the younger patient, experienced central neuropathy and stroke, which is reported in nearly one-third of DADA2 cases,[13] with a higher incidence associated with childhood-onset compared to adulthood-onset.[14] Peripheral and cranial nerve neuropathy is common in DADA2, aiding in distinguishing it from childhood PAN.[15] The clinical heterogeneity of DADA2 may be attributed to various factors, including the degree of ADA2 enzyme activity. According to one investigation, those with the least activity were more likely to have strokes.[4] Establishing a definitive genotype-phenotype correlation in DADA2 has been challenging, as even identical mutations can manifest differently clinically.[4] The works of Ozen and Lee offer some support for the genotype-phenotype relationship in DADA2. According to research by Ozen et al, DADA2 patients who presented with Diamond-Blackfan anemia or immunodeficiency were more likely to have heterogeneous mutations in the catalytic domain of the ADA2 enzyme than those who had mutations in the dimerization domain.[16] Conversely, Lee et al. found that those missense mutations linked with vasculitis exhibited considerably more residual ADA2 enzyme activity than those associated with hematologic manifestation, even though all DADA2 patients had low levels of ADA2 enzyme activity. However, mutations related to each phenotype were distributed throughout the gene, lacking preferential localization to specific domains.[4] Take care that phenotyping based on initial presentation must not mislead clinicians in patient treatment. For example, P2's progressive illness, evolving from systemic inflammation to severe neutropenia and recurrent infections, made him a candidate for HSCT.

Our patients presented with elevated acute phase reactants at the time of presentation and during the disease flares, consistent with existing reports on DADA.[3] P1 carries the G47R mutation, one of the most prevalent mutations found across various ancestries.[7,8] His clinical presentation aligns with numerous studies indicating that G437R mutations predominantly associate with vasculitis manifestation.[3,16] However, Ozen et al[16] noted that the vasculitis presentation in their DADA2 patients differed from classical PAN, where reactive changes typically lead to thrombocytosis. In our case, P1 presented with thrombocytosis alongside elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) during febrile episodes, prior to the initiation of anti-TNF medication.

P2 in our study has a reported likely pathogenic variant (P193L) according to the American Academy of Medical Genetics (ACMG) score.[12] This variant has been reported in both homozygous and heterozygous forms, with the heterozygous state combined with two different variants. All affected patients exhibited ADA2 deficiency and vasculitis.[17-19] According to The Human Gene Database (Genecards), a total of 497 distinct variants across the DADA2 gene have been linked to ADA2 deficiency. These variants include missense mutations, frameshift alterations, and splice site mutations, each contributing to the diverse phenotypic manifestations of the condition. Disease severity and age of onset vary widely even among patients of the same family. Notably, those presenting with pure red cell aplasia typically do so early in childhood,[13,20] while patients with vasculitis or bone marrow failure commonly presented later, including in adulthood.[14,15] Our patients exemplify differences in clinical manifestations at varying ages of onset, suggesting a role for genetic, epigenetic, and environmental factors in disease expression.[21]

Both patients exhibited normal T lymphocyte counts with a reversed CD4 to CD8 ratio. P2 presented with severe neutropenia in addition to lymphopenia affecting both B and NK cells. Immunoglobulin levels were

within normal range in both patients. But specific antibody production was variable; for example, P1 can produce isohemagglutinin, but he has impaired and normal specific antibody responses to vaccines. Also, P2 has normal and impaired specific antibody production to vaccines. Severe neutropenia has been reported in up to 10% of patients,[7] and approximately 10% of DADA2 patients showed low B cell counts and diminished switched memory B cells. Furthermore, hypogammaglobulinemia occurs in about 25% of DADA2 patients, with impaired vaccine responses documented in some instances. Recurrent infections are also a concern, affecting 15-20% of patients. Additionally, a low number of T cells and NK cells has been observed in DADA2, with overall lymphopenia reported in approximately 15%.[6,7,8]

Our treatment strategy for our patients was based on their predominant signs and symptoms and included consideration of stroke prophylaxis. P1 is responding well to anti-TNF medication, and his symptoms have subsided. However, he is closely monitored for new symptoms or potential HSCT need. P2 receives G-CSF and prophylactic antibiotics while awaiting HSCT.

Although several reports showed that hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for DADA2.[9,22] Most authors advocate for anti-TNF therapy as a first-line treatment for inflammatory presentations. In contrast, HSCT is recommended for patients presenting with bone marrow failure syndrome, autoimmune cytopenia, lymphoproliferation (both benign and malignant), immunodeficiency phenotypes, and those refractory to anti-cytokine therapies. According to Hashem et al., the overall survival rate of their 30 DADA2 patients after two years of follow-up was 97%, with the ADA2 enzyme being restored to normal levels as early as two weeks after transplant and the cure of hematologic and vasculopathy symptoms.[20] For individuals with inflammatory presentations, thalidomide has proven to be an alternate, cost-effective treatment option compared to anti-TNF drugs.[2]

DADA2 is characterized by phenotypic variability, ranging from asymptomatic cases to fetal vasculitis events, fetal bone marrow aplasia, and severe immunodeficiency. This disease poses therapeutic challenges, including determining when to initiate the treatment, when to introduce etanercept, the appropriate dosage and intervals, and how to taper the medication. It is necessary to evaluate all family members to prevent morbidity and mortality among those closely related to patients. Timely management of the disease leads to improved quality of life for patients. Moreover, genetic counseling provides prenatal and early diagnosis of the disease in families with affected members.

STATEMENT OF ETHICS

This study was approved by Ethics Committee of Immunology, Asthma and Allergy Research Institute (IR.TUMS.IAARI.REC.1397.001).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The data will be available upon reasonable request by mail from corresponding author.

AI ASSISTANCE DISCLOSURE

Not applicable.

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