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Atypical adult polyarteritis nodosa unmasking deficiency of adenosine deaminase 2: a case report about the importance of genetic testing in adults

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Abstract
Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive autoinflammatory disorder caused by biallelic mutations in the *ADA2* gene. It presents as a monogenic vasculitis with heterogeneous manifestations that often resemble small- and medium-vessel vasculitis, particularly polyarteritis nodosa (PAN)-like disease, leading to frequent misdiagnosis, especially in adults. Early recognition of DADA2 is crucial, as prompt treatment can control inflammation, preserve vascular integrity, and prevent irreversible organ damage.
Rising awareness of the wide clinical spectrum of DADA2 is fundamental to improve recognition and facilitate timely diagnosis, ultimately enhancing prognosis. We herein describe the case of a middle-aged woman with skin lesions, central nervous system, peripheral nervous system, and gastrointestinal tract ischemic manifestations who was initially diagnosed with PAN. The patient was treated with glucocorticoids as well as several steroid-sparing immunosuppressive agents (methotrexate, azathioprine, rituximab, tocilizumab, and cyclophosphamide), which all proved to be ineffective. Meanwhile, the patient developed cytopenias and hypogammaglobulinemia. Subsequent genetic testing identified a homozygous missense mutation in the *ADA2* gene (c.1358A>G, p.Tyr453Cys), supporting the diagnosis of DADA2 and enabling the initiation of effective therapy with the tumor necrosis factor-α inhibitor etanercept. This case underscores the importance of considering DADA2 in adult patients presenting with recurrent vasculitic manifestations refractory to conventional immunosuppressive therapy, as timely genetic testing can be pivotal in redirecting treatment toward targeted and effective therapy.

Introduction

Deficiency of adenosine deaminase 2 (DADA2) is a monogenic autoinflammatory disorder caused by biallelic pathogenic variants in the *ADA2* (CECR1) gene (OMIM 607575), which encodes the adenosine deaminase 2 enzyme, a key regulator of endothelial and hematopoietic cell differentiation (1-3). Although the disease is typically diagnosed in childhood, it may present less commonly in adulthood. DADA2 is characterized by recurrent constitutional symptoms (*e.g.*, fever, myalgia, and arthralgia) and systemic vasculitis, primarily affecting the skin (*e.g.*, livedo racemosa and erythematous nodules), the central nervous system (CNS) (typically ischemic and lacunar strokes), and the gastrointestinal system (GI) with mesenteric vasculitis and intestinal ischemia. Additional hallmarks include signs of bone marrow failure (manifesting as anemia, neutropenia, Evans syndrome, or immune thrombocytopenia) and immunodeficiency, often associated with hypogammaglobulinemia. The clinical spectrum is therefore highly variable.

Due to its overlapping features with polyarteritis nodosa (PAN), DADA2 is often misdiagnosed, resulting in inappropriate treatment and progressive, and sometimes irreversible, organ damage (2, 4).

This case highlights the importance of considering genetic testing at an early stage in selected cases of adult-onset vasculitis, when the clinical presentation is atypical, as in the presence of hematologic abnormalities and bone marrow involvement, and/or when conventional therapy proves ineffective.

Case Report

A 57-year-old Thai woman reported a lifelong history of nonspecific systemic symptoms, including intermittent fever and arthralgias with onset in childhood. These symptoms had been managed with intermittent courses of glucocorticoids (GC) in her country of origin. Furthermore, her family history was unremarkable in terms of hereditary disorders. Upon relocating alone to Italy at the age of 30, she developed recurrent vascular skin lesions, predominantly affecting the lower extremities (livedo racemosa and erythematous nodules). Additionally, she experienced CNS, peripheral nervous system (PNS), and GI ischemic complications, leading to multiple hospital admissions.

Diagnostic assessment and therapeutic intervention

In 2000, the clinical picture included constitutional symptoms (arthromyalgia, fever, fatigue), livedo and nodular skin lesions, episodes of GI vasculitis (requiring multiple intestinal resections due to ischemia), CNS and PNS involvement (signs of lacunar ischemia at brain magnetic resonance imaging, left-sided sensorimotor hemiparesis, seventh cranial nerve palsy, and multiple ulnar mononeuropathies with electromyographic alteration), and renal ischemic changes evident on scintigraphy with vascular stenosis on angiography. A small-bowel biopsy was performed, which showed only ischemic damage. Moreover, the autoantibody panel was negative, and the patient resulted positive for past viral hepatitis B (HBV) infection, while screening for hepatitis C virus, HIV, and tuberculosis was negative. At that time, based on the multisystem involvement, fulfillment of the 1990 American College of Rheumatology classification criteria, and a favorable response to GC therapy, a diagnosis of PAN was established.

Initial therapy consisted of continuous GC use at moderate-to-high doses (never below 25 mg/day prednisone equivalent), with dose escalation during ischemic relapses. Over the following years, multiple immunosuppressive agents were sequentially administered to facilitate steroid tapering, including methotrexate (12.5 mg weekly), azathioprine (150 mg daily), rituximab (1000 mg intravenously on days 0 and 15, for a total of two cycles 6 months apart from each other), tocilizumab (8 mg/kg intravenously monthly for 1 year), and finally cyclophosphamide (500 mg/m² monthly for a total of three infusions). However, none of these treatments achieved durable disease control, and long-term use was associated with significant biochemical and hematologic abnormalities, including elevated hepatic enzymes and cytopenias. The patient continued to experience recurrent GI and cutaneous vasculitic relapses, necessitating repeated GC pulses and hospitalizations.

Throughout her life, the patient developed multiple comorbidities: femoral head osteonecrosis (possibly compounded by ischemic vasculopathy), type 2 diabetes mellitus, arterial hypertension with cardiac hypertrophy, and severe osteoporosis. Additionally, the patient developed infectious complications, comprising HBV and cytomegalovirus (CMV) reactivation, which required antiviral therapy with oral entecavir and intravenous ganciclovir. Chronic GC exposure may have plausibly contributed to these events.

During follow-up, progressive signs of bone marrow dysfunction became evident, such as persistent normocytic anemia [hemoglobin (Hb) 12.8 g/dL in 2019, 8.5 g/dL in 2025] and mean corpuscular volume 91 fL, and absolute lymphopenia (1.3×10^9/L in 2019, 0.43×10^9/L in 2025), accompanied by hypogammaglobulinemia [immunoglobulin G (IgG) 4.11 g/L, immunoglobulin M (IgM) 0.12 g/L, immunoglobulin A (IgA) 0.25 g/L in 2025]. These abnormalities were initially attributed to prior cytotoxic therapies, particularly rituximab and cyclophosphamide, but persisted despite drug discontinuation and appropriate supportive measures, among which were blood component transfusions and immunoglobulin supplementation. The persistence of these hematological and immunological abnormalities suggested an underlying primary disease component, as PAN does not typically cause cytopenias or immunoglobulin deficiencies (5).

Given the refractory disease course, as well as the combination of systemic vasculitic involvement and bone marrow failure with immunodeficiency, a reassessment of the diagnosis was undertaken. Whole-exome sequencing was performed to investigate potential genetic causes, including DADA2, which could explain the patient's overall clinical presentation. Genetic analysis identified a homozygous missense variant in the *ADA2* gene, c.1358A>G (p.Tyr453Cys), which has previously been reported as a pathogenic variant in both homozygous and compound heterozygous states (6), confirming the DADA2 diagnosis. From an epidemiological perspective, most affected individuals in the West Asia region are homozygous for the founder variant p.Gly47Arg, with the highest carrier frequency observed among the Georgian Jewish population (approximately 1:10) (7). Genomic databases suggest that the Tyr453Cys variant is rare in East Asian, South Asian, and other Asian populations. Most reported cases of DADA2 in Asian individuals involve other rare or novel variants. Nevertheless, the Tyr453Cys variant has been reported in a Chinese case report and case series, indicating that, although uncommon, it may also occur in Asian populations (1, 8). Variant classification was performed according to the American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology guidelines. The homozygous ADA2 c.1358A>G (p.Tyr453Cys) variant was classified as pathogenic based on previously reported clinical and genetic evidence, its rarity in population databases, and supporting computational evidence (ACMG criteria PM3, PM2, and PP3) (see *Supplementary File 1* for further technical details) (9).

Unfortunately, familial segregation analysis could not be performed due to the unavailability of blood samples from relatives. Similarly, enzymatic activity could not be measured, as the required assays were not feasible at that time within the laboratory. Nevertheless, assessment of enzyme activity would have provided valuable information regarding residual *ADA2* function, potentially contributing to a more accurate estimation of disease severity and a better understanding of the genotype–phenotype correlation. Although the diagnosis of DADA2 can be established either by identifying biallelic pathogenic variants in the *ADA2* gene or by demonstrating reduced *ADA2* enzymatic activity, confirmation by both molecular genetic testing and functional enzymatic analysis, when available, is recommended to strengthen diagnostic confidence and support clinical interpretation (10).

Follow-up and outcomes

After decades of therapeutic challenges and unsuccessful treatment attempts, revision of her diagnosis led to the initiation of tumor necrosis factor (TNF)-α inhibitor therapy with etanercept (50 mg subcutaneously once weekly), resulting in progressive and marked clinical improvement. The patient achieved remission of cutaneous lesions (Figure 1a and b) and normalization of inflammatory biomarkers. GC were gradually tapered from 25 mg/day to 5 mg/day (prednisone equivalent) over 9

months, without disease flares. At 12 months of follow-up, no vascular exacerbations had occurred, and no therapy-related adverse events were reported. The patient was able to travel to Thailand, a trip previously deferred due to her condition. HBV and CMV prophylaxis were continued throughout. Furthermore, hematological parameters stabilized or even showed modest improvement (Hb 9.4 g/dL, lymphocytes 0.61 $\times 10^9$/L; IgG 4.46 g/L, IgM 0.08 g/L, IgA 0.15 g/L) (see *Supplementary Table 1*). As hematological manifestations are known to be typically unresponsive to conventional immunosuppressants, long-term management will focus on close monitoring and targeted interventions (immunoglobulin replacement, routine administration of inactivated vaccines, and prophylactic antimicrobial therapy).

Discussion and Conclusions

This case highlights the importance of considering DADA2 in adults presenting with atypical or treatment-refractory vasculitis (*Supplementary Figure 1*). Although classically a pediatric disorder, DADA2 can also manifest later in life and closely mimic PAN, both clinically and histopathologically. PAN is a necrotizing vasculitis of medium-sized arteries characterized by heterogeneous organ involvement, such as the skin, GI tract, and peripheral nerves (11), features that substantially overlap with DADA2.

First described in 2014, DADA2 is now recognized as a monogenic autoinflammatory vasculopathy and part of the expanding spectrum of inborn errors of immunity (12, 13). The estimated prevalence is approximately 4 per 100,000 individuals (2). Although most cases begin in childhood, approximately 8-10% present after 18 years of age (14). Clinical presentations are highly variable, ranging from early-onset systemic vasculitis and recurrent stroke to isolated cutaneous disease in adults, along with immuno-hematologic abnormalities.

The pathophysiology involves endothelial dysfunction and dysregulated immune signaling, including polarization of macrophages toward an M1 pro-inflammatory phenotype, activation of the type I interferon pathway, and neutrophil-driven vascular injury. Hematologic abnormalities such as lymphopenia, cytopenias, and hypogammaglobulinemia are also frequent (2, 3).

Marked intrafamilial variability in disease severity and age at onset has been observed even among individuals with the same mutation (15), which suggests that additional genetic, epigenetic, or environmental modifiers may influence disease expression (16).

Due to its broad and heterogeneous phenotype, DADA2 is often misclassified as PAN, particularly in adults with systemic vasculitis. Clinically, several features may help distinguish between the conditions (Figure 2). DADA2 more frequently presents with CNS involvement, livedo racemosa, and recurrent fever, reflecting systemic inflammation. Conversely, classic PAN usually involves PNS and kidneys, with hypertension and mononeuritis multiplex, whereas cerebrovascular events are uncommon. Myalgia and arthralgia are nonspecific symptoms common to both conditions (2, 14, 16, 17).

Early recognition is therefore critical, since TNF inhibitors are highly effective in controlling vascular inflammation, reducing systemic inflammation, and preventing ischemic complications, such as stroke (2). Given the vasculitis-like manifestations and hematological involvement, it is also essential to consider alternative diagnoses, such as VEXAS syndrome, particularly in elderly male patients. Although the epidemiology of this condition is increasingly well characterized, exclusion of *UBA1* variants through genetic testing is important, given the overlap in several clinical domains between these entities (18).

TNF inhibitors currently represent the standard of care for vasculitic DADA2, as endorsed by recent international consensus recommendations (10). In patients with profound cytopenias or bone marrow failure, TNF inhibitors alone may be insufficient, and hematopoietic stem cell transplantation should be considered, alongside conventional measures for infection risk prevention, including antimicrobial prophylaxis and vaccination (10).

In our case, the genetic test performed allowed for a diagnostic reassessment and the prompt administration of the appropriate therapy to achieve disease control. Although the enzymatic activity was not assessed, representing a significant limitation of our evaluation, the overall clinical presentation, together with the identification of a pathogenic biallelic *ADA2* variant and the substantial clinical improvement achieved with TNF inhibitor therapy, which had not been observed with previous treatments, strongly supports our diagnostic conclusion.

Limitations

This report has several limitations. First, ADA2 enzymatic activity was not assessed due to the unavailability of the assay in our laboratory. Although the identification of such *ADA2* variant, together with the highly suggestive clinical phenotype and the marked clinical response to TNF inhibitors strongly supports the diagnosis, functional confirmation would have further strengthened the diagnostic workup. Second, the long retrospective disease course limited the availability of standardized clinical disease activity measures and serial imaging data. Third, the patient received multiple immunosuppressive agents over time, making it challenging to distinguish disease-related hematologic and immunologic manifestations from treatment-related toxicity. However, the persistence of cytopenias and hypogammaglobulinemia after treatment discontinuation supports their interpretation as part of the underlying DADA2 phenotype.

In conclusion, clinicians should consider DADA2 in adults presenting with overlapping features of vasculitis, immunodeficiency, and hematologic abnormalities, particularly in cases refractory to conventional therapies. In this context, early genetic testing is essential for establishing an accurate diagnosis and guiding appropriate treatment, preventing irreversible complications and improving long-term outcomes. Therefore, integrating genetic testing into diagnostic algorithms for systemic vasculitis, supported by multidisciplinary collaboration among rheumatologists, immunologists, and geneticists, can reduce diagnostic delays and optimize patient care.

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Online supplementary material
Supplementary File 1. Detailed description of genetic analysis.
Supplementary Figure 1. A brief summary of the main clinical events, vasculitic manifestations, therapies, genetic diagnosis and clinical outcomes of our patient.
Supplementary Table 1. Summary of treatment, prednisone dosage, and key laboratory parameters at baseline and during follow-up.



Figure 1. a) Cutaneous manifestations of adenosine deaminase 2 deficiency before the initiation of tumor necrosis factor inhibitor therapy showing vascular skin lesions, including livedo racemosa and erythematous nodules on both legs. Significant skin involvement with painful nodules and erythema is present. b) Complete resolution of cutaneous lesions after 6 months of etanercept therapy, during glucocorticoid tapering (prednisone equivalent to 7.5 mg/day). The nodules have fully resolved and the skin exhibits a healthy, rosy appearance.

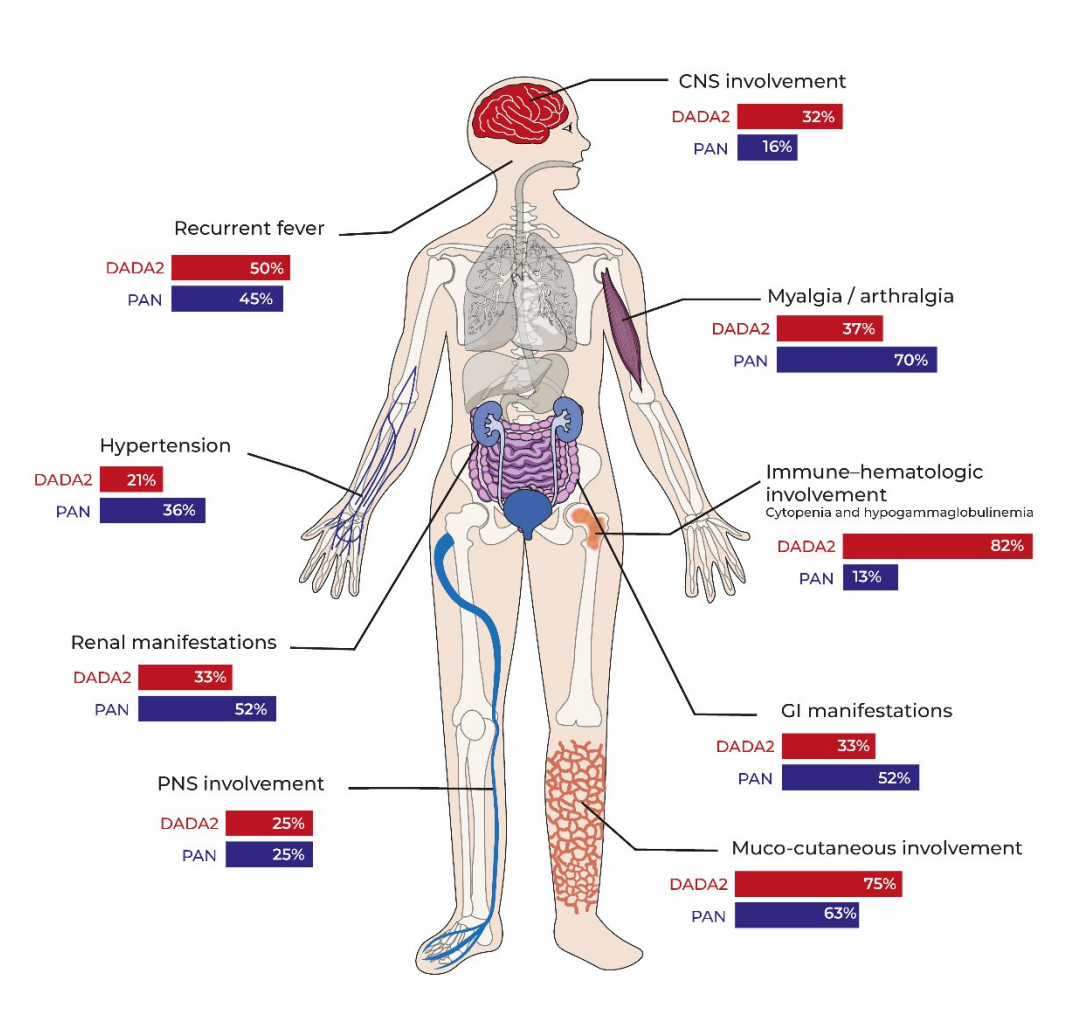


Figure 2. Schematic overview of the frequency of organ involvement in polyarteritis nodosa (PAN) (blue) and adenosine deaminase 2 deficiency (DADA2) (red), based on current available data from clinical cohorts of the diseases. While both share systemic vasculitic features, DADA2 more often presents with recurrent fever, central nervous system involvement, cutaneous manifestations and bone marrow failure along with hematologic abnormalities, whereas PAN typically shows renal and peripheral nerve involvement with hypertension (17, 18). CNS, central nervous system; PNS, peripheral nervous system; GI, gastrointestinal.