Deficiency of Adenosine Deaminase 2 Presenting as Periodic Fever at the Mainland of Familial Mediterranean Fever

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To the Editor

Deficiency of adenosine deaminase 2 (DADA2) is a monogenic disease caused by mutations in the *adenosine deaminase 2* (*ADA2*) gene. It was first described in 2014, in patients with predominantly treatment-resistant vasculitis phenotype, namely, polyarteritis nodosa [1, 2]. It is probably the most cited disease among newly described diseases in medicine because several new cases were described just after the initial description of the disease. The clinical spectrum of the disease was expanded with each publication including patients presenting with immunodeficiency, leukopenia, pure red cell aplasia, or lymphoproliferation. Most of the patients in the literature have recurrent fever attacks accompanied by one or more clinical features [1–5]. Herein, we describe a case of DADA2 presenting as periodic fever and provisionally diagnosed as familial Mediterranean fever (FMF).

A 4-year-old boy was referred to pediatric rheumatology clinic with complaints of recurrent fevers, arthralgia, and myalgia for the last 3 months. He was the first child of healthy, non-consanguineous parents and had a healthy 1-year-old sister. Family history was unremarkable for any rheumatic disease. The family stated that the fever attacks started 3 months ago, recurring every 2–3 weeks, lasting for 3–5 days, and accompanied by mild abdominal pain, arthralgia, and myalgia. There was no history of recent or distant COVID-19 infection in the family. Physical examination was normal without any rash, arthritis, lymphadenopathy, or hepatosplenomegaly. Initial laboratory tests at the time of fever revealed mild anemia (white blood cell count: 8400/mm³, neutrophil count: 5600/mm³, lymphocyte count: 2100/mm³, hemoglobin: 10.8 g/dL, platelets: 324,000/mm³) and high acute phase reactants [C-reactive protein (CRP): 74.8 mg/L, erythrocyte sedimentation rate (ESR): 83 mm/h, serum amyloid A (SAA): 314 mg/L] with normal biochemistry and urinalysis. The fever episodes continued in the next months and acute phase reactants remained high in between fever episodes. Viral serology tests, blood, and urine cultures were all negative for an infectious etiology. Flow cytometric analysis of lymphocytes and serum immunoglobulins were normal. Bone marrow aspiration and ultrasound screening studies were negative for malignancies like leukemia, lymphoma, or neuroblastoma. Bone marrow examination showed normal trilineage hematopoiesis without any sign of hemophagocytosis, eosinophilia, or lymphoid aggregates. *MEFV* mutation analysis showed heterozygous M680I mutation in exon 10. Colchicine and prednisolone (2 mg/kg/day) were started with the working diagnosis of FMF and protracted febrile myalgia syndrome (PFMS). On the 2nd week of this regimen, the fever episodes continued, and acute phase reactants remained elevated (CRP: 86.4 mg/L, ESR: 44 mm/h, SAA: 556 mg/L). The work-up for vasculitis including thoracoabdominal magnetic resonance angiography was normal. Anakinra (2 mg/kg/day) was added to the treatment regimen. On the 2nd week of anakinra, the child had another fever episode, and the dose was increased to 5 mg/kg/day which led to partial resolution of fever attacks for 3 weeks but the fever episodes eventually recurred. Auto-inflammatory disease gene panel (including genes for *MVK, TNFRSF1A, NLRP3, ADA2*) showed a homozygous mutation in exon 2 of *ADA2* gene [c.144del; p.(Arg49Glyfs*4)]. The child had final diagnosis of DADA2, and etanercept treatment was started. He is being followed for 1.5 years under etanercept and colchicine treatments and did not have any fever episodes since the first dose of etanercept with normalization of acute phase reactants. Both parents were heterozygous, but healthy younger sister was homozygous for the same mutation in the *ADA2* gene. She did not have any *MEFV* gene mutation. Plasma ADA2 activity of the
index patient was 0.2%, and it was 0.6% in the healthy sister. Even though she was asymptomatic, preemptive etanercept treatment was initiated and being followed for 1 year without any complaints.

Familial Mediterranean fever is highly endemic in our country. We consider FMF always in the first place in children with recurrent unexplained fever and/or abdominal pain complaints. Even though it is an autosomal recessive disease, 20–25% of FMF patients have only one mutation. PFMS is the most devastating manifestation of FMF, and there are reports that PFMS may be the first clinical manifestation of FMF [6]. Digenic inheritance refers to the interaction of two genes resulting in the expression of a phenotype [7]. Our patient’s phenotype and genotype were compatible with FMF and PFMS, but the unresponsiveness of the patient to colchicine, corticosteroids, and anakinra made us search for another disease. We believe that MEFV gene mutation had some degree of contribution to the phenotype.

The recent review done by Pinto et al. [4] included 316 DADA2 patients, and fever was observed in 51.8% of the cases. But nearly all of the patients described in the literature have accompanying signs or symptoms like livedoid skin rash, Raynaud’s phenomenon, stroke, recurrent infections, or lymphadenopathy that are suggestive of vasculitis, autoimmunity, immunodeficiency, or lymphoproliferation [1–5]. Our case had pure autoinflammatory manifestations. Nihira et al. [8] presented a 3-month-old girl with fever of unknown origin and erythema multiforme-like eruptions that had final diagnosis of DADA2. The authors concluded that DADA2 should be in the differential diagnosis list of children with fever of unknown origin, even in the absence of vasculopathy. Also, Navon-Alkan et al. [2] described 24 DADA2 patients and 11 of them had only fever and skin involvement.

There are asymptomatic cases with pathogenic homozygous mutations in the ADA2 gene, and it is highly recommended to search for ADA2 mutations in the family members. Preemptive treatment is also recommended in asymptomatic cases if plasma ADA2 enzyme activity is low because the disease might have irreversible consequences like stroke [4, 5].

In conclusion, DADA2 may manifest with pure autoinflammatory manifestations. If possible, all family members should be checked for ADA2 mutations and plasma ADA2 enzyme activity after the definition of an index patient in the family.

Author Contribution All the authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Mustafa Çakan and Betül Sözeri. The first draft of the manuscript was written by Mustafa Çakan, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent to Participate Written informed consent was obtained from the parents.

Competing Interests The authors declare no competing interests.

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