Editorial

Novel pathogenic *ADA2* mutations: alert to diagnosis challenge of ADA2 deficiency

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Autoinflammatory and autoimmune diseases often present with complex and variable clinical manifestations, leading to challenges in making a diagnosis, particularly in cases that present with atypical clinical features. Somatic mutations contributing to rheumatologic diseases have been largely identified by sequencing approaches with advances and widespread availability of genomic DNA sequencing (1-5). Genotype-driven approaches have been used to delineate human diseases with diverse clinical features by looking for pathogenic variants in patients with or without particular clinical characteristics (6,7). This genotype-driven approach is particularly helpful in identifying rheumatologic diseases due to their heterogenous clinical presentations. Most recently, this approach has been successful in identifying VEXAS syndrome, a monogenic disease of adulthood caused by somatic mutations in *UBA1* in hematopoietic stem and progenitor cells leading to both hematological and inflammatory manifestations (8).

Identification of adenosine deaminase 2 deficiency (DADA2) should be approached similarly. First reported in 2014, inflammation leading to tissue damage is a key clinical feature of this rare autosomal recessive monogenic disease due to loss-of-function mutations of *ADA2* (9,10). DADA2 deficiency typically presents in childhood and is characterized by vasculopathy, stroke, inflammation, immunodeficiency, and hematologic manifestations (11-14).

In a recent study published on *Translational Paediatrics*, Yin and colleagues (15) reported a 3-year-old boy with DADA2 who initially presented with nonspecific clinical manifestations including recurrent fever, mildly enlarged lymph nodes, and elevated acute phase reactants, with an initial diagnosis of systemic onset juvenile idiopathic arthritis. The key events leading to a re-evaluation of the initial diagnosis were the presence of intractable hypertension and gastrointestinal complications suspicious for underlying vasculopathy, and an unsustained response to immunosuppressive treatments. This case report should alert clinicians to consider genetic testing in patients with nonspecific autoimmune or autoinflammatory disease phenotypes, especially in those who present in early childhood. Misdiagnosis is not unexpected when a patient presents with a wide spectrum of clinical manifestations and atypical features of DADA2.

Study of Yin *et al.*, which was published on *Translational Paediatrics*, identified a novel compound heterozygous mutation in *ADA2* gene (15), c.737 G>C (p. Arg246Thr) located in exon 3 and c.827 T>C (p.Phe276Ser) located in exon 4. Their experimental data revealed ADA2 enzyme activity was almost completely lost in this patient. These novel compound heterozygous variants are likely

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pathogenic due to their association with established disease phenotypes, family history, and functional studies showing reduced ADA2 enzyme activity. These novel mutations are likely associated with vasculitis rather than hematologic phenotypes as this patient did not have any hematological manifestations. This report expands our current knowledge of disease-causing variants in DADA2; future studies will help better characterize the genotype-phenotype relationship.

In conclusion, the study by Yin and colleagues presented a case of suspected juvenile idiopathic arthritis with atypical clinical features that led to the identification of novel disease-causing *ADA2* variants. This case highlights the importance for clinicians to consider monogenic inherited autoinflammatory disorders when systemic vasculitis occurs in early childhood, patients who develop atypical manifestations of their suspected diagnosis, or have a suboptimal response to treatment. Whole genome sequencing is powerful in disease diagnosis and in recognizing novel pathogenic mutations and should be highly considered in these circumstances.

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