DADA2 deficiency caused by new homozygous variation in 22q11.1

Sirs,

Adenosine deaminase 2 (DADA2) deficiency is a monogenic auto-inflammatory syndrome first described in 2014. It is characterised by a polyarteritis nodosa-like vasculopathy with livedo reticularis, skin ulcers, subcutaneous rashes, aphthous ulcers, and leukocytoclastic vasculitis, as well as early-onset neurological symptoms such as stroke and polyneuropathy.

Although the exact incidence of DADA2 is unknown, it can be as high as 4 per 100,000. Two of the most common pathogenic variants of DADA2 are p.G47R and p.R169Q. Recent studies have revealed that mutations in cat eye chromosome region 1 (CECR1) gene, which encodes a defect in DADA2, are associated with vascular inflammatory lesions such as polyarteritis nodosa.

Here, we report a 16-year-old adolescent followed up as having Raynaud's phenomenon, with green reticular spots of the lower limbs for many years. The patient was lymphopenic and had low serum immunoglobulin A levels. Laboratory tests showed anaemia, severe neutropenia, lymphopenia, moderately elevated erythrocyte sedimentation rate, and a positive C-reactive protein level. ANA and ANCA were not detected. Anti-ds-DNA and aPL antibodies were normal. CTA of the entire aorta showed multiple small aneurysms in branches that were less than grade 3 of the intra-abdominal arteries (Fig. 1). Furthermore, computed tomography scans of the brain, chest, and abdomen showed no abnormal enlargement of lymph nodes or solid masses.

Given his Raynaud's phenomenon, reticular green spots, and small aneurysms, we performed genetic analysis of mutations in the DADA2 gene. Whole-exome sequencing revealed a homozygous mutation: c.97(exonl)_c98(exonl)insA (Fig. 2). No DADA2 mutations were detected in his parents' DNA. Our patient had significantly lower 0.5 and 1 h DADA2 enzyme activity compared with the control and his father's samples, suggesting that our patient had DADA2 enzyme deficiency (Fig. 3).

In this case, the symptoms of an inflammatory reaction were consistent with the diagnosis of DADA2, ultimately leading to the initiation of appropriate DADA2 treatment. We started treatment with methylprednisolone (40 mg per day). After one month of treatment, we started to reduce the dose of methylprednisolone due to decreased in ESR and CRP. We were able to reduce the methylprednisolone dosage to 32 mg per day and added 20 mg of leflunomide per day. The ESR and CRP decreased to normal. The methylprednisolone dose of 32 mg was changed to oral hormone, and cyclophosphamide was successively given, but the effect was unsatisfactory. Treatment was challenging and the effectiveness of immunosuppressants was limited. TNF antibodies have been proposed as a first-line therapy for vasculitis. Thus, we switched to the anti-tumour necrosis factor alpha antagonist at 25 mg per week, and the patient's condition stabilised.

As previously reported, missense mutations in CECR1 are typically associated with the clinical phenotype of vasculitis. However, insertion, deletion, and frameshift mutations often manifest as hematopoietic dysfunction (3). Conversely, the present case suggested that even homozygous insertion and shift mutations may produce severe systemic vasculitis, thereby warranting clinical attention. Experts suggest that DADA2 activity dosage can be a complementary tool for diagnosing DADA2 deficiency in cases with suggestive clinical picture and inconclusive genetic testing (4). Inflammatory features usually respond to anti-TNF agents, but bone-marrow failure and severe immunodeficiency may require haematopoietic stem-cell transplantation. The relationship between the genotype and clinical phenotype of DADA2 has yet to be studied in depth through family-lineage investigations and mechanistic studies. Notably, the possibility of identifying DADA2 deficiency can be considered in adolescents presenting clinically with vasculitis who also have an immunodeficiency.

In 2023, Lee *et al.* (5) of Harvard Medical School formulated the first expert consensus on the diagnosis and treatment of DADA2, He provides a standardised framework for the management of DADA2 patients by outlining the definition, diagnosis, screening, clinical diagnosis, and management of the disease phenotype. The aim of this study was to improve awareness of DADA2 among clinicians and patients and to better promote the treatment and management of DADA2.

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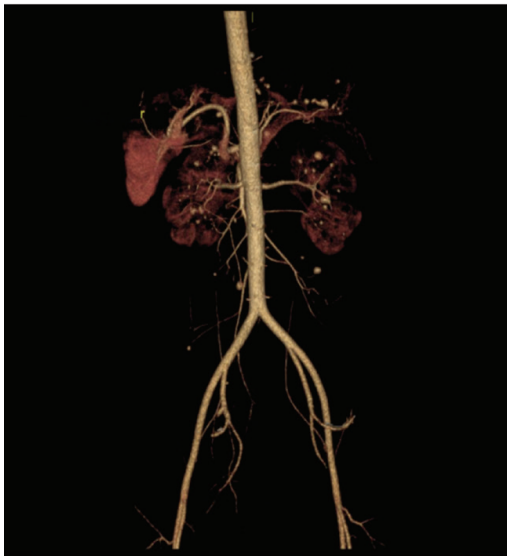

Fig. 1. CTA of the whole aorta showed multiple small aneurysms below grade 3 branches of intra-abdominal arteries.

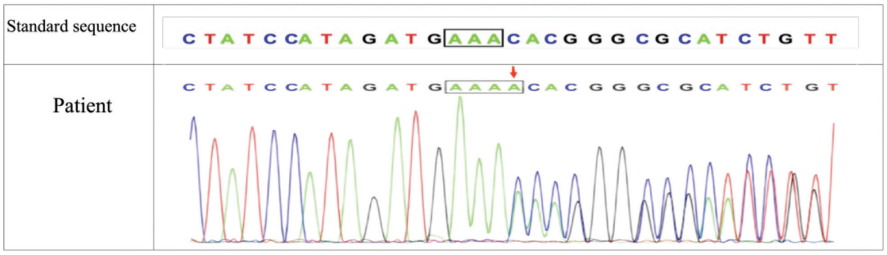

Fig. 2. Patient's peripheral blood whole-exon gene test results.

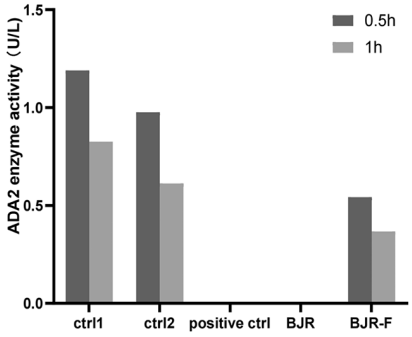

Fig. 3. Defective detection of adenosine deaminase 2 (DADA2) activity in the patient.
ctrl1: control 1; ctrl2: control 2; positive ctrl: positive control; BJR: patient; BJR-F: patient's father.

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