Diagnosis of deficiency of adenosine deaminase 2 with early onset polyarteritis nodosa in an adult patient with a novel compound heterozygous *CECR1* mutation

Sirs,

Polyarteritis nodosa (PAN) is a rare systemic necrotising vasculitis affecting medium and small arteries without glomerulonephritis or vasculitis of arterioles, capillaries and venules (1). While most cases are considered idiopathic, a minority of cases is associated with hepatitis B or hepatitis C virus infection or other infections (1, 2). Notably, childhood PAN takes a more benign course compared to adult onset PAN (3). More recently, homozygous or compound heterozygous loss-of-function mutations of the *cat eye syndrome chromosome region 1 (CECR1)* gene resulting in deficiency of adenosine deaminase 2 (DADA2) have been reported in association with early onset PAN (4, 5).

Here we report on a 30-year old patient who was admitted to our hospital for the first time for further diagnosis and treatment. She had suffered from recurrent ischaemic strokes and splenic, intestinal and renal infarction between her 4th and 11th year of age. Elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was repeatedly reported. A heterozygous factor V Leiden mutation and reduced serum-levels of immunoglobulin (Ig)G, IgM and IgA had also been found. At the age of 10 she underwent laparotomy for intestinal infarction. Intimal proliferation with luminal confinement of small intestinal vessels was described in a histological specimen. Vasculitis without further specification was diagnosed at that time. The patient was treated with glucocorticoids, methotrexate and cyclosporine A for about 5 years, followed by glucocorticoid and low-molecular-weight heparin treatment. On admission to our hospital, the patient had a spastic haemiparesis as consequence of former strokes. She complained about severe weakness and myalgia. Under the current treatment with 30 mg prednisolone daily, ESR and CRP were elevated with 69 mm/h and 47.3 mg/l, respectively. Circulating interleukin (IL)-6 (54.2 ng/l; normal range <7 ng/l) and IL-2R (1308 kU/l; normal range <623 kU/l) levels were elevated. While the white blood cell count was within normal range, the number of circulating B-cells was severely reduced (11/µl; normal range 100–500/µl). Serum levels of IgG (4.44 g/l; normal range 7-16 g/l), IgA (<0.14 g/l; normal range 0.7–5.0 g/l) and IgM (<0.05 g/l; normal range 0.4–2.3 g/l) were low. Magnetic resonance imaging (MRI) showed residual cerebral infarct lesions, a stenosis of the left vertebral artery and increased signal intensity attributable to oedema and possible vasculitic inflammation of skeletal muscles. Based on the patient's medical history, we diagnosed childhood onset PAN in accordance with the EULAR/PRINTO/PRES criteria (6). Sanger-sequencing of the *CECR1* gene disclosed a novel compound heterozygous mutation: c.139G>T (p.G47W) and c.1367A>G (p.Y456C). Upon molecular genetic confirmation of DADA2, we started treatment with etanercept (50 mg subcutaneously per week). Within days, the patient reported complete relief of weakness and myalgia. The prednisolone dosage could be tapered to 5 mg daily. ESR and CRP levels were normal, whereas the number of circulating B-cells and serum levels of IgG, IgA and IgM remained unchanged upon follow-up 6 months later.

DADA2 causes endothelial cell damage, necrotising arteritis, activation of monocytes and macrophages, peripheral B-cell deficiency and hyogammaglobulinaemia (4, 5, 7, 8). Other variants (G47A, G47R, G47V) of the *CECR1* mutation than the one found in our patient (G47W) have been reported previously. The Y456C has not been reported before (4, 5, 7 – 9). Cytotoxic immunosuppression is often insufficient to control inflammation, whereas tumour necrosis factor (TNF)α-blockade rapidly induces remission (4, 5, 7-9). Haematopoietic stem cell transplantation can be considered for severe bone marrow dysfunction (10). As demonstrated by our case, the rarity of DADA2 and lack of exclusive features distinguishing it from other forms of early onset PAN impedes timely diagnosis and requires a high degree of suspicion.

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