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 thrombosis or phlebitis 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 (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 IgG, 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 hemiparesis as consequence of former strokes. She complained about severe myalgia. Under the current treatment with 30 mg prednisolone daily, ESR and CRP were elevated with 69 mm/h (normal range <623 kU/l; normal range <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 resulted in the discovery of 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 following 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)-r-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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References