Hyper-IgD syndrome in a patient with IgA immunodeficiency

Sir,

A 9-year-old Greek girl, presented with a three-day history of myalgias, fever up to 40 °C and erythematous cutaneous plaques. Family history was unremarkable. From her past medical history, she had recurrent infections (pneumonia, staphylococcus dermatitis, tonsillitis), transient knee monarthrosis and selective IgA immunodeficiency, which was revealed five years ago during investigation for febrile cervical lymphadenopathy.

Physical examination showed warm, erythematous plaques on her upper and lower extremities. Blood tests revealed neutrophil leucocytosis, normochromic, normocytic anaemia and elevated acute phase reactants (Table I). Repeated blood, throat and urine cultures as well as the antibodies against Mycoplasma pneumoniae, Adenovirus and Epstein-Barr were all negative. Chest x-ray, abdominal ultrasound and an-giotensin-converting enzyme (ACE) were normal. Antinuclear and anti-neutrophil cytoplasmic antibodies were not detected and C3 and C4 serum levels were within normal limits. Polyclonal hypergammaglobulinemia was noticed and measurement of serum immunoglobulins showed elevated IgD levels: 880 IU/ml (normal value: <100 IU/ml) and very low IgA levels: 6 mg/dl (normal value: 34-305 mg/dl). Peripheral blood genetic analysis revealed two heterozygous mutations, p.C376S and p.V377I, on exon 11 of the Mevalonate Kinase (MVK) gene, which confirmed the diagnosis of hyper-IgD syndrome (HIDS). Spontaneous recovery was noticed awaiting laboratory results. Next flare was treated with Canakinumab, with very good response. Clinical symptoms included leukocytosis and elevated acute-phase reactants. Mevalonic acid may be detected in urine during febrile episodes (2).

Treatment could be challenging. Non-ste-roidal anti-inflammatory drugs and disease modifying antirheumatic drugs have been used with limited success. Steroids given early at attack onset seem to be beneficial. Biologic treatment with anti-IL-1 regimes (Anakinra, Canakinumab) and Etanercept, appears to be the most effective, while Tocilizumab has also been used (7).

Serum IgD levels are elevated in about 80% of the patients (6), while IgA is also increased in more than half of HIDS patients (6). Interestingly, our patient had selective IgA deficiency. The latter has a large variety of clinical manifestations, like allergies, gastrointestinal disorders and recurrent sinopulmonary infections, as in our case, but most patients are asymptomatic (8). Its pathogenesis is largely unclear, however there seems to be an impaired ability for B cells to be switched to IgA secreting plasma cells. Aberrancies in T cells and in various cytokines as well as several mutations associated with sIgA immunodeficiency have also been described (9). sIgA immunodeficiency has been associated with a variety of autoimmune diseases (10) but it has not been described in patients with auto-inflammation syndromes.

In conclusion, we describe the first patient with HIDS combined with sIgA deficiency, highlighting that these are not mutually-exclusive diagnoses.

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