Recurrent macrophage activation syndrome in spondyloarthritis and monoallelic missense mutations in PRF1: a description of one paediatric case

Sirs,

Macrophage activation syndrome (MAS) is a serious, potentially fatal complication of paediatric rheumatic diseases, which is seen most commonly in systemic juvenile idiopathic arthritis (sJIA) (1). We report the case of a girl affected by B27-positive Spondyloarthritis (SpA) who developed recurrent episodes of MAS. The genetic analysis revealed the presence of a monoallelic missense mutation in the perforine gene (*PRF1*).

A 16-year-old girl was referred to us because of 2-week fever, unresponsive to oral antibiotics, dysuria, urticarial rash and buttock pain.

The history until the age of 5 years as the familiar history are unknown because she was adopted. At the age of 11, she presented fever for 2 weeks with arthralgia and rash. In few days she developed a MAS according to the current criteria (2), characterised by urticarial rash, hepatosplenomegaly, hyperferritaemia, hypertransaminasaemia, hypertrigliceridaemia, hyponatraemia, decrease in platelet count, confirmed by the presence of macrophage haemophagocytosis on bone marrow aspirate. The patient was successfully treated with steroids (3 pulses of methylprednisolone 30 mg/kg/day followed by prednisone 2 mg/kg/day), intravenous immunoglobulins (IVIG) 2 g/kg/day per 3 days and cyclosporine 4 mg/kg/day, progressively tapered and discontinued in 2 years.

After 6 months the patient presented a second episode of MAS and she was treated with steroids and cyclosporine achieving disease remission. Cyclosporine was discontinued 9 months before the present hospitalisation.

At present admission, the patient had fever, dysuria, urticarial rash, buttock pain on the right side, psoriatic lesions on the forehead and acute bilateral uveitis.

Pelvic magnetic resonance imaging (MRI) disclosed right sacroiliitis (Fig. 1). HLA analysis revealed positive HLA-B27.

According to the current International League of Associations for Rheumatology (ILAR) classification of JIA (3), the patient was classified in the group of undifferenciated arthritis.

Blood and urine cultures, collected in course of oral antibiotics, were negative, but the high phase reactants associated with microhaematuria and leukocyturia, led us to suspect a urinary tract infection and an intravenous antibiotic was stared with disappearance of fever and progressive normalisation of laboratory tests.

Three days after the discharging, she presented again with unremitting fever, polyarthralgia and increased acute phase reactants and a full-blown picture of MAS (2) with hyperferritaemia, hypertransaminasaemia, hypertrigliceridaemia, hyponatraemia, reduction in platelet counts and hypofibrinogenaemia. She was started on 3 pulses of intravenous methylprednisolone and cyclosporine. The fever reoccurred at discontinuation of the pulses and she was started on dexametasone 10 mg/m^2 for 2 weeks plus IVIG for 3 days, achieving the complete remission.

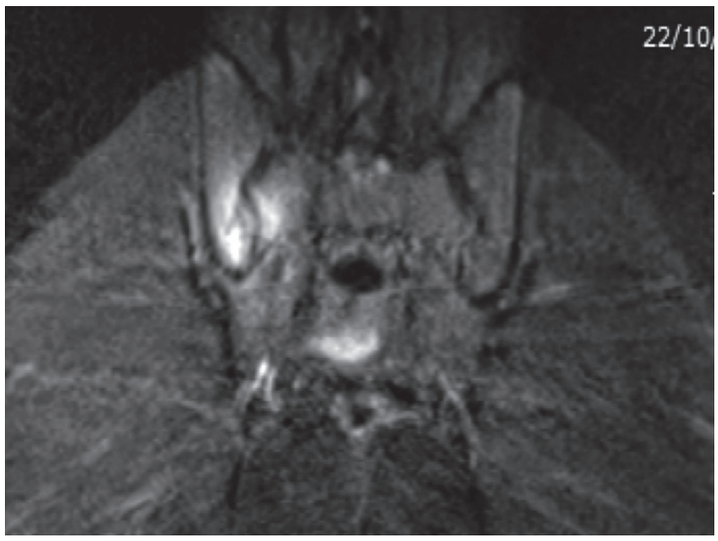

Fig. 1. Magnetic resonance image. Coronal/Axial STIR images show diffuse periarticular bone marrow oedema of the right sacroiliac joint, consisting of sacroiliitis.

The cytotoxic lymphocyte function was assessed by flow cytometry (4), which revealed reduced perforin expression (30%) and normal NK cell and CTL degranulation. Based on these findings, direct sequencing of the perforine gene (*PRF1*) was carried out, which showed the presence of an heterozygous single nucleotide substitution (c.1262T>G, p.F421C).

Research for monoallelic inflammasome defect affecting the NLRC4, recently identified in a patient with recurrent MAS and "normal NK cell function and genetic testing for haemophagocytic lymphohistiocytosis (HLH)" (5) were not performed.

We can not exclude a possible role of an hypothetical inflammasome defect also in this case.

MAS bears strong similarity to the group of HLH (6). The familiar form of HLH (FHL) is caused by bi-allelic mutations which result in severe defect in cytotoxic activity. Mutations in FHL-related genes have been identified in patients with MAS occurring in the context of sJIA in independent cohorts of children (7, 8). We identified a monoallelic missense mutation in the *PRF1* gene, that was previously reported in Childhood Anaplastic Large Cell Lymphoma (9), in a patient with recurrent episodes of MAS in a full-blown picture of peripheral SpA (10) and classified in the group of undifferentiated arthritis according to the ILAR criteria.

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