Development of spondyloarthropathy following episodes of macrophage activation syndrome in children with heterozygous mutations in haemophagocytic lymphohistiocytosis-associated genes

Sirs,

We read with interest Filocamo and colleagues' report describing a child with spondyloarthritis and recurrent macrophage activation syndrome (MAS) who had a monoallelic missense mutation in the perforin gene (*PRF1*) (1). A PUBMED literature search, revealed only 1 other child with spondyloarthropathy and MAS (2), or the related condition of secondary haemophagocytic lymphohistiocytosis (sHLH) (3). At our institution, we have seen 2 previously well children hospitalised with MAS who later developed spondyloarthritis, both with associated uveitis, after recovery from MAS but while on tapering immunosuppressive treatment. Both children possessed monoallelic missense mutations in genes involved in the perforin-mediated cytolytic pathway employed by cytotoxic CD8 T cells and natural killer (NK) cells (4).

The first child was a 21-month-old African-American boy who presented with fever, oral bleeding, hepatomegaly, thrombocytopenia, anaemia, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, elevated sCD25 level, and haemophagocytosis on bone marrow biopsy, thus, fulfilling HLH criteria (3). He was found to have a monoallelic missense mutation in *MUNC13-4* (*c.847 A>G*, p.I283V) (5), whose gene product is critical to perforin mediated cytolytic activity, and HHV-6 was identified as a possible trigger of his HLH (6). He was treated with a combination of high dose methylprednisolone (30 mg/kg/day for 3 days before tapering doses), cyclosporine A (5 mg/kg/day), and recombinant interleukin-1 receptor antagonist (anakinra, 15 mg/kg/day), and he quickly and remarkably improved (Fig. 1), leading to hospital discharge within 10 days. Three weeks after hospitalisation he developed bilateral anterior uveitis while on tapering immunosuppression. The uveitis responded to topical corticosteroid eye drops, and systemic corticosteroids and cyclosporine A were discontinued within 3 months of hospitalisation. Four months after the MAS episode, he developed enthesitis (metatarsal heads, inferior and superior poles of patellae, and Achilles insertions), and eventually knee and wrist arthritis, prompting the diagnosis of enthesitis-related arthritis/juvenile idiopathic arthritis (7) and treatment with weekly methotrexate. Methotrexate (for arthritis) and anakinra (maintained to allow for tapering immunosuppression without MAS flare) were discontinued 2.5 years after hospitalisation, and there have been no further episodes of MAS, uveitis, or arthritis in the 3+ years since discontinuing therapy.

During the same time frame of the young boy's hospitalisation, an 18-year-old Caucasian girl was admitted to the same hospital for prolonged fever and liver failure. A detailed clinical history has been previously reported (8). She met 7 of 8 HLH criteria, and was found to have a *RAB27A* mutation (*c.259G>C*, p.A87P), another gene product critical to perforin-mediated cytolysis. She was treated with high dose corticosteroids, cyclosporine A, and anakinra, and promptly responded to therapy. Within 2 weeks of hospital discharge she also developed bilateral anterior uveitis (painful, erythematous, photophobic) requiring periocular corticosteroid injections to control the inflammation. Her immunosuppression was tapered off over one year, but a few years later she developed spondyloarthritis (ANA and HLA-B27 negative). She has had no further MAS episodes in the 5+ years since her hospitalisation.

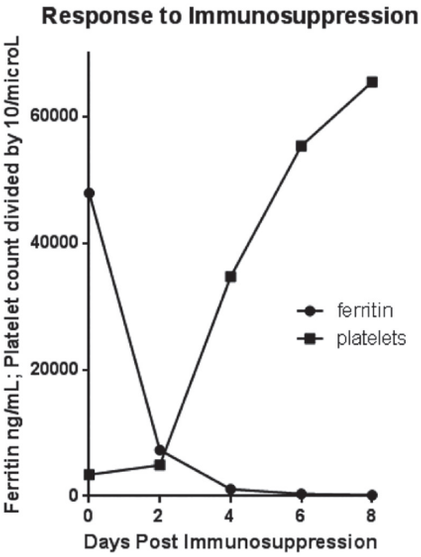

Fig. 1. Rapid clinical response of MAS to immunosuppression with corticosteroids, cyclosporine A, and anakinra. Serum ferritin (•) and circulating platelet count (▪) are graphed before (day 0) and after immunosuppression for the 21-month-old boy with the *MUNC13-4* mutation.

These 2 MAS cases followed by uveitis and spondyloarthritis provide additional support for the association of childhood spondyloarthritis and MAS. It is possible inflammation associated with emerging spondyloarthropathy combined with an HLH-associated gene defect allows for reaching a threshold where MAS becomes clinically evident (9). They also suggest monoallelic mutations in perforin pathway HLH-associated genes are risk factors for MAS/sHLH development (4). We recently demonstrated the *RAB27A c.259G>C* (p.A87P) mutation from the teenage girl functions as a partial dominant-negative protein by disrupting the interaction with Munc13-4, delaying granzyme B polarisation to the NK cell immunologic synapse, and decreasing NK cell lytic function (8). We and others demonstrated similar dominant-negative effects of monoallelic mutations in other perforin pathway genes (*e.g. MUNC18-2*) from secondary HLH patients on NK cell function (4, 10). Even common mutations, like *PRF1* (*c.272C>T*, p.A91V), can have partial dominant-negative effects, and may contribute to MAS in the setting of influenza infection (11). Fortunately, immunosuppression, including interleukin-1 blockade, can resolve MAS, even in those with monoallelic mutations in familial HLH-associated cytolytic pathway genes. This is consistent with the benefit of anakinra in treatment-refractory patients with MAS (12).

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