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

Sirs,
We read with interest Filocamo and colleagues’ report describing a child with spondyloarthrits 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 haemagglutocytic lymphohistiocytosis (HLH) (3). At our institution, we have seen 2 previously well children hospitalised with MAS who later developed spondyloarthrits, 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 cytolitic 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.547 A>G, p.1283V) (5), whose gene product is critical to perforin mediated cytolitic 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 encephalitis (metatarsal heads, inferior and superior poles of patellae, and Achilles insertions), and eventually knee and wrist arthritis, prompting the diagnosis of encephalitis-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 3.5 years since discontinuing therapy. During the same time frame of the young boy’s hospitalisation, an 18-year-old Cauca-