

Letters to the Editor

Dramatic efficacy of cyclosporine A in macrophage activation syndrome

Sir,

Macrophage activation syndrome (MAS) is a potentially life threatening complication of chronic rheumatic disorders characterised by fever, cytopenia, deranged liver function and, frequently, coagulopathy and neurological involvement (1). Because MAS may have a fatal outcome, prompt recognition and treatment are of upmost importance. However, corticosteroids are effective in most but not all cases, and the use of high-dose intravenous immunoglobulins, cyclophosphamide, plasma exchange, and etoposide has provided conflicting results. We report 2 cases of MAS occurring in children with systemic inflammatory disorders that was refractory to high-dose corticosteroid therapy, but responded dramatically to cyclosporine A (CyA).

A 9-year-old boy presented with an unspecified systemic inflammatory syndrome that went into remission with prednisone therapy. Three months after corticosteroid discontinuation, he developed a thrombotic thrombocytopenic purpura with severe neurological involvement. Plasma exchange therapy led to progressive clinical improvement. Five days after the last plasma exchange, he experienced intermittent high fever, enlarged tender liver, splenomegaly, and scleral icterus. Laboratory studies disclosed pancytopenia, elevated liver trans-

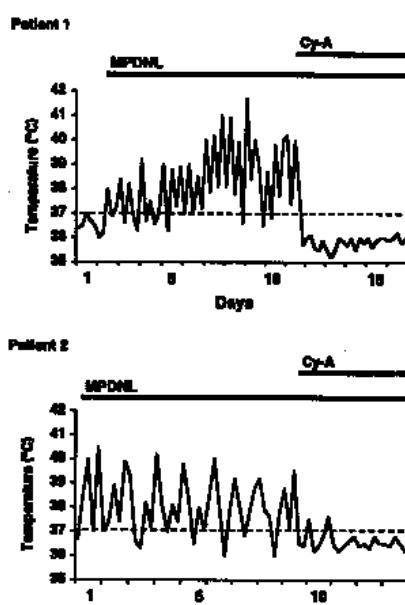


Fig. 1. Time course of fever before and after the start of cyclosporine A. CyA: cyclosporine A; MPDNL: methylprednisolone.

aminases, bilirubin, triglycerides and ferritin, and evidence of intravascular coagulation. The bone marrow aspirate revealed macrophage hemophagocytosis. Intravenous methylprednisolone, 4 mg/kg/day, was begun. Because the fever did not respond and the liver failure progressed, we initiated intravenous CyA, 3 mg/kg/day. The result was disappearance of the fever within 6 hours (Fig. 1) and the prompt improvement of laboratory abnormalities.

An 11-year-old girl was diagnosed as having systemic lupus erythematosus (SLE) in October, 1997. Prednisone therapy led to rapid improvement of the clinical and laboratory abnormalities. Six weeks later, she was readmitted with a one-week history of intermittent high fever. Physical examination was negative, serum complement levels were normal and anti-DNA antibodies were absent. No microbiological evidence of infection was found and fever was unaffected by a 7-day treatment course with ceftriaxone, 2 g/day. Over the following days, she developed pancytopenia and increased levels of liver transaminases, triglycerides and ferritin. A bone marrow aspirate revealed macrophage hemophagocytosis. Intravenous methylprednisolone, 2 mg/Kg/ day, was begun and a single infusion of intravenous immunoglobulins, 2 g/Kg, administered. Because this treatment did not affect the course of MAS, oral CyA, 5 mg/kg/day, was added. This resulted in resolution of the fever within 24 hours (Fig. 1) and prompt improvement of laboratory abnormalities.

The treatment strategy for MAS is usually based on the parenteral administration of high doses of corticosteroids. However, there have been some fatalities in reported series, even among patients treated with massive doses of corticosteroids. The use of CyA was recently advocated based on the proven benefit of this drug in the management of disorders affecting macrophages, such as haemophagocytic lymphohistiocytosis (2). A rapid response to CyA in severe or corticosteroid-resistant MAS occurring in children with systemic juvenile idiopathic arthritis has been reported (3, 4). In both of the patients reported here, the introduction of CyA exerted a dramatic ("switch-off") effect on the disease process, with disappearance of the fever and improvement of the laboratory abnormalities within a few hours. The striking time course of these events further supports the distinctive efficacy of this drug in this clinical syndrome. The second patient, who had SLE, developed MAS while the systemic disease was quiescent, serum complement levels were normal and anti-DNA antibodies absent. In lupus patients, MAS is exceedingly rare. It

can occur acutely at disease presentation or may develop, as in our case, more subtly as unexplained fever and cytopenia without evidence of lupus exacerbation or infection. In a study of bone marrow specimens from 28 patients with SLE obtained during 30 episodes of cytopenia, Morales *et al.* (5) found that 22 specimens exhibited hemophagocytosis uncorrelated with the severity of the lupus, complement levels, or anti-DNA titres. This suggests that in lupus this clinical syndrome may be more common than previously realised. In patients with SLE, the diagnosis of MAS can be particularly difficult since it may mimic the clinical features of the underlying disease. We conclude from our observations that therapy with CyA should be further explored as a first line therapy for MAS occurring in children with chronic rheumatic diseases.

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