Macrophage Activation Syndrome and Multisystem Inflammatory Syndrome

Angelo Ravelli, *IRCCS Istituto Giannina Gaslini and Università degli Studi di Genova, Genoa, Italy*

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of systemic juvenile idiopathic arthritis (JIA). Its hallmark is an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, which leads to marked hypercytokinemia. Clinically, the syndrome is characterized by prolonged fever, pancytopenia, hepatosplenomegaly, elevated liver enzyme levels, neurologic symptoms, coagulation abnormalities, and hyperferritinemia. A characteristic feature may be seen on bone marrow examination, which often reveals numerous morphologically benign macrophages exhibiting hemophagocytic activity. The mainstay of the therapy of MAS is based on the parenteral administration of high doses of corticosteroids. In the mid-1990s, the use of cyclosporine was advocated, based on its proven benefit in the management of familial hemophagocytic lymphohistiocytosis. With the recent advent and use of a variety of biologic agents, novel therapeutic approaches are being evaluated as first-line therapy for MAS. The most promising results have been obtained with the administration of the IL-1 inhibitor anakinra. The role of other therapeutic options, particularly the anti-IFNγ antibody and IL-18 inhibitors, is being explored.

The emergence of the multisystem inflammatory syndrome in children (MIS-C) is one of the most worrying and mysterious phenomena observed during the COVID-19 pandemic. The signs and symptoms of this hyperinflammatory condition are a mix of those of Kawasaki disease (KD) and toxic shock syndrome, and are characterized, among others, by fever, gastrointestinal symptoms (nausea, vomiting and abdominal pain), and cardiac involvement, especially myocarditis. Many of these children have required urgent Intensive Care Unit admission because of the development of multiorgan failure and circulatory shock, usually of myocardial origin. Laboratory abnormalities include markedly increased acute phase reactants, raised ferritin and D-dimer, hypoalbuminemia, lymphopenia and relative thrombocytopenia. Patients with myocarditis have elevated levels of pro-B-type natriuretic peptide (proBNP) and troponin. Treatment is based on the administration of intravenous immunoglobulin and corticosteroids. Anakinra was found to be beneficial in patients refractory to first-line therapy or with severe myocarditis. The clinical similarities between MIS-C and KD have stimulated an intense debate about whether MIS-C and KD represent different illnesses with overlapping clinical features or are on the same disease spectrum.