Case Report

Methotrexate as a Possible Trigger of Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

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ABSTRACT. Macrophage activation syndrome (MAS) is a potentially life threatening complication of chronic rheumatic diseases, particularly systemic juvenile idiopathic arthritis (JIA). A number of triggers have been related to the development of MAS, including viral infections, nonsteroidal antiinflammatory drug therapy, and gold salt injections. We describe a patient with systemic JIA who developed MAS shortly after receiving methotrexate, suggesting that this drug can be regarded as a potential trigger of MAS in children with JIA. (J Rheumatol 2001;28:865–7)

Key Indexing Terms:
METHOTREXATE
MACROPHAGE ACTIVATION SYNDROME
HEMOPHAGOCYTOSIS
JUVENILE ARTHRITIS

Macrophage activation syndrome (MAS) is a severe, potentially life threatening complication of chronic rheumatic diseases in childhood, particularly systemic juvenile idiopathic arthritis (JIA). It is secondary to the excessive activation of well differentiated macrophages and is characterized by serious liver disease, cytopenia, intravascular coagulation syndrome, and neurological involvement[1,2]. A number of triggers have been related to the development of MAS, including viral infections, aspirin, other nonsteroidal antiinflammatory drugs (NSAID), sulfasalazine, and gold salt injections[3-10]. We describe a patient with systemic JIA who developed MAS shortly after administration of methotrexate (MTX), suggesting that MTX can be regarded as a potential trigger of MAS.

CASE REPORT

A 6-year-old girl was admitted to her local hospital with a 2 week history of high spiking intermittent fever, evanescent morbilliform rash, and swelling and pain in both wrists. Laboratory investigation revealed hemoglobin 92 g/l, white blood cells 18.4×10^9/l with 84% neutrophils, platelets 580×10^9/l. Erythrocyte sedimentation rate (ESR) was 120 mm/h and C-reactive protein (CRP) 40 mg/l. A bone marrow aspirate yielded normal findings. Aspirin therapy (100 mg/kg/day) was ineffective in controlling symptoms and had to be discontinued after one week because of the occurrence of liver toxicity. Treatment with prednisone (2 mg/kg/day) was started, which led to improvement of clinical manifestations and laboratory abnormalities. She was discharged with tapering prednisone and naproxen (15 mg/kg/day). Five months after the onset of symptoms and 2 weeks after prednisone discontinuation, she had a recurrence of rash and joint symptoms, with swelling and pain in knees, wrists, and right elbow. This was accompanied by an increase of the laboratory indicators of systemic inflammation. Prednisone was restarted at 1 mg/kg/day, together with naproxen.

One month later, she was admitted to our department. Examination revealed an evanescent morbilliform rash over the trunk, arms, and face and arthritis in both wrists, knees, and the right elbow. There was neither generalized lymphadenopathy nor hepatosplenomegaly, and temperature was normal. Laboratory investigation disclosed hemoglobin 121 g/l, white blood cells 22.5×10^9/l with 88% neutrophils, platelets 603×10^9/l, ESR 89 mm/h, CRP 99 mg/l, fibrinogen 462 mg/dl, and serum ferritin 207 ng/ml (normal range 8–400). Liver and kidney function tests, serum total proteins and electrophoresis, serum complement levels, urinalysis, rheumatoid factor, and antinuclear and antineutrophil cytoplasmic antibodies were normal or absent. Over the next 3 weeks the prednisone dose was gradually decreased from 1 to 0.3 mg/kg/day and naproxen was substituted with ibuprofen (40 mg/kg/day). This was followed by recurrence of intermittent fever and worsening of joint pain, particularly in the wrists. A diagnosis of systemic JIA was made and, based on the presence of persistent polyarthritis and corticosteroid dependent systemic manifestations and the inefficacy of NSAID therapy, a second line treatment with oral MTX at 10 mg/m^2/week was begun; simultaneously, the dose of prednisone was increased to 1 mg/kg/day.

Twenty-four hours after the first MTX dosing she experienced a sharp rise of fever to 40.2°C and complained of intense and generalized pruritus. There were no signs of a flare of rash or articular symptoms, but a slight liver enlargement was detectable. Two days later, blood tests showed a fall in white blood cell count to 2.34×10^9/l (neutrophils 43%, lymphocytes 51%, eosinophils 2%, and monocytes 4%), hemoglobin to 94 g/l, platelets

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to 200×10^9/l, and ESR 46 mm/h, and an increase in the levels of aspartate aminotransferase to 177 IU/l (normal 11–34), alanine aminotransferase to 122 IU/l (11–39), lactic dehydrogenase to 2172 IU/l (230–460), triglycerides to 464 (40–160), and ferritin to 10,143 ng/ml; there was evidence of intravascular coagulation with decreased fibrinogen to 140 mg/dl (normal 170–410) and increased fibrin split products (> 40 μg/ml; normal < 10). No microbiological or serological evidence of infection, including Epstein-Barr virus and cytomegalovirus, was found. The clinical and laboratory features were consistent with MAS. Confirmation of the diagnosis through a bone marrow aspirate was considered unnecessary. Treatment with oral cyclosporin A (4 mg/kg/day) was initiated. The result was disappearance of fever within 24 h and prompt improvement of laboratory abnormalities (Table 1). The girl was discharged 2 weeks after the onset of MAS with a regimen of tapering prednisone, cyclosporin A, and ibuprofen.

DISCUSSION

Macrophage activation syndrome is increasingly recognized as a possible complication of childhood rheumatic diseases, particularly systemic JIA[1,2]. Prompt recognition and treatment of this syndrome are imperative because the risk of a fatal outcome is high[11]. Although MAS can occur with no apparent precipitating event or be associated with an exacerbation of the underlying disease, a number of triggering factors have been identified, including viral infections, aspirin toxicity, a recent change or dose increase of NSAID therapy, sulfasalazine therapy, or a second injection of gold salts[3-10]. We recently reported a boy with systemic JIA who developed MAS following MTX toxicity[12]. However, although the time course of MTX side effects and MAS suggested a link between the 2 clinical events, their relationship remained uncertain.

This patient developed MAS shortly after first MTX dosing in the apparent absence of any triggering event, suggesting that MAS could have been a direct result of MTX toxicity. Although we cannot rule out that the NSAID therapy or a viral infection could have played a role in inducing this complication, a responsibility of ibuprofen is unlikely because the patient had been shifted from naproxen to this drug 3 weeks before and continued taking it during the whole course of MAS; on the other hand, serologies for viral infections previously associated with the development of MAS were negative and the shortness of the time interval and the characteristics of clinical symptoms argue for a hypersensitivity or idiosyncratic reaction to MTX as the inciting factor of MAS. A similar mechanism has been hypothesized for development of MTX associated lung disease, which is a known, although rare, complication of MTX therapy in chronic rheumatic diseases[13,14]. Another drug induced MAS that can occur in JIA and is thought to be idiosyncratic is that observed after the second injection of gold salts. This form of MAS usually occurs one to 6 days after gold injection and is often accompanied by the development of a new rash that is not typical of JIA and can be itching[7-10].

The management of MAS in childhood rheumatic disorders is commonly based on parenteral administration of high doses of corticosteroids, which, however, are not always effective[9,15]. Recently, it has been reported that cyclosporin A can be very effective in severe or corticosteroid resistant MAS[12,15]. As a result, cyclosporin A has been proposed as first line treatment in MAS[11,12]. In our patient, administration of cyclosporin A resulted in prompt improvement of the clinical and laboratory features of MAS, thus supporting its distinctive efficacy in this clinical syndrome.

In summary, because MTX is increasingly used to treat childhood rheumatic disorders, this report should alert physicians to the possible development of macrophage activation syndrome in children with systemic JIA taking weekly MTX therapy.

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Table 1. Results of laboratory studies before onset and during the course of MAS.

Laboratory Test	Normal Values	On Admission	Onset of MAS	After 1 week
White blood cells, $\times 10^9$/l	4.0–9.0	22.5	2.3	9.9
Hemoglobin, g/l	129 ± 23	121	94	98
Platelets, $\times 10^9$/l	250–400	603	200	562
ESR, mm/h	< 20	89	46	68
Aspartate aminotransferase, IU/L	11–34	19	177	40
Alanine aminotransferase, IU/l	11–39	14	122	83
Lactate dehydrogenase, IU/l	320–460	647	2172	765
Triglycerides, mg/dl	40–160	90	464	182
Fibrinogen, mg/dl	170–410	462	140	332
Fibrin split products, μg/ml	< 10	—	> 40	< 10
Ferritin, ng/ml	8–120	207	10,143	1916

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