Case Report

Favorable Outcome in Patients with Renal Involvement Complicating Macrophage Activation Syndrome in Systemic Onset Juvenile Rheumatoid Arthritis

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ABSTRACT. Systemic-onset juvenile rheumatoid arthritis (SoJRA) constitutes about 10-20% of all JRA. However more than two-thirds of the mortality seen in JRA patients is accounted for by SoJRA. Macrophage activation syndrome (MAS), which can also be considered as a form of secondary hemophagocytic lymphohistiocytosis, is a major cause of morbidity and mortality in children with SoJRA. MAS is characterized by persistent high fever, pancytopenia, mild to serious derangements of liver cell function, encephalopathy, and disseminated intravascular coagulation. Renal involvement in MAS is a rarely recognized feature. In 2 recently reported case series of MAS in SoJRA, renal involvement appeared to be associated with poor prognosis. We describe 3 children with SoJRA who had renal involvement complicating MAS and had a favorable outcome. (J Rheumatol 2004;31:2068–70)

Key Indexing Terms:
MACROPHAGE ACTIVATION SYNDROME SYSTEMIC ONSET JRA
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Systemic-onset juvenile rheumatoid arthritis (SoJRA) constitutes about 10-20% of all JRA[1]. However more than two-thirds of the mortality seen in JRA patients is accounted for by SoJRA[2]. Macrophage activation syndrome (MAS), which can also be considered as a form of secondary hemophagocytic lymphohistiocytosis, is a major cause of morbidity and mortality in children with SoJRA. MAS is characterized by persistent high fever, pancytopenia, mild to serious derangements of liver cell function, encephalopathy and disseminated intravascular coagulation[3,4].

Renal involvement in MAS is a rarely recognized feature. In 2 recently reported case series of MAS in SoJRA, renal involvement appeared to be associated with poor prognosis[4,5].

We describe 3 children with SoJRA who had renal involvement complicating MAS and had a favorable outcome.

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CASE REPORTS

Case 1. A 14-year-old girl was diagnosed with SoJRA at 8 years of age. She developed an episode of MAS at 11 years of age (3 years after diagnosis) and was treated with pulse methylprednisone followed by high dose oral prednisone. At age 13 while in remission, off all medications, she developed a second episode of MAS. The diagnosis of MAS was made on the basis of anemia (hemoglobin, Hb, 107 g/l), thrombocytopenia (platelets 106×10^9/l), coagulopathy with an international normalized ratio (INR) of 1.50 (normal: 0.90-1.10), partial thromboplastin time (PTT) of 57 seconds (normal: 25-35), extreme hyperferritinemia, high LDH, hypofibrinogenemia, and bone marrow evidence of hemophagocytosis. Further investigations including a peripheral smear did not reveal any other etiology for this presentation. There were no identifiable infectious or drug precipitants except for ibuprofen taken for back pain 2 days before she presented with MAS. There was no hypocomplementemia or any other clinical or serological evidence for lupus. MAS was characterized by multiorgan involvement including central nervous system, cardiac, and renal involvement requiring admission to the pediatric intensive care unit (PICU). The features of MAS and renal involvement are listed in Tables 1 and 2. She was treated with supportive management and intravenous (IV) pulse methylprednisolone (1000 mg/day for 3 days). IV cyclosporine 50 mg (dose adjusted for renal failure) was commenced 24 h after admission and was discontinued after 1 dose following a generalized tonic-clonic seizure. She was subsequently treated according to a modified HLH-94 protocol[6] with 6 doses of etoposide and oral prednisone that was tapered over the subsequent 10 months. Renal biopsy was not done on account of the risk of bleeding associated with the coagulopathy. Her creatinine normalized over 7 days with improvement in the rest of her clinical and biochemical status. She made a full recovery from the MAS with normal renal function. Currently, she is free of symptoms and off all medication.

Case 2. A 15-year-old girl was diagnosed with SoJRA at the age of 4. Her disease was controlled with oral prednisone, IV immunoglobulin, and methotrexate (MTX). She presented with MAS at 14 years of age (11 years

Table 1. Features of MAS.

	Patient 1	Patient 2	Patient 3
Fever	–	+	+
Splenomegaly	–	+	+
Hepatomegaly	–	–	+
Cytopenia (more than 2 cell lines)	+	+	+
Hemoglobin g/dl	107	66	106
White cell count × 10^9	9.5	1.7	4.8
Platelet count × 10^9	106	77	68
ALT (0–40)	54	120	187
AST (0–45)	498	210	124
Triglycerides (0.4–1.3 mmol/l)	3.03	2.38	3.15
Ferritin (22–400 µg/l)	52,010	22,504	13,380
LDH (470–900 U/l)	13,785	1414	4705
Coagulopathy*	+	+	–
Fibrinogen (1.6–4.0 g/l)	0.87	1.26	2.84
Bone marrow biopsy evidence of hemophagocytosis	+	–	–

LDH: lactate dehydrogenase. * Elevated INR or PTT.

Table 2. Features of renal disease, therapy, and outcome.

	Patient 1	Patient 2	Patient 3
Proteinuria	+	+	+
Urinary protein (mg/m^2/h)	ND	18.80	890.11
Hematuria	+	+	+
Urinary casts	WBC casts	RBC casts	RBC casts
Peak creatinine (0–106 µmol/l)	348	449	64
Time to normal creatinine, days	7	24	NA
Hypertension	–	–	+
Renal outcome	Full recovery	Full recovery	Full recovery
MAS outcome	Full recovery	Full recovery	Full recovery
Corticosteroids	+	+	+
Cyclosporine	+	–	–
Etoposide	+	–	–

NA: not applicable; ND: not done.

after diagnosis). MAS was diagnosed on the basis of anemia (Hb 66 g/l), low white cell count of 1.7 × 10^9/l, thrombocytopenia (platelets 77 × 10^9/l), coagulopathy with an INR of 1.83, PTT of 68.3 seconds, hypofibrinogenemia, hyperferritinemia, and raised LDH. A bone marrow aspirate did not show hemophagocytosis. No infectious or drug precipitants were identified. There was no hypocomplementemia and her autoantibody profile was negative. Her peripheral blood smear showed polychromasia and some fragments, but there was no other biochemical evidence of hemolysis. On presentation she was in renal failure. She was admitted to the PICU with hypotension requiring treatment with inotropes. The features of her MAS and renal disease are shown in Tables 1 and 2. There was no evidence of neurological or cardiac involvement. She was treated with pulse IV methylprednisolone (1000 mg/day for 3 days) followed by oral prednisone which was tapered over 7 months. She had a full recovery with normal renal function (creatinine normalized over 24 days). A renal biopsy was not done because of the dramatic response to therapy. Currently, she receives maintenance doses of MTX for active joint disease.

Case 3. A 10-year-old boy was diagnosed with SoJRA at 9 years of age. The diagnosis was made on the basis of fever, classic rash, polyarthritis, and hepatosplenomegaly. Three days after diagnosis he developed hematuria and proteinuria with definite red cell casts in the urine and laboratory features of MAS. No precipitants were identified. His complement levels, peripheral smear, and autoantibody profile were normal and there were no clinical or serological features to suggest lupus. There was no derangement in serum creatinine at any time during admission. There was no other organ involvement, but he did have mild hypertension requiring anti-hypertensive treatment for a short period of time. His MAS and renal features are shown in Tables 1 and 2. He was treated with pulse IV methylprednisolone (1000 mg/day for 3 days) followed by oral prednisone, which was tapered over the subsequent 10 months. Since he initially had a significant coagulopathy and the proteinuria decreased rapidly, renal biopsy was not performed. He is currently symptom free, off all medication.

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is classified as a macrophage-related histiocytic disorder[6]. It has been suggested that MAS falls under the broad umbrella of secondary HLH disorders[7-9]. There are few reports of renal involvement in HLH. In one series of 57 patients with reactive MAS (23 had adult Still's disease or SoJRA), 62% (35/57) had evidence of renal impairment with 17% (10/57) requiring dialysis[10]. The authors reported that patients with more severe renal impairment had a worse outcome.

We describe 3 patients with SoJRA with renal involvement complicating MAS. While severe renal involvement in MAS/HLH and SoJRA is unusual, it has been associated with a poor prognosis. In a series of 9 patients with MAS, 3 patients with SoJRA had renal involvement, and 2 of these patients died[5]. In another series of 24 patients with reactive hemophagocytosis, 2 children with SoJRA had renal involvement, one of whom died[4]. In all these patients the renal disease was associated with multiorgan involvement. Two of the 3 patients we describe had multiorgan involvement.

Although renal biopsy would have been helpful in understanding the underlying pathology, it was not done in our patients because of either the risks associated with deranged coagulation or the rapid response to therapy. The presence of proteinuria, hematuria, and abnormal cellular casts strongly suggests that the renal dysfunction observed in our patients was due to intrinsic renal damage and was not attributable to pre-renal failure. A glomerulopathy is suggested by the presence of red cell casts and significant proteinuria in 2 of the 3 patients. While the nature of this glomerulopathy cannot be determined by the clinical and urinary features alone, the presence of disseminated intervascular coagulation (DIC) raises the possibility of microangiopathy. While a prerenal component cannot be strictly ruled out in these cases, there was no indication of prerenal disease as evidenced by indices including an elevated urea:creatinine ratio. Moreover, the presence of renal casts clearly indicates intrarenal pathology.

Renal involvement can occur in the absence of multiorgan involvement and may carry a good outcome as observed in one of our patients. While the other 2 patients had renal involvement in association with multiorgan failure, they also had a good outcome in terms of renal func-

tion and overall survival. Our experience suggests that renal involvement, like other manifestations of MAS, has a spectrum of severity and even severe renal involvement does not always portend a bad prognosis. The clinical presentation of these 3 cases would suggest heterogeneity in the underlying renal pathology. Early treatment with high dose corticosteroids with or without other immunosuppressive agents may be important in determining a good outcome.

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