ARTHRITIS & RHEUMATISM
Vol. 60, No. 11, November 2009, pp 3388–3399
DOI 10.1002/art.24883

Macrophage Activation Syndrome in Juvenile Systemic Lupus Erythematosus

A Multinational Multicenter Study of Thirty-Eight Patients

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Objective. **To describe the clinical and laboratory features of macrophage activation syndrome as a complication of juvenile systemic lupus erythematosus (SLE).**

Methods. **Cases of juvenile SLE–associated macrophage activation syndrome were provided by investigators belonging to 3 pediatric rheumatology networks or were found in the literature. Patients who had evidence of macrophage hemophagocytosis on bone marrow aspiration were considered to have definite macrophage activation syndrome, and those who did not have such evidence were considered to have probable macrophage activation syndrome. Clinical and laboratory findings in patients with macrophage activation syndrome were contrasted with those of 2 control groups composed of patients with active juvenile SLE without macrophage activation syndrome. The ability of each feature to discriminate macrophage activation syndrome from active disease was evaluated by calculating sensitivity, specificity, and area under the receiver operating characteristic curve.**

Results. **The study included 38 patients (20 with definite macrophage activation syndrome and 18 with probable macrophage activation syndrome). Patients with definite and probable macrophage activation syndrome were comparable with regard to all clinical and laboratory features of the syndrome, except for a greater frequency of lymphadenopathy, leukopenia, and throm-**

Dr Pringe is recipient of an Alpha Scholarship from the European Union (contract no. AML/B7-311/970666/II-0246-FI).

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Submitted for publication March 9, 2009; accepted in revised form July 11, 2009.

bocytopenia in patients with definite macrophage activation syndrome. Overall, clinical features had better specificity than sensitivity, except for fever, which was highly sensitive but had low specificity. Among laboratory features, the best sensitivity and specificity was achieved using hyperferritinemia, followed by increased levels of lactate dehydrogenase, hypertriglyceridemia, and hypofibrinogenemia. Based on the results of statistical analysis, preliminary diagnostic guidelines for macrophage activation syndrome in juvenile SLE were developed.

Conclusion. **Our findings indicate that the occurrence of unexplained fever and cytopenia, when associated with hyperferritinemia, in a patient with juvenile SLE should raise the suspicion of macrophage activation syndrome. We propose preliminary guidelines for this syndrome in juvenile SLE to facilitate timely diagnosis and correct classification of patients.**

Macrophage activation syndrome is a severe, potentially life-threatening complication of childhood systemic inflammatory disorders. The hallmark of this syndrome is excessive activation and proliferation of T lymphocytes and macrophages with massive hypersecretion of proinflammatory cytokines, including interleukin-1β (IL-1β), IL-6, interferon-γ, and tumor necrosis factor α. Macrophage activation syndrome may occur spontaneously, as a complication of active underlying disease, or may be triggered by an infection or a change in therapy. Clinically, patients with macrophage activation syndrome present with nonremitting high fever, pancytopenia, hepatosplenomegaly, hepatic dysfunction, encephalopathy, coagulation abnormalities, and sharply increased levels of ferritin. The pathognomonic feature of the syndrome is seen on bone marrow examination, which reveals numerous morphologically benign macrophages actively phagocytosing hematopoietic cells (1–4). Because macrophage activation syndrome bears a close resemblance to the group of hemophagocytic lymphohistiocytosis syndromes, it is currently classified among the secondary, or acquired, forms of hemophagocytic lymphohistiocytosis (5,6).

Among pediatric rheumatic disorders, macrophage activation syndrome occurs much more frequently, for unknown reasons, in systemic juvenile idiopathic arthritis (JIA) (1–4). However, in recent years this syndrome has been increasingly reported in patients with juvenile systemic lupus erythematosus (SLE) (7–11). Furthermore, it has been suggested that macrophage activation syndrome in juvenile SLE may be underrecognized (12). Because macrophage activation syndrome is a serious condition that can follow a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are imperative. However, the diagnosis of macrophage activation syndrome in patients with SLE may be challenging because it may mimic the clinical features of the underlying disease or be confused with an infectious complication. Differentiation of macrophage activation syndrome from these conditions is critical to select the appropriate therapeutic approach. Recently, preliminary diagnostic guidelines for macrophage activation syndrome as a complication of systemic JIA have been developed (13). However, it is unclear whether these guidelines may be applied to patients with juvenile SLE. Other potentially suitable diagnostic guidelines are those developed for hemophagocytic lymphohistiocytosis (14).

Because little information exists on macrophage activation syndrome in juvenile SLE, we undertook a multinational, multicenter collaborative study, with the primary aim of describing the clinical and laboratory features of this complication in patients with juvenile SLE. Secondary objectives were to investigate whether this complication may be regarded as underdiagnosed in juvenile SLE and whether the diagnostic guidelines for systemic JIA–associated macrophage activation syndrome or hemophagocytic lymphohistiocytosis may be used to identify macrophage activation syndrome in patients with juvenile SLE. An additional purpose of the study was to attempt development of diagnostic guidelines for macrophage activation syndrome as a complication of juvenile SLE.

PATIENTS AND METHODS

Patient selection. Clinical information on patients with juvenile SLE–associated macrophage activation syndrome was collected from several sources. All investigators belonging to the Italian Pediatric Rheumatology Study Group (IPRSG), the Pediatric Rheumatology International Trials Organization (PRINTO), and the Pediatric Rheumatology Collaborative Study Group (PRCSG) were contacted by e-mail and asked whether they had seen any cases of macrophage activation syndrome in juvenile SLE and, if so, whether they were willing to enroll their patients in the study. Those who responded positively were asked to complete a structured case report form with each patient's anonymous data and to send the completed form to the coordinating center (Istituto G. Gaslini). In addition, the clinical database at the coordinating center was scrutinized to identify patients with juvenile SLE who had macrophage activation syndrome. Finally, a systematic review of the literature was conducted to identify published cases of macrophage activation syndrome in patients with juvenile SLE with sufficient information available. The Medline database was searched using a strategy that included

the following medical subject headings: systemic lupus erythematosus, children, childhood, pediatric, macrophage activation syndrome, and hemophagocytic syndrome. This screening was supplemented by a manual search of references in the articles.

To be included in the study, patients had to have been diagnosed as having SLE according to the American College of Rheumatology (ACR) 1997 revised criteria (15), have been younger than 18 years at diagnosis, and have had an episode of macrophage activation syndrome diagnosed and treated as such by the attending physician. The diagnosis of macrophage activation syndrome had to be based on the typical clinical and laboratory picture of the syndrome, irrespective of evidence of macrophage hemophagocytosis in the bone marrow aspirate. However, patients who had such evidence were considered to have definite macrophage activation syndrome, whereas those who lacked it because bone marrow aspiration was not performed or did not show hemophagocytosis were considered to have probable macrophage activation syndrome. Patients who had an infection at the time of macrophage activation syndrome were not excluded because it is known that infections are common triggers of this syndrome in patients with rheumatic diseases (1).

Control groups. To identify the clinical and laboratory features with the greatest sensitivity and specificity for the diagnosis of macrophage activation syndrome in juvenile SLE, we followed the classification criteria approach, as was done for the development of preliminary diagnostic guidelines for macrophage activation syndrome as a complication of systemic JIA (13,16,17). The purpose of this approach is to separate patients with a particular disease from patients without the disease. Ideally, classification criteria have high sensitivity for the disease in question and high specificity against other diseases (that is, a high proportion of patients with the disease are found to be positive and a high proportion of patients without the disease are found to be negative). These criteria are generally created by comparing patient groups with the index disease with control patients who have a "confusable" disease. In our study, the index disease was represented by macrophage activation syndrome as a complication of juvenile SLE and the confusable condition by active juvenile SLE without macrophage activation syndrome.

Two control groups of patients with active SLE without macrophage activation syndrome were selected. The first group consisted of 29 consecutive patients seen at the Istituto G. Gaslini (IGG control sample) between 2002 and 2006 who had 33 instances of active disease. Active disease was defined as either the time of diagnosis, before the start of a disease-specific treatment; or the first disease flare, defined as an increase in the SLE Disease Activity Index 2000 score of ≥ 3 points compared with a previous assessment (18), requiring an increase in prednisone dosage of >0.5 mg/kg/day or 20 mg/day or the start of cyclophosphamide therapy. The second group was composed of 387 patients enrolled in a multinational study to investigate cumulative damage in juvenile SLE (multinational control sample) (19). These patients had clinical manifestations recorded within the first month after disease onset, a time period that was thought to imply the presence of active disease. Laboratory findings were not available in this control group. The study protocol was approved by the Ethics Committee of the Istituto G. Gaslini.

Statistical analysis. Comparison of the frequencies of demographic and clinical features and of laboratory findings between patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome and between patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome combined and controls was made by chi-square test or Fisher's exact test in cases of expected frequencies of <5. Comparison of mean values of laboratory parameters was performed using the Mann-Whitney U test. The ability of each feature to discriminate instances of macrophage activation syndrome from instances of active disease was evaluated by calculating sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve (16). The discriminative ability of laboratory tests was assessed using either the standard threshold, i.e., the threshold reported in the literature or judged to be clinically meaningful, or the best threshold, i.e., the threshold obtained through the ROC curve analysis that produced the most appropriate tradeoff between sensitivity and specificity.

To devise the preliminary diagnostic guidelines for macrophage activation syndrome as a complication of juvenile SLE, we sought the best classification/diagnostic rule. This requires making a specific tradeoff between sensitivity and specificity, through changing the definition of a positive. To reach this goal, we used the "number of criteria present" approach, which is done by varying l, the minimum number of criteria required to be present for a patient to be classified as positive (16). In other words, if any l or more of a list of criteria are present in a patient, then the patient can be classified as positive. Notably, all criteria must be able to be judged as being either present or absent (that is, they must be dichotomous) to allow using this method. The lower the decision threshold, the larger the number of patients that will be judged to be positive, resulting in high sensitivity and low specificity. Conversely, if the threshold chosen is high, then more patients will be judged to be negative, resulting in low sensitivity and high specificity. By varying the threshold, a table can be produced that allows for the selection of the combination of variables that shows the "best" diagnostic accuracy. For each combination of variables tested, sensitivity, specificity, and diagnostic odds ratio (OR) (20) were calculated.

RESULTS

A total of 38 patients with juvenile SLE and macrophage activation syndrome were included in the study; 14 patients were enrolled by PRINTO investigators, 7 patients were enrolled by IPRSG investigators, 5 patients were enrolled by PRCSG investigators, 6 patients were seen at the coordinating center, and information on 6 patients was found in the literature (9–11). Twenty patients had definite macrophage activation syndrome, and 18 patients had probable macrophage activation syndrome.

The main demographic features and the frequency of ACR criteria for SLE in patients with macrophage activation syndrome and controls at the time of

Table 1. Demographic characteristics and frequency of ACR criteria at diagnosis in patients with definite and probable macrophage activation syndrome and in patients with active juvenile SLE without macrophage activation syndrome*

	Patients with definite macrophage activation syndrome (n = 20)†	Patients with probable macrophage activation syndrome (n = 18)	All patients with macrophage activation syndrome (n = 38)‡	IGG controls (n = 29)	*P*§	Multinational controls (n = 387)¶	*P*#
Female	18 (90.0)	16 (88.9)	34 (89.5)	23 (79.3)	0.31	330 (85.3)	0.48
White	9 (69.2)	14 (77.8)	23 (74.2)	29 (100.0)	0.005	140 (36.2)	<0.0001
Age at diagnosis of SLE, mean ± SD years	12.6 ± 3.7	12.7 ± 3.4	12.6 ± 3.5	12.2 ± 2.7	0.46	12.1 ± 3.4	0.39
Time from SLE diagnosis to onset of macrophage activation syndrome, mean ± SD years**	0.4 ± 0.9	1.0 ± 1.7	0.7 ± 1.3	–	–	–	–
ACR criteria at diagnosis							
Malar rash	13 (68.4)	12 (66.7)	25 (67.6)	24 (82.8)	0.16	245 (63.3)	0.61
Discoid rash	1 (5.3)	2 (11.1)	3 (8.1)	1 (3.4)	0.62	20 (5.2)	0.44
Photosensitivity	8 (42.1)	5 (27.8)	13 (35.1)	7 (24.1)	0.33	118 (30.5)	0.56
Oral or nasal ulcers	8 (42.1)	11 (61.1)	19 (51.4)	7 (24.1)	0.01	77 (19.9)	<0.0001
Arthritis	14 (73.7)	13 (72.2)	27 (73.0)	19 (65.5)	0.51	200 (51.7)	0.013
Nephritis	15 (79.0)	11 (61.1)	26 (70.3)	8 (27.6)	0.0006	195 (50.5)	0.022
CNS disease	5 (26.3)	4 (22.2)	9 (24.3)	0 (0.0)	0.0036	28 (7.2)	0.0004
Serositis	9 (47.4)	10 (55.6)	19 (51.4)	5 (17.2)	0.004	53 (13.7)	<0.0001
Hematologic involvement	18 (94.7)	16 (88.9)	34 (91.9)	21 (72.4)	0.05	271 (70.0)	0.005
Positive immunoserology	19 (95.0)	18 (100.0)	37 (97.4)	27 (93.1)	0.57	351 (90.7)	0.16
Antinuclear antibody positive	20 (100.0)	18 (100.0)	38 (100.0)	29 (100.0)	–	382 (98.7)	1.00

* Except where indicated otherwise, values are the number (%). There were no significant differences between patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome. ACR = American College of Rheumatology; – = not applicable.
† Data were available for 13 patients for race and for 19 patients for malar rash, discoid rash, photosensitivity, oral or nasal ulcers, arthritis, nephritis, central nervous system (CNS) disease, serositis, and hematologic involvement.
‡ Data were available for 31 patients for race and for 37 patients for malar rash, discoid rash, photosensitivity, oral or nasal ulcers, arthritis, nephritis, CNS disease, serositis, and hematologic involvement.
§ All patients with macrophage activation syndrome versus Istituto G. Gaslini (IGG) controls, by Fisher's exact test for sex, race, frequency of discoid rash, frequency of CNS disease, and immunoserology (positivity for anti–double-stranded DNA, anti-Sm, or antiphospholipid antibodies), by the Mann-Whitney U test for age at diagnosis, and by chi-square test for all other parameters.
¶ Data were available for 382 patients for age at diagnosis and for 386 patients for nephritis.
# All patients with macrophage activation syndrome versus multinational controls, by Student's *t*-test for age at diagnosis, by Fisher's exact test for frequency of discoid rash and antinuclear antibodies, and by chi-square test for all other parameters.
** One patient was excluded from the probable macrophage activation syndrome group because macrophage activation syndrome occurred before diagnosis of juvenile systemic lupus erythematosus (SLE).

diagnosis are shown in Table 1. Patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome were comparable with regard to all demographic features and the frequency of all ACR criteria at diagnosis. All patients with macrophage activation syndrome (patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome combined) were comparable with both control groups with regard to the proportion of female patients and mean age at diagnosis of juvenile SLE. Compared with control groups, patients with macrophage activation syndrome had greater frequencies of the ACR criteria oral/nasal ulcers, nephritis, central nervous system (CNS) disease, arthritis, serositis, and hematologic involvement at diagnosis.

Table 2 shows the frequency of typical clinical features of macrophage activation syndrome, fulfillment of systemic JIA–associated macrophage activation syndrome or hemophagocytic lymphohistiocytosis diagnostic criteria, occurrence of macrophage activation syndrome within 1 or 6 months after diagnosis of juvenile SLE, triggering factors, admission to the intensive care unit (ICU), death, and therapeutic interventions in patients with macrophage activation syndrome and in control groups. All clinical features were comparable between patients with definite and probable macrophage activation syndrome, except lymphadenopathy, which was more common in the former group. The same clinical features were much more common in all patients with macrophage activation syndrome combined than in the control groups.

Table 2. Frequency of clinical features of macrophage activation syndrome in patients with definite and probable macrophage activation syndrome and in patients with active juvenile SLE without macrophage activation syndrome*

	Patients with definite macrophage activation syndrome (n = 20)†	Patients with probable macrophage activation syndrome (n = 18)‡	All patients with macrophage activation syndrome (n = 38)§	IGG controls (n = 33)¶	*P*#	Multinational controls (n = 386)	*P***
Fever	19 (95.0)	15 (83.3)	34 (89.5)	7 (21.2)	<0.0001	248 (64.2)	0.002
Hepatomegaly	9 (47.4)	10 (55.6)	19 (51.4)	4 (12.1)	0.0005	40 (10.4)	<0.0001
Splenomegaly	8 (42.1)	6 (33.3)	14 (37.8)	5 (15.1)	0.033	32 (8.3)	<0.0001
Lymphadenopathy	14 (70.0)	6 (33.3)	20 (52.6)	11 (33.3)	0.10	69 (17.9)	<0.0001
Hemorrhagic manifestations	8 (40.0)	6 (33.3)	14 (36.8)	3 (9.1)	0.006	–	–
CNS disease	8 (40.0)	6 (33.3)	14 (36.8)	1 (3.0)	0.0005	33 (8.5)	<0.0001
Patients with macrophage activation syndrome within 1 month after diagnosis	13 (65.0)	11 (61.1)	24 (63.2)	–	–	–	–
Patients with macrophage activation syndrome within 6 months after diagnosis	17 (85.0)	12 (66.7)	29 (76.3)	–	–	–	–
Triggers	11 (68.8)	15 (83.3)	26 (76.5)	–	–	–	–
Active disease/flare	9 (81.8)	12 (80.0)	21 (80.8)	–	–	–	–
Infection	4 (36.4)	3 (20.0)	7 (26.9)	–	–	–	–
Therapeutic change	1 (9.1)	0	1 (3.8)	–	–	–	–
ICU admission	8 (57.2)	6 (33.3)	14 (43.7)	–	–	–	–
Death	2 (10.5)	2 (12.5)	4 (11.4)	–	–	–	–
Treatment							
Corticosteroids	20 (100.0)	18 (100.0)	38 (100.0)	–	–	–	–
Cyclosporine	7 (36.8)	7 (38.9)	14 (37.8)	–	–	–	–
IV immunoglobulin	9 (47.4)	3 (16.7)	12 (32.4)	–	–	–	–
Cyclophosphamide	4 (21.1)	4 (22.2)	8 (21.6)	–	–	–	–
Azathioprine	1 (5.3)	3 (16.7)	4 (10.8)	–	–	–	–
Plasma exchange	3 (15.8)	1 (5.6)	4 (10.8)	–	–	–	–
Rituximab	2 (10.5)	0 (0.0)	2 (5.4)	–	–	–	–
Mycophenolate mofetil	0 (0.0)	1 (5.6)	1 (2.7)	–	–	–	–
Etoposide	1 (5.3)	0 (0.0)	1 (2.7)	–	–	–	–
Patients meeting systemic JIA–associated criteria	19 (100)	17 (100)	36 (100)	22 (71.0)	0.0005	–	–
Patients meeting hemophagocytic lymphohistiocytosis criteria	13 (81.3)	9 (52.9)	22 (66.7)	0 (0.0)	<0.0001	–	–

* Values are the number (%). The only significant difference between patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome was for lymphadenopathy ($P = 0.024$). SLE = systemic lupus erythematosus; – = not applicable.
† Data were available for 19 patients for hepatomegaly and splenomegaly, for 16 patients for triggers, for 11 patients for active disease/flare, infection, and therapeutic changes, for 14 patients for intensive care unit (ICU) admission, for 19 patients for death, for 19 patients for cyclosporine, intravenous (IV) immunoglobulin, cyclophosphamide, azathioprine, plasma exchange, rituximab, mycophenolate mofetil, and etoposide, for 19 patients for systemic juvenile idiopathic arthritis (JIA) criteria, and for 16 patients for hemophagocytic lymphohistiocytosis criteria.
‡ Data were available for 15 patients for the triggers active disease/flare and infection, for 16 patients for death, and for 17 patients for systemic JIA criteria and hemophagocytic lymphohistiocytosis criteria.
§ Data were available for 37 patients for hepatomegaly and splenomegaly, for 34 patients for triggers, for 26 patients for active disease/flare, infection, and therapeutic change, for 32 patients for ICU admission, for 35 patients for death, for 37 patients for cyclosporine, IV immunoglobulin, cyclophosphamide, azathioprine, plasma exchange, rituximab, mycophenolate mofetil, and etoposide, for 36 patients for systemic JIA criteria, and for 33 patients for hemophagocytic lymphohistiocytosis criteria.
¶ The n value represents the number of assessments. (Some patients were assessed at both time of diagnosis and first disease flare.) Data were available for 31 assessments for systemic JIA criteria and for 32 assessments for hemophagocytic lymphohistiocytosis criteria.
# All patients with macrophage activation syndrome versus Istituto G. Gaslini (IGG) controls, by chi-square test.
** All patients with macrophage activation syndrome versus multinational controls, by Fisher's exact test for central nervous system (CNS) disease and by chi-square test for all other parameters.

Overall, clinical features had better specificity than sensitivity, except for fever, which was highly sensitive but had poor specificity versus the multinational control group. Hepatomegaly, splenomegaly, hemorrhages, and CNS dysfunction were effective in discriminating macrophage activation syndrome from

Table 3. Laboratory findings in patients with definite and probable macrophage activation syndrome and in patients with active juvenile SLE without macrophage activation syndrome*

	Patients with definite macrophage activation syndrome (n = 20)	Patients with probable macrophage activation syndrome (n = 18)	All patients with macrophage activation syndrome (n = 38)	IGG controls (n = 33)†	P‡
White blood cell count, $\times 10^9$/liter	2.4 ± 1.4	4.5 ± 2.4	3.4 ± 2.1	4.4 ± 3.1	0.12
Hemoglobin, gm/liter	79 ± 16	88 ± 18	83 ± 17	109 ± 20	<0.0001
Platelet count, $\times 10^9$/liter	95.7 ± 78.3	146.3 ± 99.3	119.7 ± 91.3	221.4 ± 109.1	<0.0001
Aspartate aminotransferase, units/liter	327.1 ± 376.7	170.9 ± 129.6	246.5 ± 284.4	38.5 ± 30.7	<0.0001
Alanine aminotransferase, units/liter	131.3 ± 143.6	192.4 ± 296.1	162.9 ± 233.3	52.1 ± 45.0	0.0002
Bilirubin, mg/dl	0.6 ± 0.4	1.1 ± 1.7	0.9 ± 1.4	0.4 ± 0.2	0.09
Lactate dehydrogenase, units/liter	1,953.5 ± 1,649.9	1,254.9 ± 624.7	1,604.2 ± 1,277.5	430.5 ± 134.0	<0.0001
Albumin, gm/dl	2.3 ± 0.5	2.7 ± 0.7	2.5 ± 0.6	3.7 ± 0.7	<0.0001
Fibrinogen, gm/liter	2.03 ± 0.98	2.25 ± 1.13	2.13 ± 1.03	3.61 ± 1.13	<0.0001
Triglycerides, mg/dl	397.2 ± 412.3	428.9 ± 228.3	413.5 ± 325.6	132.6 ± 99.0	<0.0001
Serum sodium, mmoles/liter	134.1 ± 8.6	132.7 ± 5.4	133.3 ± 6.8	136.8 ± 3.2	0.0054
Ferritin, μg/liter	3,829.9 ± 5,039.1	2,071.8 ± 2,603.4	2,840.9 ± 3,892.4	84.6 ± 78.0	<0.0001

* Values are the mean ± SD. The only significant difference between patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome was for white blood cell count ($P = 0.03$). SLE = systemic lupus erythematosus.
† The n value represents the number of assessments. (Some patients were assessed at both time of diagnosis and first disease flare.)
‡ All patients with macrophage activation syndrome versus Istituto G. Gaslini (IGG) controls, by Mann-Whitney U test.

active disease. However, their sensitivity was low to moderate (data not shown). Diagnostic guidelines for systemic JIA–associated macrophage activation syndrome (13) were fulfilled by all patients with macrophage activation syndrome and by 22 (71%) of 31 IGG control patients. Hemophagocytic lymphohistiocytosis diagnostic criteria (14) were met by 22 (66.7%) of 33 patients with macrophage activation syndrome and by none of the IGG control patients. Diagnostic guidelines could not be assessed in the multinational control sample due to the lack of laboratory data.

As many as 63.2% and 76.3% of patients with macrophage activation syndrome developed this syndrome within 1 and 6 months, respectively, after diagnosis of juvenile SLE. A triggering factor was suspected in 76.5% of instances, with macrophage activation syndrome occurring much more commonly in the setting of disease activity or flare; an associated infection was reported in 26.9% of instances. Fourteen (43.7%) of 32 patients had to be admitted to the ICU, and 4 (11.4%) of 35 patients died (2 of multiple organ failure, 1 of acute respiratory distress syndrome, and 1 of pneumococcal sepsis). The frequencies of these events were comparable between the definite and probable macrophage activation syndrome groups. All patients received systemic corticosteroid therapy, most frequently intravenously. Cyclosporine was the most commonly administered immunosuppressive medication, followed by cyclophosphamide, azathioprine, and mycophenolate mofetil. Intravenous immunoglobulin, plasma exchange, rituximab, and etoposide were used in 12, 4, 2, and 1 patients, respectively. Overall, frequency of therapeutic choices was similar in patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome.

The mean values of laboratory parameters of macrophage activation syndrome in patients with macrophage activation syndrome and in control samples are presented in Table 3. Patients with definite and probable macrophage activation syndrome were comparable with regard to all laboratory values, with the exception of white blood cell count, which was lower in the former group. All laboratory values were markedly worse in all patients with macrophage activation syndrome combined than in the IGG control group, except white blood cell count and bilirubin, which were comparable between the 2 groups.

Table 4 shows the frequency of laboratory features of macrophage activation syndrome in patients with macrophage activation syndrome and in control groups. Patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome were comparable with regard to all laboratory features, with the exception of a greater frequency of leukopenia and a borderline greater frequency of thrombocytopenia in patients with definite macrophage activation syndrome. As with the mean values for the laboratory parameters described above, the frequency of laboratory abnormalities was much greater in all patients with macrophage activation syn-

Table 4. Frequency of laboratory features of macrophage activation syndrome in patients with definite and probable macrophage activation syndrome and in patients with active juvenile SLE without macrophage activation syndrome*

	Patients with definite macrophage activation syndrome (n = 20)†	Patients with probable macrophage activation syndrome (n = 18)‡	*P*§	All patients with macrophage activation syndrome (n = 38)¶	IGG controls (n = 33)#	*P***
White blood cell count $\leq 4.0 \times 10^9$/liter	18 (90.0)	8 (44.4)	0.003	26 (68.4)	21 (63.6)	0.67
Hemoglobin ≤90 gm/liter	14 (70.0)	10 (55.6)	0.36	24 (63.2)	5 (15.2)	<0.0001
Platelet count $\leq 150 \times 10^9$/liter	18 (90.0)	11 (61.1)	0.04	29 (76.3)	6 (18.2)	<0.0001
Aspartate aminotransferase >40 units/liter	12 (80.0)	15 (93.8)	0.27	27 (87.1)	10 (30.3)	<0.0001
Alanine aminotransferase >40 units/liter	11 (78.6)	14 (87.5)	0.43	25 (80.6)	15 (45.5)	0.0037
Bilirubin >1.0 mg/dl	1 (12.5)	3 (21.4)	0.53	4 (18.2)	0 (0.0)	0.12
Lactate dehydrogenase >400 units/liter	15 (93.8)	15 (93.8)	0.76	30 (93.8)	12 (52.2)	0.0003
Albumin ≤3.0 gm/dl	10 (100.0)	9 (64.3)	0.05	19 (79.2)	5 (20.0)	<0.0001
Fibrinogen ≤1.5 gm/liter	6 (37.5)	6 (42.9)	0.76	12 (40.0)	0 (0.0)	0.0003
Triglycerides >160 mg/dl	12 (75.0)	15 (88.2)	0.30	27 (81.8)	3 (20.0)	<0.0001
Serum sodium <135 mmoles/liter	7 (63.6)	10 (66.7)	0.60	17 (65.4)	5 (19.2)	0.0008
Ferritin >500 μg/liter	13 (92.9)	17 (94.4)	0.69	30 (93.8)	0 (0.0)	<0.0001

* Values are the number (%). SLE = systemic lupus erythematosus; IGG = Istituto G. Gaslini.
† Data were available for 15 patients for aspartate aminotransferase, 14 patients for alanine aminotransferase, 8 patients for bilirubin, 16 patients for lactate dehydrogenase, 10 patients for albumin, 16 patients for fibrinogen and triglycerides, 11 patients for serum sodium, and 14 patients for ferritin.
‡ Data were available for 16 patients for aspartate aminotransferase and alanine aminotransferase, 14 patients for bilirubin, 16 patients for lactate dehydrogenase, 14 patients for albumin and fibrinogen, 17 patients for triglycerides, and 15 patients for serum sodium.
§ Patients with definite macrophage activation syndrome versus patients with probable macrophage activation syndrome, by chi-square test for white blood cell count, hemoglobin, and fibrinogen and by Fisher's exact test for all other parameters.
¶ Data were available for 31 patients for aspartate aminotransferase and alanine aminotransferase, for 22 patients for bilirubin, for 32 patients for lactate dehydrogenase, for 24 patients for albumin, for 30 patients for fibrinogen, for 33 patients for triglycerides, for 26 patients for serum sodium, and for 32 patients for ferritin.
# The n value represents the number of assessments. (Some patients were assessed at both time of diagnosis and first disease flare.) Data were available for 17 assessments for bilirubin, for 23 assessments for lactate dehydrogenase, for 25 assessments for albumin, for 26 assessments for fibrinogen, for 15 assessments for triglycerides, for 26 assessments for serum sodium, and for 24 assessments for ferritin.
** All patients with macrophage activation syndrome versus controls, by Fisher's exact test for bilirubin and by chi-square test for all other parameters.

drome combined than in the IGG control group, with the exception of a comparable frequency of leukopenia and bilirubin increase.

The sensitivity, specificity, and area under the ROC curve for each laboratory feature, assessed using the standard threshold or the best threshold obtained through ROC curve analysis, are shown in Table 5. Platelet count, liver transaminases, serum albumin, triglycerides, serum sodium, and ferritin yielded similar levels of sensitivity and specificity using either the standard or the best threshold. White blood cell count, hemoglobin, bilirubin, lactate dehydrogenase, and fibrinogen yielded different levels of sensitivity and specificity depending on whether the standard or best threshold was used. Overall, hyperferritinemia had the best sensitivity and specificity, followed by increased lactate dehydrogenase level, hypertriglyceridemia, and hypofibrinogenemia. Thrombocytopenia was a better indicator of macrophage activation syndrome than leukopenia or anemia, and aspartate aminotransferase was slightly superior to alanine aminotransferase. An examination of the abnormalities of the 3 blood cell lines (leukopenia, anemia, and thrombocytopenia) in various combinations revealed that the greatest sensitivity and specificity (both ~80%) were obtained when any 2 of the 3 abnormalities were simultaneously present (data not shown).

The frequencies of traditional laboratory indicators of SLE activity, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, C3, C4, and antinuclear and anti-DNA antibodies, were comparable between patients with definite macrophage activation syndrome and patients with probable macrophage activation syndrome. All patients with macrophage activation syndrome combined had a borderline lower frequency of increase in ESR, but had a much greater frequency of increase in CRP level compared with the IGG control group. The frequencies of hypocomplementemia and antinuclear antibody positivity were comparable between patients with macrophage activation syndrome and patients with active SLE without macro-

Table 5. Sensitivity and specificity of laboratory parameters analyzed for ability to discriminate macrophage activation syndrome from active juvenile SLE without macrophage activation syndrome*

	Standard threshold	Sensitivity	Specificity	Best threshold	Sensitivity	Specificity	AUC (95% CI)
White blood cell count, $\times 10^9$/liter	≤4.0	68.4	36.4	≤1.9	34.2	100	0.61 (0.48–0.72)
Hemoglobin, gm/liter	≤90	63.2	84.8	≤112	100	57.6	0.84 (0.74–0.92)
Platelet count, $\times 10^9$/liter	≤150	76.3	81.8	≤149	76.3	81.8	0.77 (0.66–0.86)
Aspartate aminotransferase, units/liter	>40	87.1	69.7	>33	93.5	66.7	0.87 (0.76–0.94)
Alanine aminotransferase, units/liter	>40	83.3	54.5	>48	80.6	66.7	0.77 (0.65–0.86)
Bilirubin, mg/dl	>1.00	18.2	100	>0.34	81.8	52.9	0.66 (0.49–0.81)
Lactate dehydrogenase, units/liter	>400	93.8	47.8	>567	90.6	95.7	0.94 (0.84–0.99)
Albumin, gm/dl	≤3.0	79.2	80.0	≤3.4	91.7	68.0	0.87 (0.74–0.95)
Fibrinogen, mg/dl	≤150	40.0	100	≤290	80.0	76.9	0.84 (0.71–0.92)
Triglycerides, mg/dl	>160	81.8	80.0	>178	78.8	93.3	0.87 (0.75–0.95)
Serum sodium, mmoles/liter	<135	65.4	80.8	<135	65.4	80.8	0.72 (0.58–0.84)
Ferritin, μg/liter	>500	93.8	100	>249	96.4	100	0.99 (0.92–0.99)

* Sensitivity and specificity were obtained for the standard threshold (the threshold reported in the literature or judged to be clinically meaningful) and for the best threshold (the threshold obtained through the receiver operating characteristic curve analysis that produced the most appropriate tradeoff between sensitivity and specificity). SLE = systemic lupus erythematosus; AUC = area under the curve; 95% CI = 95% confidence interval.

phage activation syndrome, whereas the latter group had a borderline greater prevalence of positive anti-DNA antibodies (data not shown).

Using the "number of criteria present" approach, we sought the combination of clinical and laboratory variables that had the greatest diagnostic accuracy, that is, the best ability to discriminate macrophage activation syndrome from active disease without macrophage activation syndrome. Only variables that revealed strong discriminating properties, were not duplicative, and were available for a sufficient number of patients were examined. The clinical variables included were fever, hepatomegaly, splenomegaly, hemorrhages, and CNS dysfunction, and the laboratory variables included were cytopenia (affecting 2 or more cell lineages), aspartate aminotransferase increase, lactate dehydrogenase increase, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia. For each laboratory variable, the most discriminating threshold, either standard or best, was used. Evidence of hemophagocytosis in the bone marrow was not included because it was regarded as a confirmatory criterion rather than a first-line diagnostic criterion.

The study variables were combined in the following 3 ways: clinical variables only, laboratory variables only, and clinical and laboratory variables. For each combination of variables, sensitivity, specificity, and diagnostic OR were calculated. The best results were obtained using the simultaneous presence of any 1 or more clinical criteria and any 2 or more laboratory criteria, which yielded a sensitivity of 92.1%, a specificity of 90.9%, and a diagnostic OR of 116.7 (95% confidence interval 21.9–621.6). Based on these results, we set up diagnostic guidelines for macrophage activation syndrome as a complication of juvenile SLE (Table 6).

Table 6. Preliminary diagnostic guidelines for macrophage activation syndrome as a complication of juvenile SLE*

Clinical criteria
1. Fever (>38°C)
2. Hepatomegaly (≥3 cm below the costal arch)
3. Splenomegaly (≥3 cm below the costal arch)
4. Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding)
5. Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)

Laboratory criteria
1. Cytopenia affecting 2 or more cell lineages (white blood cell count ≤4.0 $\times 10^9$/liter, hemoglobin ≤90 gm/liter, or platelet count ≤150 $\times 10^9$/liter)
2. Increased aspartate aminotransferase (>40 units/liter)
3. Increased lactate dehydrogenase (>567 units/liter)
4. Hypofibrinogenemia (fibrinogen ≤1.5 gm/liter)
5. Hypertriglyceridemia (triglycerides >178 mg/dl)
6. Hyperferritinemia (ferritin >500 μg/liter)

Histopathologic criterion
Evidence of macrophage hemophagocytosis in the bone marrow aspirate

* The diagnosis of macrophage activation syndrome requires the simultaneous presence of at least 1 clinical criterion and at least 2 laboratory criteria. Bone marrow aspiration for evidence of macrophage hemophagocytosis may be required only in doubtful cases. These criteria were developed using patients with active juvenile systemic lupus erythematosus (SLE) without macrophage activation syndrome as a control group. As such, they may not be powerful enough to distinguish macrophage activation syndrome from particular infectious complications.

DISCUSSION

Although no specific data exist for juvenile SLE, the reported prevalence of macrophage activation syndrome in SLE ranges from 0.9% to 4.6% (21). However, it has been suggested that macrophage activation syndrome in SLE may be more common than previously recognized. Morales et al (22) evaluated bone marrow specimens from 28 patients with SLE obtained during 30 episodes of cytopenia. They found that 22 specimens (73.3%) exhibited hemophagocytosis, which was not correlated with severity of SLE, serum complement levels, or anti-DNA antibody titers. Tsuji et al (23) reported that 7 (9.6%) of 73 patients with SLE and liver dysfunction had hemophagocytic syndrome.

We compared the typical clinical and laboratory features of macrophage activation syndrome in patients who had evidence of macrophage hemophagocytosis on bone marrow aspirate (definite macrophage activation syndrome) with those in patients who lacked such evidence (probable macrophage activation syndrome). It was hypothesized that the latter group of patients might not have true macrophage activation syndrome or might have a more subtle form that could have been overlooked in the absence of a specific suspicion. However, the 2 patient groups were comparable with regard to demographic characteristics, most clinical and laboratory features, frequency of ACR criteria at diagnosis, fulfillment of diagnostic criteria for systemic JIA–associated macrophage activation syndrome and hemophagocytic lymphohistiocytosis, admission to the ICU, death, and drug therapies.

This finding suggests that macrophage activation syndrome in juvenile SLE may be diagnosed in the absence of evidence of macrophage hemophagocytosis in the bone marrow. As noted in patients with hemophagocytic lymphohistiocytosis (24) and macrophage activation syndrome as a complication of systemic JIA (13), the bone marrow aspirate does not always show hemophagocytosis, and furthermore, hemophagocytosis is not always demonstrable at onset. The failure to demonstrate hemophagocytosis does not negate the diagnosis of hemophagocytic lymphohistiocytosis. However, a bone marrow aspirate would be required to rule out a condition that may induce a macrophage activation syndrome by itself, such as *Leishmania* infection (25,26).

The clinical and laboratory spectrum of macrophage activation syndrome in our patients with juvenile SLE is similar to that observed in macrophage activation syndrome occurring in the course of adult-onset SLE (9,27) and systemic JIA (1–4). The similarity with systemic JIA–associated macrophage activation syndrome was strengthened by the finding that its diagnostic guidelines were met by 100% of juvenile SLE patients with macrophage activation syndrome. However, these guidelines did not demonstrate sufficient diagnostic specificity, since they were also met by 71% of patients with active juvenile SLE without macrophage activation syndrome. The main shortcoming of systemic JIA–associated macrophage activation syndrome guidelines is that certain thresholds of laboratory parameters do not apply to patients with juvenile SLE. Because of the prominent inflammatory nature of systemic JIA, the occurrence of a relative decrease in leukocyte count, platelet count, or fibrinogen may be more relevant in making an early diagnosis of macrophage activation syndrome in that disease. However, since cytopenia is a frequent feature of active juvenile SLE, an absolute decrease in blood cell lineages would be required. Other diagnostic guidelines that might be useful to identify macrophage activation syndrome in juvenile SLE are those developed for hemophagocytic lymphohistiocytosis (14). These guidelines proved highly specific, since they were met by no patient in the control group. However, sensitivity was not satisfactory; 33.3% of patients with macrophage activation syndrome did not fulfill the criteria for hemophagocytic lymphohistiocytosis.

In the patients with juvenile SLE in the present study, fever discriminated macrophage activation syndrome from active disease well when the IGG control sample was used as comparator. However, diagnostic strength was lower in the comparison with the multinational control sample. Nevertheless, the fact that fever was present in as many as 90% of patients with macrophage activation syndrome suggests that it is a key component of the clinical picture of macrophage activation syndrome in juvenile SLE. All of the other clinical features provided high specificity rates, but were not as good in terms of sensitivity.

Laboratory features showed excellent discriminating properties, with the use of the standard threshold being more advantageous in some cases, and the use of the best threshold more advantageous in other cases. This is in keeping with clinical experience indicating that early suspicion of macrophage activation syndrome is most commonly raised by the detection of subtle changes in laboratory parameters, whereas clinical symptoms are often delayed or not specific. The most notable exception was leukopenia, which was detected with similar frequency in macrophage activation syndrome and active disease without macrophage activation syndrome. However, the frequency of leukopenia was greater and

its mean value was lower in patients with macrophage activation syndrome who had evidence of macrophage hemophagocytosis on bone marrow aspiration than in those who lacked such evidence. This suggests that the diagnostic validity of leukopenia is poor in the more subtle or initial stages of macrophage activation syndrome, whereas it becomes a central laboratory feature in the acute phase of the syndrome.

Thrombocytopenia was a better indicator of macrophage activation syndrome than leukopenia or anemia. Of the laboratory features of macrophage activation syndrome, the strongest ability to discriminate this complication from active SLE was shown by hyperferritinemia, whose sensitivity and specificity were both equal to or nearly 100%. As many as 78.6% of patients with macrophage activation syndrome and only 33.3% of patients with active disease had elevated CRP levels. This suggests that increased CRP level may be useful to distinguish macrophage activation syndrome from active juvenile SLE, although it might not discriminate it from an infection (28).

On the basis of the results of statistical analysis and considering the clinical importance of the different features, we selected 5 clinical criteria and 6 laboratory criteria to be included in the preliminary guidelines for macrophage activation syndrome in juvenile SLE (Table 6). Using the "number of criteria present approach," we found that the best separation between patients and control subjects occurred when any 1 or more clinical criteria and any 2 or more laboratory criteria were simultaneously present. The strong discriminating ability shown by this definition led us to suggest that demonstration of macrophage hemophagocytosis in the bone marrow aspirate should be reserved for diagnostic confirmation only in doubtful cases. It should be recognized, however, that the statistical power provided by the relatively small size of the patient samples was limited. Furthermore, the guidelines were developed using patients with active disease as a control group. It remains to be established whether these guidelines are powerful enough to distinguish macrophage activation syndrome from other confusable conditions, namely infectious complications. Future modifications of guidelines should consider inclusion of novel parameters, such as soluble IL-2 receptor α (CD25) and soluble CD163, which reflect activation and expansion of T cells and macrophages, respectively, and may help identify subclinical cases (29).

As observed in adult patients with SLE (9,27), macrophage activation syndrome was associated with disease onset in the majority of patients. This represents a difference from systemic JIA, in which macrophage activation syndrome has been more commonly described in patients with advanced disease (1–4). Furthermore, it suggests that immune derangement induced by systemic disease is the major determinant of macrophage activation syndrome in juvenile SLE. In the present study, macrophage activation syndrome represented a serious complication, since 43.7% of the patients required admission to the ICU, and 11.4% died.

The therapeutic strategies for macrophage activation syndrome in juvenile SLE are not well established. With regard to systemic JIA–associated macrophage activation syndrome, treatment is primarily based on the parenteral administration of high doses of corticosteroids. However, fatal cases of macrophage activation syndrome in spite of the use of massive doses of corticosteroids have been reported (2,4,7). Early introduction of cyclophosphamide has been advocated as soon as corticosteroids seem to be insufficient, since this drug is a recognized treatment of severe SLE (9,10). Cyclosporine has been found to be dramatically effective in severe or corticosteroid-resistant instances of macrophage activation syndrome in children with systemic JIA (30,31) and children with juvenile SLE (32). Cyclophosphamide and cyclosporine were given to 21.6% and 37.8% of the patients in our study, respectively. There were no differences in outcome between patients who did or did not receive such treatments. Etoposide, which is the mainstay of therapeutic protocols in hemophagocytic lymphohistiocytosis, was used in 1 patient. Recently, a favorable outcome was reported in an adult patient with refractory lupus-associated macrophage activation syndrome who was treated with infliximab (33). The only biologic medication used to treat patients included in the present study was the anti–B cell agent rituximab, which was administered to 2 patients, both of whom had severe pancytopenia.

Our study should be interpreted in the light of several potential limitations. We should acknowledge that it is difficult to truly determine the sensitivity and specificity of diagnostic criteria without a gold standard for diagnosis, and considering that many clinicians already use versions of these criteria when determining a clinical diagnosis of macrophage activation syndrome. Data collection was conducted retrospectively. A retrospective study is subject to missing and possibly erroneous data. Some laboratory measurements were not available in some patients. Although most of the laboratory tests examined are widely standardized routine procedures, their execution in different laboratories and at different times may have affected their reliability.

The low frequency of renal and CNS disease seen in the control group with active disease enrolled at the coordinating center may be partially due to most of these patients having been assessed at disease onset. It is known that kidney and CNS disease may occur late in the disease course (34). Another possible explanation is that patients with juvenile SLE who are prone to develop macrophage activation syndrome have a greater multisystem involvement at disease onset. That the control group with laboratory data available comes from a single center may raise a potential referral bias. We should acknowledge that findings in these patients may not be generalizable to patients seen in other tertiary pediatric rheumatology centers. The multinational sample, which was more representative, lacked laboratory data. The main strengths of our study lie in the multicenter nature of the data collection and in the sample size of patients with juvenile SLE and macrophage activation syndrome, which is the largest collected to date.

In conclusion, macrophage activation syndrome is a life-threatening and probably underdiagnosed complication of juvenile SLE. When a patient with juvenile SLE presents with unexplained fever and cytopenia, an evaluation for macrophage activation syndrome, including assessment for hyperferritinemia, should be carried out. Diagnostic confirmation through the demonstration of macrophage hemophagocytosis in the bone marrow may not be necessary in the presence of the typical clinical and laboratory features of the syndrome. Although first-line treatment is based on the parenteral administration of high-dose corticosteroids, cyclosporine, and perhaps etoposide, may play a role when disease is refractory to corticosteroid treatment. Further studies in larger numbers of patients and using different control groups are needed to investigate the validity of these preliminary diagnostic guidelines for macrophage activation syndrome as a complication of juvenile SLE.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ravelli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Parodi, Davì, Pistorio, Ruperto, Martini, Ravelli.

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