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Arthritis and Use of Hydroxychloroquine Associated with a Decreased Risk of Macrophage Activation Syndrome among Adult Patients Hospitalized with Systemic Lupus Erythematosus

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Abstract

Background—Macrophage activation syndrome (MAS) is an uncommon but serious complication of systemic lupus erythematosus (SLE). We aimed to identify factors associated with MAS among adult hospitalized SLE patients.

Methods—Within the Brigham and Women's Hospital (BWH) Lupus Center Registry, we identified adult SLE patients > age 17 who had been hospitalized from 1970–2016, with either ferritin > 5,000 ng/mL during admission or “macrophage activation syndrome” or “MAS” in discharge summary. We confirmed MAS by physician diagnosis in medical record review. We matched each hospitalized SLE patient with MAS to 4 SLE patients hospitalized without MAS (by SLE diagnosis date $\pm$ 1 year). We employed conditional logistic regression models to identify clinical factors associated with MAS among hospitalized SLE patients.

Results—Among 2094 patients with confirmed SLE, we identified 23 who had a hospitalization with MAS and compared them to 92 hospitalized without MAS. Cases and controls had similar age at SLE diagnosis (29.0 vs. 30.5, $p = 0.60$), and hospital admission (43.0 vs. 38.3, $p = 0.80$), proportion female (78% vs. 84%, $p = 0.55$), and time between SLE diagnosis and hospitalization (1,971 vs. 1,732 days, $p = 0.84$). Arthritis (OR 0.04 [95% CI 0.004–0.35]) and hydroxychloroquine use (OR 0.18 [95% CI 0.04–0.72],) on admission were associated with decreased MAS risk. Admission SLEDAI scores (30 vs. 19, $p = 0.002$) and lengths of stay (16 days vs. 3 days, $p < 0.0001$) were much higher among cases. Death during hospitalization was 19% among cases and 3% among controls ($p = 0.03$).

Conclusions—In this case-control study of hospitalized adult SLE patients, arthritis and hydroxychloroquine use at hospital admission were associated with decreased MAS risk. Further studies are needed to validate these factors associated with lowered MAS risk.

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Keywords

macrophage activation syndrome; systemic lupus erythematosus; hemophagocytosis; hemophagocytic syndrome

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with myriad manifestations characterized by circulation of autoantibodies, complement activation and infiltration of T-cells with associated tissue damage¹. It may affect virtually any system of the body, and frequently has hematologic manifestations, with anemia, thrombocytopenia, lymphopenia and leukopenia². Macrophage activation syndrome (also known as hemophagocytic syndrome) is a sepsis-like condition associated in some cases with rheumatic diseases such as adult Still's disease and SLE and marked by hypercytokinemia, cytopenias, splenomegaly, and less commonly, disseminated intravascular coagulation and neurological involvement. It is thought to be on the spectrum of hemophagocytic lymphohistiocytosis (HLH)³. MAS that is secondary to a rheumatic condition is most effectively treated with immunosuppressive medicines appropriate for the underlying disease and no firm guidelines exist⁴.

Several different versions of diagnostic criteria for MAS in rheumatologic conditions, mainly in children, have been published⁵. The most recent definition of HLH put forth by the Histiocyte Society in 2004 describes HLH as fulfilling five of the following eight criteria: fever $\geq 38.5^{\circ}\text{C}$, splenomegaly, cytopenia in at least two cell lines, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis on biopsy, low or absent NK cell activity, ferritin $>500\text{ ng/mL}$, and elevated soluble CD25⁶. With the realization that patients with rheumatologic conditions may present with hemophagocytic syndrome but not fulfill criteria for HLH, several groups have developed diagnostic criteria for MAS in rheumatologic conditions⁵. The most recent criteria from 2009 for MAS in pediatric SLE ("the Ravelli criteria") require one of five clinical and two of seven lab criteria⁷. To date, there are no corresponding criteria for adults with SLE and MAS.

MAS is an infrequent complication of SLE. However, it may have severe consequences and has been associated with increased mortality among SLE patients⁸. Given that MAS is a rare complication of SLE, we endeavored to identify clinical and laboratory factors that could be associated with its development. To avoid the obvious finding that SLE patients with MAS are more severely ill than those without MAS, we conducted a case-control study, comparing SLE patients admitted to the hospital with and without MAS. Case-control studies are more efficient than cohort studies, having more relative power to detect differences between groups, but the selection of appropriate controls is of paramount importance.

Methods

Study Population

Within the Brigham & Women's Hospital (BWH) Lupus Registry, we identified 2094 patients with SLE, validated by expert rheumatologist opinion and 4 American College of

Rheumatology (ACR) updated criteria for the classification of SLE⁹, followed at BWH from 1972–2016. We linked these patients to their BWH electronic medical records. We searched all hospital admissions for laboratory ferritin values > 5,000 ng/mL or the words “macrophage activation syndrome” or “MAS” within the discharge summaries¹⁰. We excluded patients if high ferritin was due to cirrhosis, ESRD, or iron overload. We matched each SLE patient with MAS to four randomly-selected SLE patients with date of SLE diagnosis $\pm$ 1 year who were hospitalized, but did not have MAS.

Data Collection

We collected demographic and clinical data from the BWH Lupus Registry and BWH electronic medical records, including age, race, sex, zip code of residence, dates of SLE diagnosis and hospital admission in question. Medication use and dosing at hospital admission were also obtained by medical record review. Cause of hospitalization, laboratories, and serologies on admission, as well as medications on admission and during hospitalization were collected. Number of ACR criteria manifesting prior to admission and SLE Disease Activity Indices (SLEDAI) scores¹² on admission were calculated. Zip code at time of hospitalization was used if available; otherwise most current zip code was used. Area-level median incomes were derived from zip codes using the 2010 U.S. Census data. For zip codes too small to obtain an estimate, median incomes from neighboring towns were used (1 observation). For the MAS cases, we collected data for the classification of MAS by Ravelli criteria⁷ and HLH-2004 criteria¹¹: fever, hepatomegaly, splenomegaly, hemorrhagic manifestations, CNS dysfunction, cytopenia in two or more cell lines, AST elevation, LDH elevation, hypofibrinogenemia, and hypertriglyceridemia⁷. SLE manifestations were identified and dated according to first mention in medical record and considered to be present before hospitalization if occurring >30 days before hospitalization date. The gold standard for MAS was the diagnosis made by the treating medical team.

Statistical Analyses

Fisher’s exact tests and Mann-Whitney U tests were used in unadjusted analyses to compare variables between cases and controls. We first performed univariable conditional logistic regression analyses, conditioned on matching, with case status as an outcome variable and the following exposure variables: age at SLE diagnosis, sex, race, median household income from zip code, length of hospital stay, SLEDAI¹² upon admission, SLE manifestations and ACR criteria⁹ present before hospitalization, and medications upon admission. We then performed multivariable conditional logistic regression, including age, sex and variables with $p < 0.10$. Associations between these variables and case status were described as odds ratios (OR) with 95% confidence intervals. The level of significance was set as a two-tailed $p < 0.05$. All statistical analyses were performed using Stata version 14.0. This study was approved by the Partners’ Institutional Review Board.

Results

Patient Characteristics

We identified 76 potential MAS cases (of whom 69 had ferritin > 5000 IU/ml during hospital admission and 7 of whom had the words “macrophage activation summary” or

“MAS” within their discharge summaries). After medical record review, we confirmed 23 SLE patients with MAS according to physician diagnosis. We matched these SLE MAS cases to 92 SLE controls with similar age at diagnosis who had a hospitalization without MAS. Cases and controls had similar age at SLE diagnosis (29.0 vs. 30.5, $p = 0.60$), age at admission (43.0 vs. 38.3, $p = 0.80$), proportion female (78.3% vs. 83.7%, $p = 0.55$), median income (\$59,770 vs. \$64,796, $p = 0.43$) and days between SLE diagnosis and hospitalization for SLE or MAS (1,971 vs. 1,732 days, $p = 0.84$) (Table 1). The proportion of black patients was higher among those with SLE, but not significantly so (47.8% vs. 32.6%, $p = 0.22$). Median age at the hospital admission under investigation was 43.0 in cases and 38.3 in matched controls, $p = 0.22$. In addition, while the number of ACR SLE criteria present before the time of hospitalization was similar, MAS cases were less likely to have arthritis (52.2% vs. 80.4%, $p = 0.01$) and more likely to have SLE hematologic manifestations (91.3% vs. 67.4%, $p = 0.02$) than controls. The most common causes of admission among the 92 SLE controls included lupus flare (46.7%, 30.2% of which had nephritis), infection (29.3%) and bleeding (4.3%).

The SLEDAI scores of MAS cases on admission were higher than the controls (30 vs. 19, $p = 0.002$). Additionally, 39.1% of cases and 23.9% of controls had active neurologic SLE manifestations ($p = 0.19$), while 87.0% of cases and 65.2% of controls had active renal disease ($p = 0.05$). Prescribed medications on admission were similar between groups, except that cases were much less likely than controls to be receiving hydroxychloroquine (26.1% vs. 59.8%, $p = 0.005$). Two of 23 patients presented with MAS prior to diagnosis of SLE (1,457 days and 262 days prior), and two were diagnosed with SLE during the admission with MAS. Among MAS cases, maximum laboratory values (medians) were: ferritin 8,111 ng/mL, LDH 671.5 U/L and triglycerides 239 mg/dL. Minimum WBC value was 2.02 K/uL, for Hct was 20.2%, and for platelets it was 41 K/uL (medians, Table 2). They had a mean number of 2.3 clinical criteria and 3.7 laboratory criteria per Ravelli⁷. Of note, only 39.1% met HLH-2004 criteria¹¹, with a mean criteria number of 4.0. Less than half underwent bone marrow biopsies (43.5%), and of those biopsied, 60% had hemophagocytosis identified on pathology.

Outcomes of MAS in SLE

Hospital length of stay was higher among the MAS cases than controls (16 days vs. 3 days, $p < 0.0001$). Most MAS patients were treated with IV steroids, IVIG and cyclophosphamide, with fewer numbers receiving anakinra, rituximab, hydroxychloroquine, mycophenolate, cyclosporine and etoposide (Table 3). Two underwent bone marrow transplant and were both alive at time of review. Overall, there were 4 deaths in the MAS group (19%) and 3 in the control group during hospitalization (3%). Within 5 years of hospitalization, there were 7 deaths in the case group (acute liver failure, sepsis in 4, and respiratory failure in 2). In the same time period, there were 6 deaths in the control group (septic shock in 2, myocardial infarction, breast cancer, pneumococcal sepsis, and one of unknown cause).

Factors associated with MAS in SLE

In univariable conditional logistic regression models, presence of arthritis (OR 0.25 [95% CI 0.09–0.71]) and use of hydroxychloroquine on admission (OR 0.25 [95% CI 0.09–0.70])

conferred decreased risk (Table 4). Higher SLEDAI scores were associated with an increased risk of MAS (OR 1.07 per point [95% CI 1.02–1.11]). In the multivariable analysis including age, sex and SLEDAI score, arthritis and hydroxychloroquine on admission, presence of arthritis (OR 0.04 [95% CI 0.004–0.35]), and use of hydroxychloroquine on admission (OR 0.18 [95% CI 0.04–0.72]) were significantly associated with decreased risk of MAS, while higher SLEDAI scores were associated with an increased risk of MAS (OR 1.10 [95% CI 1.02–1.19]).

Discussion

Using a case-control study design with matched hospitalized SLE controls, we found that high SLEDAI score was associated with increased risk of MAS, while hydroxychloroquine use and presence of arthritis were strongly associated with a decreased risk of MAS development. As expected, MAS cases had markedly elevated ferritin levels, significant cytopenias, high inflammatory markers and liver dysfunction. The in-hospital case mortality rate was 19%, compared to the mortality rate of 3% for a matched SLE hospitalized cohort. The SLE MAS patients in this case-control study had a lower five-year mortality than has been previously reported⁸. It is difficult to compare, however, as the past study was conducted in a Korean cohort given racial influences on disease activity as well as geographic differences between the cohorts.

A few past studies have investigated factors that may be associated with MAS among SLE patients ill enough to be hospitalized. A recent retrospective cohort study by Ahn *et al.* examined 157 hospitalized febrile adults with SLE and found that those with MAS (n=54) had lower CRP and C3 and higher liver function tests, ferritin and other markers of MAS⁸. In addition, MAS was associated with mortality with an OR of 64.5 (95% CI 7.6–544.4). A systematic review by Takahashi *et al.* included a total of 93 adult patients diagnosed with both SLE and MAS. In 53% of these patients, MAS was the first manifestation of SLE¹⁴. Within our sample, four patients presented with MAS as their earliest SLE manifestation (17%), but the median time between SLE diagnosis and presentation with MAS was 5.4 years.

The association between elevated SLEDAI and increased risk of MAS is important for clinicians given that SLE patients with the most active disease may be at highest risk of MAS. The finding that arthritis prior to hospitalization was associated with a reduced risk of MAS supports the hypothesis that the presence of a musculoskeletal manifestation such as arthritis may signify an SLE phenotype with lower risk of hematologic manifestations, specifically MAS, an extreme hematologic manifestation of SLE. This observation has been made for other SLE manifestations. For example, in a study by Karassa *et al.*, presence of arthritis was negatively associated with development of central nervous system lupus¹⁵.

Our finding that receipt of hydroxychloroquine was associated with a reduced risk of MAS is novel. Given the retrospective nature of our investigation, it is difficult to identify reasons for this finding. Hydroxychloroquine is a highly important disease-stabilizing medication for SLE, and its use has been associated with a delayed onset of SLE as well as fewer organ complications^{16,17}. The pathogenesis of MAS has been increasingly elucidated over the last

decade, and is driven in part by the production of IL-1, IL-6 and TNF-alpha¹⁸. In addition, toll-like (TLRs) receptors are thought to play a significant role, especially when MAS is virally-triggered. One possible explanation as to why hydroxychloroquine might be associated with a decreased odds of developing MAS is related to its effects on cytokine production. Specifically, there is evidence that hydroxychloroquine decreases the secretion of IL-6 and TNF-alpha, and that it may lead to inhibition of TLR-3 and TLR-7¹⁹. These changes in cytokine production may reduce the risk of MAS in susceptible individuals. It is difficult to know why the number of patients in the case group had such a low percentage of hydroxychloroquine, but one possible explanation is that 4 of 23 cases received a lupus diagnosis at the time of or after MAS diagnosis, so they were unlikely to be on hydroxychloroquine. It is also difficult to know why the overall rate of hydroxychloroquine use was low, but medication adherence and lack of access to care are possible explanations.

The patients in our study were treated primarily with corticosteroids and cyclophosphamide, which are frequently used in severe SLE. However, 19% of patients were treated with IVIG, which is not commonly used to treat SLE. This may be because there is anecdotal evidence of efficacy in early reactive MAS¹³, and because it is relatively safe compared to alternative immunosuppression. Few patients with clinical MAS in our study met HLH-2004 criteria, and even fewer underwent a bone marrow biopsy. This underscores the importance of establishing separate criteria for MAS as a complication of SLE for future clinical trials and studies. Clinically, a MAS diagnosis is a signal to the provider that strong immunosuppressive and antiproliferative medications may be required (e.g. anakinra, cyclosporine, etoposide)^{20,21}.

This study has a few limitations. First, patients were drawn from an academic medical center with a large referral base, which may limit generalizability. Interestingly, although SLEDAI scores were higher in the MAS case than control groups, SLE ACR criteria manifesting before time of hospitalization were not, suggesting perhaps that cases had more active disease but not necessarily a greater number of manifestations in total, past and present. It is important to note that SLEDAI scores, although lower, were still significantly elevated in the control group (21), indicating very active SLE, which is consistent with a population of patients hospitalized for SLE, with a significant proportion having CNS and renal disease. Age at SLE diagnosis was also similar by study design. As MAS is a rare complication of SLE, a matched design enabled us to examine MAS risk factors with greater power than would be possible in an unmatched study and also allowed selection of more appropriate controls than healthy outpatients. As some individuals presented with SLE and MAS simultaneously or were followed outside of our system, we lacked some laboratory data in the months preceding hospitalization, and thus we were not able to evaluate whether laboratory features prior to onset of MAS were associated with MAS development. Additionally, because this is a case-control study, we were unable to estimate the incidence of MAS in SLE, and this incidence is not well-known from any existing study⁸. In identifying patients with MAS through their elevated ferritin levels, it is possible that we introduced a bias toward very severe cases. This problem was mitigated by including patients with diagnosis codes for macrophage activation syndrome. However, it is possible we may have missed patients with lower ferritins who went undiagnosed by their physician team.

In this case-control study of hospitalized adults with SLE, we found a history of arthritis and prior use of hydroxychloroquine were strongly associated with decreased risk of MAS when compared to hospitalized patients diagnosed with SLE within the same year. MAS was also associated with higher SLEDAI scores, length of stay and mortality, but not increased number of SLE manifestations prior to admission. Our findings underscore the importance of vigilance in diagnosing this potentially devastating complication of SLE, given its high mortality and the lack of formal consensus criteria.

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Table 1

Characteristics of Adults with SLE with MAS compared to those without MAS

	MAS Cases (n = 23)	Non-MAS Controls (n = 92)	p value [*]
Median age at SLE diagnosis, years, (IQR) [†]	29.0 (18.6–47.9)	30.5 (22.5–44.2)	0.60
Median age at hospital admission, years, (IQR) [†]	43.0 (26.2–53.8)	38.3 (28.1– 52.6)	0.80
Female, %	78.3	83.7	0.55
Median income, dollars (IQR) ^{‡,§}	59,770 (48,350–78,133)	64,796 (48,350–85,833)	0.43
Race/Ethnicity			
Black (%)	47.8	32.6	0.22
White (%)	30.4	41.3	0.47
Hispanic/Latino (%)	4.4	6.5	1.00
Asian (%)	13.0	7.6	0.42
Other (%)	4.4	8.7	0.69
Days between SLE diagnosis and hospitalization, (IQR) [‡]	1,971 (90–4,546)	1,732 (134–4,579)	0.84
Median length of stay, days (IQR)	16 (9–33)	3 (1–6)	<0.0001
SLEDAI	30 (17–41)	19 (12–29)	0.004
Number of ACR criteria (SD) [†]	5.8 (2.4)	5.5 (2.0)	0.62
ACR criteria at hospitalization, (%)			
Malar rash	56.5	48.9	0.64
Discoid lesions	21.7	18.5	0.77
Photosensitivity	30.4	31.5	1.00
Oral ulcers	26.1	22.8	0.79
Arthritis	52.2	80.4	0.01
Serositis	34.8	44.6	0.48
Renal involvement	73.9	56.5	0.16
CNS involvement	26.1	20.7	0.58
Hematologic disorders	91.3	67.4	0.02
Immunologic disorders	73.9	68.5	0.80
Antinuclear antibody	91.3	94.6	0.63
Medications on Admission			
All immunosuppressants (except prednisone and hydroxychloroquine)	17.4	21.7	0.63
Hydroxychloroquine	26.1	59.8	0.005
Prednisone	52.3	43.5	0.49
Azathioprine or 6-MP	4.4	5.4	1.00
Rituximab	0	1.1	1.00
Cyclophosphamide	0	3.3	1.00
Mycophenolate mofetil	4.4	9.8	0.68
Methotrexate	4.4	2.2	0.49

	MAS Cases (n = 23)	Non-MAS Controls (n = 92)	p value *
Anakinra	4.4	0	0.20
Cyclosporine	0	2.2	1.00

* T-test and Mann-Whitney used for continuous and Fisher's exact test for categorical data comparisons.

[†]SD = standard deviation

[‡]IQR= interquartile range

No patients were receiving IVIG or tacrolimus upon admission, although some received these for treatment.

Table 2

Laboratory Values and MAS/HLH Criteria of 23 Adults with SLE and MAS

Maximum Laboratory Values during episode	Adults, n=23
Ferritin, ng/mL (normal 20–400) *	8,111 (5,670–22,070)
LDH, U/L (107–231) n = 13	671.5 (486–1,443)
AST, U/L (9–30)	161 (68–475)
ALT, U/L (10–50)	68 (38–228)
CRP, mg/L (0.0–3.0) n=15	60.5 (24.9–155.5)
ESR, mm/hr (0–18) n=14	72 (53–101)
Triglycerides, mg/dL (35–135)	239 (155–446)
Minimum labs during episode, mean (range)	
WBC, K/uL (4–10)	2.02 (1.04–4.84)
Hematocrit, % (36–48)	20.2 (18.5–24.4)
Platelets, K/uL (150–450)	41 (21–122)
Classification Systems	
Number of Ravelli clinical criteria [†]	2.3 (1.0)
Number of Ravelli laboratory criteria	3.7 (1.0)
Number of HLH-2004 criteria ^{‡,§}	4.1 (1.3)
Percentage who met HLH-2004 criteria	39.1
Percentage with bone marrow biopsy ^{//}	43.5
Percentage of bone marrow biopsies with hemophagocytosis	60

* All lab values are median with inter-quartile range

[†] MAS by Ravelli criteria: 1 clinical and 1 laboratory criteria. Mean (standard deviation).

[‡] SD = Standard deviation

[§] HLH-2004 guidelines: 5 of 8 criteria.

^{//} Percentages for bone marrow biopsy positivity are based upon those with bone marrow biopsy during hospitalization.

Table 3

Additional Treatments for MAS Administered In Hospital

Medications	%
IV steroids	47.8
Intravenous Immunoglobulin	17.4
Cyclophosphamide	13.0
Rituximab	8.7
Cyclosporine	8.7
Anakinra	8.7
Etoposide	8.7
Allogeneic BMT	8.7
Mycophenolate mofetil	8.7
Hydroxychloroquine	8.7
Alemtuzumab	4.3

Table 4

Conditional Logistic Regression comparing Characteristics of SLE in Adult MAS cases and Matched Hospitalized SLE Patients without MAS, Odds Ratios and 95% Confidence Intervals (95%CI) *

	Univariable Models, OR and 95%CI (N=106)	Multivariable Models, OR and 95%CI (N=106) [‡]
Age at SLE diagnosis (years)	1.00 (0.96–1.02)	1.00 (0.95–1.05)
Age at admission (years)	1.00 (0.96–1.03)	
Female	0.71 (0.23–2.18)	3.51 (0.46–26.45)
Median Income	0.99 (0.99–1.01)	
Asian	1.77 (0.44–7.23)	
Black	1.94 (0.75–5.00)	
Hispanic/Latino	0.63 (0.07–5.89)	
Other	0.48 (0.06–4.01)	
White	0.60 (0.22–1.65)	
Number of ACR criteria at time of hospitalization	1.06 (0.84–1.35)	
SLEDAI score on admission	1.07 (1.02–1.11)	1.10 (1.02–1.19)
Malar rash	1.41 (0.53–3.76)	
Discoid lesions	1.24 (0.39–3.92)	
Photosensitivity	0.95 (0.36–2.52)	
Oral ulcers	1.21 (0.41–3.59)	
Arthritis	0.25 (0.09–0.71)	0.04 (0.004–0.35)
Serositis	0.66 (0.26–1.71)	
Renal involvement	2.15 (0.78–5.92)	
CNS involvement	1.45 (0.45–4.64)	
Hematologic	4.59 (1.04–20.3)	
Immunologic disorders	1.32 (0.46–3.78)	
Antinuclear antibody	0.63 (0.12–3.22)	
Medications upon admission[‡]		
Hydroxychloroquine	0.25 (0.09–0.70)	0.18 (0.04–0.72)
Prednisone	1.40 (0.57–3.42)	
Azathioprine or 6-MP	0.80 (0.09–6.85)	
Mycophenolate mofetil	0.40 (0.05–3.45)	
Methotrexate	2.00 (0.18–22.06)	

* Cases and controls matched on year of SLE diagnosis

[‡] Age, sex and variables with p<0.10 (SLEDAI score, arthritis and hydroxychloroquine on admission) were included in the multivariable model (empty cell if variable not included in analysis).

[‡] Rituximab, cyclophosphamide, anakinra, cyclosporine, tacrolimus and IVIG omitted from the analysis as numbers too small.