Severe Hematologic Manifestations Among Filipino Patients With Systemic Lupus Erythematosus: a 5-Year Retrospective Cohort Study

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ABSTRACT

Objective: Determination of the prevalence of severe hematologic manifestations among Filipino patients with systemic lupus erythematosus (SLE) and analysis of any association with organ involvement and serology.

Methods: This cross-sectional study included SLE patients 19 years old and above seen at the UST Hospital from 2012 to 2017. Patients with severe hematologic manifestations (severe hemolytic anemia, severe thrombocytopenia, and Evans syndrome (ES)) were identified and their prevalence determined. Independent t-test was used to compare continuous variables. Categorical variables were measured using the chi-square test; odds ratios (OR) with their corresponding 95% confidence interval were calculated using the SPSS software version 21. This study has been approved by the Institutional Review Board.

Results: Of the 253 patients (238 females, 94.07%), the mean age at diagnosis was 27.04 (SD 9.96) years. Severe hematologic involvement was noted in 12.26% (n=31); severe hemolytic anemia was the most prevalent (14, 5.53%), followed by severe thrombocytopenia (13, 5.14%) and ES (4, 1.58%). Higher prevalence of major organ involvement was observed among patients who manifest with severe hematologic disease. Severe thrombocytopenia was more likely to have cardiac involvement (OR 7.39, 95% CI 1.90 to 28.81, p=0.004). A higher prevalence of negative baseline anti-dsDNA serology was seen among patients who developed ES.

Conclusion: Severe hematologic involvement was noted in 12.26% of Filipino SLE patients, with hemolytic anemia as the most frequently recorded. Severe thrombocytopenia was associated with cardiac involvement among these patients. Patients developing ES tend to have a negative anti-dsDNA serology.

Keywords: systemic lupus erythematosus, severe hematologic manifestations, hemolytic anemia, thrombocytopenia

INTRODUCTION

Hematologic abnormalities are commonly seen among patients with SLE. They may present as an isolated abnormality or may occur in conjunction with other manifestations.

The presence of hematologic abnormalities may indicate disease activity in SLE. They may present with varying manifestations affecting all three hematologic cell lineages. The American College of Rheumatology (ACR) defines hematologic disorder in SLE as any of the following: hemolytic anemia

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with reticulocytosis, leukopenia <4000/mm^3, lymphopenia <1500/mm^3, or thrombocytopenia <100,000/mm^3 in the absence of offending drugs. [1]

A study has demonstrated more frequent organ-threatening manifestations among patients with severe hematologic manifestations.[2] Another study has shown that severe hematologic manifestations are associated with a high rate of in-hospital mortality.[3]

We determined the prevalence of severe hematologic manifestations (severe hemolytic anemia, severe thrombocytopenia and ES) among Filipino patients with SLE. In addition, the association between these hematologic manifestations and the presence of organ-threatening complications, namely: mucocutaneous, musculoskeletal, renal, neurologic, cardiovascular, and pulmonary involvement was also determined. Furthermore, we found out whether certain serological parameters were associated with severe hematologic disease.

METHODOLOGY

Data Collection

Medical records of SLE patients aged 19 years and older who were seen at the UST Hospital from January 2012 to December 2017 were reviewed. The included patients fulfilled either the 1997 ACR criteria or the 2012 Systemic Lupus Collaborating Clinics (SLICC) classification criteria for SLE. Severe hematologic manifestations were either in the form of autoimmune hemolytic anemia, thrombocytopenia or both and must satisfy the criteria defined by Sultan [1] as follows: hemolytic anemia with hemoglobin <8 g/dl in the presence of a positive Coombs test and reticulocytosis; thrombocytopenia with platelet count <50 x 10^9/L; and ES with hemolytic anemia and thrombocytopenia with any of the counts below the aforementioned threshold. Excluded patients were those who had overlapping autoimmune diseases such as scleroderma, primary Sjogren's syndrome, rheumatoid arthritis (RA), mixed connective tissue disease (MCTD), idiopathic inflammatory myopathy (IIM), as well as infectious processes mimicking lupus.

Statistical Analysis

Descriptive statistics for continuous variables were expressed in mean and standard deviation; categorical variables were expressed in frequencies and percentages. An independent sample t-test was used to compare continuous variables, while chi-square test was utilized for comparison of dichotomous variables. Variables with statistical significance were further explored using the multivariate logistic regression analysis. A p-value of ≤0.05 was considered statistically significant. Results were presented as odds ratio (OR) along with their 95% confidence intervals. All statistical tests were performed using statistical software SPSS version 21.

Ethical Considerations

This study has been approved by the UST Research Ethics Committee in accordance with the ethical principles set out in the Declaration of Helsinki 2015. Waiver of consent was obtained from the Medical Director as well as the attending rheumatologists prior to the review of patient medical records. Strict confidentiality has been observed.

RESULTS

A total of 253 adult SLE patients were included. There was female predominance (94.07%). The mean age at diagnosis was 27.03 (SD 9.96) years. Most of the patients had positive antinuclear antibody (ANA) and baseline anti-dsDNA, while only 28% had low C3. Mucocutaneous involvement was the most common manifestation, which was seen in 92% of patients. This was followed by musculoskeletal symptoms (68%). More than half of the patients had renal involvement (57%). Neurologic involvement was noted more frequently than cardiac and pulmonary involvement. Baseline characteristics of study participants was summarized in Table 1.

The prevalence of severe hematologic manifestations in 253 adult SLE patients was 12.26% (n=31). This included severe hemolytic anemia (5.53%, n=14), severe thrombocytopenia (5.14%, n=13), and ES (1.58%, n=4).

Patients with severe hematologic manifestations had a higher cumulative organ involvement compared to those who did not (mean number of organs involved: 2.968 vs 2.410, p=0.001).

There was a higher prevalence of major organ involvement (renal, neurologic, cardiac and pulmonary) as well as hypocomplementemia at baseline among patients who had severe hemolytic

Table 1. Baseline demographic and clinical characteristics of all study patients.

Variables	Values	
Demographic data		
Female n, (%)	238	94.07
Age at diagnosis (mean, SD)	27.03	(9.96)
Disease duration (mean, SD)	8.23	(5.94)
Clinical and Serologic Features	**Number**	**Percentage**
Serology		
ANA-positive	250	98.81
Anti-dsDNA positive	226	89.32
Low C3	71	28.06
Clinical Manifestations		
Mucocutaneous	234	92.49
Musculoskeletal	174	68.77
Severe hematologic disease	31	12.26
Renal disease	144	56.92
Neurologic disease	34	13.44
Cardiac disease	20	7.91
Pulmonary disease	21	8.3
Mortality n, (%)	17	6.72

anemia compared to those who did not as depicted in the odds ratio shown in Table 2. These figures, however, did not reach statistical significance.

Higher prevalence of major organ involvement was likewise seen among patients who manifested with severe thrombocytopenia compared to those who did not as shown in Table 3. Among the variables, age, cardiac and pulmonary involvement was initially seen to be correlated. Upon multivariate analysis, however, only cardiac involvement demonstrated statistically significant association with severe thrombocytopenia.

Table 2. Demographic, clinical and serologic associations with severe hemolytic anemia among Filipino SLE patients.

	OR	95% CI	P value
Demographic			
Age			0.651
Female Sex	0.937	0.907-0.968	0.334
Immunologic			
ANA	0.987	0.973-1.002	0.673
Anti-dsDNA	0.701	0.148-3.313	0.652
Low C3	2.008	0.671-6.008	0.205
Clinical			
Mucocutaneous	1.059	0.131-8.560	0.957
Musculoskeletal	1.143	0.347-3.763	0.826
Renal	1.959	0.598-6.422	0.259
Neurologic	1.830	0.483-6.927	0.367
Cardiac	2.046	0.425-9.857	0.363
Pulmonary	1.930	0.402-9.263	0.404

There were only four patients who manifested ES. A higher trend of renal involvement was seen among patients who had ES compared to those without ES. On the other hand, cardiac, pulmonary and neurologic involvement was similar among patients with and without ES. The statistical analysis was not feasible due to the small number of cases with ES.

Analysis of the serology demonstrated a low prevalence of anti-dsDNA positivity and higher prevalence of baseline hypocomplementemia among patients with ES.

DISCUSSION

Hematologic disorders are common in SLE. Earlier studies have observed neutropenia to be the most common followed by thrombocytopenia and hemolytic anemia with prevalence of 47%, 27% and 13%, respectively.[4] This has been reaffirmed by a more recent cohort study showing similar trends in prevalence.[5] Although hematologic disorders are relatively common among patients with SLE, the occurrence of severe hematologic disorder is relatively less prevalent compared to other major organ involvement.

The prevalence of severe hematologic manifestations among Filipino SLE patients was slightly higher at 12.26%. This is in comparison with the study by Sultan [2] wherein the prevalence was 9.8% in a British lupus cohort. Similar to this study, severe hemolytic anemia was the most prevalent, followed by severe thrombocytopenia. The prevalence of ES was similar to a study by Costallat, wherein the prevalence among SLE patients was 2.7%.[6] A lower prevalence of ES was, however, reported by Zhang in a Chinese lupus registry with a prevalence rate of 0.47%.[7]

Higher number of organ involvement was noted among patients with severe hematologic manifestations. This implies that patients with severe hematologic disorders have more severe disease activity compared to those who did not.

Severe hemolytic anemia was not associated with any organ involvement in our study. This is in contrast with existing literatures involving foreign lupus cohorts. Sultan was able to demonstrate association between hemolytic anemia and renal as well as

Table 3. Demographic, clinical and serologic associations with severe thrombocytopenia among Filipino SLE patients.

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P value	OR	95% CI	P value
Demographic						
Age			0.043			0.052
Female Sex	0.743	0.090-6.133	0.782			
Immunologic						
ANA	0.988	0.974-1.002	0.685			
Anti-dsDNA	0.370	0.095-1.439	0.137			
Low C3	0.759	0.203-2.842	0.681			
Clinical						
Mucocutaneous	0.973	0.120-7.912	0.980			
Musculoskeletal	1.545	0.413-5.774	0.515			
Renal	2.637	0.708-9.823	0.135			
Neurologic	1.182	0.250-5.579	0.833			
Cardiac	9.375	2.731-32.188	<0.001	7.389	1.895-28.81	0.004
Pulmonary	5.830	1.626-20.903	0.003	0.294	0.069-1.26	0.099

CNS involvement.[2] Neurologic involvement was further supported by a multivariate analysis in a more recent study by Aleem.[8]

Severe thrombocytopenia was found to have higher prevalence of cardiac and pulmonary involvement in our study. Cardiac manifestations were observed presenting more often as pericarditis with pericardial effusion or cardiomyopathy in our population. Pulmonary manifestations observed were pulmonary hypertension and pleuritis with pleural effusion. Ultimately, cardiac manifestations were found to have significant association with severe thrombocytopenia after adjustment of possible confounders. No existing literature had established this type of association. This could be attributed to possible secondary antiphospholipid syndrome (APS). SLE patients who are positive for antiphospholipid (aPL) antibodies are at a 2- to 4-fold increased risk for thrombocytopenia.[9] Unfortunately, there is paucity of data on patients' records regarding antiphospholipid antibody panel which could have been utilized for analysis. A meta-analysis had shown increased risk of pulmonary hypertension in aPL-positive vs aPL-negative patients with an overall OR of 2.28 (95% CI, 1.65 to 3.15, P<0.0001).[10] Secondary APS also plays a role in the development of cardiovascular disease in patients with SLE. The presence of aPL is an independent predictor of vascular events among patients with SLE [11] and patients with lupus anticoagulant are significantly more likely to develop myocardial infarction, [12] which may eventually progress to cardiomyopathy.

In other studies, thrombocytopenia was more often associated with renal disease.[2, 13] Aleem demonstrated that thrombocytopenia was associated with arthritis and neurologic disorder among Arabian patients.[8] Furthermore, thrombocytopenia was associated with decreased survival, although a study by Nossent had found that the severity of thrombocytopenia had no significant influence.[4, 14]

ES demonstrated higher prevalence of nephritis. This is in correlation to the findings by Costallat [6], wherein it was found to be associated with nephritis, serositis and mucocutaneous involvement.

Serological analysis found no significant association between severe hemolytic anemia or severe thrombocytopenia with baseline anti-dsDNA, or hypocomplementemia. ES, however, showed a trend towards negative baseline anti-dsDNA. Existing studies on serology and hemolytic anemia have conflicting results. Cervera [15] noted that patients with high titers of anti-dsDNA antibodies had higher incidence of hemolytic anemia. Sultan, however, found no significant association;[2] neither did he find significant association between anti-dsDNA and thrombocytopenia. Furthermore, anti-

Sm and anti-RNP were associated with hemolytic anemia.[16] Our study, however, did not have complete serologic data to test these parameters. An analysis of complement activity showed that patients with low C3 were more likely thrombocytopenic.[13] In addition, patients with hematologic manifestations also had significantly lower levels of serum complement C4.[3]

CONCLUSION

In this population of Filipino patients with SLE, severe hematologic disorder was observed in 12.26%, with hemolytic anemia being the most frequently encountered. Higher prevalence of major organ involvement was seen among patients with severe hematologic disorders, but statistically significant associations were only observed between severe thrombocytopenia and cardiac involvement. A negative baseline anti-dsDNA was found to be more prevalent among patients who developed ES.

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Conflict of Interest

None declared.

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