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"Unmasking the Hemolytic Face of Lupus: A Retrospective Study on AIHA and Disease Activity"

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ABSTRACT

Background: Autoimmune hemolytic anemia (AIHA) is a significant hematologic complication in systemic lupus erythematosus (SLE), often associated with heightened disease activity and immune dysregulation. Objective: To determine the incidence of AIHA in SLE patients and analyze its clinical and serological correlations in a tertiary care setting in India

Methods: This retrospective observational study reviewed medical records of 80 SLE patients diagnosed using the 2012 SLICC criteria between January 2020 and December 2023. AIHA was defined by anemia with hemolysis markers and a positive direct antiglobulin test. Clinical, hematologic, and immunologic parameters were compared between patients with and without AIHA.

Results: AIHA was observed in 15% (12/80) of patients. Compared to non-AIHA patients, those with AIHA had significantly lower hemoglobin, higher reticulocyte counts, elevated LDH, and 100% Coombs positivity. AIHA patients also exhibited a significantly higher frequency of anti-dsDNA positivity (91.7% vs. 70.6%), low complement levels (C3 and C4), and higher SLEDAI scores (14.2 vs. 8.6; $p<0.001$), indicating more active disease.

Conclusion: AIHA is a prominent haematologic symptom of SLE that is closely linked to serologic markers and disease activity. Timely and effective care of SLE requires early identification and distinction from other causes of anaemia..

Keywords: *Systemic lupus erythematosus, autoimmune hemolytic anemia, Coombs test, anemia, disease activity, anti-dsDNA, hypocomplementemia.*

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1. INTRODUCTION

Multisystem involvement and a broad range of clinical symptoms are hallmarks of systemic lupus erythematosus (SLE), a chronic autoimmune illness. One important factor in the presentation and categorisation of the illness is haematological abnormalities. One of these, autoimmune haemolytic anaemia (AIHA), is a serious but little-discussed side effect of SLE. Reduced serum haptoglobin, reticulocytosis, increased lactate dehydrogenase (LDH), indirect hyperbilirubinemia, and anaemia are all symptoms of AIHA, which is defined by the immune system's destruction of red blood cells (RBCs).[1,2].

Depending on the demographic and diagnostic standards used, the incidence of AIHA in SLE patients varies greatly in the literature, ranging from 5% to 25% [3]. Ethnic variations, disease activity, genetic predispositions, and environmental triggers might all be responsible for this heterogeneity. AIHA frequently indicates significant disease activity and can happen during flare-ups or at the beginning of SLE [4]. In order to lower morbidity and enhance patient outcomes, early.,

identification and care of AIHA are essential

Pathophysiologically, the main cause of AIHA in SLE is the generation of warm autoantibodies (IgG type) that target red blood cells. These autoantibodies attach to erythrocytes and cause the reticuloendothelial system, especially in the spleen, to destroy them. Cold agglutinins (IgM) are less often implicated. The hallmark of diagnosis for haemolysis is still a positive direct antiglobulin (Coombs) test, which supports the immune-mediated aetiology of haemolysis [5]. Clinically, splenomegaly, pallor, tiredness, and jaundice can all be signs of AIHA in SLE. Cardiovascular strain and an elevated risk of thromboembolic events can result from severe instances. Crucially, AIHA may be misdiagnosed as chronic illness anaemia or other anaemia causes in lupus patients, such renal disease or nutritional deficits, which might postpone necessary treatment.[6].

In order to diagnose AIHA, laboratory tests are essential. Supporting evidence of haemolysis is provided by the Coombs test, peripheral smear, reticulocyte count, LDH levels, indirect bilirubin, and serum haptoglobin. Additionally, AIHA has been linked to serological indicators of active lupus, such as low complement levels and anti-double stranded DNA (anti-dsDNA) antibodies (C3, C4), indicating a connection between humoral autoimmune and haematologic symptoms.[7,8].

High-dose corticosteroids are usually used as the first-line treatment for AIHA in SLE. In refractory instances, immunosuppressive drugs such as rituximab, mycophenolate mofetil, and azathioprine are used. AIHA can return even after therapy, which can have a major effect on the prognosis of the illness [9]. Western populations have been the focus of the majority of research examining the relationship between AIHA and SLE. Data from South Asia, especially India, where environmental and genetic variables may affect the manifestation of illness, is scarce. The purpose of the current retrospective investigation was to ascertain the prevalence of AIHA in tertiary care centre patients with SLE and to examine its clinical and serological correlations.

2. MATERIALS AND METHODS

Study Design and Setting: This retrospective observational study was conducted in the Department of Internal Medicine at [Institution Name], a tertiary care center in India. The study period ranged from January 2020 to December 2023.

Sample Size: A total of 80 patients with a confirmed diagnosis of SLE were included based on a review of hospital medical records.

Inclusion Criteria:

Patients diagnosed with SLE based on the 2012 SLICC classification criteria.

Age ≥15 years.

Availability of complete clinical and laboratory data.

Exclusion Criteria:

Patients with known hereditary hemolytic anemias.

Evidence of nutritional anemia (iron, B12, or folate deficiency).

Patients with chronic kidney disease stage 4 or above.

Definition of AIHA: AIHA was defined as anemia (hemoglobin <11 g/dL) with:

Reticulocytosis (>2.5%).

Elevated LDH and indirect bilirubin.

Low serum haptoglobin (when available).

Positive direct Coombs (DAT) test.

Data Collection: Demographic information, the length of the disease, clinical symptoms, the SLEDAI-2K score, laboratory results (CBC, reticulocyte count, LDH, bilirubin levels, Coombs test), and immunological parameters (ANA, anti-dsDNA, complement levels) were all gathered from both electronic and physical medical records.

Statistical Analysis: SPSS version 26 was used to analyse the data. For baseline characteristics, descriptive statistics (mean, SD, and percentage) were employed. The chi-square and t-tests were used to compare the groups. P-values less than 0.05 were regarded as statistically significant.

3. RESULTS

Table 1: Demographics and Clinical Features

Parameter	Total (n=80)	AIHA (n=12)	Non-AIHA (n=68)

Mean Age (years)	30.5 ± 6.9	29.8 ± 7.2	30.7 ± 6.7
Female (%)	72 (90%)	11 (91.7%)	61 (89.7%)
Mean Disease Duration	3.1 ± 2.2	3.3 ± 2.1	3.0 ± 2.2

The baseline features of the 80 patients with a diagnosis of systemic lupus erythematosus (SLE) are shown in this table, which also compares the 68 patients who did not develop autoimmune haemolytic anaemia (AIHA) with the 12 patients who did. In line with the established female preponderance in SLE, the majority of patients in both groups were female, and the mean age of participants was comparable between the two groups (29.8 vs. 30.7 years). The AIHA group had a little longer average illness duration (3.3 vs. 3.0 years), but this difference was not statistically significant. These results suggest that age, gender, or length of disease do not seem to be significant predictors of AIHA in SLE patients.

Table 2: Hematologic Parameters

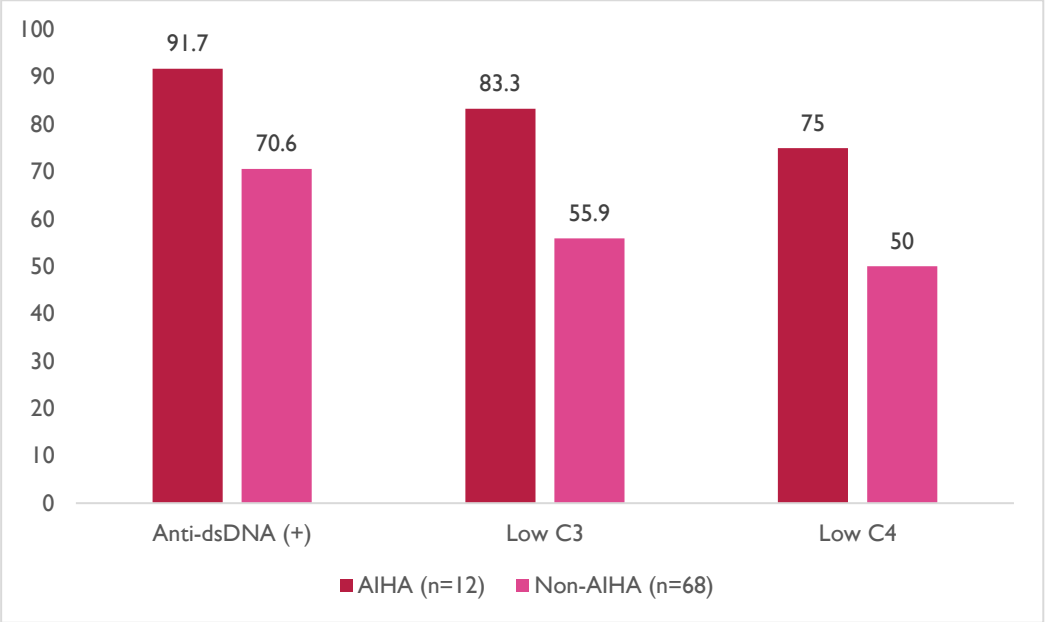
Parameter	AIHA (n=12)	Non-AIHA (n=68)	p-value
Hemoglobin (g/dL)	7.9 ± 1.2	10.9 ± 1.3	<0.001
Reticulocyte (%)	3.2 ± 0.6	1.5 ± 0.4	<0.001
LDH (IU/L)	568 ± 123	295 ± 90	<0.001
DAT Positive (%)	12 (100%)	0 (0%)	--

Key haematologic indicators are compared between SLE patients with and without AIHA in this table. Haemoglobin levels, reticulocyte counts, and lactate dehydrogenase (LDH) levels all showed statistically significant differences ($p<0.001$ for all), with AIHA patients exhibiting the usual haemolysis symptoms of decreased haemoglobin, increased reticulocyte counts, and high LDH. The autoimmune character of anaemia in the afflicted subgroup was further supported by the fact that all patients in the AIHA group exhibited direct antiglobulin (DAT) positivity, but none of the non-AIHA patients did.

Table 3: Immunological Parameters

Parameter	AIHA (n=12)	Non-AIHA (n=68)	p-value
Anti-dsDNA (+)	11 (91.7%)	48 (70.6%)	0.03
Low C3	10 (83.3%)	38 (55.9%)	0.04
Low C4	9 (75%)	34 (50%)	0.05

The immunologic profiles of SLE patients with AIHA and those without are shown in this table. A far greater percentage of AIHA patients exhibited low complement levels, including C3 (83.3% vs. 55.9%, $p=0.04$) and C4 (75% vs. 50%, $p=0.05$), and tested positive for anti-dsDNA antibodies (91.7% vs. 70.6%, $p=0.03$). These results highlight the use of serological markers in identifying individuals at risk for haematologic problems and corroborate the link between AIHA and active immunologic illness.



Figure

Table 4: Disease Activity and Organ Involvement

Parameter	AIHA (n=12)	Non-AIHA (n=68)	p-value
SLEDAI Score	14.2 ± 3.6	8.6 ± 2.9	<0.001
Renal Involvement	5 (41.7%)	18 (26.5%)	0.29

This table contrasts renal involvement and disease activity, as determined by the SLE Disease Activity Index (SLEDAI), between the AIHA and non-AIHA groups. More active illness was indicated by substantially higher SLEDAI scores (14.2 ± 3.6 vs. 8.6 ± 2.9, $p<0.001$) in patients with AIHA. Even while the AIHA group experienced renal involvement more frequently (41.7% vs. 26.5%), the difference was not statistically significant ($p=0.29$). These results demonstrate the robust correlation between AIHA and overall disease activity; however, more research in bigger cohorts is necessary to determine the relationship with particular organ involvement.

4. DISCUSSION

Our study's results show that, with an observed prevalence of 15% in our cohort, autoimmune haemolytic anaemia (AIHA) is a rather prevalent haematologic symptom among individuals with systemic lupus erythematosus (SLE). This is consistent with earlier research that found that the incidence varied significantly depending on the diagnostic criteria, geographic location, ethnicity, and patient selection, with ranges of 5% to 25%.Bertsias GK et a.; Giannouli S et al. [1,2].

In SLE, AIHA is seen as a sign of elevated illness severity and activity. SLEDAI scores were considerably higher in individuals with AIHA in our research (14.2 ± 3.6 vs. 8.6 ± 2.9), indicating a clear connection with current illness. This is corroborated by earlier research showing that haematologic symptoms, especially AIHA, frequently accompany lupus flare-ups and are indicative of increased immunological dysregulation. Piga M et al.; Reveille JD et al. [3,4].

Our findings show that individuals with AIHA had greater levels of reticulocytes, LDH, and indirect bilirubin—all of which are indicators of hemolysis—and considerably lower levels of haemoglobin. The autoimmune cause of the anaemia is supported by the AIHA group's 100% positive direct antiglobulin (Coombs) test result. Notably, these laboratory characteristics aid in distinguishing AIHA from renal anaemia or anaemia of chronic illness, which frequently coexist in SLE patients. Hill QA et al. [5].

Our study found a strong correlation between AIHA and immunological profile indicators of active SLE, including hypocomplementemia and anti-dsDNA positive. In particular, low C3 and C4 levels were substantially more common in the AIHA group, and anti-dsDNA antibodies were present in 91.7% of AIHA patients as opposed to 70.6% of non-AIHA patients. These results support previous research, highlighting the interaction between complement consumption, autoantibody synthesis, and haematologic involvement. Moyo VM et al.; Kamesh L et al. [6,7].

Interestingly, renal involvement was more common in AIHA patients (41.7% vs. 26.5%), although this did not reach

statistical significance. This trend suggests that multi-organ disease may cluster in more severe SLE phenotypes. Other studies have similarly reported an association between AIHA and lupus nephritis, although the strength of this association varies Tselios K et al. [8].

Our cohort's demographics (mean age 30.5 years, 90% female) are in line with worldwide epidemiologic trends for SLE, which show that young, reproductive-age females comprise the majority of those afflicted. This trend is mirrored by the small majority of AIHA in females (91.7%), which emphasises the importance of being vigilant when assessing haematologic abnormalities in this patient population.Lisnevskaia L et al. [9].

From a clinical standpoint, any patient who presents with unexplained anaemia should have AIHA in SLE diagnosed, particularly if haemolysis is evident. Since AIHA can cause serious morbidity, such as cardiovascular strain, transfusion dependency, and thromboembolic consequences, early detection is essential. When AIHA is mistakenly attributed to renal anaemia or iron shortage, proper immunosuppressive treatment may be delayed. Sultan SM et al. [10].

With positive results in most patients, corticosteroids continue to be the cornerstone of AIHA therapy in SLE. Steroid dependency and relapses are not unusual, though. Agents like mycophenolate mofetil, azathioprine, or rituximab may be used for refractory patients. Although this retrospective investigation did not include treatment data, further prospective research is required to assess therapy responses and results. Michel M et al.; Barcellini W et al.[11,12].

There are important clinical implications of our findings. First, routine haemolysis screening in anaemic SLE patients can help with early AIHA diagnosis. Second, the association between AIHA and markers of disease activity emphasises the need for comprehensive lupus care during haemolytic events. Finally, understanding the frequency of AIHA in different groups might assist direct resource allocation and regional policy. Berentsen S et al. [13].

Our study has a number of limitations that might impact how broadly the results can be applied, such as its retrospective design, single-center setting, and small sample size. Furthermore, we were unable to evaluate the prognostic implications due to the lack of data on treatment results and long-term follow-up. However, this study highlights the need for increased clinical awareness and prompt care and adds useful data to the little literature on AIHA in Indian SLE patients. Naqi M et al.; Ramos-Casals M et al. [14,15].

5. CONCLUSION

With a 15% frequency in our research group, autoimmune haemolytic anaemia is a significant and clinically relevant haematologic symptom of systemic lupus erythematosus. Higher disease activity and serologic indicators like hypocomplementemia and anti-dsDNA antibodies are closely linked to it. In order to start therapy on time and avoid problems, prompt detection by suitable laboratory assessment is crucial. Clinicians should keep a high index of suspicion for AIHA in any SLE patient who presents with anaemia and haemolysis symptoms because of the possibility of misdiagnosis and underreporting.

Our research emphasises how crucial it is to include haemolytic screening in the standard assessment of individuals with SLE. The results highlight the clinical burden of AIHA and its function as a marker of active and potentially severe lupus, despite the small sample size and the lack of treatment data assessment. To validate these findings and investigate long-term results, treatment approaches, and recurrence rates, larger multicentric prospective studies are necessary. Enhancing knowledge of AIHA across a range of populations can lead to more individualised treatment plans, lower morbidity, and better patient care.

6. LIMITATIONS OF THE STUDY

Retrospective Design: Selection bias and dependence on pre-recorded data are two intrinsic drawbacks brought about by the study's retrospective design. It limits the capacity to identify causal links between factors like disease activity and AIHA development.

Incomplete Medical Records: Existing hospital records, which could have been inconsistently or incompletely documented, were the source of the data. Important metrics such as haemolysis severity grading, haptoglobin levels, and therapy response were not consistently documented.

Single-Center Setting: Because the study was limited to a single tertiary care institution, it might not accurately represent the prevalence of illness or diagnostic procedures in other healthcare environments. This restricts the findings' external validity and capacity to be applied to larger or more varied groups.

Small Sample Size: The study may not have the power to identify less frequent connections, such the effect of AIHA on certain organ systems, given its small sample size of 80 patients. More thorough statistical comparisons and subgroup analysis would be possible with a bigger cohort.

Lack of Longitudinal Follow-Up: The long-term clinical outcomes of AIHA patients, including recurrence rates, survival, and treatment-related problems, were not evaluated in this study. The prognostic implications of AIHA in SLE are yet

unknown given the absence of follow-up data.

No Analysis of Treatment Modalities: Information about treatments (such as corticosteroids, immunosuppressants, or biologics) was not recorded in the research. Consequently, it does not offer information on the effectiveness of treatment or the best ways to manage AIHA in patients with SLE.

Limited Immunological Profiling: Conventional haematological and serological criteria were used to make the diagnosis. Neither flow cytometry nor advanced immunological markers, which might more accurately describe autoantibody patterns or lymphocyte subsets, were used.

Uncontrolled Confounding Variables: Potential confounding factors such as concomitant infections, drug-induced hemolysis, or coexisting autoimmune disorders were not fully evaluated or excluded.

Ethnic and Geographic Limitation: Generalisability may be impacted by regional and ethnic differences in illness phenotype or genetic predisposition since all patients were from a certain geographic area.

No Quality-of-Life Assessment: It was not evaluated how AIHA affected patients' functional level, hospital stay, or quality of life—all of which are critical for a thorough clinical viewpoint.

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