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ORIGINAL ARTICLE

Hematological Disorders in patients with Connective Tissue Diseases

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ABSTRACT

Background: This study describes connective tissue diseases, including systemic lupus erythematous, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease and overlap syndrome, and their associations with hematologic disorders. Consequently, anemia, leukopenia, thrombocytopenia, and antiphospholipid antibody (APLA) are included as morbidity indicators and can be used to determine further treatment strategies for this disease.

Methods: Therefore, a cross-sectional study was performed for six months from August 2024 to January 2025 at PAF Hospital Islamabad. Two hundred consecutive patients met the classification criteria for CTDs, including 50% SLE, 20% SSc, 15% Sjögren syndrome, 10% overlap syndrome, and 5% MCTD. The data gathered from the files consisted of demographic data, complete blood count (CBC) data, autoantibody profiles and clinical data. According to the ISTH, hematologic disorders were diagnosed, whereas APLA testing was performed via ELISA and coagulation tests. The descriptive statistical tests were computed through the Statistical Package of the Social Sciences (SPSS) software version 26.0 and the level of significance was considered to be 0.05.

Results: We reported that 78% of the patients had at least one altered hematologic parameter. Approximately 52% of the study subjects were found with anemia, 33% with leukopenia, 32.5% had lymphopenia, and 15% had thrombocytopenia, whereas pancytopenia was found in only 6.5% of the patients. With respect to hematologic changes, SLE patients manifested the greatest percentage of anemia at 70%, leukopenia at 40% and thrombocytopenia at 20%. Therefore, 33.5% of the patients were positive for APLA, and 10% of the total group fulfilled the criteria for secondary APS.

Conclusion: Cryptogenic hematology is common in patients with CTDs and more common in patients with SLE and MCTD. Therefore, it is crucial in CTD that blood counts should be researched on a regular basis together with APLA antibodies because their shifts indicate some issues.

Keywords: Systemic lupus erythematosis, systemic sclerosis, sjogrens syndrome, mixed connective tissue disorders and antiphospholipid antibody syndrome.

INTRODUCTION

Systemic autoimmune diseases can be referred to as diseases that are characterized by autoimmune inflammation or attack on different organs or tissues in the body (A). Among the clinically significant outcomes of these diseases, hematological changes are the most conspicuous (B). This can be attributed to SLE having genetic, autoimmune, or infectious origins like anemia, which is observed in more than half of patient with leukopenia, particularly lymphopenia and thrombocytopenia[1,2] (2). Such cytopenias could be due to autoimmune hemolysis, chronic inflammation, the impact of the disease, and/or the effects of immunosuppressive drugs on the bone marrow (1). Anemia and/or leukopenia are detected in Sjögren's syndrome, systemic sclerosis (SSc), and mixed connective tissue disease (MCTD) patients and in patients with overlapping syndromes but the prevalence and/or severity of these conditions vary according to the disease[3-5]. Thus, the interaction of the hematologic system can be considered not only diagnostic but also prognostically significant. For example, cytopenias are conducive to active disease and the frequency of infection and thrombotic events associated with antiphospholipid antibody APLA in patients with SLE[6]. Another cause of anemia in systemic sclerosis is gastrointestinal blood loss and anemia associated with chronic disease, which, although is common, has been established as portending a poor survival prognosis[7]. Finally, cytopenias in MCTD and overlap syndromes seems to indicate an aggressive disease state and the need for intervention[8,9]. Although hematological abnormalities are considered a common feature of CTDs, there are findings that lack sufficient data available from real-life experiences with patients from South Asia. This study was also conducted to obtain updated clinical information about the proportion and types of hematologic abnormalities present among CTD patients in a tertiary center in Islamabad, Pakistan. Understanding these patterns will aid clinicians in the assessment of risk, which will enable them to develop a suitable course of action to foster the development of clients[10,11].

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METHODS

Study design and setting: This cross-sectional study was carried out at PAF Hospital Islamabad which is a teaching and tertiary care hospital from 1st August, 2022 to 31st January, 2023. The study protocol was approved by the Institutional Ethics Committee and since it is a retrospective study, informed consent was absent. All procedures during the study were performed in accordance with Helsinki's declaration and other regulations of the country[12].

Patient Population: We subsequently recruited two hundred consecutive patients who presented with CTDs according to major classification criteria from the hospital. The patients were categorized according to the diagnosis they received during their regular visits.

SLE: This condition was diagnosed on the basis of the 2019 EULAR/ACR criteria for SLE classification[13].

Primary Sjögren's syndrome: Diagnosis per the 2016 ACR-EULAR criteria[14].

Systemic sclerosis (SSc): Again, as per the ACR/EULAR classification criteria set in 2013[15].

Mixed Connective Tissue Disease (MCTD): The criteria used in diagnosis include those proposed by Alarcón-Segovia and Fleischmann et al.

Overlap syndrome: Patients who fulfilled the recommendations of at least two other CTDs in addition to rheumatoid arthritis[17].

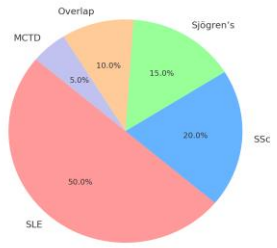
Patients with undifferentiated CTD, rheumatoid arthritis or cytopenias secondary to other underlying diseases such as malignancies or chronic infections, among others were excluded.

Data collection: Electronic medical records were used and data were extracted from these records. The collected data included patient demographics, such as patient age, sex, CTD subtype, duration of the disease, and general CBC, including Hb, WBC count, WBC differential and platelet count. Abnormalities in the blood count were defined via the following criteria:
Iron deficiency anemia is detected via the daily recommended intake DRI, but moderate/severe anemia DRI Hb levels are <10 g/dl for males and <12 g/dl for females[18].
Leucopenia was defined as total WBC count $<4.0\times10^9$/L lymphopenia was defined as a lymphocyte count $<1.0\times10^9$/L [19].
Petitioned thrombocytopenia was defined as a platelet count less than 100×10^9/L. it was classified as mild if it is in the range of 50–99×10^9/L; moderate if it was 30–49×10^9/L; and severe if it was less than 30×10^9/L[20].
Pancytopenia: concurrent anemia, leukopenia, and thrombocytopenia.
Autoimmune hemolytic anemia: AIHA was considered if the direct antiglobulin test was positive together with hemolysis. Antiphospholipid antibodies were determined by ELISA (anticardiolipin-aCL IgG/IgM and anti-β2 glycoprotein-β2GPI) and coagulation assays of the lupus anticoagulant-LA test. Patients were diagnosed with antiphospholipid antibody syndrome (APS) using the repeat APLA test criteria involving APLA positivity on two occasions performed at least 12 weeks apart and clinical manifestations that involved thrombosis or pregnancy morbidity on the basis of the Sydney classification[21].
Sample size justification: The sample comprises 200 qualified patients within the 6-month period of the study. The post hoc power calculation revealed that a target sample of 200 participants has the ability to estimate the prevalence of anemia to be within a 7% margin of error around the hypothesized 50% with 95% confidence. Additionally, this study can compare the frequencies of hematologic abnormalities within CTD subgroups with 95% confidence intervals and a preset two-sided alpha of 0.05[22].
Statistical analysis: These data were analyzed via the Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables are described as the means ± standard deviations (SDs) or medians with interquartile ranges (IQRs) if they did not follow a normal distribution. Frequencies and percentages were the measures used to present the categorical variables. Between-group comparisons (for example, between SLE patients and other CTDs) were performed via the chi-square test or Fisher's test. Tests were deemed meaningful only when the overall value of $p < 0.05$. Where laboratory values were missing, such cases were also omitted in the specific analysis in which the data were missing.

RESULTS

Patient characteristics: Thus, the sample for the study consisted of 200 patients with CTDs. The distribution was as follows:
SLE: 100 patients (50%)
Systemic Sclerosis: 40 patients (20%)
Primary Sjögren's syndrome: 30 patients (15%)
Overlap syndrome: 20 patients (10%)
MCTD: 10 patients (5%)
Furthermore, the mean age was 36.8 ± 12.4 years and the group was mainly female with only 10% male participants. The duration of the disease has also been found to differ according to the subtype and the mean durations for SLE and SSc patients were 3 years and 5 years respectively. As noted in Figure 1, a breakdown of CTD diagnoses among the study population is shown below.

Figure 1: On the basis of the collected data, a pie chart showing the percentage distributions of CTD groups such as SLE 50%, SSc 20%, Sjögren's 15%, Overlap 10%, and MCTD 5% was prepared.



Prevalence of Hematological Abnormalities: Overall 156 (78%) patients presented with at least one hematologic abnormality. Table 1 summarizes the frequencies of anemia, leukopenia, thrombocytopenia, pancytopenia, and aPL positivity stratified by CTD subtype.

Table 1: Prevalence of hematological abnormalities stratified by CTD diagnosis.

Hematological Abnormality	SLE (n=100)	SSc (n=40)	Sjogren's (n=30)	MCTD (n=10)	Overlap (n=20)	Total (N=200)
Anemia (Hb <12 g/dL F, <13 g/dL M)	70 (70%)	10 (25%)	9 (30%)	7 (70%)	8 (40%)	104 (52%)
Leukopenia (<4×10^9/L)	40 (40%)	6 (15%)	9 (30%)	7 (70%)	4 (20%)	66 (33%)
Lymphopenia (<1×10^9/L)	50 (50%)	2 (5%)	3 (10%)	6 (60%)	4 (20%)	65 (32.5%)
Thrombocytopenia (<100×10^9/L)	20 (20%)	2 (5%)	4 (13%)	3 (30%)	1 (5%)	30 (15%)
Pancytopenia	10 (10%)	1 (2.5%)	0 (0%)	1 (10%)	1 (5%)	13 (6.5%)
aPL Positivity (any aCL, β2GPI, or LA)	40 (40%)	10 (25%)	10 (33%)	2 (20%)	5 (25%)	67 (33.5%)

Note: Overlap syndromes include patients meeting the criteria for ≥2 CTDs (excluding isolated rheumatoid arthritis).In our study, anemia was present in 52% of the 104 patients. Anemia of chronic disease was the most common type (≈60%), followed by iron deficiency anemia (≈25%), while autoimmune hemolytic anemia was observed in a smaller proportion of patients (≈14%), as shown in Table 2.

Table 2. Distribution of anemia types among CTD patients (n = 104)

Type of Anemia	Number of Patients	Percentage (%)
Anemia of Chronic Disease (ACD)	70	67.3
Iron Deficiency Anemia (IDA)	20	19.2
Autoimmune Hemolytic Anemia (AIHA)	14	13.5
Total	104	100

Figure 2 presents a bar graph showing the percentage frequency of each hematologic abnormality across the entire cohort. In addition, a pie chart (Figure 3) visually displays the distribution of APLA positivity among the different CTD groups.
Figure 2
X-axis: Hematologic abnormality (anemia, leukopenia, lymphopenia, thrombocytopenia, pancytopenia, aPL positive)
Y-axis: percentage of patients
The bars indicate: Anemia (52%), leukopenia (33%), lymphopenia (32.5%), thrombocytopenia (15%), pancytopenia (6.5%), and aPL positivity (33.5%).
Detailed Findings by CTD Subtype
Systemic lupus erythematosus (SLE): Among the 100 SLE patients, 70.0% had anemia, the mean of which was 10.5 ± 1.8 g/dL. The common side effects reported were leukopenia in 40 (40%) patients and lymphopenia in 50 (50%) patients. Thrombocytopenia was observed in 20 (20%) patients, and 10 patients (10%) had pancytopenia. Significantly 14% of the SLE patients had AIHA, as evidenced by positivity in the direct Coombs test. Additionally, 40

patients with SLE fulfilled the APAH serology criteria; 10 of them (10% of the total number of patients with SLE) fulfilled the clinical criteria for APS. These frequencies are in agreement with previous studies that estimated the anemia prevalence to be between 70-72%, leukopenia 32-40% and thrombocytopenia 20-23% in SLE patients[1,2,14,20].

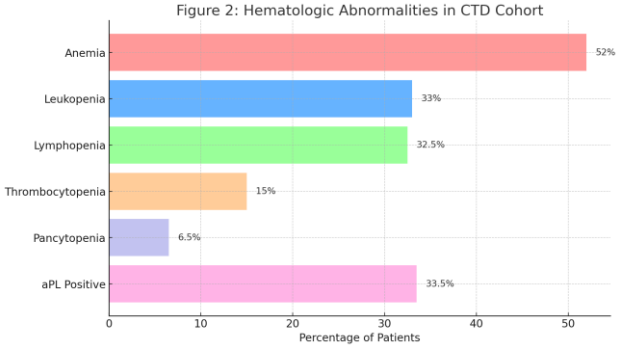
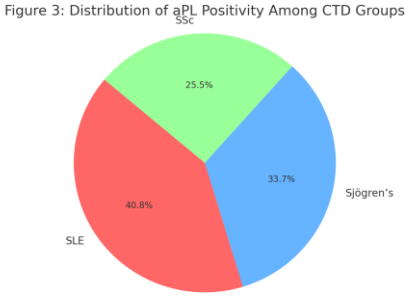


Figure 3: Pie chart demonstrating that among the total CTD cohort, approximately one-third (33.5%) were aPL positive, with SLE patients accounting for the largest portion (40% of SLE patients), followed by Sjögren's (33%) and SSc patients (25%).



Systemic Sclerosis (SSc): Among 40 SSc patients, anemia was present in 10 (25%) patients, 5% of whom had moderate anemia and 20% of whom had mild anemia, with a mean Hb of approximately 11.0 g/dL. Leukopenia was less common, and thrombocytosis occurred in only two patients (5%). Similarly, ten out of forty patients were positive for APLA but only one patient had clinical APS. These findings are consistent with published literature with regard to the prevalence of anemia in SSc patient populations, in which anemia rates range from 20 to 25%.

Primary Sjögren's syndrome: Among the 30 patients in the Sjögren subgroup, 9 (30%) had anemia, whereas 9 (30%) had leukopenia. Lymphopenia was documented in 3 of the patients in the study (10%), whereas thrombocytopenia was observed in 4 of the patients (13%). Positivity for aPL was noted in 10 of the patients (33%). These statistics correlate with other data that state that anemia is present in 20–50% of Sjögren's syndrome cases, whereas leukopenia is present in up to 42% of cases[6,7,13].

Mixed Connective Tissue Disease (MCTD): Hematologic manifestations were observed in all 10 patients diagnosed with MCTD and 7 of them had renal complications. A total of 78% of them had anemia, and leukopenia was observed in 70% of the patients; the most common type of leukopenia was lymphopenia. Thrombocytopenia occurred in 3 patients (30%). Taken together, despite the low number of patients in the sample, these data are in accordance with previous research on MCTD with a cytopenias incidence of approximately 75%[8,10].

Overlap syndrome: In the case of 20 patients with overlapping syndromes, the hematological changes were less severe. Anemia was observed in 8 (40%) patients, leukopenia in 4 (20%) patients, and thrombocytopenia in only 1 (5%) patient. Of the 20 patients, 5 (25%) were APLA positive. These rates are lower than those in the groups with SLE or MCTD of pure forms, which may indicate that the overlap syndromes are less severe in terms of hematologic manifestations[9,17].

DISCUSSION

The present study aims to present data on hematological compensation in patients with various confirmed CTDs in a tertiary health care facility in Islamabad. Study revealed that 78% of these patients had at least one form of hematologic derangement and that the most prevalent form was anemia (52%), leukopenia (33%), lymphopenia (32.5%), thrombocytopenia (15%), and pancytopenia (6.5%). Specifically, 33.5% of the patients were seropositive for APLA, and 10% had APS according to the categorized classification criteria. These findings are in agreement with those of studies described in the recent literature[1-3,14,20].

The finding of anemia prevalence of 70% in SLE patients is in agreement with other cross-sectional and longitudinal studies that reported anemia in 70–72% of SLE patients. The same situation was observed for leukopenia and lymphopenia, which were detected in 40% and 50% of this study's SLE cohort, respectively. All types of cytopenias can occur when the immune system attacks its own bone marrow[1,2]. The platelet count deficiency in this study SLE subpopulation (20%) can also be explained by the data in the abovementioned references, which varied within the range of 14–30%. With respect to anemia, the systemic sclerosis detected in our study was present in 25% of the Libyan patients, which is consistent with studies conducted on European patient cohorts. Among patients with primary Sjögren's syndrome, 30% had anemia and a 30% leukopenia rate, whereas 30 patients were free of these manifestations[6,13]. In our small MCTD group, 70% of the patients had anemia and 70% had leukopenia; these findings are similar to those of other centers[8,10]. Since overlap syndromes are heterogeneous, there are lower above-normal prevalence rates of cytopenias, thus indicating that the degree of hematologic manifestations may depend on the predominant disease process[9,17].

The high prevalence of hematological abnormalities in CTDs underscores the need for routine monitoring of complete blood counts and APLA. Early detection of cytopenias can prompt timely interventions either by modifying immunosuppressive therapy or initiating treatment for APS to reduce complications such as severe bleeding, infections, or thrombotic events[12,20]. For example, in SLE, timely management of autoimmune hemolytic anemia (AIHA) with corticosteroids and immunosuppressant has shown to improve patient outcomes[2,14]. In addition, the presence of APLA in one-third of our patients indicates that regular screening for APS is warranted, as only a subset of aPL-positive patients develop clinical thrombosis[8,12].

Our results also have prognostic implications. Several studies have demonstrated that cytopenias, particularly severe thrombocytopenia, are associated with increased disease activity and poorer outcomes in patients with CTDs[12,14,20]. The association between APLA positivity and thrombocytopenia in our cohort further suggests that hematologic parameters can serve as surrogate markers for immune dysregulation and may aid in risk stratification[8,12]. For clinicians, these findings highlight the importance of incorporating routine hematologic evaluation into management protocols for CTD patients.

importantly, this study has certain limitations that are worth mentioning. This is mostly because the retrospective study design does not focus on possible transient or subclinical cytopenias. One limitation pertinent to the use of chart review is that certain variables (such as other medications or comorbid diseases affecting the blood count results) may not have been adequately controlled. However, to some extent, the small subgroup of MCTD and/or overlap syndromes may affect the generalizability of the findings derived from this study. However, because our data were collected from actual clinical practice settings, they offer useful information on hematologic findings in various CTDs in a South Asian population.

Further prospective research is needed to strengthen these observations and analyze changes in hematologic abnormalities associated with CTD and vice versa. Future studies investigating the immunopathogenic pathways that result in cytopenias in these disorders, as well as the possible positive impact of early therapeutic interventions on the basis of complete blood count and other hematologic abnormalities, are needed. Perhaps extending the biomarkers that already exist and bone marrow assessment will help to reveal the etiology of such observations.

CONCLUSION

Notably, the actual prevalence of hematologic disorders in the present study was high, where almost 80% of the 200 patients attending PAF Hospital, Islamabad, who suffer from connective tissue diseases, had hematologic abnormalities. The most common abnormalities detected were anemia, followed by leukopenia and thrombocytopenia, including lymphopenia. Anemias were the most common in patients with SLE and MCTD; the other two common findings were leukopenia more specifically lymphopenia and thrombocytopenia. Indeed, we identified APLA in approximately one-third of our cohort, and approximately one-quarter of those subjects developed clinical APS. These data confirm the need for close observation and timely intervention in patients with hematologic disorders associated with CTDs with the purpose of enhancing patient prognosis and providing profound therapeutic strategies. In conclusion, the current study contributes to the knowledge of the role of hematologic factors in the management of CTDs and incorporates them as useful biomarkers in the management of these diseases.

Availability of Data and Materials: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, subject to institutional and ethical regulations.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: NS conceptualized the study and drafted the manuscript. SN and ZUH, ZS contributed to data collection and clinical interpretation. NAL provided supervision and critical revision of the manuscript. LM and KS assisted in data acquisition, statistical analysis, and literature review. All authors read and approved the final manuscript.

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