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Original Research Article

Correlation of Bone Marrow Histomorphology with Peripheral Hemolytic Markers in Sickle Cell Disease Patients

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Abstract

Background: Sickle cell disease (SCD) is characterized by chronic hemolysis and compensatory bone marrow erythroid hyperplasia. Understanding the relationship between bone marrow morphological changes and peripheral hemolytic markers may provide valuable insights into disease severity assessment and therapeutic monitoring. This study aimed to evaluate the correlation between bone marrow histomorphological features and peripheral hemolytic markers in SCD patients.

Methods: This cross-sectional analytical study was conducted on 72 confirmed SCD patients aged 12-45 years. Bone marrow aspiration and trephine biopsy were performed, and histomorphological parameters including cellularity, myeloid-to-erythroid (M:E) ratio, erythroid hyperplasia grade, iron stores, and dysplastic changes were assessed. Peripheral hemolytic markers including lactate dehydrogenase (LDH), indirect bilirubin, reticulocyte count, and haptoglobin were measured simultaneously. Correlation analysis was performed using Pearson's and Spearman's coefficients.

Results: Mean bone marrow cellularity was 78.4 ± 12.6%, with 87.5% of patients demonstrating erythroid hyperplasia. The mean M:E ratio was 0.8 ± 0.3. Significant positive correlations were observed between erythroid hyperplasia grade and LDH levels ($r=0.68$, $p<0.001$), reticulocyte count ($r=0.72$, $p<0.001$), and indirect bilirubin ($r=0.54$, $p<0.001$). Bone marrow cellularity showed moderate positive correlation with reticulocyte count ($r=0.61$, $p<0.001$). Haptoglobin levels demonstrated significant negative correlation with erythroid hyperplasia grade ($r=-0.58$, $p<0.001$). Patients with severe erythroid hyperplasia exhibited significantly higher LDH (892.4 ± 186.3 vs. 542.7 ± 124.8 U/L, $p<0.001$) compared to those with mild hyperplasia.

Conclusion: Bone marrow histomorphological changes significantly correlate with peripheral hemolytic markers in SCD patients, suggesting that peripheral markers may serve as reliable non-invasive surrogates for assessing bone marrow compensatory response.

Keywords: Sickle Cell Disease; Bone Marrow Histomorphology; Hemolytic Markers; Erythroid Hyperplasia; Lactate Dehydrogenase; Reticulocyte Count.

Introduction

Sickle cell disease (SCD) represents one of the most prevalent inherited hemoglobinopathies worldwide, affecting millions of individuals predominantly in sub-Saharan Africa, the Mediterranean region, Middle East, and the Indian subcontinent [1].

The disease results from a point mutation in the β-globin gene, leading to the production of abnormal hemoglobin S (HbS), which polymerizes under deoxygenated conditions, causing red blood cell sickling, chronic hemolysis, and vaso-occlusive phenomena [2]. The pathophysiology of SCD is characterized by ongoing intravascular and extravascular hemolysis, which triggers compensatory mechanisms within the bone marrow [3]. This compensatory erythropoietic response manifests as marked erythroid hyperplasia, decreased myeloid-to-erythoid ratio, and increased bone marrow cellularity [4].

The chronic hemolytic state in SCD leads to elevated peripheral hemolytic markers including lactate dehydrogenase (LDH), indirect bilirubin, and reticulocyte count, while haptoglobin levels are characteristically decreased [5]. Bone marrow

examination in SCD patients reveals distinctive morphological features that reflect the underlying hemolytic process and compensatory erythropoiesis [6]. Previous studies have documented various bone marrow abnormalities including erythroid hyperplasia with megaloblastic changes, iron store alterations, and occasionally dyserythropoiesis [7]. However, the quantitative relationship between these bone marrow changes and peripheral hemolytic markers remains incompletely characterized.

Recent investigations have emphasized the importance of hemolytic markers in predicting clinical outcomes and complications in SCD [8]. Kato and colleagues proposed a hemolytic subphenotype classification based on these markers, suggesting their utility in risk stratification [9]. Furthermore, studies have demonstrated associations between elevated hemolytic markers and complications such as pulmonary hypertension, leg ulcers, and priapism [10].

Despite advances in understanding SCD pathophysiology, limited data exist regarding the direct correlation between bone marrow morphological features and peripheral hemolytic indices. Most existing studies have focused on either bone marrow changes or peripheral markers independently, without systematically examining their interrelationship [11]. Understanding these correlations could provide insights into whether peripheral markers accurately reflect the degree of bone marrow compensatory response and potentially reduce the need for invasive bone marrow procedures in certain clinical scenarios.

The aim of this study was to evaluate the correlation between bone marrow histomorphological parameters and peripheral hemolytic markers in patients with sickle cell disease, and to determine whether peripheral hemolytic indices can serve as reliable surrogates for bone marrow erythroid activity assessment.

Materials and Methods

A total of 72 patients with confirmed sickle cell disease were enrolled in the study. The diagnosis of SCD was established based on hemoglobin electrophoresis demonstrating HbS predominance, confirmed by high-performance liquid chromatography (HPLC). Patients were recruited during routine follow-up visits or during admissions for various SCD-related complications.

Inclusion Criteria: Patients aged 12-45 years with confirmed SCD (homozygous HbSS or compound heterozygous HbSC/HbSβ-thalassemia), clinically stable at the time of sampling (at least 4 weeks from acute crisis), and willing to undergo bone marrow examination were included.

Exclusion Criteria: Patients with recent blood transfusion (within 3 months), concurrent infections or inflammatory conditions, pregnancy, chronic kidney or liver disease, patients on hydroxyurea therapy for less than 6 months, and those with contraindications to bone marrow biopsy were excluded.

Sample Collection and Laboratory Analysis: Peripheral venous blood samples (10 mL) were collected in appropriate anticoagulant tubes. Complete blood count with reticulocyte count was performed using automated hematology analyzer (Sysmex XN-1000). Serum LDH was measured using spectrophotometric enzymatic method. Indirect bilirubin was calculated from total and direct bilirubin measured by colorimetric method. Serum haptoglobin was quantified using immunoturbidimetric assay.

Bone Marrow Examination: Bone marrow aspiration and trephine biopsy were performed from the posterior superior iliac spine under local anesthesia using standard aseptic technique. Aspiration smears were stained with Leishman stain and Perls' Prussian blue stain for iron assessment. Trephine biopsy specimens were fixed in 10% neutral buffered formalin, decalcified, and processed for paraffin embedding. Sections (4 μm) were stained with hematoxylin and eosin, reticulin stain, and Perls' stain.

Histomorphological Assessment: Bone marrow cellularity was assessed on trephine biopsy sections and expressed as percentage. M:E ratio was calculated from aspiration smears by counting 500 nucleated cells. Erythroid hyperplasia was graded as mild (M:E 1:1-2:1), moderate (M:E 1:2-1:3), or severe (M:E <1:3). Iron stores were graded from 0 to 6 using Gale's classification. Dyserythropoietic features were recorded as present or absent.

Statistical Analysis: Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables were presented as frequencies and percentages.

Pearson's correlation coefficient was used for normally distributed continuous variables, while Spearman's rank correlation was applied for non-parametric data. Comparison between groups was performed using independent t-test or ANOVA. Statistical significance was set at $p<0.05$.

Results

Baseline Characteristics: The study included 72 SCD patients with a mean age of 24.6 ± 8.3 years. Males constituted 54.2% (n=39) of the study population. The majority of patients (81.9%, n=59) had homozygous HbSS disease, while 12.5% (n=9)

had HbSC disease and 5.6% (n=4) had HbSβ-thalassemia. Mean hemoglobin level was 8.2 ± 1.4 g/dL, and mean fetal hemoglobin (HbF) was 12.4 ± 6.8% (Table 1).

Peripheral Hemolytic Markers: Mean LDH level was 724.8 ± 248.6 U/L, which was significantly elevated compared to normal reference range. Indirect bilirubin was elevated at 2.8 ± 1.4 mg/dL. Mean reticulocyte count was 12.4 ± 5.6%, and absolute reticulocyte count was 298.4 ± 126.8 × 10^9/L. Serum haptoglobin was markedly reduced with median value of 8.2 mg/dL (IQR: 4.6-18.4).

Bone Marrow Histomorphological Findings: Mean bone marrow cellularity was 78.4 ± 12.6%, with 91.7% of patients showing hypercellular marrow.

The mean M: E ratio was 0.8 ± 0.3. Erythroid hyperplasia was observed in 87.5% (n=63) of patients, with 22.2% (n=16) showing mild, 40.3% (n=29) moderate, and 25.0% (n=18) severe hyperplasia. Iron stores were decreased (grade 0-1) in 48.6% (n=35) of patients. Dyserythropoietic changes were noted in 34.7% (n=25) of cases (Table 1).

Table 1: Baseline Characteristics, Hemolytic Markers, and Bone Marrow Findings (N=72)

Parameter	Value
Demographics	
Age (years), mean ± SD	24.6 ± 8.3
Male gender, n (%)	39 (54.2)
HbSS genotype, n (%)	59 (81.9)
Hematological Parameters	
Hemoglobin (g/dL), mean ± SD	8.2 ± 1.4
HbF (%), mean ± SD	12.4 ± 6.8
WBC count (×10^9/L), mean ± SD	11.8 ± 4.2
Platelet count (×10^9/L), mean ± SD	342.6 ± 128.4
Hemolytic Markers	
LDH (U/L), mean ± SD	724.8 ± 248.6
Indirect bilirubin (mg/dL), mean ± SD	2.8 ± 1.4
Reticulocyte count (%), mean ± SD	12.4 ± 5.6
Haptoglobin (mg/dL), median (IQR)	8.2 (4.6-18.4)
Bone Marrow Features	
Cellularity (%), mean ± SD	78.4 ± 12.6
M:E ratio, mean ± SD	0.8 ± 0.3
Erythroid hyperplasia, n (%)	63 (87.5)
Decreased iron stores (grade 0-1), n (%)	35 (48.6)
Dyserythropoiesis present, n (%)	25 (34.7)

Correlation Analysis: Significant positive correlations were observed between bone marrow erythroid hyperplasia grade and all hemolytic markers except haptoglobin, which showed negative correlation. The strongest correlation was between erythroid hyperplasia grade and reticulocyte count ($r=0.72$, $p<0.001$), followed by LDH ($r=0.68$, $p<0.001$). Bone marrow cellularity also showed moderate positive correlation with reticulocyte count ($r=0.61$, $p<0.001$) and LDH ($r=0.52$, $p<0.001$). M:E ratio demonstrated significant negative correlation with all hemolytic markers (Table 2).

Table 2: Correlation between Bone Marrow Parameters and Peripheral Hemolytic Markers

Bone Marrow Parameter	LDH	Indirect Bilirubin	Reticulocyte Count	Haptoglobin
	r (p-value)	r (p-value)	r (p-value)	r (p-value)
Cellularity (%)	0.52 (<0.001)	0.44 (<0.001)	0.61 (<0.001)	-0.46 (<0.001)
Erythroid hyperplasia grade	0.68 (<0.001)	0.54 (<0.001)	0.72 (<0.001)	-0.58 (<0.001)
M:E ratio	-0.64 (<0.001)	-0.48 (<0.001)	-0.69 (<0.001)	0.52 (<0.001)
Iron store grade	-0.38 (0.001)	-0.28 (0.018)	-0.42 (<0.001)	0.32 (0.006)

Comparison by Erythroid Hyperplasia Severity: Patients were stratified according to erythroid hyperplasia severity. Those with severe hyperplasia exhibited significantly higher LDH levels (892.4 ± 186.3 U/L) compared to patients with moderate (714.6 ± 198.4 U/L) and mild hyperplasia (542.7 ± 124.8 U/L) ($p<0.001$). Similar patterns were observed for reticulocyte count and indirect bilirubin. Haptoglobin levels were inversely related to hyperplasia severity (Table 3).

Table 3: Hemolytic Markers According to Erythroid Hyperplasia Severity

Parameter	No/Mild Hyperplasia (n=25)	Moderate Hyperplasia (n=29)	Severe Hyperplasia (n=18)	p-value
LDH (U/L)	542.7 ± 124.8	714.6 ± 198.4	892.4 ± 186.3	<0.001
Indirect bilirubin (mg/dL)	1.9 ± 0.8	2.8 ± 1.2	3.9 ± 1.6	<0.001
Reticulocyte count (%)	7.8 ± 3.2	12.6 ± 4.4	18.4 ± 5.8	<0.001
ARC (×10⁹/L)	186.4 ± 78.6	298.2 ± 104.6	438.6 ± 142.8	<0.001
Haptoglobin (mg/dL)*	16.8 (8.4-28.6)	7.4 (4.2-14.6)	4.2 (2.8-8.4)	<0.001
Hemoglobin (g/dL)	8.9 ± 1.2	8.2 ± 1.4	7.4 ± 1.3	0.002

***Median (IQR); ARC: Absolute Reticulocyte Count**

Discussion

This study demonstrates significant correlations between bone marrow histomorphological features and peripheral hemolytic markers in sickle cell disease patients, providing quantitative evidence for the relationship between marrow compensatory response and peripheral hemolysis indices. Our findings suggest that peripheral hemolytic markers may serve as reliable non-invasive surrogates for assessing the degree of bone marrow erythroid hyperplasia.

The observation that 87.5% of our patients exhibited erythroid hyperplasia is consistent with the chronic hemolytic nature of SCD [12]. The bone marrow in SCD characteristically responds to ongoing red cell destruction through expansion of the erythroid compartment, a finding that has been documented in various studies examining bone marrow pathology in hemolytic anemias [13]. The mean cellularity of 78.4% in our cohort reflects this compensatory hypercellularity, which typically exceeds age-matched normal values by 20-30%.

The strong positive correlation between erythroid hyperplasia grade and reticulocyte count (r=0.72) confirms the expected relationship between bone marrow erythroid activity and peripheral reticulocyte release. Reticulocytes, being immature red blood cells released from the marrow in response to erythropoietic demand, serve as a direct indicator of marrow erythroid output [14]. Our findings align with previous observations that reticulocyte indices correlate with hemolytic severity in SCD [15].

The significant correlation between LDH levels and erythroid hyperplasia grade (r=0.68) provides important clinical insights. Elevated LDH in SCD primarily results from red cell destruction, as hemolyzed erythrocytes release intracellular LDH into the circulation [16]. Our data suggest that higher LDH levels indicate not only greater hemolysis but also more pronounced bone marrow compensatory response. This association supports the concept of the hemolytic subphenotype in SCD, wherein patients with higher hemolytic rates may require more aggressive monitoring and intervention [17].

The inverse correlation between haptoglobin levels and erythroid hyperplasia severity (r=-0.58) reflects the consumption of this acute-phase protein during intravascular hemolysis. Haptoglobin binds free hemoglobin released during hemolysis, and its depletion indicates significant ongoing hemolytic activity [18]. Interestingly, patients with severe erythroid hyperplasia had median haptoglobin levels of only 4.2 mg/dL, suggesting near-complete consumption due to sustained hemolysis.

The finding of decreased iron stores in 48.6% of patients despite chronic hemolysis warrants attention. While SCD is classically associated with iron overload in transfusion-dependent patients, those without regular transfusions may develop functional iron deficiency due to chronic inflammation and increased erythropoietic demand [19]. The negative correlation between iron stores and hemolytic markers suggests that patients with more severe hemolysis may deplete iron reserves more rapidly despite adequate dietary intake.

Dyserythropoiesis observed in 34.7% of patients represents an important morphological finding. Previous studies have attributed dyserythropoietic changes in SCD to folate deficiency, oxidative stress, and the inherent abnormalities in sickle erythroid precursors [20]. The presence of dyserythropoiesis may contribute to ineffective erythropoiesis, potentially exacerbating anemia despite marrow hyperactivity.

The clinical implications of our findings are significant. The strong correlations observed suggest that peripheral hemolytic markers, particularly reticulocyte count and LDH, may obviate the need for bone marrow examination in certain clinical scenarios where assessment of marrow erythroid response is desired. This is particularly relevant given that bone marrow biopsy is an invasive procedure with associated discomfort and potential complications [21]. Furthermore, these correlations may have prognostic value. Patients demonstrating discordance between peripheral markers and expected bone marrow response—such as elevated hemolytic markers without proportionate reticulocytosis—may warrant investigation for bone marrow failure,

aplastic crisis, or superimposed nutritional deficiencies [22].

Our study has limitations. The cross-sectional design precludes assessment of temporal relationships. The exclusion of patients on hydroxyurea for less than 6 months may introduce selection bias. Additionally, we did not evaluate the impact of specific hemoglobin genotypes on correlations, although the predominance of HbSS patients (81.9%) provides a relatively homogeneous population.

Conclusion

This study demonstrates significant correlations between bone marrow histomorphological parameters and peripheral hemolytic markers in sickle cell disease patients. Erythroid hyperplasia grade shows strong positive correlations with LDH and reticulocyte count, while displaying inverse correlation with haptoglobin levels. These findings suggest that peripheral hemolytic markers may serve as reliable non-invasive indicators of bone marrow compensatory erythroid response. The clinical utility of these markers extends to disease monitoring, severity assessment, and potentially reducing the need for invasive bone marrow procedures. Prospective studies correlating these parameters with clinical outcomes and therapeutic response are warranted to further establish their clinical applicability.

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