

Etiological Spectrum and Diagnostic Accuracy of Peripheral Smear and Bone Marrow Evaluation in Patients with Pancytopenia at a Tertiary Care Center in India: A Cross-Sectional Observational Study

Aditi N. Patel¹, Akshi Y. Patel², Naushin A. Ghori³

¹Assistant Professor, Department of Pathology, Gujarat Medical Education & Research Society (GMERS), Dharpur, Patan, Gujarat, India

²Assistant Professor, Department of Pathology, Nootan Medical College and Research Centre, Visnagar, Gujarat, India

³Tutor, Department of Pathology, Narendra Modi Medical College, Maninagar, Ahmedabad, Gujarat, India

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Corresponding author: Dr. Aditi N Patel

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Abstract

Introduction: Pancytopenia, the reduction of all three blood cell lines, presents with varied etiologies that differ regionally. In India, nutritional anemias, marrow failure, and hematological malignancies are most common. This study evaluated the etiological spectrum of pancytopenia and the diagnostic utility of peripheral smear versus bone marrow examination.

Methods: A cross-sectional study was conducted in the Department of Pathology, Medical College & S.S.G. Hospital, Baroda, from October 2018 to October 2020. A total of 190 patients aged 17–76 years with pancytopenia were analyzed through clinical evaluation, hematological parameters, peripheral smear, and bone marrow examination.

Results: Of 190 patients (M:F ratio 1.1:1), the 27–36 years group was most affected (28.9%). Weakness (28.9%) and fever (16.3%) were common symptoms; pallor was the leading sign (56.8%). Severe anemia and thrombocytopenia were frequent. Peripheral smear most often showed microcytic hypochromic anemia (43.7%). Bone marrow (n=58) revealed megaloblastic anemia (18.9%), aplastic anemia (17.2%), dimorphic anemia (12.1%), and acute leukemia (8.6%). Smear correlated well with nutritional anemias but marrow was essential for marrow failure and malignancies.

Conclusion: Megaloblastic anemia remains the leading and reversible cause of pancytopenia in India. Peripheral smear aids initial assessment, but bone marrow examination is crucial for definitive diagnosis.

Keywords: Pancytopenia, Peripheral Smear, Bone Marrow, Etiological Spectrum, Megaloblastic Anemia.

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Introduction

Pancytopenia is a common but challenging clinico-hematological presentation characterized by the simultaneous reduction of all three major blood cell lines—erythrocytes, leukocytes, and platelets, resulting in anemia, leukopenia, and thrombocytopenia, respectively. Patients typically present with fatigue, pallor, and weakness attributable to anemia; recurrent infections due to leukopenia; and bleeding manifestations associated with thrombocytopenia. [1,2] It is not a disease entity per se but a manifestation of various underlying disorders that primarily or secondarily affect the bone marrow. [3] The etiological spectrum of pancytopenia varies widely across regions, shaped by genetic, nutritional, environmental, and socioeconomic factors.

Globally, the incidence is estimated at 2–5 cases per million population per year, with higher prevalence reported in Asian countries, approximately double that of Western nations. [4] In India, multiple regional studies consistently identify megaloblastic anemia due to vitamin B12 or folate deficiency as the leading cause, followed by aplastic anemia, hypersplenism, and hematological malignancies. [5–7] In contrast, studies from Nepal and Bangladesh report aplastic anemia and infections such as malaria and leishmaniasis as major contributors, [8,9] whereas in Europe and Israel, neoplastic infiltration and therapy-related marrow suppression predominate. [10] These regional differences underscore the importance of institutional data to guide diagnostic

priorities and therapeutic strategies. Peripheral smear evaluation is a simple, inexpensive, and minimally invasive tool that provides essential preliminary information. However, bone marrow aspiration and trephine biopsy remain the gold standards, offering detailed assessment of marrow cellularity, morphology, and infiltrative processes. [2,11] Aspiration smears provide superior cytological detail, while trephine biopsies allow reliable evaluation of overall marrow architecture and cellularity. [12] The diagnostic value of marrow evaluation lies in its ability to distinguish between reversible causes such as nutritional deficiencies and irreversible marrow failure syndromes or infiltrative malignancies. [13,14]

Given the heterogeneity of underlying causes and the critical role of timely diagnosis in improving patient outcomes, institutional studies remain relevant in defining the clinico-hematological profile of pancytopenia. The present study was undertaken to evaluate the etiological spectrum of pancytopenia and to assess the diagnostic accuracy of peripheral smear findings in comparison with bone marrow examination among patients at a tertiary care center in India.

Materials and Methods

Study Design and Setting: This was a cross-sectional observational study conducted in the Department of Pathology, Medical College & S.S.G. Hospital, Baroda, Gujarat, India, a tertiary care referral center, from October 2018 to October 2020.

Study Population: A total of 190 patients with pancytopenia, admitted under the Department of General Medicine and referred for hematological evaluation, were included.

Inclusion criteria:

- Patients >12 years of age with pancytopenia, defined as:
 - Hemoglobin <9 g/dL
 - Total leukocyte count (TLC) <4,000/mm³
 - Platelet count <150,000/mm³
- Patients who gave informed consent for peripheral smear and/or bone marrow examination.

Exclusion criteria:

- Patients <12 years or >65 years
- Pregnant women with pancytopenia
- Patients with recent acute blood loss
- Decompensated chronic liver disease
- Known genetic causes of pancytopenia

Data Collection and Clinical Evaluation:

Detailed clinical history and physical examination findings were recorded in all cases, including presenting complaints (fever, weakness, bleeding tendencies, etc.) and physical signs (pallor, hepatosplenomegaly, and lymphadenopathy).

Laboratory Investigations: Venous blood samples were collected in EDTA vacutainers for complete blood counts, performed on an automated hematology analyzer. Peripheral smears were prepared and stained with Leishman/Giemsa stains and systematically examined for red cell morphology, leukocyte differentials, platelet estimation, and abnormal cells. Reticulocyte count, malarial parasite smear, and coagulation profiles were performed as required.

Bone Marrow Examination: Bone marrow aspiration (BMA) was performed using Salah's needle from the posterior superior iliac spine under aseptic precautions, after informed consent. Aspirate smears were air-dried and stained with Giemsa stain. Trephine biopsy was performed in selected cases using Jamshidi's needle; sections were fixed in 10% buffered formalin, decalcified in formal-EDTA, processed, paraffin-embedded, and stained with hematoxylin and eosin (H&E). Perl's Prussian blue iron stain was done routinely. Touch imprints of biopsy cores were also prepared whenever feasible. In cases of "dry tap," reporting was based on trephine biopsy findings.

Data Analysis: Data were compiled and analyzed according to age, sex, presenting complaints, hematological parameters, peripheral smear findings, bone marrow morphology, and etiological diagnosis. Frequencies and percentages were used for categorical variables, and results were tabulated for descriptive comparison with similar Indian and international studies.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee for Human Research (IECHR-PGR), Medical College Baroda [IECBHR/04-2020]. Written informed consent was obtained from all participants.

Results

Demographic Characteristics [Table 1]: A total of 190 patients with pancytopenia were evaluated. Of these, 99 (52.1%) were males and 91 (47.9%) were females, with a male-to-female ratio of 1.1:1. The age of patients ranged from 17 to 76 years, with the 27–36 years age group being most common (28.9%), followed by 17–26 years (26.3%). The least affected group was 67–76 years (1.0%).

Table 1: Age and sex distribution of pancytopenia patients (n=190)

Age group (years)	Male	Female	Total (%)
17–26	23	27	50 (26.3)
27–36	29	26	55 (28.9)
37–46	19	16	35 (18.4)
47–56	17	15	32 (16.8)
57–66	10	06	16 (8.4)
67–76	01	01	02 (1.0)
Total	99	91	190 (100)

Clinical Presentation [Table 2]: The most frequent presenting symptom was generalized weakness (28.9%), followed by fever (16.3%) and abdominal pain (7.4%). Pallor was the most common clinical sign, present in 108 (56.8%)

cases. Splenomegaly and hepatomegaly were observed in 11.6% and 9.5% cases, respectively.

Less frequent findings included jaundice (4.7%), bleeding manifestations (4.2%), and pedal edema (2.1%).

Table 2: Clinical features of patients with pancytopenia (n=190)

Clinical feature	No. of patients	%
Pallor	108	56.8
Generalized weakness	55	28.9
Fever	31	16.3
Splenomegaly	22	11.6
Hepatomegaly	18	9.5
Abdominal pain	14	7.4
Jaundice	9	4.7
Bleeding manifestations	8	4.2
Pedal edema	4	2.1

Hematological Parameters [Table 3]

- Hemoglobin (Hb): The majority of patients (51.0%) had Hb between 5.1–7.0 g/dL; 27.9% had Hb 3.1–5.0 g/dL.

- Total leukocyte count (TLC): More than half (51.0%) had TLC between 1,001–2,500/mm³.
- Platelets: Most cases (73.2%) had <50,000/mm³, confirming severe thrombocytopenia.

Table 3. Hematological parameters of pancytopenia patients (n=190)

Parameter	Range	No. of cases	%
Hb (g/dL)	1.5–3.0	40	21.1
	3.1–5.0	53	27.9
	5.1–7.0	97	51.0
TLC (/mm ³)	100–1000	39	20.5
	1001–2500	97	51.0
	2501–4000	54	28.4
Platelets (/mm ³)	<50,000	139	73.2
	51,000–100,000	41	21.6
	100,000–150,000	10	5.3

Peripheral Smear Findings [Table 4]: The predominant peripheral blood picture was microcytic hypochromic anemia (43.7%), followed

by macrocytic (21.0%), dimorphic (18.9%), and normocytic normochromic (14.7%). Only 1.6% showed a normocytic hypochromic picture.

Table 4: Peripheral smear patterns (n=190)

Smear pattern	No. of cases	%
Microcytic hypochromic	83	43.7
Macrocytic	40	21.0
Dimorphic	36	18.9
Normocytic normochromic	28	14.7
Normocytic hypochromic	3	1.6

Bone Marrow Examination [Table 5]: Bone marrow evaluation was done in 58 patients. Among them, 29 (50.0%) had hypercellular marrow, 16 (27.6%) hypocellular, and 13 (22.4%) normocellular.

Table 5: Bone marrow cellularity (n=58)

Cellularity	No. of cases	%
Hypercellular	29	50.0
Hypocellular	16	27.6
Normocellular	13	22.4

Etiological Spectrum [Table 6]: Bone marrow findings established the following etiologies:

- Normal trilineage maturation (NTM): 15 (25.9%)
- Megaloblastic anemia: 11 (18.9%)
- Aplastic anemia: 10 (17.2%)
- Dimorphic anemia: 7 (12.1%)
- Acute leukemia: 5 (8.6%)

- Iron deficiency anemia: 3 (5.2%)
- Rare causes (1 case each; 1.7%): metastatic malignancy, anemia due to pregnancy, hemophagocytic lymphohistiocytosis, Parvovirus B19 infection, hematolymphoid neoplasm, myelodysplastic syndrome, ineffective hematopoiesis.

Table 6: Etiological distribution in pancytopenia cases with bone marrow evaluation (n=58)

Etiology	No. of cases	%
Normal trilineage maturation	15	25.9
Megaloblastic anemia	11	18.9
Aplastic anemia	10	17.2
Dimorphic anemia	7	12.1
Acute leukemia	5	8.6
Iron deficiency anemia	3	5.2
Others (metastatic malignancy, anemia of pregnancy, HLH, Parvovirus B19, hematolymphoid neoplasm, MDS, and ineffective hematopoiesis)	7	12.1

Correlation of Peripheral Smear with Bone Marrow: Peripheral smear showed strong correlation in nutritional anemias (megaloblastic, dimorphic, and iron deficiency anemia), where smear morphology was highly predictive of marrow findings. In contrast, aplastic anemia, acute leukemia, MDS, and infiltrative disorders required bone marrow confirmation for definitive diagnosis.

Discussion

Pancytopenia is a frequent hematological problem with a wide etiological spectrum, ranging from reversible nutritional deficiencies to life-threatening bone marrow failure syndromes and malignancies. In the present study of 190 patients, the most common cause identified was megaloblastic anemia (18.9%), followed by aplastic anemia (17.2%), dimorphic anemia (12.1%), and acute leukemia (8.6%). This pattern is largely consistent with other Indian studies, though with some regional variations.

Age and Sex Distribution: In the present study, pancytopenia was most frequently observed in the 27–36 years age group (28.9%), with a slight male predominance (M: F = 1.1:1). Similar demographic trends have been reported by Gayathri and Rao (54.8% males, mean age 24 years) [2] and Sweta et al. (61% males, commonest age 21–34 years) [5]. In contrast, Agarwal et al. reported a female

predominance (54.3%) with maximum incidence in the second decade. [15] These findings reflect regional and dietary influences, particularly in relation to nutritional anemias.

Clinical Features: The most common presenting feature in our study was pallor (56.8%), followed by generalized weakness (28.9%) and fever (16.3%). This is comparable with findings of Sharma et al. (pallor 88.6%, fever 59.8%), [6] Jella et al. (pallor 73.2%, fever 46.4%), [14] and Mittal et al. (pallor 95.2%). [7] Bleeding manifestations and hepatosplenomegaly were less frequent, which aligns with earlier Indian cohorts but contrasts with Bangladeshi studies where splenomegaly due to infections was more prevalent. [8]

Hematological Findings: The peripheral smear in our series most often revealed microcytic hypochromic anemia (43.7%), whereas Gayathri and Rao [2] and Agarwal et al. [15] reported dimorphic anemia as the predominant pattern (37.5% and 35.7%, respectively). The variation may be attributed to regional nutritional deficiencies, particularly iron and folate, which commonly coexist in Indian patients.

Bone Marrow Cellularity: Bone marrow examination in 58 cases revealed hypercellular marrow in 50%, hypocellular marrow in 27.6%, and normocellular in 22.4%. Similar findings were

reported by Mittal et al., who observed hypercellularity in 57% of cases. [7] Agarwal et al., however, reported hypocellularity in 44% cases. [15] These differences highlight the variability of etiologies across study populations, with aplastic anemia contributing to higher hypocellular rates in some regions.

Etiological Spectrum: Our study established megaloblastic anemia as the leading cause of pancytopenia, consistent with Sweta et al. (66%), [5] Sharma et al. (50.7%), [4] Mittal et al. (33.3%), [7] and Varma et al. (39%). [16] This supports the continuing burden of nutritional deficiencies in India, despite improvements in healthcare. In contrast, studies from Nepal [14] and Bangladesh [8] reported aplastic anemia and infections (malaria, leishmaniasis) as predominant causes. A study from Europe emphasized marrow infiltration and therapy-related suppression as major contributors. [9]

The second most common cause in the present study was aplastic anemia (17.2%), in line with reports by Mansuri et al. (8%) [17] and Sharma et al. (7.5%), [6] but lower than Santra et al., who reported it in 25% of cases. [11] Acute leukemia was seen in 8.6% of our cases, comparable to Sharma et al. (9%) [4] but higher than Santra et al. (1.8%). [11]

Rare causes such as hemophagocytic lymphohistiocytosis, myelodysplastic syndrome, metastatic malignancy, and parvovirus B19 infection were also identified in our study. These rare etiologies have also been sporadically reported in Indian cohorts, [2,10,11] underlining the need for bone marrow examination in unexplained cases.

Diagnostic Accuracy: Peripheral smear correlated strongly with marrow findings in megaloblastic and dimorphic anemia, where morphological changes (macrocytosis, hypersegmented neutrophils, tear-drop cells) were diagnostic. However, in aplastic anemia, acute leukemia, MDS, and infiltrative malignancies, bone marrow was indispensable for definitive diagnosis. This observation is consistent with prior studies, [1,10,11] confirming that while peripheral smear is an excellent first-line tool, marrow examination remains the diagnostic gold standard.

Strengths and Limitations: The strength of this study lies in its large cohort size (190 patients) and comprehensive evaluation with both peripheral smear and marrow correlation. Limitations include its single-center design, and lack of biochemical assays for vitamin B12 and folate, which could have further substantiated cases of megaloblastic anemia.

Conclusion

Pancytopenia represents a common yet diagnostically challenging hematological condition with a wide etiological spectrum. In this study, megaloblastic anemia emerged as the most frequent cause, followed by aplastic anemia, dimorphic anemia, and acute leukemia. While peripheral smear provided valuable preliminary insights, especially in nutritional anemias, bone marrow examination was indispensable for establishing definitive diagnoses in marrow failure syndromes, leukemias, and rare infiltrative conditions.

The study emphasizes the continued burden of nutritional deficiencies such as vitamin B12 and folate deficiency in the Indian population, highlighting the need for routine dietary supplementation and early screening. At the same time, the identification of less common but clinically significant etiologies such as hemophagocytic lymphohistiocytosis, myelodysplastic syndrome, metastatic malignancy, and parvovirus B19 infection underscores the importance of a comprehensive diagnostic approach.

In conclusion, a combination of clinical evaluation, hematological parameters, peripheral smear, and bone marrow examination remains the cornerstone of accurate diagnosis in pancytopenia. Early identification of the underlying cause not only facilitates timely treatment but also significantly impacts patient prognosis.

Use of Generative AI: Generative artificial intelligence (ChatGPT) was utilized to support drafting and language refinement of this manuscript. All content was thoroughly reviewed, validated, and revised by the authors to ensure accuracy, originality, and consistency with the study data. The AI tool had no role in study design, data collection, analysis, interpretation, or final decision-making.

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