Section: Pathology

Original Research Article

UTILITY OF PERIPHERAL BLOOD MORPHOLOGY IN THE EARLY RECOGNITION OF ACUTE PROMYELOCYTIC LEUKEMIA: A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia characterized by abnormal promyelocytes in peripheral blood and/or bone marrow. Early recognition is crucial because of life-threatening hemorrhagic complications, particularly disseminated intravascular coagulation. This study evaluated the utility of peripheral blood smear morphology as an early indicator of APL in patients presenting with bicytopenia or pancytopenia. **Materials and Methods:** This retrospective observational study was conducted at the Department of Pathology, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur, from 2023 to 2025. A total of 150 cases of bicytopenia and pancytopenia were evaluated. Peripheral blood smear and bone marrow findings were reviewed for morphological features suggestive of APL and correlated with PML: RARA molecular confirmation. Data were analyzed descriptively because of the small APL sample. **Results:** Of 150 cases, 81 (54.0%) had bicytopenia and 69 (46.0%) had pancytopenia. Acute leukemia accounted for 58 cases (38.7%). Ten cases (6.7% of the total cohort; 17.2% of acute leukemia cases) were confirmed as APL. Median age was 37.5 years (range, 3–59 years), with female predominance (male-to-female ratio, 1:4). Eight patients (80.0%) had pancytopenia, while two (20.0%) had bicytopenia with leukocytosis. Characteristic abnormal promyelocytes were identified in seven cases (70.0%), including hypergranular promyelocytes, microgranular promyelocytes, bilobed or folded nuclei, deeply indented or angel-wing nuclei, Auer rods, and faggot cells. All cases were confirmed by PML: RARA molecular testing. **Conclusion:** Peripheral blood smear examination can provide an important early morphological clue to APL and facilitate urgent confirmatory testing, particularly in settings where molecular diagnostics are unavailable or not immediately accessible. However, the absence of characteristic abnormal promyelocytes in peripheral blood does not exclude APL, and definitive diagnosis requires appropriate confirmatory testing for PML: RARA.

INTRODUCTION

Acute promyelocytic leukemia (APL) represents a distinct clinicopathologic entity within Acute myeloid leukemia (AML) with t(15;17) (q24;q21) translocation, which results in the formation of the PML::RARA fusion gene. The fusion gene encodes a chimeric protein that disrupts normal myeloid differentiation, leading to promyelocyte accumulation in the peripheral blood and bone marrow[1,2] APL constitutes only 5%-15% of AML cases. However, it is a critical focus in hematology because targeted therapies like all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) provide remarkable curability with long-term remission rates exceeding 90%.[3]

Although APL has one of the most favorable prognoses among AML subtypes when treated promptly, it constitutes a medical emergency because of its severe bleeding diathesis and risk of early mortality. Up to one-third of patients succumb before therapy initiation. Consequently, diagnosis must be established promptly, preferably within a day of clinical suspicion. Morphological assessment of

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peripheral blood and bone marrow smears serves as the initial diagnostic approach to recognize APL.[4]

Early stage APL often presents with leukopenia, requiring extensive manual screening of peripheral smear to locate rare abnormal promyelocytes.[5] Clinically, APL frequently presents with cytopenia, often accompanied by bleeding manifestations. In resource-limited settings, definite diagnosis by cytogenetics or molecular studies is not always immediately available. Therefore, morphological evaluation of peripheral blood and bone marrow remains the cornerstone for a rapid provisional diagnosis. The characteristic hypergranular variant shows abnormal promyelocytes with bilobed nuclei, dense azurophilic granules and multiple Auer rods including faggot cells, while the microgranular variant can pose diagnostic challenges.[6] The confirmation and subtyping of APL depends on hematopathologists, who integrate morphological review, flow cytometric immunophenotyping and molecular genetic testing.[7,8]

This study aimed to evaluate the utility of peripheral blood smear morphology as an early indicator of APL among patients presenting with bicytopenia or pancytopenia when molecular and cytogenetic results are not readily available.

MATERIALS AND METHODS

A hospital-based retrospective observational study was conducted in the Department of Pathology, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Porompat, Manipur, a tertiary care referral center. The study period extended from 2023 to 2025. A total of 150 cases of bicytopenia and pancytopenia were retrospectively reviewed from departmental records and laboratory archives. Of these, 81 cases had bicytopenia and 69 had pancytopenia. Patients of all age groups and both sexes were included. Leishman-stained peripheral blood smears were examined for morphological features suggestive of APL, including abnormal promyelocytes with abundant azurophilic granules, bilobed or folded nuclei, deeply indented or "angel-wing" nuclei, reniform nuclei, Auer rods, and faggot cells. Detailed morphological assessment was performed using a high-power microscope with the 100× oil-immersion objective.

Cases showing morphological features suggestive of APL were subsequently evaluated by bone marrow examination and PML: RARA molecular testing for confirmation. In cases in which characteristic abnormal promyelocytes were not evident in the peripheral blood smear, APL was considered when there was strong clinical and hematological suspicion, particularly in patients presenting with bleeding manifestations such as epistaxis, petechiae, or purpura, together with cytopenia on complete blood count. These cases were further evaluated by bone marrow examination and PML: RARA molecular testing for confirmation.

Demographic, clinical, and hematological data were retrieved from patient records and departmental archives. Data were analyzed descriptively using frequencies and percentages for categorical variables and median and range for age. Because only 10 cases of APL were identified, no inferential statistical analysis was performed.

Inclusion Criteria

Patients of all age groups and both sexes presenting with bicytopenia or pancytopenia were included. Cases were included when adequate peripheral blood smear findings and corresponding bone marrow examination findings were available for evaluation.

Exclusion Criteria

Cases with technically inadequate peripheral blood smears, incomplete laboratory data, or inadequate bone marrow aspirate and/or biopsy samples were excluded.

RESULTS

Among the 150 retrospectively evaluated cases, 81 (54.0%) had bicytopenia and 69 (46.0%) had pancytopenia (Figure 1). Acute leukemia was the most frequent diagnostic category, accounting for 58 cases (38.7%). Other diagnoses included myelofibrosis in 17 cases (11.3%), erythroid hyperplasia in 13 cases (8.7%), myelodysplastic syndrome in 11 cases (7.3%), plasma cell myeloma in 4 cases (2.7%), aplastic anemia in 2 cases (1.3%), non-Hodgkin lymphoma in 2 cases (1.3%), and metastatic adenocarcinoma in 2 cases (1.3%). The remaining 41 cases (27.3%) were classified as cytopenia, not otherwise specified. The diagnostic distribution is presented in. [Table 1]

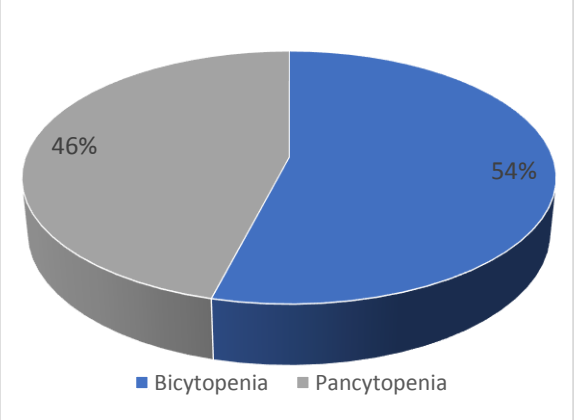

Figure 1: Pie chart showing distribution of bicytopenia and pancytopenia among 150 cases.

Among the 58 cases of acute leukemia, 10 (17.2%) were diagnosed as APL, representing 6.7% of the total study cohort. The median age of patients with APL was 37.5 years (range, 3–59 years). Nine patients were adults and one was a child aged 3 years. A female predominance was observed, with a male-to-female ratio of 1:4. All 10 patients had anemia, absolute neutropenia, and thrombocytopenia. Eight patients (80.0%) presented with pancytopenia, whereas two (20.0%) had bicytopenia accompanied

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by leukocytosis. The demographic and hematological characteristics of the APL cases are summarized in [Table 2].

Table 1: Etiological Spectrum of Bicytopenia and Pancytopenia

Diagnosis	Number (n)	Percentage (%)
Acute Leukemia	58	38.7
Myelofibrosis	17	11.3
Erythroid hyperplasia	13	8.7
Myelodysplastic syndrome	11	7.3
Plasma cell myeloma	4	2.7
Aplastic anemia	2	1.3
Non-Hodgkin lymphoma	2	1.3
Metastatic adenocarcinoma	2	1.3
Cytopenia, NOS	41	27.3
Total	150	100

Characteristic abnormal promyelocytes were identified in the peripheral blood of seven of the 10 patients with confirmed APL (70.0%). The observed morphological features included abundant azurophilic granules, mononuclear and binucleated forms, bilobed or folded nuclei, deeply indented or "angel-wing" nuclei, Auer rods, and faggot cells. [Figure 2A–U]

In the remaining three patients (30.0%), characteristic abnormal promyelocytes were not identified in the peripheral blood smear. In these cases, APL was suspected on the basis of the overall clinical and hematological findings, including bleeding manifestations such as epistaxis, gingival bleeding, and purpura, together with pancytopenia. Bone marrow examination subsequently supported the diagnosis, which was confirmed by PML::RARA molecular testing.

Table 2: Demographic and Hematological Profile of the Study Cases

Case	Age (years)	Sex	HGB (g/dL)	TLC (×109/L)	ANC (×109/L)	PLT (×109/L)	Cytopenia pattern
1.	39	F	6.4	0.46	0.04	15	Pancytopenia
2.	35	F	7.8	1.86	0.22	72	Pancytopenia
3.	37	F	7.5	3.72	0.74	15	Pancytopenia
4.	3	F	7.1	24.80	0.50	18	Bicytopenia+ leukocytosis
5.	59	M	7.0	2.30	0.51	20	Pancytopenia
6.	48	F	6.1	10.35	1.14	20	Bicytopenia+ leukocytosis
7.	40	F	7.5	3.00	0.60	22	Pancytopenia
8.	57	F	7.5	1.08	0.13	33	Pancytopenia
9.	27	F	8.6	0.98	0.08	28	Pancytopenia
10.	21	M	5.0	1.80	0.27	14	Pancytopenia

Abbreviation: TLC, total leukocyte count; HGB, hemoglobin; PLT, platelet count; ANC, absolute neutrophil count.

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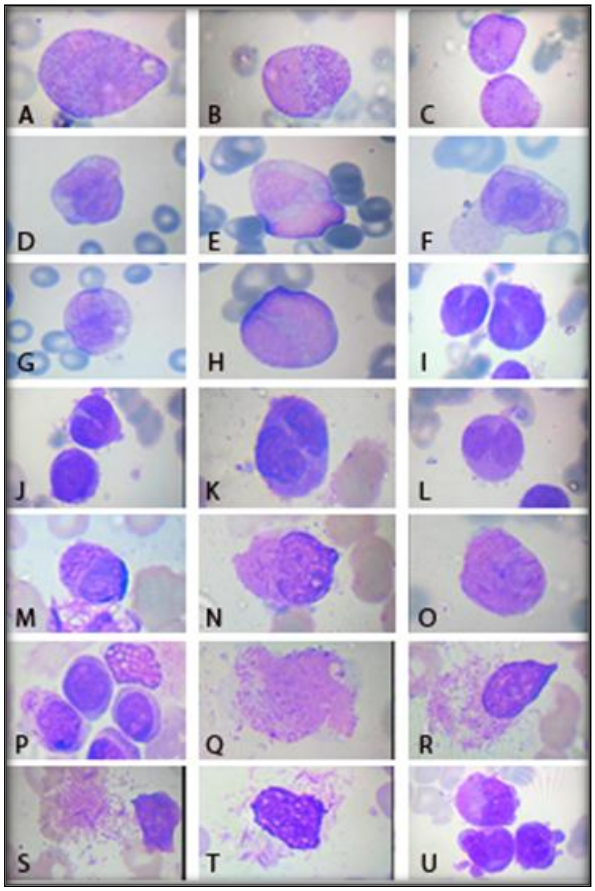

Figures 2: Morphological spectrum of abnormal promyelocytes. (A-C)Hypergranular promyelocytes with abundant azurophilic granules and eccentric nuclei. (D-H) Microgranular promyelocytes with folded nuclei. (I-L) Abnormal promyelocytes with deeply indented nuclei mimicking "angel-wing" appearance. (M-P) Faggot cells showing multiple Auer rods. (Q-T) Burst cells with abundant azurophilic granules, irregular nuclei, and Auer rods. (U) Abnormal promyelocytes with reniform nuclei and dusky-hued cytoplasm.

DISCUSSION

Acute promyelocytic leukemia (APL) is a hematological emergency due to its rapid progression and serious consequences like disseminated intravascular coagulation. Confirmatory diagnosis of APL depends on morphological analysis, immunophenotyping by flow cytometry, and detection of the t(15;17) translocation or PML::RARA fusion through molecular testing. These methods are time consuming and are often unavailable in centers with limited resources.[9-11] Patients outcomes in APL are adversely affected by delayed diagnosis and treatment initiation, often resulting from limited access to specialized healthcare.[12,13] Risk stratification using the presenting white blood cell count guides therapy, with count ≥10,000/μL defining high risk disease.[14] In this series, peripheral smear morphology provided an important early diagnostic clue that could facilitate urgent clinical evaluation and confirmatory testing.

APL is categorized into two morphological variants: the classic hypergranular form and the microgranular subtype. The hypergranular type typically manifests with leukopenia and is characterized by atypical promyelocytes exhibiting bilobed or folded nuclei, abundant azurophilic granules, and frequent Auer rods. In contrast, the microgranular variant tends to present with leukocytosis and comprises promyelocytes with reniform or bilobed nuclei, scant submicroscopic granules that are positive for myeloperoxidase (MPO) staining.[15] This cohort demonstrated a female predominance, while other literature describes a slight male predominance, the small sample size limits demographic interpretation. The median age of patient with APL is 37.5 years, which is comparable to the findings of Tripathi and Kular, who reported a median age of 37 years.[12]

Study limitations include the retrospective design, single-center setting, and small number of confirmed APL cases, which limit the generalizability of the findings, particularly demographic observations. Characteristic APL morphology was not evident in the peripheral blood of all confirmed cases, highlighting the limitations of peripheral blood morphology as a as the sole diagnostic approach. Because PML: RARA molecular testing was performed for confirmation of suspected APL rather than systematically in all 150 patients, the study could not determine the sensitivity, specificity, or predictive values of peripheral blood morphology.

CONCLUSION

Peripheral blood smear examination can provide an important early morphological clue to acute promyelocytic leukemia and facilitate urgent confirmatory testing, particularly in settings where molecular diagnostics are unavailable or not immediately accessible. However, the absence of characteristic abnormal promyelocytes in peripheral blood does not exclude APL, and definitive diagnosis requires appropriate confirmatory testing for PML: RARA.

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