Section: Pathology

Case Series

FROM INFANCY TO OLD AGE: PURE ERYTHROID LEUKEMIA AT THE EXTREMES OF LIFE — A FIVE-CASE SERIES

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ABSTRACT

Pure erythroid leukemia (PEL) is a rare and aggressive subtype of acute myeloid leukemia arising from erythroid lineage transformation, and its rarity together with its morphological overlap with other erythroid-rich myeloid neoplasms makes integration of morphology, immunophenotype, and cytochemistry essential for accurate diagnosis. We reviewed five patients diagnosed with PEL according to the 2022 World Health Organization (fifth edition) criteria, which require bone marrow erythroid precursors comprising at least 80% of marrow cellularity with proerythroblasts accounting for at least 30% of cells. Clinical presentation, peripheral blood and bone marrow parameters, morphology, flow cytometric immunophenotype, periodic acid-Schiff (PAS) cytochemistry, treatment, and outcome were correlated for each case. Patients ranged from two to seventy-one years of age (median 32 years; four males, one female). All presented with cytopenia-related symptoms or with abdominal symptoms related to organomegaly, and one elderly patient presented with facial palsy suggesting extramedullary or cranial nerve involvement. All five cases met the WHO diagnostic thresholds, with erythroid precursors of 80-89% and proerythroblasts of 33-41%. Marrow morphology showed multinucleation, binucleation, cytoplasmic blebbing or bridging, and megaloblastoid change in varying combinations. Flow cytometry was uniformly positive for CD235a, CD36, CD33, and CD117, and negative for myeloperoxidase, CD34, HLA-DR, and lymphoid markers in all cases, with aberrant CD13 co-expression noted in two of five cases. PAS cytochemistry was positive in all five cases. One patient received intensive anthracycline-cytarabine induction and four received azacitidine; at last follow-up, two patients had succumbed (the youngest and the oldest in the cohort), two had achieved remission, and one remained on treatment. This series supports the characteristic CD235a-positive/ CD36-positive/ CD117-positive/ myeloperoxidase-negative immunophenotype of PEL with PAS positivity, and shows that outcome remained poor at the extremes of age despite therapy. Cytogenetic and molecular correlation, not available for this cohort, is recommended in future work to refine prognostic stratification.

Keywords: Pure erythroid leukemia, acute myeloid leukemia, erythroid precursors, flow cytometry, periodic acid-schiff stain, hematopathology.

INTRODUCTION

Pure erythroid leukemia (PEL) is a rare and biologically aggressive subtype of acute myeloid leukemia (AML) characterized by a proliferation of immature cells committed exclusively to the erythroid lineage. Erythroid leukemias have undergone repeated reclassification: the 2008 World Health Organization (WHO) scheme recognized two subtypes, erythroleukemia (erythroid/myeloid type) and pure erythroid leukemia, whereas the 2016 revision eliminated the erythroid/myeloid subtype,

reclassifying most such cases as myelodysplastic syndrome or AML based on blast percentage, and retaining PEL as the sole erythroid-lineage entity.[1-3] The 2022 WHO fifth edition (WHO-HAEM5) further refined the diagnostic threshold for PEL, requiring bone marrow erythroid precursors comprising at least 80% of marrow cellularity with proerythroblasts accounting for at least 30% of cells, in the absence of an increased myeloblast population.[1,4]

PEL accounts for well under 5% of all AML cases and is often, though not always, secondary to prior cytotoxic therapy or an antecedent myeloid neoplasm.[5,6] It carries a characteristic immunophenotype (CD235a/glycophorin A, CD36, CD117, and E-cadherin positivity with myeloperoxidase and CD34 negativity), a distinctive block-pattern periodic acid-Schiff (PAS) positivity, and a strong association with complex karyotype and TP53 mutation, translating into a dismal prognosis with reported median survival of only a few months.[5-7] Because its morphology can overlap with other erythroid-predominant myeloid neoplasms and even with erythroid maturation arrest of non-neoplastic causes, an integrated diagnostic approach combining morphology, immunophenotyping, cytochemistry, and cytogenetics is essential.[6,8]

Given the rarity of this entity, published experience largely comprises single case reports or small retrospective series. We present a case series of five patients diagnosed with PEL, correlating morphological, flow cytometric, and PAS cytochemical findings with clinical presentation, treatment, and outcome, with the aim of reinforcing recognition of this uncommon but aggressive leukemia.

CASE PRESENTATION

This is a retrospective review of five patients diagnosed with pure erythroid leukemia at Kidwai Memorial Institute of Oncology over the period of two years. Informed consent was [obtained from patients or legal guardians / waived owing to the retrospective, de-identified nature of the study – specify]. Diagnosis was established on bone marrow aspirate and trephine biopsy according to the WHO fifth edition (2022) criteria described above.[1,4] For each patient, we recorded age, sex, presenting symptoms, examination findings (including lymphadenopathy and organomegaly), complete blood counts, peripheral smear blast percentage, bone marrow erythroid precursor and proerythroblast percentages, bone marrow morphology, PAS cytochemical staining pattern, immunophenotype by multiparameter flow cytometry, immunohistochemistry for CD117 and p53 on trephine sections, treatment administered, and clinical outcome at last follow-up [Figure 1]. Formal cytogenetic analysis (karyotype/FISH) and molecular sequencing were not available for this cohort at the time of this report; this is addressed as a limitation in the discussion below.

Five patients (four male, one female) with a diagnosis of PEL were included, ranging in age from two to seventy-one years (median 32 years). Presenting complaints were predominantly related to cytopenias (fever, fatigue, gum bleeding) or organomegaly (abdominal pain, blood in stools); one elderly patient presented with facial palsy in association with fever and headache, raising the possibility of cranial nerve or extramedullary involvement. Lymphadenopathy was present in only the youngest (pediatric) patient. Hepatosplenomegaly was present in the same pediatric patient, isolated splenomegaly was noted in two adult patients, and no organomegaly was detected in the remaining two. Demographic and clinical findings are summarized in [Table 1].

All patients were anemic (hemoglobin 7.0-10.2 g/dL) and thrombocytopenic (platelets 8,000-63,000/µL), and all had a total leukocyte count below the lower limit of normal (1,200-3,800/µL), reflecting the ineffective, erythroid-restricted hematopoiesis characteristic of this entity. Peripheral smear blast percentage was low in all cases (3-10%), consistent with the predominantly marrow-based nature of the disease. Bone marrow erythroid precursors ranged from 80-89% of marrow cellularity and proerythroblasts from 33-41%, and all five cases therefore met the WHO 2022 morphological threshold for PEL [Table 2].

Table 1: Demographic and clinical features

Case	Age / Sex	Presenting symptoms	Examination finding	Lymphadenopathy	Organomegaly
1	2 years, Male	Fever with gum bleeding	Pallor	Present	Hepatomegaly & splenomegaly
2	26 years, Female	Fever with fatigue	Pallor	Absent	None
3	33 years, Male	Abdominal pain	Organomegaly	Absent	Splenomegaly
4	32 years, Male	Blood in stools with abdominal pain	Organomegaly	Absent	Splenomegaly
5	71 years, Male	Headache with fever	Facial palsy	Absent	None

Table 2: Hematological and bone marrow parameters

Case	Hb (g/dL)	TLC (/µL)	Platelets (/µL)	PS blasts (%)	BM erythroid precursors (%)	BM proerythroblasts (%)
1	7.9	1,200	52,000	5	87	35
2	10.2	2,100	63,000	3	86	39
3	8.9	3,100	23,000	8	82	33

4	8.2	3,800	51,000	10	80	36
5	7	2,900	8,000	6	89	41

Hb, hemoglobin; TLC, total leukocyte count; PS, peripheral smear; BM, bone marrow.

Bone marrow morphology in the erythroid series showed multinucleation in three of five cases, binucleation in three of five, cytoplasmic blebbing in two of five, cytoplasmic bridging in three of five, and megaloblastoid change in two of five, with most cases showing more than one of these features in combination. Flow cytometric immunophenotyping was remarkably consistent: all five cases were positive for CD235a, CD36, CD33, and CD117, and negative for myeloperoxidase, CD34, HLA-DR, and lymphoid lineage markers. Aberrant co-expression of CD13, a myeloid-associated antigen, was noted in two cases (Cases 4 and 5). PAS cytochemistry was positive in all five cases. Findings are summarized in [Table 3].

Table 3: Morphology, immunophenotype, PAS, treatment, and outcome

Case	Bone marrow morphology	FCM positive	FCM negative	PAS	Treatment	Outcome
1	Multinucleation, binucleation, cytoplasmic blebbing	CD235a, CD36, CD33, CD117	MPO, CD34, HLA-DR & lymphoid markers	Positive	Daunorubicin + Cytarabine (intensive induction)	Succumbed
2	Cytoplasmic bridging, megaloblastic change	CD235a, CD36, CD33, CD117	MPO, CD34, HLA-DR & lymphoid markers	Positive	Azacitidine	On treatment
3	Multinucleation, cytoplasmic blebbing	CD235a, CD36, CD33, CD117	MPO, CD34, HLA-DR & lymphoid markers	Positive	Azacitidine	In remission
4	Cytoplasmic bridging, binucleation	CD235a, CD36, CD33, CD117 with aberrant CD13	MPO, CD34, HLA-DR & lymphoid markers	Positive	Azacitidine	In remission
5	Multinucleation, cytoplasmic bridging, binucleation, megaloblastic change	CD235a, CD36, CD33, CD117 with aberrant CD13	MPO, CD34, HLA-DR & lymphoid markers	Positive	Azacitidine	Succumbed

FCM, flow cytometry; PAS, periodic acid-Schiff stain.

Treatment was individualized: the youngest patient (Case 1) received intensive induction chemotherapy with daunorubicin and cytarabine, while the remaining four patients received the hypomethylating agent azacitidine. At last follow-up, two patients (Cases 1 and 5, the youngest and the oldest in the cohort) had succumbed to their disease, two (Cases 3 and 4) had achieved remission on azacitidine, and one (Case 2) remained on treatment.

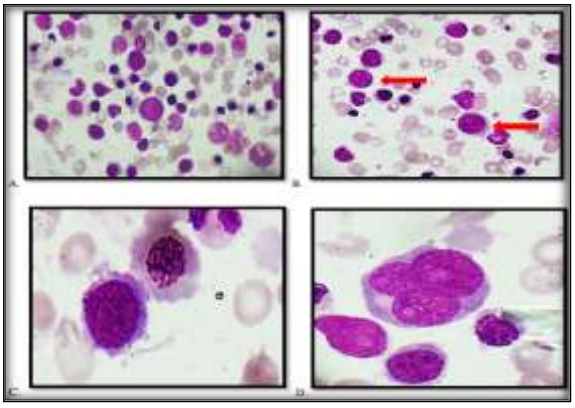
Case 1: A two-year-old boy presented with fever and gum bleeding, with pallor, generalized lymphadenopathy, and hepatosplenomegaly on examination. Investigations revealed severe pancytopenia (hemoglobin 7.9 g/dL, total leukocyte count 1,200/µL, platelets 52,000/µL). Bone marrow showed 87% erythroid precursors with 35% proerythroblasts exhibiting multinucleation, binucleation, and cytoplasmic blebbing; flow cytometry and PAS positivity supported the diagnosis of PEL. He was treated with daunorubicin and cytarabine induction but succumbed to the disease.

Case 2: A 26-year-old woman presented with fever, fatigue and pallor without lymphadenopathy or organomegaly. Bone marrow showed 86% erythroid precursors with 39% proerythroblasts showing cytoplasmic bridging and megaloblastic change. She was started on azacitidine and remains on treatment.

Case 3: A 33-year-old man presented with abdominal pain and splenomegaly. Bone marrow showed 82% erythroid precursors with 33% proerythroblasts displaying multinucleation and cytoplasmic blebbing. He achieved remission on azacitidine.

Case 4: A 32-year-old man presented with blood in stools, abdominal pain and splenomegaly. Bone marrow showed 80% erythroid precursors with 36% proerythroblasts showing cytoplasmic bridging and binucleation; flow cytometry additionally showed aberrant CD13 co-expression. He achieved remission on azacitidine.

Case 5: A 71-year-old man presented with headache and fever. On examination patient had facial palsy, without lymphadenopathy or organomegaly. Bone marrow showed 89% erythroid precursors with 41% proerythroblasts showing multinucleation, cytoplasmic bridging, binucleation, and megaloblastic change; flow cytometry showed aberrant CD13 co-expression. Despite azacitidine therapy, he succumbed to disease.



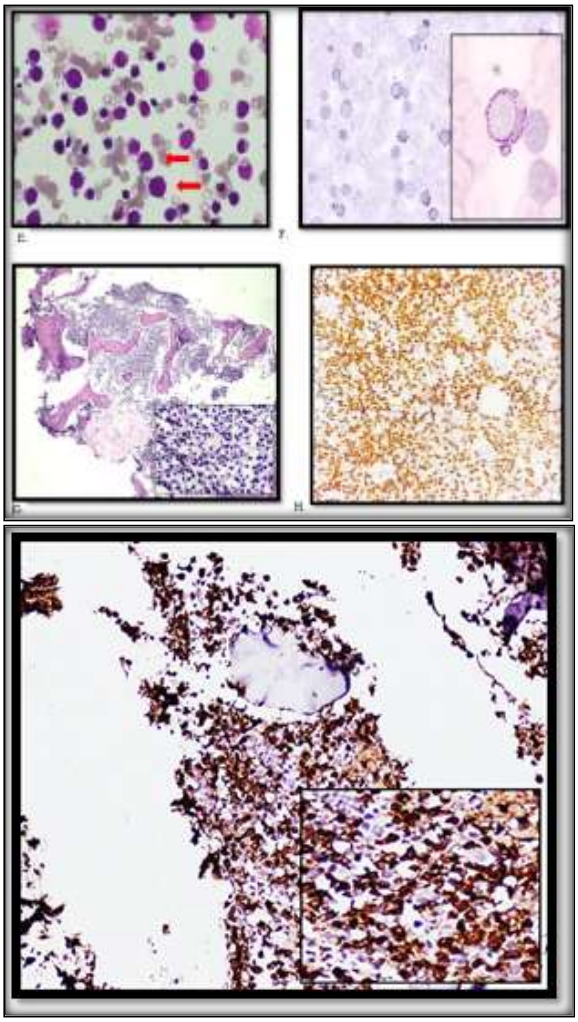


Figure 1: Representative bone marrow morphology, periodic acid–Schiff (PAS) cytochemistry, and immunohistochemistry, showing findings common across the case series (not attributed to a single case). A. Low-power view of a bone marrow aspirate smear showing erythroid predominance with numerous proerythroblasts. B. High-power view of the erythroid series; red arrows indicate proerythroblasts. C. Oil-immersion view showing megaloblastoid change. D. Oil-immersion view showing multinucleation. E. Low-power view; red arrow indicates a cell with binucleation and cytoplasmic blebbing. F. PAS stain showing block-pattern cytoplasmic positivity (Inset). G. Bone marrow trephine biopsy showing a single core of tissue with approximately five intertrabecular spaces; paratrabecular areas show atypical cells arranged in diffuse sheets. H. Immunohistochemistry showing a mutant-type p53 expression pattern (diffuse, strong nuclear positivity). I. Immunohistochemistry showing CD117 positivity.

DISCUSSION

All five patients in this series met the WHO 2022 (fifth edition) morphological criteria for PEL, with bone marrow erythroid precursors of 80-89% and proerythroblasts of 33-41%, both comfortably above the respective 80% and 30% thresholds.[1,4] This internal consistency across a small but complete cohort illustrates that, when applied rigorously, the current quantitative criteria identify a morphologically homogeneous group of markedly immature, erythroid-restricted proliferations, distinguishing PEL from erythroid-rich myelodysplastic syndrome and other AML subtypes with secondary erythroid hyperplasia.[2,3]

The morphological features observed, namely multinucleation, binucleation, cytoplasmic blebbing, cytoplasmic bridging, and megaloblastoid change, are the classic diagnostic hallmarks of PEL described in prior series and reviews.[5,6] The immunophenotypic profile in this cohort (CD235a-positive, CD36-positive, CD117-positive, myeloperoxidase-negative, CD34-negative, HLA-DR-negative) closely mirrors that reported by Wong et al., who found glycophorin (CD235a-related) positivity in 100% and CD117 positivity in 83% of PEL cases, with myeloperoxidase negativity in the majority.[6] Aberrant co-expression of the myeloid marker CD13, observed in two of our five cases, has similarly been described as an occasional finding in PEL and is a recognized diagnostic pitfall that can lead to misclassification as AML with myeloid differentiation if immunophenotyping is not interpreted alongside morphology and erythroid-specific markers.[5,6] Uniform PAS positivity across all five cases in a block-like pattern is consistent with the cytochemical signature of erythroid leukemic cells and remains a useful, low-cost adjunct in settings where flow cytometry is not immediately available, particularly given the myeloperoxidase-negative, blast-poor peripheral smear that can otherwise mimic acute lymphoblastic leukemia or an aplastic process.[5,7]

Immunohistochemistry performed on trephine sections showed CD117 positivity in the erythroid precursor population and a mutant-type p53 expression pattern (diffuse, strong nuclear positivity; [Figure 1H-I]), a recognized immunohistochemical surrogate for TP53 mutation. Formal cytogenetic analysis (karyotype/FISH) and molecular sequencing were not performed in this cohort, which is a notable limitation, since PEL is strongly associated with complex karyotype (reported in up to 83% of cases), monosomy 5/deletion 5q, monosomy 7/deletion 7q, and biallelic TP53 mutation, all of which portend a particularly poor prognosis and are increasingly incorporated into risk stratification.[5-9] The mutant-pattern p53 immunostaining observed here is consistent with, though not a substitute for, the TP53 alterations reported in this literature. We were unable to correlate formal cytogenetic risk with outcome in the present cohort; incorporation of karyotype, FISH, and TP53 mutation testing is recommended for future prospective evaluation of this cohort and is planned as an extension of this work.

The clinical course in this series reflects the aggressive natural history of PEL reported in the literature, with two of five patients (40%) succumbing to disease. Notably, the two fatalities occurred at the extremes of age in this cohort, the youngest (two years) and the oldest (71 years), while

the three patients of intermediate age (26-33 years) achieved remission or remained stable on treatment. Pediatric PEL/erythroleukemia is exceedingly rare, and although historical pediatric series report a similarly guarded prognosis, our single pediatric case adds to the limited literature on this age group.[10] The elderly patient's presentation with facial palsy is noteworthy and may reflect cranial nerve or extramedullary leukemic infiltration, a rare but recognized manifestation of aggressive myeloid leukemias; this patient also had the lowest platelet count in the cohort (8,000/μL) and succumbed despite hypomethylating therapy. Four of five patients received azacitidine, reflecting the shift toward hypomethylating agents in this typically therapy-intolerant, often elderly or comorbid population, consistent with reports that intensive chemotherapy is poorly tolerated and that allogeneic transplantation, when feasible, remains the only potentially curative option.[4,9]

This series is limited by its small sample size (five patients), single-centre retrospective design, absence of formal cytogenetic (karyotype/FISH) and molecular sequencing correlation, variable duration of follow-up, and incomplete documentation of antecedent hematologic disease or prior cytotoxic exposure, which is relevant given the recognized association between PEL and secondary/therapy-related leukemogenesis. These limitations preclude definitive statistical conclusions, and the observations here should be regarded as descriptive and hypothesis-generating.

CONCLUSION

Pure erythroid leukemia is a rare, morphologically and immunophenotypically distinctive AML subtype characterized by multinucleation, cytoplasmic blebbing/bridging, and megaloblastoid change on morphology; a consistent CD235a-positive/CD36-positive/CD117-positive/myeloperoxidase-negative/CD34-negative immunophenotype, occasionally with aberrant myeloid antigen co-expression; and block-pattern PAS positivity. In this series of five patients, integration of these parameters reliably established the diagnosis in cases meeting the WHO 2022 quantitative erythroid/proerythroblast thresholds, while clinical outcome remained poor, particularly at the extremes of age.

Cytogenetic and molecular characterization, not available in this cohort, should be incorporated in future work to refine prognostication, and larger multi-institutional series are needed to better define optimal treatment strategies for this aggressive leukemia.

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