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Case Series

Acute Erythroid Leukemia as a Diagnostic Challenge for Myelodysplastic Syndrome and Other Acute Myeloid Leukemia: Three Cases with Review of Literature

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Abstract

Acute Erythroid Leukemia (AEL) is a rare and aggressive subtype of acute myeloid leukemia (AML), characterized by prominent erythroid precursors and often associated with biallelic TP53 mutation. It has evolved through various terminologies and classification over the years. AEL shows overlap with other hematologic disorders such as AML and myelodysplastic syndromes (MDS) therefore diagnosis of these entities remains challenging. We describe three patients who presented with cytopenias and history of prior cytotoxic therapy showing dominance of erythroid precursors while manifesting three distinct hematological diagnoses. The diagnosis requires an integrated approach involving morphology, immunohistochemistry, flow cytometry, and molecular techniques. The role of immunohistochemistry, including p53, was critical in distinguishing these conditions. TP53, a key tumor suppressor gene, maintains genomic integrity and regulates cellular responses to stress. Mutations in TP53 are frequently associated with therapy-related myeloid neoplasms, aggressive morphology and poor prognosis. TP53 mutation is commonly found in AEL and is associated with poor prognosis whilst providing crucial diagnostic and prognostic information. The frequent association of AEL with TP53 mutation underscores its dismal prognosis. This case series highlights the diagnostic complexities, the need for comprehensive diagnostic tools and emphasizes the subtleties in differentiating AEL from other two entities.

Keywords: Acute erythroid leukemia; Acute myeloid leukemia; Myelodysplastic Syndrome; TP53 mutation

Abbreviations

AELP: Acute Erythroid Leukemia; AML: Acute Myeloid Leukemia; FAB: French-American-British; IHC: Immunohistochemistry; ITP: Immune Thrombocytopenic Purpura; MDS: Myelodysplastic Syndrome; MPO: Myeloperoxidase; NGS: Next-Generation Sequencing; Nrbc: Nucleated Red Blood Cells; PARP: Poly ADP-Ribose Polymerase; PAS: Periodic Acid Schiff; VAF: Variant Allele Frequency; WBC: White Blood Cells.

Introduction

Acute Erythroid Leukemia (AEL) is a subtype of acute myeloid leukemia (AML) characterised by prominent erythroid precursors and often associated with biallelic TP53 mutation [1]. It was first described as Di Guglielmo Syndrome in 1923 [2]. Once classified under French-American-British (FAB) as M6b subtype, thereafter renamed Pure erythroid leukemia and later came to be known as AEL. This changing WHO classification reflects the evolving understanding of this lesser-known entity. It can arise de novo or secondary to cytotoxic therapy. Its frequent association with TP53 mutation underscores its dismal prognosis [3]. It shows diagnostic overlap with AML and MDS with increased erythroid precursors. Hereby we discuss three cases highlighting the nuances in differentiating AEL from other two entities.

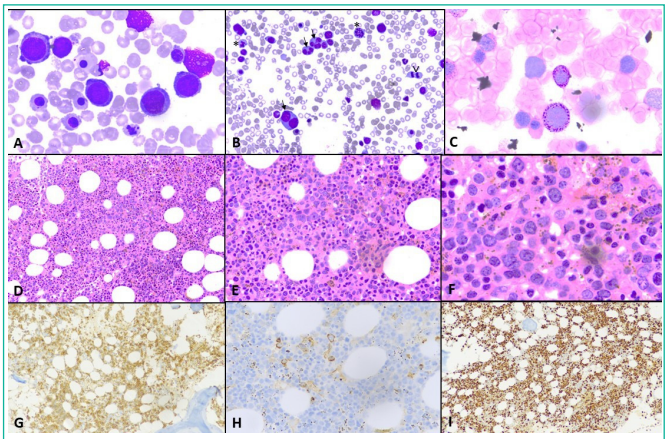

Figure 1: A. Bone marrow smear shows proerythroblasts with large size, round nucleus, open chromatin with prominent 1-3 nucleoli and deep basophilic cytoplasm. B. Erythroid precursors showed significant dyserythropoiesis in the form of multinucleation (arrow), budding, karyorrhexis, membrane irregularity (asterisk) and nuclear bridging (arrow head). (Giemsa stain, 1000x magnification). C. Proerythroblast shows characteristic magenta globules in cytoplasm on Periodic acid Schiff stain (Periodic acid Schiff stain, 200x magnification). D, E, F. Bone marrow biopsy shows hypercellular marrow with erythroid hyperplasia and increased proerythroblasts. (H&E stain; 100x, 200x, 400x magnification respectively). On immunohistochemistry (G) E-cadherin highlights the proerythroblasts and CD34 highlights the scattered myeloblasts (H) in background. P53 (I) shows nuclear positivity in >90% of cells.

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Case 1

A 69-year-old lady presented to the hospital with generalised weakness and patches of bluish discoloration on the skin. On physical examination ecchymotic patches were observed. The patient was a known case of ITP and was on Azoran for 8 years.

The peripheral smear showed pancytopenia with 5-6% blasts and 11 nucleated red cells (nRBC) per 100WBC. No significant dysgranulopoiesis was seen. Bone marrow aspirate smears were cellular and showed preponderance of erythroid precursors (>80%) of which 32% were proerythroblasts showing marked dyserythropoiesis (Figure 1). Maturing myeloid precursors were reduced and there was increase in blasts (8%). Megakaryocytes were reduced. Sample for flow cytometry was not available. In view of >80% erythroid precursors, >30% proerythroblasts and <20% blasts, diagnosis of acute erythroid leukemia was suspected. On further evaluation Periodic acid Schiff stain validated the suspicion by showing coarse globular cytoplasmic staining in proerythroblasts. Bone marrow biopsy was hypercellular (~75-80%) for age showing erythroid hyperplasia predominantly including proerythroblasts which were highlighted by E-cadherin, CD117 and negative for CD34, CD61. Scattered CD34 positive cells (7-8%) were seen. Strong nuclear expression of p53 was seen in >90% of cells (Figure 1). NGS showed missense TP53 p. (Arg273His) mutation (VAF 77%). Hence a final diagnosis of acute erythroid leukemia with mutated TP53 was established.

Case 2

A 74-year-old man presented with fever, cough and expectoration with pancytopenia for two months. The patient was operated for carcinoma rectum 16 years back with history of radiotherapy.

The peripheral smear showed pancytopenia with 7% blasts and 5nRBCs per 100WBCs. Bone marrow aspirates were cellular and showed erythroid preponderance (65%) with features of significant dysplasia (Figure 2). There were 21% cells with abnormal morphology characterised by medium sized cells with round nuclei, dispersed fine chromatin, one to three nucleoli and blue agranular cytoplasm leading to a morphological dilemma of myeloblast or proerythroblast. These cells were negative for both MPO and PAS. Megakaryocytes were adequate and showed hypolobation. Considering pancytopenia, dysplasia in erythroid lineage and negative special stains our diagnosis hinged on characterisation of 21% cells with abnormal morphology which was aided by flow cytometry. These cells were positive for immaturity (CD45, CD34, CD117) and myeloid markers (CD13, CD33, CD117) while negative for erythroid (CD71, CD36) and other lineage markers (CD3, CD19) (Figure 3). These findings were corroborated by the biopsy which showed clusters of blasts on CD34 and CD117. P53 IHC showed scattered positivity in ~5-6% cells favouring wildtype (Figure 2). However, NGS could not be done. Therefore, a diagnosis of Acute Myeloid Leukemia was established.

Case 3

A 69-year-old lady presented to the OPD with generalised weakness with a past history of treatment with PARP inhibitors for carcinoma breast (5 years back). The peripheral smear showed bicytopenia with mild left shift and features of dysgranulopoiesis in about 6% neutrophils with no blasts seen. Bone marrow aspirates were non-contributory due to marked hemodilution and flow cytometry could not be done. Biopsy was hypercellular (~65-70% cellularity) with areas of fibrosis and streaming of the cells. Erythroid hyperplasia with increased proerythroblasts was noted. These cells comprised ~22% when highlighted by E-cadherin, CD117 and CD71 with negative CD34. Myeloids were adequate with maturation up to neutrophils. Blasts were not increased on IHC for CD34. Megakaryocytes were prominent and showed focal clustering, mild pleomorphism and atypia. There was significant dysmegakaryopoiesis in about 45% cells. P53 showed strong nuclear positivity in >80% cells. Masson trichrome and reticulin stains showed grade 2 fibrosis (Figure 4). In view of erythroid hyperplasia, <30% proerythroblast, significant dysmegakaryopoiesis with fibrosis and p53 positivity in >80% cells, a diagnosis of myelodysplasia with fibrosis and mutated p53 was inferred. In this case p53 positivity on IHC served as a screening tool for TP53 mutation however NGS/cytogenetics was advised to assert biallelic status of TP53 mutation (Table 1).

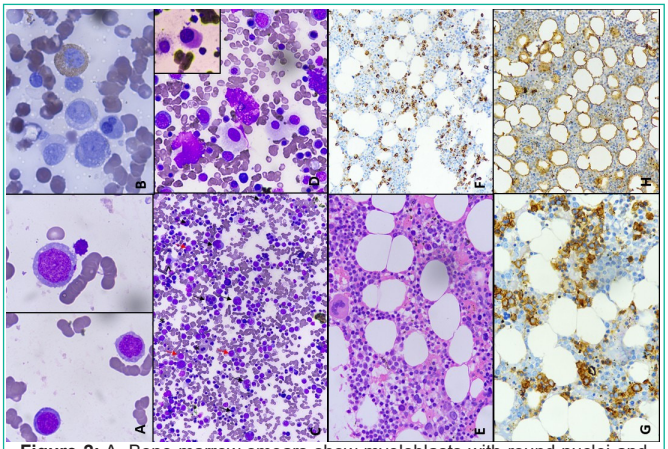

Figure 2: A. Bone marrow smears show myeloblasts with round nuclei and moderate circumferential blue agranular cytoplasm. (Giemsa stain, 1000x magnification). B. These cells were negative for MPO (Myeloperoxidase stain, 1000x magnification). C. Bone marrow aspirate smear shows cellular marrow with erythroid hyperplasia showing significant dyserythropoiesis in the form of multinucleation (black arrow), budding (asterisk) and membrane irregularity (arrow head). (Giemsa stain, 200x magnification) along with presence of 21% myeloblasts (red arrow). D. Megakaryocytes showed dysmegakaryopoiesis in the form of monolobation (Giemsa stain, 400x magnification). E. Bone marrow biopsy is hypercellular, show scattered and clusters of blasts with fine chromatin and prominent nucleoli. (H&E, 200x magnification). The myeloblasts were highlighted on immunohistochemistry for CD34 (F) while E-cadherin (H) highlighted erythroid precursors. P53 (I) was negative, 10-15% cells showed nuclear staining.

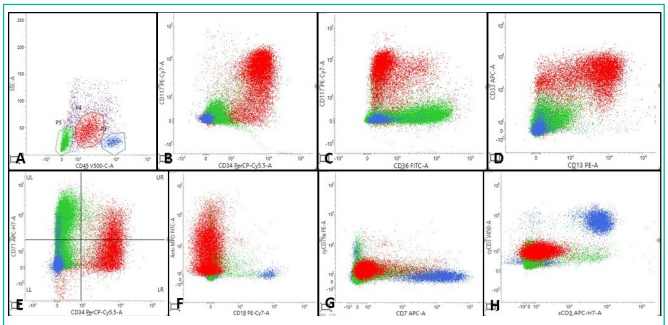

Figure 3: Flow cytometric analysis of the marrow aspirate identifies 21% myeloid blasts (red) expressing moderate CD34, CD117, CD13, CD33, dim CD45 and negative for CD71, CD36, CD19, CD7 and CD3. The scatter plots also depict erythroid precursors (green) and lymphoid population (blue).

Table 1: Summary of clinical and laboratory findings of the three cases.

	Case 1	Case 2	Case 3
Age/Gender	69/Female	74/Male	69/Female
Hemogram 1. Hemoglobin 2. TLC 3. Platelet	 70 g/L 3.2 x 10^9/L 150 x 10^9/L	 60 g/L 1.1 x 10^9/L 950 x 10^9/L	 85 g/L 9.3 x 10^9/L 320 x 10^9/L
Prior cytotoxic therapy	Present (Azathioprine)	Present (Radiotherapy)	Present (PARP inhibitors)
Peripheral smear 1. Cytopenia 2. Blasts 3. nRBC/100 WBC	 Pancytopenia 5-6% 11	 Pancytopenia 7% 5	 Bicytopenia 0 1
Bone marrow findings 1. Cellularity 2. Erythroid precursors 3. Proerythroblasts 4. Myeloid Blasts 5. Megakaryocytes	 75-80% >80% 32% 7-8% Reduced	 20-25% 65% 22% 21% Adequate	 65-70% <80% <30% <5% Adequate
Special stains 1. PAS 2. MPO	 Positive Negative	 Negative Negative	Not applied
Dysplasia	Present in erythroid precursors	Present in erythroid precursors and megakaryocytes	Present in megakaryocytes
P53 IHC/TP53 mutation	Positive on IHC and NGS (VAF 77%)	Wildtype	Positive on IHC. NGS not done
Diagnosis	Acute erythroid leukemia	Acute myeloid leukemia	Myelodysplasia with fibrosis and mutated p53

TLC- Total leucocyte count; PARP- Poly ADP-ribose polymerase; nRBC- nucleated red blood cells; WBC- White blood cells; PAS- Periodic acid Schiff; MPO- Myeloperoxidase; IHC-Immunohistochemistry; NGS- Next-Generation Sequencing; VAF- Variant Allele Frequency.

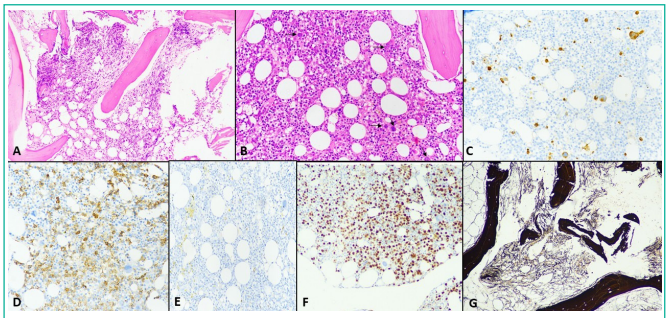

Figure 4: A. and B. Bone marrow biopsy shows hypercellular marrow with streaming of cells and many hypolobate megakaryocytes with few micromegakaryocytes (arrow) (H&E, 100x magnification) as highlighted on immunohistochemistry for CD61 (C). Erythroid precursors are highlighted on IHC E-cadherin (D) and CD34 (E) was negative. P53 (F) shows nuclear positivity in >80% cells. Reticulin stain (G) shows grade 2-3 fibrosis.

Discussion

Erythroid predominant myeloid neoplasm encompasses a diagnostically challenging and biologically heterogenous group of disorders with overlapping morphologic features. Accurate classification requires an integrated assessment of morphology, immunohistochemistry and flow cytometry.

In this case series, all the three cases presented post cytotoxic therapy with cytopenias. On marrow examination there was significant preponderance of erythroid precursors along with increased proerythroblasts and marked dyserythropoiesis. In view of these morphological features, following aided to arrive at final diagnosis: morphological enumeration, special stains, immunohistochemistry and flow cytometry. In case one, application of PAS stain helped confirm presence of >30% proerythroblast which was validated by E-cadherin, CD117 and CD34 immunohistochemistry. In case two, the morphology of the precursor cells was ambiguous, so their ontogeny was confirmed by positive CD13, CD33, CD34 and negative CD71 flow cytometry and reinstated on immunohistochemistry. In case three marrow fibrosis did not allow morphological evaluation and flow cytometry. Biopsy evaluation bore full accountability for the diagnosis. Morphology of megakaryocytes and immunhistochemistry markers like E-cadherin, CD117, CD34 helped enumerate the myeloblasts and erythroblasts. P53 immunohistochemistry was very helpful in case 1 and 3.

In the last two decades WHO classification has seen a significant evolution in the nomenclature of cases with > 50% erythroid precursors. The denominator for calculating myeloblasts was changed from nonerythroid cells to total marrow cells [4]. Post this revision the cases were either classified as MDS or AML, NOS as seen in the study conducted by Qiu S *et al*[5]. Another conceptual shift occurred in 2022 WHO revision where the term erythroleukemia was eliminated. The category "AEL" was retained but redefined more strictly as a rare and aggressive form of AML comprised entirely of immature erythroid precursors often with biallelic TP53 inactivation [6].

Post this change finite case reports have been published on AEL in the literature. Nayak MD *et al* [7] reviewed 5 cases as per FAB classification. They classified (four) cases into M6a and M6b(one case), based on the percentage of blast, erythroid precursors, morphological features showing dysplasia and special stains. Sato S *et al* [8] and Parkhi M *et al* [9] each reported one case of AEL which presented to the OPD similar to our case except for the history of prior cytotoxic therapy. Both cases showed dysplasia in erythroid lineage and >30% proerythroblasts. IHC E-cadherin helped establish the diagnosis in both the cases which was significant governing factor akin to our case. Similarly, the patient in the latter case report also had TP53 mutation with high VAF on NGS.

Akhtar K *et al* [10] described a case of a 35-year-old female who presented with pancytopenia. In this case report authors have tried to identify cases of AEL by differentiating from MDS or AML with erythroid predominance by utilising special stains (PAS and MPO) along with flow cytometry and karyotyping. Bone marrow showed 24% myeloblasts along with dysplasia in megakaryocytes and erythroid precursors. Monosomy 5q was detected on cytogenetics. All features put together helped classify it as AML with myelodysplasia related changes.

TP53 mutation is commonly encountered aberration post cytotoxic therapy. Its detection by NGS or aberrant p53 immunostaining (80% strong and diffuse nuclear stain or complete absence of nuclear stain in all cells) [11] is a poor prognostic factor with a dominant negative effect. TP53 mutation is associated with reduced overall survival and complex karyotypes [6]. It has high prevalence in AEL and MDN with biallelic TP53 inactivation. Fang H *et al* [12] studied biallelic TP53 inactivation and p53 expression in 22 cases of de novo pure erythroid leukemia by NGS and IHC. All patients had TP53 mutation, 76% cases were uniformly strongly positive for p53 while 5 showed null pattern. They emphasised critical role of biallelic loss of p53 in development of PEL. In our study positive p53 immunostaining was seen in 2 out of 3 cases, out of which NGS confirmed the p53 mutation in one case.

Given the rarity of AEL and the overlapping morphologic and immunophenotypic features with therapy-related MDS and AML accurate diagnosis is increasingly dependent on a combination of morphology, immunohistochemistry, flow cytometry and molecular-studies.

Conclusion

This case series highlights the diagnostic overlap of AEL with AML with myelodysplasia and MDS with fibrosis which is evident through evolving WHO revisions. TP53 mutation and in turn AEL have unfavourable outcome. Limited cases were studied and NGS, flow cytometry could not be done in all cases. More cases need to be studied to understand the disease and come up with therapy to improve overall survival. Despite the evolution of nomenclature some grey areas remain to be addressed. For instance, cases with ≥30% proerythroblasts and ≥20% myeloblasts or cases with ≥30% proerythroblasts but <20% myeloblast and <80% erythroid precursors. Further studies are needed to explore this middle ground.

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