

Acute Erythroid Leukemia – A Hematological review of 5 cases in a tertiary care centre

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Abstract- Acute Erythroid Leukemia (AML M6) is a rare form of acute leukemia. **Aims and Objectives:** To retrospectively evaluate 5 cases of acute erythroid leukemia reported in the department of Pathology, Kasturba Medical College and Hospital, Manipal and analyze their clinico-hematological features with the available literature. **Materials and Methods:** Case records of the 5 patients with acute erythroid leukemia, diagnosed between January 2009 and December 2012 were reviewed. Clinical details were noted and slides were reviewed. **Results:** The mean age was 43.8years (range: 12-72). Male: female ratio of 3:2. Mean duration of symptoms in the present series was 6.4 weeks. Cytogenetics available in 2 cases, were normal. Pancytopenia was seen in 4 of the 5 cases. 4 cases were typed as AML –M6a or erythroleukemia (erythroid/myeloid) while one solitary case was of pure erythroid leukemia. **Conclusion:** The features of AML M6 are different from those reported in similar studies thus far.

Index Terms- Acute Erythroid Leukemia, AML M6, clinico-hematological feature.

I. INTRODUCTION

Acute Erythroid Leukemia (AML M6) is a rare form of acute leukemia; characterized by an uncontrolled proliferation of erythroid precursors (proerythroblasts and basophilic erythroblasts) and myeloblasts. Ever since its description almost a century ago it remains an elusive diagnosis, comprising < 5 % of all Acute Myeloid Leukemia (AML) cases.¹ After Giovanni Di Guglielmo stumbled onto this rare disease in 1928, the neoplasm has borne the eponym “Di Guglielmo syndrome”.² The disease continues to evolve with time, hence providing a better understanding of the biology, clinical course and survival outcomes. To date, only few case reports of AML M6 have been reported from the Indian subcontinent.³⁻⁶ We here report a retrospective analysis, in which we evaluated the clinico-hematological features of Acute Erythroid Leukemia.

II. OBJECTIVES

To review the 5 cases of acute erythroid leukemia reported in our hospital and analyze their clinico-hematological features with the available literature.

III. MATERIALS AND METHODS

5 cases reported as acute erythroid leukemia in the Dept. of Pathology, Kasturba Medical College and Hospital, Manipal over a period of three years between January 2009 to December 2012, were reviewed. Clinical information was obtained from the Medical Records Department. The clinical details as available in the hospital records were noted. Age, sex, symptoms with duration, examination findings and any other relevant data were reviewed. Hematological review of all 5 cases (reported by an individual pathologist) was done on the bone marrow aspirate smears; including the cytochemical stains (MPO, SBB and PAS).

IV. DEFINITION OF AML M6

The current WHO classification subtypes it into two categories based on the presence or absence of significant myeloid component.¹ Erythroleukemia or Erythroid/Myeloid (FAB subtype A – M6a) comprises of more than 50% erythroid precursors among all nucleated cell population of bone marrow and more than 20% myeloblasts among non erythroid cells. Pure erythroid leukemia (FAB subtype B – M6b) comprises of more than 80% immature cells of erythroid lineage with no evidence of a significant myeloid component.

V. RESULTS

The 5 cases typed morphologically as Acute Erythroid Leukemia had distinct profiles. The clinical parameters are presented in Table 1.

Table 1: Clinical characteristics of all 5 AML M6 patients

| Case no | Age | Sex | Fever | Asthenia | Jaundice | Bleeding | Lymphadenopathy | Organomegaly | Pallor |
|---------|-----|-----|-------|----------|----------|----------|-----------------|--------------|--------|
| 1. | 72 | M | + | + | - | + | + | + | + |
| 2. | 39 | F | + | + | - | - | - | + | + |
| 3. | 43 | M | - | + | + | + | - | - | + |
| 4. | 11 | M | - | + | + | + | - | + | + |
| 5. | 51 | F | + | + | - | + | - | + | + |

+ present.
 - absent.

The hematological parameters are presented in Table 2.

Table 2: Hematological parameters in all 5 AML M6 patients

| Case no. | Hemoglobin (gm %) | Total count (x10 ⁶ / dL) | WBC | Platelets (x10 ⁶ / dL) | No. of cell lineages with dyspoiesis | Bone marrow megakaryocyte number | WHO 2008 classification | Cytogenetics |
|----------|-------------------|-------------------------------------|-----|-----------------------------------|--------------------------------------|----------------------------------|-------------------------|--------------|
| 1. | 5.5 | 2300 | | 55000 | 3(E+My+Me) | Reduced | M6a | Not done |
| 2. | 6.3 | 4000 | | 71000 | 3(E+My+Me) | Reduced | M6a | Not done |
| 3. | 2.3 | 2600 | | 30000 | 2(E+My) | Reduced | M6a | 46,XY |
| 4. | 9.3 | 7300 | | 140000 | 1 (E) | Adequate | M6b | 46,XY |
| 5. | 5.2 | 4200 | | 26000 | 3(E+My+Me) | Reduced | M6a | Not done |

E- Erythroid, My-Myeloid, Me-Megakaryocyte

M6b- Pure erythroleukemia

M6a- Erythroid/ myeloid

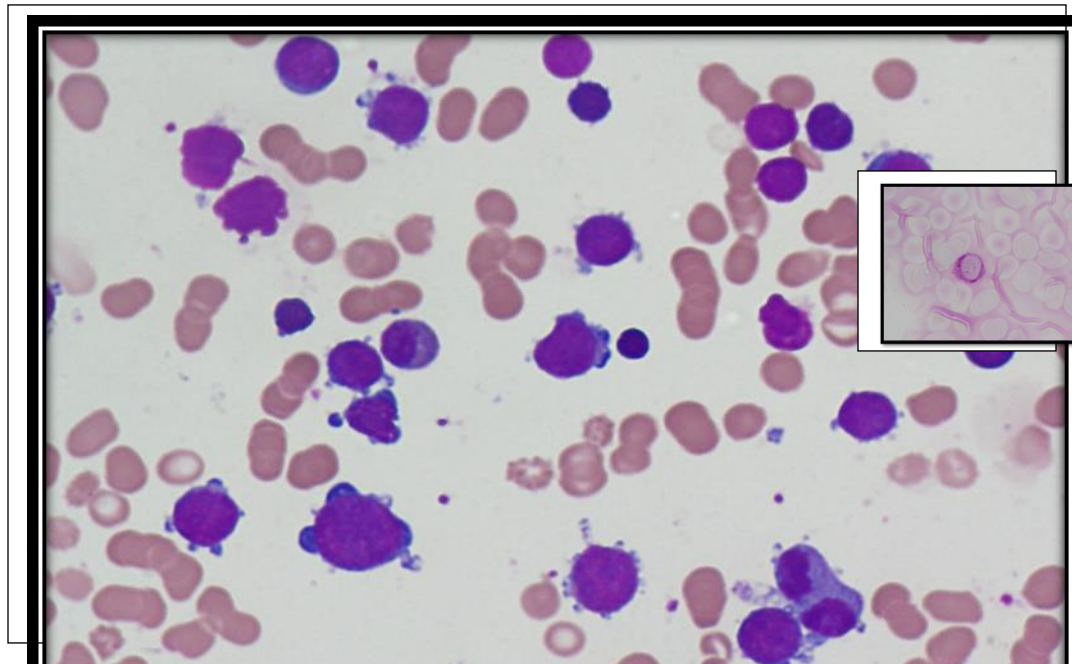


Figure 1 – Bone marrow aspirate showing erythroid hyperplasia with PAS positive erythroblast (Inset). (Leishman x200)

VI. DISCUSSION

Acute Erythroid Leukemia (AML M6) is a rare form of acute leukemia. It is a distinctive bone marrow disorder characterized by the neoplastic proliferation of the dysplastic erythroid elements mixed with blasts of myeloid origin. The cases reported from India are sparse. Recent past have had few reports including a single case in 10 years of follow up of the Tata Memorial Hospital data and 20 cases in the series from AIIMS, Delhi.^{7, 8} More recently, a case series from a south indian tertiary care hospital was also reported.⁶ AML M6 is relatively uncommon and is known to account for 3-5% of all de novo AMLs and 20-30% of secondary leukemias.⁶

Clinical parameters: The malignancy usually presents in the fifth and sixth decades, but a bimodal peak has been described in conjunction with AML M6.⁹ The smaller peak has been noted below 20 years, and a broader peak in seventh decade.¹⁰ Few pediatric cases have also been elucidated.¹¹ In the present series, the age group ranged from 11 to 72 years with a mean of 43.8 years. One pediatric case was seen in the present series as well and is an addition to this rare demographic. The reason for this could be that all the cases in the present series were de novo. In most of the series, due to unknown reasons, males have been predominant. This was the case in the present series, with a male: female ratio of 3:2.

The signs and symptoms of AML M6 are nonspecific and are attributed to the replacement of bone marrow elements by neoplastic cells. Patients rarely present with symptoms lasting longer than six months, and they are usually diagnosed within 1-3 months after the onset of symptoms.⁶ Mean duration of symptoms in the present series was 6.4 weeks, which is marginally lesser than the ones reported in literature.^{5,12-14} In many series, approximately half the cases of AML M6 are therapy-related while secondary leukemias are less frequent (10-15%).¹⁵ No history of any therapy was seen in the present series, hence they could be de novo.

Asthenia (100%), bleeding (80%) and fever (60%) were the most dominant presenting features in this study; which is fairly consistent with the other recent series.^{4,6} None of the 5 patients had significant bone pains, which have been reported in 33% of all cases.^{4,12,13,14,16} Interestingly, the other features associated with AML M6 patients presenting with bone pains include hypergammaglobulinemia, positivity for rheumatoid factor, Coombs test and anti-nuclear antibody.¹⁷

Examination findings included hepatomegaly, splenomegaly and lymphadenopathy. Pallor was consistently noted in all the 5 cases. A comparison of the examination findings in the present study is compared with other studies and the data are shown in Table 3

Table 3: Comparison of clinical findings in the earlier series and the present study

| [1] Series | [2] No. of patient s | [3] Hepatosplenomegaly | [4] Lymphadenopathy | [5] Pallor |
|---|----------------------|------------------------|---------------------|------------|
| [6] Tsuji ,et al 1995 ⁽¹⁸⁾ | [15] 20 | [24] 2 | [33] 0 | [42] 18 |
| [7] Oloapade O. et al. 1992 ⁽¹³⁾ | [16] 26 | [25] 10 | [34] 0 | [43] 26 |
| [8] Mazella, et al. 1998 ⁽⁹⁾ | [17] 21 | [26] 15 | [35] 0 | [44] 18 |
| [9] Attili, et al .2006 ⁽⁶⁾ | [18] 14 | [27] 6 | [36] 2 | [45] 14 |
| [10] Present | [19] 5 | [28] 4 | [37] 1 | [46] 5 |

Hematological profile: Pancytopenia was noted in all the cases in our study (table 2). Anemia was significant (median Hb – 6.3 gm%) Thrombocytopenia was the most consistent finding (median – 41 x 10³ /ul). The leucocyte number ranged from low normal to mildly reduced. Interestingly, the lone pediatric case had a milder cytopenia in contrast to the others. Morphological diagnosis of AML M6 was based on bone marrow aspirate and peripheral smear findings. The aspirates studied showed hyper cellularity with an increased erythroid cells showing varying degrees of dysplastic features such as megaloblastoid change, multinuclearity, inter-nuclear bridges and nuclear budding were observed (figure 1). Dyspoiesis was noted most consistently with erythroid series (100%), followed by myeloid (60%). All but one case had reduced megakaryocytes (Table 2).

But the most consistent and important is the morphological pattern based on the percentage of the erythroblasts and myeloblasts. Erythroblasts can be differentiated from other lineages by being positive for Periodic Acid Schiff (PAS), showing globular positivity and negative for Myeloperoxidase (MPO) & Sudan Black B (SBB). In flow cytometry analysis, the erythroblasts are positive for CD36 and glycophorin A, but not specific.¹⁹

The cytogenetic abnormality pattern in AML M6 is quite varied. Complex karyotypes with multiple structural abnormalities are common with del 5q and del 7q.^{1,13} The involvement of chromosomes 11 and 19 in de novo patients have recently surfaced.²⁰ In the present series, 2 of the 5 cases had a normal karyotype. The cytogenetics could not be done in the remaining 3 patients.

The differential diagnoses for AML M6 could be varied and pose diagnostic challenges.¹ With regard to erythroleukemia (erythroid/myeloid); MDS (refractory anemia with excess blasts): is a possibility but the blasts account for less than 20%. In AML with MDS related changes, >20 % blasts with multi-lineage dysplasia in >50% cases of the cells in more than 2 lineages supports the diagnosis. AML with increased erythroid precursors (lesser proerythroblasts and basophilic erythroblasts) also comes in this realm. In cases of pure erythroid leukemia, megaloblastic anemia, acute lymphoblastic leukemia (especially in pediatric age group) and lymphomas are often considered as close diagnostic parallels.²¹

Both subtypes of AML M6 are associated with an aggressive and rapid clinical course.¹ Due to poor follow-up and non-

uniformity in treatment received, the survival of the 5 patients were not charted. The study was not supported by ancillary technique such as immunophenotyping by flow- cytometry due to varied reasons (ranging from heavy cost involved to lack of consent on the part of patients/clinicians). The number of cases was a handful, but this could be debated by the sheer rarity of this entity.

VII. CONCLUSIONS

Many neoplasms continue to evolve and perplex the researchers. Acute Erythroid Leukemia (AML M6) is a rare form of acute leukemia which seems to follow that trend. The features of this entity are different from those reported in similar studies thus far.

REFERENCES

- [1] Swerdlow S H, Campo E, Harris N L, Jaffe E S, Pileri S A, et al. Acute myeloid leukemia, not otherwise specified. In: WHO classification of Tumours of Hematopoietic and lymphoid tissues. 4th edition; IARC press, Lyon, France; 2008:130-9.
- [2] Di Guglielmo G. L'eritremie. Haematologica.1928; 9:301-47.
- [3] Batra VV, Karan AS, Saxena R. Erythroleukemia: a clinico-hematological review of four cases. Indian Pediatr 2004;41:587-90.
- [4] Jogai S, Varma N, Garewal G, Das R, Varma S. Acute erythroleukemia (AML-M6) -- a study of clinico-hematological, morphological and dysplastic features in 10 cases. Indian J Cancer 2001;38:143-8.
- [5] Mohanty R, Dash B, Chawla SC, Paul HS. Acute erythroleukemia--M6B. Indian J Pathol Microbiol 2001;44:461-2.
- [6] Attili SVS, et al. A retrospective study of clinico-hematological and cytogenetic profile of erythroleukemia from South India. Turk J Hematol 2006; 23:158-63.
- [7] D'Costa GG, Siddiqui HM, Pradhan RM, Gupte SS. Pattern of leukemias: a ten-year incidence study of 242 cases. J Postgrad Med 1989;4:191-96.
- [8] Kumar L, Menon H, Sharma A, Wadhwa J, Kumar R, Kochupillai V. Acute myeloid leukemia (AML): A study of 516 patients. JCO. 2004; 22 (14): 6711.
- [9] Mazzella FM, Alvares C, Kowal-Vern A. The acute erythroleukemias. Clin Lab Med 2000;20:119-37.
- [10] Park S, Picard F, Dreyfus F. Erythroleukemia: a need for a new definition. Leukemia 2002;16: 1399-401.
- [11] Batra V V, Karan A S , Saxena R; Erythroleukemia. A clinico-hematological review of 4 cases. In brief reports: Indian Pediatrics 2004;41:587-90.

- [12] Wells AW, et al. Erythroleukaemia in the north of England: a population based study. *Clin Pathol* 2001;54:608-12.
- [13] Olopade OI, et al. Clinical, morphologic, and cytogenetic characteristics of 26 patients with acute erythroblastic leukemia. *Blood* 1992;80:2873-82.
- [14] Vardiman J. Proposed WHO classification of neoplastic diseases of hematopoietic and lymphoid tissues (acute leukemias and myeloid disorders). *Am J Surg Pathol* 1997;21:114-21.
- [15] Domingo-Claros A, Larriba I, Rozman M, et al. Acute erythroid neoplastic proliferations. A biological study based on 62 patients. *Hematologica* 2002;87: 148-53.
- [16] Peterson BA, Levine EG. Uncommon types of acute non-lymphocytic leukemia: clinical features and management of FAB M5, M6 and M7. *Semin Oncol* 1987;14: 425-34.
- [17] Hetzel P, Gee TS. A new observation in the clinical spectrum of erythroleukemia. A report of 46 cases. *Am J Med* 1978;64:765-72.
- [18] Tsuji M, Tamai M, Terada N, Tako H. An erythremic form of acute erythremic myelosis (Di Guglielmo's syndrome) causing hepatosplenomegaly due to the infiltration of hemoglobin-bearing blast cells: an autopsy case. *Pathol Int* 1995;45:310-4.
- [19] Latif N, Salazan E, Khan R et al. The pure erythroid leukemia: A case report and literature review. *Clinical Advances in Hematology and Oncology* 2010 ;8(4):283-88.
- [20] Colita A, Belhabri A, Chelghoum Y, Charrin C, Fiere D, Thomas X. Prognostic factors and treatment effects on survival in acute myeloid leukemia of M6 subtype: a retrospective study of 54 cases. *Ann Oncol* 2001;2:451-55.
- [21] Khanna R, Nayak DM, Manohar C, Seshadri S, Belurkar SV. Pure erythroleukemia- A case report and literature review. *The Internet Journal of Haematology* 2011;7(2), doi: 10.5580/feb.

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