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A RETROSPECTIVE STUDY OF THE CLINICOPATHOLOGICAL FEATURES, COURSE AND PROGNOSIS OF THREE CASES OF ERYTHROID-PREDOMINANT MYELOID NEOPLASMS, WITH A REVIEW OF THE LITERATURE IN RELATION TO AML M6 - CASE SERIES

Immunohematology

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ABSTRACT

Background: The current WHO classification of myeloid neoplasms with erythroid predominance has placed pure erythroid leukaemia as the only entity in the Acute Myeloid Leukaemia, M6 category whereas previously described subtype Erythroid/myeloid has been placed into either Myelodysplastic syndrome (MDS) with excess blasts or Acute myeloid leukaemia (AML)with myelodysplasia-related change.
Methods and materials: Out of 110 cases of AML diagnosed during a two-year period in a tertiary level hospital, three cases initially identified as AML M 6 were analysed retrospectively of their clinical history, blood and bone marrow examination, flowcytometry, course and response to treatment and finally placed them in an appropriate category.
Results: Two of the three cases, a three-year-old girl and a 29-year-old male, were initially diagnosed as AML N6 remained as pure erythroid leukemia and the third case as AML with myelodysplasia-related change. The first two cases died within 5 months of diagnosis and treatment and the third in morphological remission.
Conclusion: We are reporting these case series due to their rarity and ferocity.

KEYWORDS

Myeloid neoplasm, Acute myeloid leukemia, Myelodysplastic syndrome, Pure erythroid leukemia.

INTRODUCTION

According to the French-American-British (FAB) classification, Acute Myeloid Leukemia, M6 is a rare subtype of Acute Myeloid Leukemia, NOS.[1] In recognition of the extensive work and description by Italian hematologist, Giovanni Di Guglielmo,1917, it is also known as DI Guglielmo syndrome. However, it is stated that M. Copelli described the first known case of acute erythroid leukemia in 1912 under the label erythromatosis.[2] Traditionally, it had two subtypes: Erythroleukaemia (Erythroid myeloid) and pure erythroid leukamia (PEL), however latest WHO classification (4th edition, 2017) has removed the former subtype and placed it under MDS with excess blasts if blasts are less than 20 or AML myelodysplasia related changes if blasts are more than 20% irrespective of erythroid cell count.[3]

AIM AND OBJECTIVE

To study of clinicopathological features, course and prognosis of three cases myeloid neoplasms with erythroid predominance diagnosed at a tertiary care hospital with review of literature with respect to AML M6.

MATERIALS AND METHODS:

Out of 110 cases of AML diagnosed over a period of two years, three AML, M6 cases with marked erythroid component were studied with clinical history, blood and bone marrow examination, flowcytometry, course and response to treatment and lastly their clinical relevance with latest WHO classification.

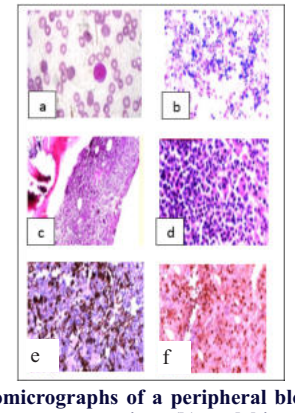

Figure 1: Photomicrographs of a peripheral blood(a)showing a blast and bone marrow aspirate(b) and biopsy(c, d) showing marked erythroid hyperplasia and immunostaining for positive Glycophorin A(e) and scattered myeloperoxidase (MPO) positive blasts (f).

Case no. 1

A three-year-old girl presented with intermittent fever and was diagnosed with leukopenia. She was pale on examination, but she had no icterus, cyanosis, lymphadenopathy, or organomegaly. Peripheral blood shows 5 % blasts. The bone marrow aspirate and biopsy revealed erythroid hyperplasia (>80%) with dysplasia in the erythroid and myeloid series, as well as the presence of more than 30% proerythroblasts that are positive for Glycophorin A, CD117, and negative for myeloperoxidase (MPO). Flowcytometry reveals that these blasts are HLADR and CD 34 negative. Diagnosed initially as AML M6 thus remained as AML, M6.

She was given induction chemotherapy as per AML protocol, but she developed neutropenic sepsis and died within four months of being diagnosed.

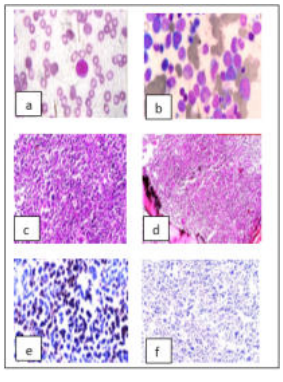

Figure 2. Photomicrographs of a peripheral blood(a) showing a blast and bone marrow aspirate(b) and biopsy (c, d) showing marked erythroid hyperplasia and immunostaining for positive Glycophorin A (e) and negative myeloperoxidase (MPO) blasts (f).

Case no 2.

A 29-year-old male, non- smoker/drinker, has had anemia for two months and has been treated with iron supplementation and multiple transfusions at a peripheral hospital. On examination, he was also pale, but he had no icterus, cyanosis, lymphadenopathy, or organomegaly. Peripheral blood showed 4 % blasts. The bone marrow aspirate and biopsy revealed significant erythroid hyperplasia (>80%) with dyserythropoeisis as well as the presence of more than 30% proerythroblasts that are positive for Glycophorin A but negative for myeloperoxidase (MPO). Flowcytometry reveals that these blasts are also HLA-DR and CD34 negative. AML M6 was diagnosed and thus

remained as AML M6. On day 9 of induction therapy with AML protocol, he also developed neutropenia with fever and a focus of infection in the right mandibular region, developed bilateral pneumonia and died within 5 months of being diagnosed.

Case no. 3

57-year-old female with a 2-year history of generalized weakness, cough and hoarseness of voice. On examination she was pale as well but no icterus, cyanosis, lymphadenopathy and organomegaly. Peripheral blood showed 23% blasts. The bone marrow aspirate and biopsy revealed significant erythroid hyperplasia (>50%), with blasts immunostaining positive for both Glycophorin A and myeloperoxidase (MPO). Flowcytometry also revealed CD 33 and HLA-DR positivity. The diagnosis of AML M6 (Erythroid/Myeloid) was changed to AML with myelodysplasia-related change.

She was begun on induction chemotherapy based on initial diagnosis and has completed three cycles. She is currently in morphological remission.

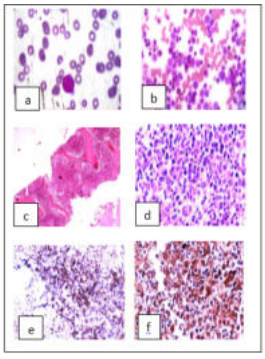

Figure 3. Photomicrographs of peripheral blood smears (a) with blasts, BM aspirate (b) with blasts, BM biopsy (c, d) with considerable erythroid hyperplasia and immunostaining for Glycophorin A (e) and strong myeloperoxidase (f).'

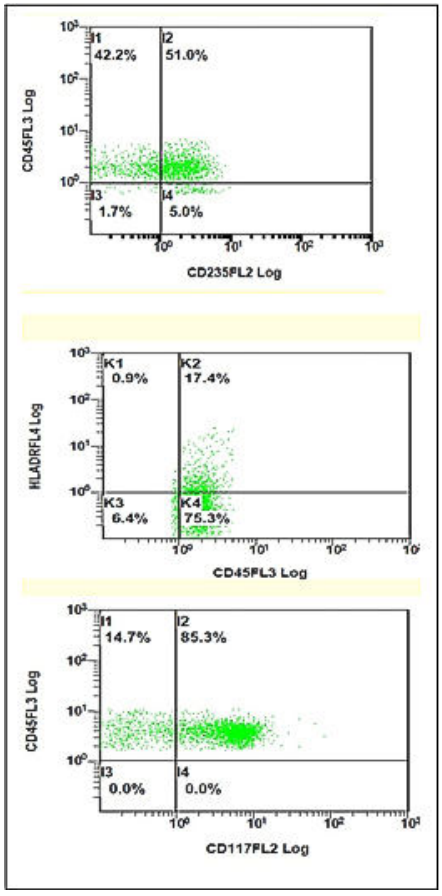

Figure 4. Flowcytometry showing positive CD235, CD117 and negative HLA DR in AML, M6 cases

DISCUSSION

Up until 2016, AML M6 had two subtypes: erythroleukemia (erythroid/myeloid) and PEL. Erythroleukemia is defined by erythroid cells accounting for 50% of total nucleated bone marrow cells and myeloblasts accounting for 20% of nonerythroid cells, whereas PEL is defined by erythroblasts accounting for up to 80% of all nucleated cells in the marrow. [4] These two categories both exhibited a large erythroid component, however in the case of PEL, erythroid cell maturation was halted, resulting in predominantly undifferentiated erythroid precursors or proerythroblast. PEL has no major myeloblast component, but erythroleukemia contains a large number of them. However, this classification has always been contentious because a slight increase or decrease in the blast percentage of nonerythroid cells or the erythroid component might have a significant impact on treatment decisions. The diagnosis of myelodysplastic syndrome (MDS) can be changed to erythroleukemia with a little increase in the blast count. A little shift in erythroid percentage can modify the diagnosis, which is frequently due to fluctuations in therapeutic nutritional deficits, EPO administration, or observer variation in counting the cells. As a result, many experts suggested that erythroleukemia be merged into the MDS category because both conditions have similar dysplastic features and the former is frequently secondary to prior MDS. As a result, the percentage of erythroid cells is no longer significant in such instances, and the blast percentage is now calculated using all nucleated cells in the marrow. Erythroleukemia has genetic abnormalities that are more similar to MDS, such as common TP53 mutations and rare FLT3 and NPM1 mutations. [5-8]

PEL is defined by the updated 4th edition WHO classification as a neoplastic proliferation made up of >80% immature erythroid precursors, of which >30% are proerythroblasts, with no prior myeloid neoplasm, chemotherapy, or radiotherapy exposure, and no recurring genetic abnormalities. [9]Microscopically, the blasts in the marrow aspirate are medium to large proerythroblasts with round nuclei, fine chromatin, 2 to 3 nucleoli, basophilic agranular cytoplasm, and vacuoles that frequently show PAS block positivity. They are also NSE and acid phosphatase positive, but MPO and Sudan black negative.

Two of the three cases reported here have been reclassified as AML, M6, however their clinical progress was so quick that they died just four months after being diagnosed and treatment. They are also of varying ages, with one being three years old and the other being 29. Our third case was reclassified as AML with Myelodysplasia-related change due to the presence of 23 percent myeloblasts despite the presence of a significant erythroid component.

Acute myeloid leukemia, M6, is a rare subtype of AML that accounts for less than 1% of all AML cases.[10] It can develop spontaneously or as a result of MDS[11]. According to Erica F Reinig et al, de novo pure erythroid leukemia is a disease of adults (median age 68 years) with a striking male predominance.[11] It can occur at any age, including children, but there is an increased incidence with age with two peaks occurring in the seventh and fourth decades.[2,12]

There have been no reports of specific genetic mutations in PEL. Mutations that are common in other types of AML, such as FLT3, NPM1, and CEBPA, appear to be very rare in PEL, but TP53 mutations are common.

PEL patients typically have anemia, pancytopenia, and circulating erythroblasts in their blood, as well as extensive bone marrow involvement. [10]

PEL patients have a clinically aggressive course with a bleak prognosis. The median survival time ranges between 3.5 and 6.6 months.[13,14,15]

CONCLUSION

In individuals with erythroid hyperplasia in the bone marrow in conjunction with severe megaloblastic anemia a high index of suspicion for AML,M6 and AML with myelodysplasia is required.

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Conflicting interests

Nil

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