RESEARCH ARTICLE

Acute Myeloid Leukemia: Clinical Spectrum of 125 Patients

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Abstract

Background: Acute myeloid leukemia is an acquired clonal heterogeneous stem cell disorder. Hence, various parameters are sought out to categorize this disease into subtypes, so that as a consequence specific treatment modalities can be offered. Conventionally, the practically used method for classification utilizes French American British (FAB) criteria based on morphology and cytochemistry. The aim of present study was to determine the current spectrum of AML sub types in patients in Karachi. Materials and Methods: This single centre cross sectional study was conducted at Liaquat National Hospital, Karachi, extending from January 2010 to December 2014. Data were retrieved from archives were analyzed with SPSS version 22. Results: A total of 125 patients were diagnosed at our institution with de novo AML during five years period, 76 males and 49 females. Median age was 34.5 years. AML-M1 was the predominant FAB subtype (23.2%) followed by M2 (18.4%), M3 and M4 (16% each), M0 (14.4%), M5 (7.2%), M6 (3.2%) and M7 (1.6%). Conclusions: AML in Pakistani patients is seen in a relatively young population. The most common FAB subtype observed in our study was acute myeloblastic leukemia, without maturation (M1).

Keywords: Acute myeloid leukemia - FAB subtypes - Karachi, Pakistan

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Introduction

Acute myeloid leukemia (AML) represents one of the most frequent, biologically and clinically diverse disorder amongst all hematopoietic malignancies. (Zhou et al., 2013; Ahmad et al., 2014). In the literature annual incidence for AML is 3-4/100,000 individuals each year (Schlenk., 2014). The incidence of AML increases gradually with age and median age of acute myeloid leukemia's patients is around 70 years internationally (Ossenkoppele and Löwenberg., 2015).

The disease biology among AML patients is highly heterogeneous (Yang et al., 2012; Su et al., 2014). Therefore certain parameters are needed to classify this disease into biologic entities to understand its pathogenesis and more importantly to determined treatment modality (Tien et al., 1995; Schoch and Haferlach., 2002).

French-American-British classification for acute myeloid leukemia had been widely accepted and applicable due to its ease and good reproducibility. Conversely, the obligation of karyotyping and immunophenotyping in WHO classification makes it difficult for developing countries like Pakistan to put this classification in routine practices. FAB classification is purely based on morphologic and cytochemical features; as they do not require advanced technology and can be easily applied in most laboratories (McKenna., 2000). It mainly categorizes according to their lineage differentiation and degree of maturation of the leukemic cells. In view of these merit, the FAB classification was implemented nationally and internationally. Previous study, reported from Pakistan was determined AML-M2 as the predominant variant in adults AML (Harani et al., 2005).

Present study is design to determine the current spectrum of AML subtypes in our population. As the patients from all over the city belonging to diverse racial groups were come to our centrally located tertiary care center, thus our study tends to establish an existing trend of AML locally.

Materials and Methods

This is a retrospective cross sectional analysis conducted at hematology department of Liaquat National Hospital. The study was extended over a period of 5 years from January 2010 to December 2014.

Socio-demographic data including age, gender and contact numbers were recorded. All patients underwent detailed history, general physical and systemic examination. Patients having history of prior hematological disorders like Myelodysplastic syndrome, Myeloproliferative neoplasm, Myelodysplastic/ Myeloproliferative entity or undifferentiated leukemia and cases of pediatrics AML were excluded from the analysis. The patients who were known cases of secondary AML were also not included. A total of 125 adults (≥15 years) with newly diagnosed

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untreated de novo AML were integrated in the study. The diagnosis of AML was established according to the customary FAB criteria, and was based on bone marrow morphology and cytochemical staining (Bennett et al., 1985).

Complete blood counts were done on Cell Dyne automated counter (Abbott, USA). All peripheral blood smears were reviewed by specialist hematopathologists. Bone marrow aspiration was done from posterior iliac crest through Jamshidi needle and was stained by Leishman's stain. Cytochemical stains were carried out on each bone marrow smears including Sudan Black B (SBB), Periodic acid-Schiff (PAS) and Alpha naphthyl acetate esterase by commercially provided kits from Merck Diagnostic, as per manufacturer's instructions. Each test results were validated by running simultaneously appropriate positive controls. Immunophenotyping was done where it was deemed necessary, in patients with diagnostic uncertainty.

Approval from the institutional ethical and research review committee was obtained prior to the study.

Data analysis

The demographic data, clinical characteristics, and laboratory results were analyzed by descriptive analysis. Data was compiled and analyzed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc, Chicago, IL, USA). The results were expressed as mean±SD for quantitative variables and qualitative variables are presented as frequency & percentages.

Results

Out of 125 patients, 76 were males (60.8%) and 49 were females (39.2%) with male to female ratio of 1.5:1. Age ranged between 15 and 85 years with a mean age of 37.97±20.12 years and median age of 34.5 years. Overall 95 (76%) patients were under 50 years of age, and only 30 (24%) patients were above 50 years.

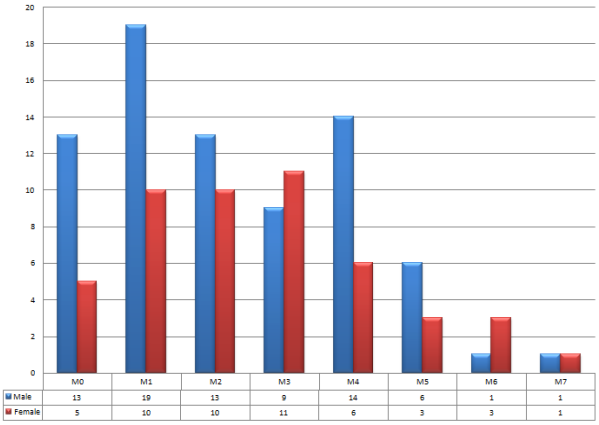

Figure 1. Spectrum of FAB Classification according to Gender

The major complaints were fever in 91 (72.8%) patients; generalized weakness in 75 (60%) patients; bleeding in 47 (37.6%) patients and dyspnea in 15 (12%) patients. Physical examination revealed pallor as a predominant finding detected in 71 (56.8%) patients followed splenomegaly and hepatomegaly in 20 (16%) and 16 (12.8%) patients respectively. Lymphodenopathy was noted in 13 (10.4%) patients.

The mean hemoglobin was 8.19±2.12 g/dl with the mean MCV of 85.98±9.83 fl. The mean total leukocyte count of 43.08±68.45x10^9/l; Absolute neutrophilic count (ANC) of 3.09±6.66 x10^9/l and the mean platelets count were 62.32±78.61x10^9/l.

Anemia was noted in 102 (81.6%) patients. Thrombocytopenia (platelets count <100x10^9/l) was detected in 105 (84%) patients.

We found Acute myeloblastic leukemia, without maturation (AML-M1) to be the commonest subtype comprising of 29 out of 125 cases (23.2%) followed by AML-M2 in 23 (18.4%) patients, M3 & M4 variants in 20 patients each (16%), M0 subtype seen in 18 (14.4%) patients, while M5 was noted in 9 (7.2%) patients. The least encountered types were M6 and M7 detected in 4 (3.2%) and 2 (1.6%) patients respectively. Comparative analyses with other regional studies are shown in table-1.

In relation to gender distribution males patients revealed predominance of AML-M1 type while female patients show AML-M3 as a frequent variant (figure1).

Discussion

AML is a disease of the elder, with a median age of around ~70 years (Juliusson et al., 2009). Surprisingly, the median age of the patients in our study is 34.5 years. When compared with international reports, our finding is in distinction with studies published from Sweden and Germany, where the median age were 71 and 60 years respectively. (Lazarevic, 2014; Pastore, 2014). However, some studies from our part earlier reported low median age (Kakepoto et al., 2002; Harani et al., 2005). Conceivably this variance may be elucidated by difference based on geographical and genetic makeup between two racial groups and also accountable is the high mean ages in western countries compared to east.

There are two standard classification systems that are widely used for the diagnosis of acute myeloid leukemia (AML). The French-American-British (FAB) classification system is based on differentiation and

Table 1. FAB Classification of Adults AML in Prior Pakistani Studies

Author/year	M0	M1	M2	M3	M4	M5	M6	M7
Hassan et al., 1993 (n=62)	1.6	22.5	32.2	9.1	22.5	8.6	1.6	1.6
Chaudry et al., 1993 (n=54)	0	13	44.4	11.1	24	3.7	3.7	0
Kakepoto et al., 2002 (n=74)	0	8.1	16	15	46	9.5	0	2.7
Harani et al., 2005 (n= 95)	1.2	9.4	30.5	12.6	36.8	6.3	0	0
Asif et al., 2013 (n=56)	1.8	32.1	14.3	19.6	19.6	9.0	1.8	1.8
Ali et al., 2013 (n=100)	NR	33	26	4	13	9	5	NR
Present study 2015 (n=125)	14.4	23.2	18.4	16	16	7.2	3.2	1.6

morphological grounds to define specific types. Whilst World Health Organization (WHO) classification are mainly reliant on immunophenotyping and conventional karyotype. FAB classification has been widely adopted in most of haematology laboratories of Pakistan.

The FAB classification of AML has been comprehensively studied at both national and international levels (Kakepoto et al., 2002; Asif et al., 2013; Walter et al., 2013). However there is a breach of a decade between prior regional (Karachi) studies and in the present study. The present study has illustrated the existing spectrum of FAB classification in Pakistani adults AML patients. We determined AML-M1 as the commonest type, followed by M2 and M3, M4 and M0 respectively. This distribution of various FAB types was partly comparable with the prior studies. Nevertheless more pertinent finding of the present study is changeover from M2 subtype towards M1 variant.

Table-1 depicted the FAB distribution in various prior studies on Pakistani patients with adult's AML. Most published data indicate the predominance of M2 (1990) and M4 (2005) as a common subtypes previously (Chaudhry et al., 1993; Hassan et al., 1993; Harani et al., 2005). However, the M1 dominance was seen in the present study which is in concurrence with the recent studies by Asif and Ali et al from Pakistan (Asif et al., 2013; Ali et al., 2013). Similarly, Hamayun et al from northern area also revealed M1 as predominant subtype accountable in 50% of their study subjects (Hamayun et al., 2005). Nevertheless it seems to have a gradual transition from AML-M2 (30-89% blast cells) towards a more advanced AML-M1 (blast cell >90%) disease phenotype.

When compared these findings with recent Indian study on a large cohort (n=209), the predominant subtypes were M5 (25.4%) and M2 (23.9%) (Sarojam et al., 2014). Studies from Saudi Kingdom reported the predominance of M4 and M5 variants (Harakati et al., 1993; Spence et al., 1988). Nakase et al showed AML-M4 as common subtype in Australian AML patients compared to Japanese, where AML-M2 is frequent (Nakase et al., 2000). However recently one study on largest cohort (n = 5848) of patients from USA disclosed M1 in 25% of AML patients (Walter et al., 2013). Present study also confirms M1 (23.2%) as the most common type followed by M2.

The differences in AML subtypes may be due to the subjectivity of morphological diagnosis, however some genetic factors may be responsible for a particular FAB subtype of AML in our population. Notably most studies at national level had small number of patients and perhaps with under exploitation of cytochemical stains. Besides these studies might not have utilized immunophenotyping that resulted in an inaccurate diagnosis.

A number of biological and clinical factors affect the outcome and response to treatment in patients with AML. The differences in prognosis have been observed among the different FAB subtypes (Asif et al., 2013). Generally cases of M5, M6, M0 and M7 have a worse prognosis than those of M2, M3 and M4 (Asif et al., 2013). It is also note worthy, that substantiation of maturation in leukemic cells, presence of granules or Auer rods and positivity of Sudan Black Band reactions are associated with a more favorable prognosis (Asif et al., 2013). In our study most common subtype was AML-M1 which lack maturation, might points towards aggressive phenotype and poor prognosis. This may also represent high disease burden in our patients could have been due to the late presentation.

Clinically, an AML patient with an increase percentage of leukemic blasts tends to have FLT3-ITD mutation (Gregory et al, 2009). Recently Mawali et al showed that half of the patients with M1-FAB subtype had FLT3/ITD positivity which has been associated with poor prognosis (Mawali et al., 2013). However we did not evaluated mutational status in our patients which is our limitation. But perhaps it would be same in our population, which needs validation.

The limitations of the study need to be mentioned; firstly karyotyping analysis was not performed, as this facility was not available at our institute. Secondly informative markers including molecular testing and mutational status were also not determined due to financial constrains.

In conclusion, AML is predominantly seen in very younger age group in Pakistan. Though, previously other national studies had reported AML-M2 as a frequent type, but present study revealed Acute myeloblastic leukemia, without maturation (M1) as a major subtype. Prospective studies should be pursueded on larger patient series to incorporate novel molecular markers and its prognostication in the local population.

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