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Pathology

Frequency of Fab Subtype and Linicohaematological Manifestation in Elderly Acute Myeloid Leukemia Patients in Tertiary Care Hospitals Peshawar

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Abstract **Original Research Article**

Aim And Objectives: AML is the most common acute leukemia affecting adults, its incidence increases with increasing age; the study aims to find out the clinical and haematological parameters of adult AML patients and the frequency of AML FAB subtype among these patients. ***Methods:*** This descriptive, cross sectional study was conducted in IRNUM; KTH and HMC tertiary care hospitals of Peshawar, 30 diagnosed AML patients of age ≥ 50 years were included in the study. The demographic details were recorded in a questionnaire, previous clinical record was obtained and the hematological findings at the diagnosis were recorded. Data was recorded in Microsoft Excel® (version 2013) data sheet, for further analysis the data was imported into Statistical Package for Social Sciences® (SPSS) version 22. ***Results:*** Overall 30 diagnosed denovo AML patients of age ≥50 years of age, included 19 male (63.3%) and 11 females (36.7%) patients were included in the study. The mean age of our study patients was 57.83 ± 5.26 years whereas the median was 59.5 years. The most common AML-FAB subtype found among study patients was AML-M2 found in 12 (40%) of patients followed by AML M4 9(30%), AML M1 6(20%) and AML M5 3(10%) in respective order. The mean hemoglobin level among the study patients was 72.10 g/L. Anaemia severity was significantly higher in AML-M2 subtype (z-score 2.0). The AML-subtypes have statistically similar pattern of WBC count (Fischer Exact P-value 0.681). Among the presenting clinical features in the study group fever, anaemia, bone pain and weakness is the most frequent presenting features in all the AML FAB subtypes. However gingivitis and hepatomegaly is the most common presenting feature in AML-M5 in the study group. ***Conclusion:*** AML M2 was the most frequent AML FAB subtype found in study patients with the male predominance M: F is (1.7:1). Anaemia, fever, weakness and bone pain was the most frequent presenting feature among the study group. Weight loss is most common presenting clinical feature in AML M4 and M5. Gingivitis and hepatomegaly was the most common presenting feature found in AML M5 in the study group.

Keywords: Acute myeloid leukemia, Tertiary Care Hospitals.

INTRODUCTION

AML represents a group of haematopoietic disorder of the myeloid lineage, characterized by uncontrolled proliferation of immature blasts and block in differentiation resulting in accumulation of these myeloblasts in the bone marrow and peripheral blood. AML is the most common acute leukemia affecting adults, its incidence increases with increasing age [1]. The peak incidence of AML occurs at approximately 80 years of age [2]. Incidence of AML varies with gender and race [2]. AML has a slight male predominance in most part of the world in all age groups [2, 3]. A geographical variation in incidence of adult AML has been reported [2]. In North America, Western Europe and Australia, AML is reported to be more common compared to the Asia and Latin America [2]. Regional differences may be caused by environmental factors or population genetics [2]. With the median age of 67 years at diagnosis, AML is uniformly a fatal disease if untreated [3]. Age has a major impact on outcome and management for patient with AML. The cares of most of the patient are complicated as they are not preferentially candidates for cytotoxic therapy mainly due to the older age, poor performance status or other associated severe medical comorbidities [2, 4]. Mortality associated with AML varies with age, race

and gender, as is the case with incidence [2]. In US mortality rate increase with age because the recorded age adjusted mortality rate shows its peak at 17.6 per 100,000 population in patients ages 80 to 84 years [2] . Survival rate has increased in the last decades for younger patients but has no change in the older age group, which is a bigger challenge to achieve therapeutic success in this older age group AML patients [2].

A high degree of heterogeneous abnormalities with respect to chromosomal abnormalities, gene mutations and change in the expression of multiple genes has been documented in AML. Cytogenetic abnormalities are detected in approximately 50 to 60% of newly diagnosed AML patients and 40 to 50% of the patients have the normal karyotype. The majority of AML cases are associated with nonrandom chromosomal translocation that often results in gene rearrangement. Cytogenetic is the most important prognostic factor for predicting remission rate, relapse and overall survival [5].

FAB classification of AML was first introduced in 1976, [6]. FAB classification system is mainly based on the morphology and the maturation of the leukemic blasts [6]. FAB system divide AML into subtypes M0 through M7 [6]. The diagnosis of AML is mainly based on presenting clinical features and laboratory findings. Patients with AML often have several non-specific (general) symptoms. These include: Weight loss, Fatigue, Fever, Night sweats and loss of appetite. Anemia and thrombocytopenia are often profound [6]. A bleeding tendency caused by thrombocytopenia and disseminated intravascular coagulation (DIC) is characteristic of the Promyelocytic variant of AML. Infections are frequent and often catastrophic. Gum, spleen, liver and lymph nodes infiltration by tumor cells and hypertrophy can occur in AML [6]. CNS Involvement can present as Headaches, Weakness, Seizures, Vomiting, Facial numbness and blurred vision [6]. The recommended European Leukemia Net (ELN) and the National Comprehensive Cancer Network (NCCN) guidelines for laboratory diagnosis of AML include Complete blood counts and differential count, Bone marrow aspirate, Bone marrow trephine biopsy, Immunophenotyping and Cytogenetics [7].

The management strategies of AML has not considerably evolved over the last 2 decades, with curative treatment still relay on the successful induction therapy to accomplish a complete remission, and a following risk adapted consolidation treatment to avoid reversion [8]. The standard induction chemotherapy is considered more challenging in older patients due to excessive toxicities linked to chemotherapy, comorbidities and treatment related mortalities.

The main purpose of this study is to find out frequency of different AML FAB subtype in elderly AML patients and their clinicohematological manifestations.

MATERIAL AND METHODS

This descriptive, cross sectional study was conducted in IRNUM, KTH and HMC tertiary care hospitals of Peshawar from January 2022 to July 2022. Ethical approval from the ethical board of Khyber Medical University (KMU) was acquired immediately after the project was approved from the Advanced Studies and Research Board (ASRB). In conformation with allocated budget and resources, the sample size for this study was set at 30 AML patients. Denovo AML patients of age ≥50 years were included in the study, which were diagnosed on the basis of bone marrow trephine biopsy. Patients with any of the following characteristics were excluded from the study: Secondary AML, relapsed AML, AML M3 and treated AML. Patients were enrolled into the study after acquisition of informed consent in writing. The demographic details were recorded in a questionnaire, which included age, gender, ethnicity and address. Besides this, previous clinical record was obtained and the hematological findings at the diagnosis were recorded. A comprehensive questionnaire depicting the clinical details regarding AML was filled out for each patient by a pre-trained physician. The details included physical examination with focus on fever, easy bruising and hepato-splenomegaly. The questionnaire also included disease history in terms of recurrent infections, bleeding symptoms, weakness, weight loss, bone pain and lymphadenopathy. Initially data was recorded in Microsoft Excel® (version 2013) data sheet, for further analysis the data was imported into Statistical Package for Social Sciences® (SPSS) version 22. Continuous variables were described using mean and standard deviation. Comparisons of mean among categorical variables were carried out employing student t- test (for two groups) and Kruskall-Wallis test (for more than two non-parametric variables). The results were presented in the form of tables, charts and graphs, which were retrieved using Microsoft excel® (version 2013).

RESULTS

Age and Gender

Age has a significant bearing on disease outcome in AML. Both disease nature and patient health are affected adversely with increasing age. The mean age of our study patients was 57.83 ± 5.26 years whereas the median was 59.5 years. These included 19 male (63.3%) and 11 females (36.7%) patients. Table 1 presents a description of various age groups among male and female study participants.

AML-FAB Subtypes among Study Patients

The most common AML-FAB subtype found among study patients was AML-M2 found in 12 (40%)

of patients followed by AML M4 9(30%), AML M1 6(20%) and AML M5 3(10%) in respective order.

Haematological Parameters

The mean hemoglobin level among the study patients was 72.10 g/L. There is no statistically significant difference in the mean Hb levels among males (70 g/dL) and females (73 g/L).

Anaemia severity was significantly higher in AML-M2 subtype (z-score 2.0). All of the cases from AML-M1 and M5 were found to have moderate anaemia.

The AML-subtypes have statistically similar pattern of WBC count (Fischer Exact P-value 0.681), however majority of the patients from AML-M1, M4 and M5 were found to have raised WBC count.

Majority of the study patient (n=16, 53.3%) were found to have mild thrombocytopenia. Only 5 patients were found to have severe thrombocytopenia.

The AML-FAB subtypes among the study population were found to have statistically comparable platelet counts. Patients with AML- M1 and M5, however, had a rather milder thrombocytopenia in comparison with the other two subtypes.

Clinical Features

The patients in the study group of the AML-subtypes presented with the clinical features of fever with or without the focus of infection, anaemia, weakness, weight loss, bone pain, bruises, splenomegaly, lymphadenopathy, gingivitis and hepatomegaly.

The AML FAB-subtypes were comparable statistically for all the clinical features except gingivitis which was statistically significant finding in the patient with AML-M5 (Fischer Exact P-value .009).

Among the presenting clinical features in the study group fever, anaemia, bone pain and weakness is the most frequent presenting features in all the AML FAB subtypes. Weight loss is most common presenting clinical feature in AML M4 and M5. Bruises, splenomegaly and lymphadenopathy is an infrequent presenting features among all the four AML FAB subtypes in the study group, however gingivitis and hepatomegaly is the most common presenting feature in AML-M5 in the study group.

Table 1: Presenting Clinical Features Among the Study Group in Different AML FAB subtypes

	M1	M2	M4	M5	TOTAL
Fever	4 66.7%	10 83.3%	8 88.9%	2 66.7%	24 80%
Fever with infection	4 66.7%	5 41.7%	7 77.8%	2 66.7%	18 60%
Pallor	5 83.3%	11 91.7%	7 77.8%	1 33.3%	24 80%
Weakness	5 83.3%	11 91.7%	9 100%	3 100%	28 93.3%
Bone Pain	5 83.3%	7 58.3%	3 33.3%	2 66.7%	17 56.7%
Weight Loss	1 16.7%	3 25.0%	5 55.6%	2 66.7%	11 36.7%
Bruises	1 16.7%	4 33.3%	5 55.6%	1 33.3%	11 36.7%
Splenomegaly	0 00.0%	1 8.3%	4 44.4%	1 33.3%	6 20.0%
Lymphadenopathy	0 00.0%	3 25%	0 00,0%	0 00.0%	3 10.0%
Gingivitis	0 00.0%	2 16.7%	1 11.1%	3 100%	6 20%
Hepatomegaly	0 00.0%	1 18.3%	2 22.2%	2 66.7%	5 16.7%

Disease Bulk Increases as the Time-to-Diagnose Increases

In this study we found that the disease bulk, defined as the conglomerate of different clinical features, corresponds directly with the time-to-diagnose, i.e. the number of clinical features in a patient increased as the time-to- diagnose increased and vice versa.

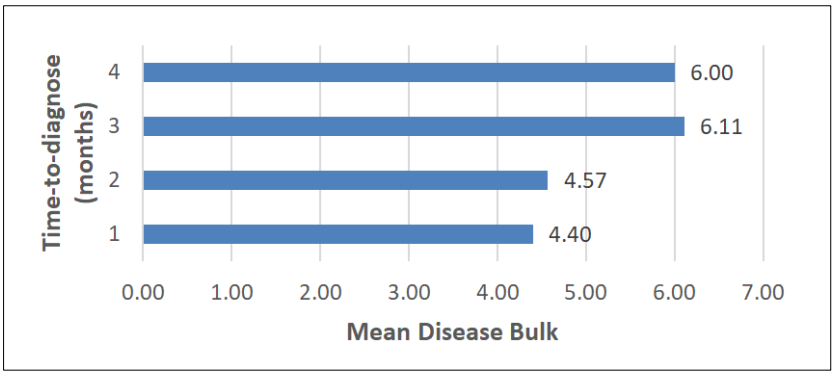

Figure 1: Presents the mean disease bulk in various time-to-diagnose categories among study patients

Figure Error! No text of specified style in document.**. 6 Disease Bulk in Various "Time-to-Diagnose" Categories**

DISCUSSION

AML is mainly a disease of old age. The global median age identified for the disease in majority of the western nations is more than 65 years. The median age found in this study was significantly higher, i.e. 59.5 years. This finding is comparable with those from neighboring developing nations [9]. A higher propensity of male gender was identified in this study (male: female = 1.7:1.0). This is consistent with findings from both developed and developing countries around the globe [10, 11].

AML-M2 was found to be the most frequent AML-FAB subtype among study patients. In a study conducted on AML patients of all age groups in the Sindh province of Pakistan in 2005, AML-M4 was found to be the most frequent AML-FAB subtype, followed by AML-M2 [12]. The disparity in findings, when compared with current study, may pertain to the differences in environmental factors, ethnicity and age categories of the study patients. Another study conducted in the same population as the current one, in the year 2005, narrated AML-M1 to be the most frequent FAB subtype followed by AML-M2 [13]. Again the study included only patients of age group <20 years. The study also did not consider testing the samples with immunocytochemistry (AML-M1 could be confused with ALL at times). More recently conducted studies in the region, however, agree with findings from the current study, with AML-M2 being the most frequent AML-FAB subtype. Similar results of higher frequency of AML-M2 have been found in studies conducted in international studies. AML-M2 has been found to associate with t (8:21) which is regarded as a good prognostic marker. A higher disease frequency is hence anticipated. This has been confirmed in several previous studies [14].

Fever was the most common clinical feature present in 24 out of 30 (80%) among the study patients in the current study. It was also found to be the most common finding among AML patients in previously conducted local studies; the study conducted by Asif N *et al*, recorded the fever in 80.4% of the study patients, another study done by Chang F, *et al*, in Sindh in 2016 reported fever in 81% of AML patients, a study done on AML patients by Mohammad B, *et al*, in the same population noted fever in 90% of the study patients.

Generalized weakness was another common presenting complaint among participants of the current study present in 28 (93.3%) out of 30 AML patients. This clinical feature has been reported in AML by several other local studies; the positive cases ranged from 38-100% [15, 16]. The lowest proportion of patients affected with this symptom among local studies was reported by Sadiq MA *et al*, in their study, weakness was found in 38% of the cases. The finding was however elicited only at presentation and it was not inquired for since appearance of the first symptoms. The mean duration of illness in our study is 68.8 days and in this study, it was 45 days.

In the current study weight loss was recorded in 37% of the patients, since inception of the disease. Only a few earlier studies have worked out this symptom among AML patients. Study conducted by Naghmi A and Hassan K in 2012 reported weight loss in 9.8% of the AML patients [17]. Chang *et al*, however, reported weight loss in 49% of the AML cases, they studied [16].

In the current study we found hepatomegaly in 5 (17%), splenomegaly in 6 (20%) and lymphadenopathy in 3 (10%) out of 30 AML study patients. Hepatosplenomegaly in the current study is found to be present in AML M4 and M5 which is also reported by an earlier study done on AML patients Asif N, *et al*, [5]. Contemporary studies have reported almost comparable findings. Table 1 presents the frequency/percentage of AML patients with Hepatomegaly, splenomegaly and lymphadenopathy at presentation.

In the present study, bone pain was found in the majority (57%) of the patients. Sadiq *et al*, reported bone pains in 14% of their AML study patients. In

another local study, the feature was reported in 18.5% of the patients. In a similar study conducted in KP, bone pains were reported in 20% of the AML study patients [6].

In the current study, gingival hyperplasia was found only in patient with AML-M5, which is also reported by Chang F, *et al*, as the most common feature present in AML M5(7). In other previous studies, the incident is reported among 7.7-27% of the study patients [16, 18].

The mean Hb found among patients in the current study was 7.2 g/dL. This is comparable to the mean Hb levels in previous local studies where these range from 6.9 to 8.6 g/dL. Since patients from current study mostly belonged from a rather lower socio-economic class, the Hb level found was lower in comparison. Findings from studies conducted in the western world are also in agreement with those from local studies. Mean Hb levels in AML patients from developed countries tend to be better in comparison with the developing countries [19, 20]. Studies conducted in Sudanese and Indian population have comparable findings [19, 20].

The mean WBC count found in the current study was 26.99+29.78. Findings from local studies vary considerably across different socioeconomic classes. Patients from relatively higher socio-economic class tend to present with a relatively low WBC count in comparison to the lower socio-economic class patients. An impact of year of study has also been noticed [21]. Those conducted earlier have deduced a higher WBC count as compared to the newer ones. This may pertain to the evolving health care system and better level of awareness among general population over the years, locally. Findings from studies conducted in developed countries contradict findings from current study [5, 22, 23]. In comparison, studies from countries with comparable socio-economic status have comparable results [19, 20].

Like Hb and WBC counts, platelet counts are also affected adversely in AML. The mean platelet count found in the current study was 41.2 x 10^9/L. This is in agreement with findings from earlier conducted local studies. Socio- economic status has no obvious bearing on platelet count (Table 1). Platelet counts from international studies also have comparable findings [5, 19, 20].

CONCLUSION

The current study concluded that AML M2 was the most frequent AML FAB subtype found in 12 (40%) followed by M4 in 9 (30%), M1 in 6 (20%) and M5 in 3 (10%) among 30 study patients in respective order. Anaemia, fever, weakness and bone pain was the most frequent presenting feature in all the four AML FAB subtypes among the study group. Weight loss is most common presenting clinical feature in AML M4 and M5. Gingivitis and hepatomegaly was the most common presenting feature found in AML M5 in the study group. In this study we found that the disease bulk, defined as the conglomerate of different clinical features, corresponds directly with the time-to-diagnose, i.e. the number of clinical features in a patient increased as the time-to-diagnose increased and vice versa.

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