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Original Article

Acute Myeloid Leukemia amongst Adults

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Abstract

Introduction: **Acute myeloid leukemia is characterized by infiltration of bone marrow and other tissues by abnormal myeloid precursors, often with appearance of these abnormal cells in the peripheral blood. AML comprises about 80% of acute leukemias in adults. Clinical features are generally ascribed to marrow failure as well as infiltration by blast cells.**

Objective: **To look into various FAB types of AML and clinically correlate them.**

Material and Methods: **This cross-sectional, descriptive study was conducted at the department of pathology, Pakistan Institute of Medical Sciences, Islamabad from July 2007 to July 2009. A total of 56 consecutive freshly diagnosed adult patients of AML were included in the study. Clinical data and Complete blood counts were studied. Bone marrow aspiration, and when required trephine biopsy were performed. Blood and bone marrow slides were stained by Wright stain; cytochemical stains were performed whenever required. Data were analyzed using SPSS version 14. Mean and ± SD were calculated for numerical values and frequencies for string values.**

Results: **In total of 56 adult cases of AML 33 (59%) were males and 23 (41%) were females. The age ranged from 16 to 79 years with mean ± SD age of 37 ± 17.19 years. The most common subtype was AML-M1 (32%) followed by M3, M4 (19.6% each), M2 (14%) and AML-M5 (9%), respectively. AML-M6, M7 and M0 were observed in one patient (1.8%) each. Hepatomegaly was observed in 48% patients, splenomegaly in 45% patients and lymphadenopathy was noted in 38% patients. Tissue infiltration was most common with AML-M4 and AML-M5 subtypes and least frequent with AML-M3 subtype. Majority of patients of AML were found to be anaemic. Leukocyte count more than 1 lack was seen in 13 (16%) patients. Majority of patients (94%) had thrombocytopenia. Pancytopenia was noticed in 13 (15.8%) patients and these included cases of M1, M2, M3 and M0. None of the Patients of AML-M4, M5, M6 and M7 presented with pancytopenia.**

Key words: **Acute myeloid leukemia, leukemia, clinical presentation, morphological features, leukemia**

Introduction

Acute myeloid leukemia (AML) is characterized by an increase in number of myeloid cells in the marrow with arrest in their maturation resulting in haemopoietic insufficiency (with or without leucocytosis) and infiltration of bone marrow and other tissues by myeloblasts.AML comprises about 80% of acute leukemias in adults and its frequency increases with advancement of age.[1] Diagnosis of AML is established when more than 30% of nucleated marrow cells are blast cells. It is further classified into 8 subtypes according to FAB (French American British Classification). According to WHO Classification however, lower percentage of blasts (20%) in blood or bone marrow is sufficient for diagnosis of acute leukemia particularly if acute leukemia is associated cytogenetic or molecular abnormalities.[2,3] It has been observed that median age at presentation in AML is 65 years with slight male predominance. Although the survival rates have improved remarkably in the younger age group, the prognosis in older patients is still poor.[4]

Clinical features of various subtypes are generally similar and are the result of marrow replacement and failure of normal haematopoiesis, resulting in anemia, bleeding and increased risk of infections. These may be general or related to specific organ system. The most common complaint is nonspecific fatigue or malaise. Anemia leads to pallor, weakness and dyspnea etc. Fever is common and is the presenting feature in 15-20% of patients. Bleeding is also a common presenting feature and can occur from nose, gums, gastrointestinal tract or urinary tract, or more commonly as petechial rash or easy brusabilty. Bone pains occur in less than 20% of patients. Organomegaly is seen in up to half of the patients with AML; however, lymphadenopathy is relatively infrequent. Skin infiltration also occurs with

involvement of extramedullary sites, including gum infiltration and CNS and is more common with AML-M5.

FAB (French American British classification) categorizes AML into 8 subtypes. In most cases, the diagnosis of these subtypes can be accomplished by careful morphological assessment of blood and bone marrow smears and cytochemistry.[5] However, there remains a significant number of cases that cannot be definitively diagnosed by these methods. In such cases immunological markers are an important diagnostic tool.

A number of clinical and biologic factors affect the outcome and response to treatment in AML patients. The differences in prognosis have been observed among the different FAB categories. Cases of M5, M6, M0 and M7 generally have a worse prognosis than those of M1-M4, and M2. AML-M3 (particularly with 15;17 translocation) has the best prognosis (if it is not associated with DIC) as they respond very well to ATRA (al trans-retinoic acid analogue). A poor prognosis is also associated with the presence of trilineage myelodysplasia" and with PAS positive erythroblasts. Conversely, evidence of maturation of leukemic cells, such as the presence of granules or Auer rods, strong positivity of Sudan Black B and positive reactions for non-specific esterase, is associated with a more favorable prognosis. Other adverse prognostic factors include an age over 60 years, a poor performance score before treatment, AML resulting from prior chemotherapy or an antecedent hematologic disorder such as MDS, white-cell count of more than 20,000/µl or an elevated serum lactate dehydrogenase level at presentation. Furthermore, an assessment for multidrug resistance and immunophenotyping may provide prognostic information. Detailed cytogenetic analysis of the leukemic blasts has also been demonstrated to be a very important prognostic factor.

The objectives of this study were to look into various types of AML according to FAB classification and their clinic-morphological presentation in adults.

Materials and Methods

This cross-sectional, descriptive study was conducted at the department of pathology, Pakistan Institute of Medical Sciences (PIMS), Islamabad from July 2007 to July 2009. A total of 56 consecutive freshly diagnosed adult patients of AML at the department of pathology, PIMS were included in the study. Patients already diagnosed as AML, and receiving cytotoxic therapy were excluded. A detailed clinical history of patients especially regarding age, sex, duration of symptoms, fever, pallor, bone pain, bleeding and various constitutional symptoms were entered in the performa. Physical examination was performed taking into account the presence of lymphadenopathy, hepatomegaly, splenomegaly, purpura, petechiae and gum hyperplasia etc. Complete blood counts were performed on a fully automated blood cell counter (Sysmex KX-21) using freshly obtained EDTA-blood sample in vacutainers.

All the patients were subjected to bone marrow aspiration, under aseptic precautions, using disposable lumbar puncture needle size 16 for adults and size 18 for children. Blood and Bone marrow Smears were stained by Wright stain. In all cases cytochemical stains (Sudan Black B, Non-specific esterase and PAS) were performed. Myelogram was done by counting 500 marrow cells. Number and morphology of the blast cells, typing according to FAB classification and final diagnoses were entered into the Performa.

All the results were then entered on SPSS version 14 for final analysis. Mean and $\pm$ SD were calculated for numerical values and frequencies were calculated for string values.

Results

In a total of 56 adult AML patients (>15 years age), 33 (59%) were males and 23 (41%) females with a male to female ratio of 1.4:1**.** Their ages ranged from 16 to 79 years with mean $\pm$ SD age of 37 $\pm$ 17.19 years. The majority of patients was between 15 and 40 years, and only 1.8% were > 70 years age (Table 1).

As shown in table 2, pallor and fever were observed in 80% and 46% patients respectively. Weight loss and bone pains were relatively less frequent. Lymphadenopathy and hepatomegaly were almost equally frequent, and were closely followed by presence of a palpably enlarged spleen. Gum hyperplasia was observed only in AML-M4 and M5 patients. The most frequent sites of bleeding were skin, gums and nose. None of the patients had history of intracranial bleeding. Bleeding was characteristically a prominent presentation in patients of AML-M3 patients (89%). Hepatomegaly and splenomegaly were observed in AML-M5 and M4 in 100% and 83% patients respectively. Gum hyperplasia was observed in AML-M5 (50%) and M4 (20%) cases.

Table 3 shows findings of complete blood picture in our patients. As shown in the table, majority of patients of AML were found to be anemic. Their mean hemoglobin levels ranged from 2.0-13.6 g/dl with

Table 1: Age Range in Adults		
Age Range (in years)	**Number of patients**	**%**
15-40	37	66
41-60	13	23
> 60	06	11

Table 2: Clinical Features of AML (n 56)	
Clinical Feature	**No (%)**
Fever	45 (80.4)
Pallor	26 (46.4)
Bleeding	25 (44.5)
Weight loss	07 (12.5)
Weakness	26 (46.4)
Bone pains	09 (16.1)
Lymphadenopathy	22 (39.3)
Hepatomegaly	21 (37.5)
Splenomegaly	19 (33.9)
Gum Hyperplasia	06 (10.7)

Table 3: Complete Blood Picture in AML Patients	
Hematological Parameter	**Mean (Range) ± SD**
Hemoglobin (g/dl)	7.44 (2-13.6) ± 2.16
White Cell Count (x10³/µl)	52.35 (1.3-272) ± 33.33
Platelet count (x10³/µl)	56.53(3-392) ± 60.55

Table 4: AML Subtypes (n 56)	
Subtype	**No (%)**
AML-M1	18 (32.1)
AML-M2	08 (14.3)
AML-M3	11 (19.6)
AML-M4	11 (19.6)
AML-M5	05 (09)
AML-M6	01 (1.8)
AML-M7	01 (1.8)
AML-M0	01 (1.8)

Table 5: Frequencies of AML Subtypes Comparison with other studies	
Author, Year	**Frequent Subtypes**
Naghmi et al	M1,M3,M4
Swirsky et al, 1986	M1,M2,M4
Callera F ET AL, 2006	M1, M2
Raina et al, 1990	M2, M3,M4
Spence et al, 1988	M4,M2,M5
Hassan et al, 1993	M2, M1,M4
Chaudry et al, 1993	M2,M4,M1
Harakati et al, 1998	M4,M5,M3
Khalidi et al, 1998	M2,M4,M1
Arber et al, 2003	M2, M4, M1
Kakepoto et al 2002	M4, M2, M3
Kumar L et al, 2004	M2,M4,M5
Hamayun M et al, 2005	M1,M2

Harani MS et al, 2005	M4,M2,M3
Mohammad SE et al, 1998	M4,M5
Rego FN et al, 2003	M4, M3, M2
Nakase et al, 2004	M4

mean of 7.4 g/dl ± 2.16 SD. The white cells had a wide range from 1.3 to 272 x10^3/µl with a mean of 52.35± 33.33 SD. Leucopenia was observed in 16% patients. Leukocytes count more than 100 x10^3/µl (hyperleukocytosis) was seen in 11% patients. Platelet count ranged from 3 and 392 x10^3/µl with mean value of 56.5310^3/µl ± 60.55xSD. Majority of patients (68.3%) had platelet count less than 50 x10^3/µl.

As shown in table 4, the most common subtype was AML-M1 (32%) followed by M3, M4 (19.6% each. In patients >60 years age, majority was diagnosed as AML-M4 and AML-M5.

Discussion

Acute Myeloid Leukemia is a group of disorders characterized by a spectrum of clinical, morphological, immunophenotypic and chromosomal abnormalities. It accounts for approximately 25% of all leukemias in adults in the western world, and therefore is the most frequent form of leukemia in this age group. [6, 7] It has the lowest survival rate of all leukemias.

In this study, among 56 adult patients male to female ratio was 1.4:1. Regarding age it was observed that at the time of presentation majority of patients (89%) was less than 60 years and only 1.8% cases were above 70 years. The same trend has also been reported in many other studies done on adult patients showing mean age of 67 years [8] with majority of their patients below 60 years (68%). Similar observations were made by N Braham-Jmili et al; they noted that 77% of their patients were less than 60 years age.[9]

The FAB classification has been the major system used by hematologists for more than 20 years. This classification is best suited for places where sophisticated investigations like cytogenetic studies and molecular studies are not available. In our study most common subtype was AML-M1 followed by equal number of M3 and M4. According to a study done in Japan on adult patients of AML, the most frequent subtype was M2 followed by M3 and M4. Table 5 shows comparison of AML subtypes with our study. As we look into the frequency of FAB types in different age groups, it was noted that AML-M3 subtype though common below 50 years of age, not a single case of M3 was seen in patients older than 50 years, the finding comparable with a study done in Japan on elderly patients of Acute Myeloid Leukemia.[10]

Disrupted hematopoiesis leads to the most common presenting manifestations, i.e. anemia, infection, and bleeding tendency. Among our patients majority presented with pallor and fever. Bleeding was also a common presenting feature. Similar findings have been reported in other studies on AML.[11,12] Rogers et al have documented that pallor and fever were prominent feature in majority of subtypes. Bleeding however was a prominent symptom in AML-M3. Most common types of bleeding were epistaxis, gum bleeding and easy bruisibilty.[13] According to Hassan et al feeling of weakness; easy fatigability and pallor were invariably present in all FAB types. In their study on clinico-hematological features of AML, majority of patients presented with fever. Bleeding manifestations were most frequent in AML-M3 cases followed by M5, M1, M4 and M2, respectively.[14] Ghosh et al from Tata Memorial hospital reported that majority of their patients presented with fatigue and pallor. They also reported that bleeding was most commonly seen in acute promyelocytic leukemia and monocytic leukemia.[15]

Patients with AML-M3 have significantly higher risks for intracranial haemorrhage than those patients with other subtypes of AML. In our series, none of the patients presented with intracranial bleeding. In AML-M3, there is also risk of bleeding from other sites and the bleeding diathesis is either due to thrombocytopenia alone or as a part of DIC. In one of the local studies done by Qazi et al on bleeding diathesis in acute myeloid leukemia it was noted that DIC was the most frequent in AML M3, followed by M5. [17] In another study done at Queen Elizabeth Central Hospital Malawi, to look for the pattern and clinico- morphological features of different leukemias it was reported that among their AML patients, majority presented with pallor and weakness and fever was noted in 32% patients.

In Acute myeloid leukemia extramedullary infiltration by leukemic cells may cause lymphadenopathy, splenomegaly or hepatomegaly. Lymphadenopathy is not as common as seen in acute lymphoblastic leukemia. Hepatosplenomegaly however is more frequent but massive hepatosplenomegaly is uncommon. In our patients, hepatomegaly and splenomegaly were observed in 48% and 45% patients respectively. Majority had mild to moderate hepatosplenomegaly. Lymph node enlargement was

noted in 33% patients. Gum hyperplasia was seen in only 10% cases and majority of them belonged to FAB types M4 and M5. Almost similar observations were made in other studies.[11,12] Gum hyperplasia however was more frequent in both the studies (seen in 23%, 24% patients) as compared to our results and majority of their patients were diagnosed as AML-M4, M5 and M1 subtype.

Anemia is a constant feature in all acute leukemias and in majority of cases is due to bone marrow infiltration leading to decreased production and rarely due to decreased red cell life span and autoimmune destruction. Evaluation of complete blood picture of our cases showed that mean hemoglobin was quite low. Our results are comparable with other studies.[15]

Amongst adult patients with acute leukemias, 5 to 30% present with hyperleukocytosis and symptoms of leukostasis. Hyperleukocytosis is defined as a total peripheral WBC above 100 x 10^9/L. Hyperleukocytosis increases the blood viscosity and is associated with the aggregation of leukemic cells in the microcirculation. Complications from hyperleukocytosis are much more common in AML than in ALL. In our study 11% of patients showed hyperleukocytosis. One interesting finding in our study was that majority of patients with hyperleukocytosis were AML-M1 cases. In one of the studies on the clinical course of patients with AML looked for the impact of WBC count on the initial course and overall outcome of these patients it was observed that white cell count greater than 100 x 10^9/l /l had lead to significantly more deaths during the first week of therapy than did patients with count less than 50 x 10^9/l.

Thrombocytopenia is a well known manifestation of acute leukemias. In our study, 95% patients developed thrombocytopenia and a low platelet count was observed consistently in AML-M2 and M3.The association of bleeding with platelet count has been well documented in the literature. Gaydos et al. were the first to document this finding in patients with acute leukemia in 1962. They demonstrated that there was a linear relationship between bleeding and platelet count. [19] It is generally noted that clinically significant bleeding occurs in approximately 20% to 32% of thrombocytopenic patients with AML (excluding patients with Promyelocytic leukemia).[20] In addition to thrombocytopenia, numerous factors have been suggested to increase the risk of bleeding including fever, sepsis, infection, anticoagulant therapy, medications, coagulation abnormalities, platelet function defects, hyperleukocytosis or recent bone marrow transplantation. [21] Qazi et al conducted a study to look into the problem of bleeding in cases of AML. They correlated this feature with thrombocytopenia alone or DIC. All their cases had thrombocytopenia. It was present alone in 70 % and as a part of DIC in the remaining 30 % of cases. DIC was the most frequent in AML M3 followed by AML-M5 and M2, respectively. Relationship to age in their study showed that DIC was the most frequent in the old age group (23.3 %), i.e. between 65 & 75 years.[17]

Pancytopenia is not a common finding in AML as majority of patients have high leukocyte count though platelet counts and hemoglobin are decreased in majority of patients. Pancytopenia is associated complications of susceptibility to life threatening infections and bleeding tendency. It is not a disease entity itself but a hematological manifestation of several different disease processes. These disorders may affect bone marrow either primarily or secondarily, resulting in the manifestation of pancytopenia. In our study pancytopenia was noticed in 19.6% patients and bicytopenia in 68% patients. A study done in Nepal to look into the causes of pancytopenia showed that 3.7% of AML patients .[22]

Hypocellular acute myeloid leukemia and hypocellular myelodysplastic syndrome represent a small (10-15%) but a significant number of patients diagnosed with myeloid malignancies. In this study bone marrow was hypocellular in 12.5% cases. Hypocellular AML mainly affects elderly and account for 5--10% cases of de-novo AML. Both these conditions are associated with pronounced pancytopenia and it is sometimes difficult to separate these disorders from aplastic anemia. If not carefully examined, separation between these conditions can be problematic. We also had one case which was diagnosed previously as aplastic anemia and later it was diagnosed at our centre as a case of AML-M2 with hypocellular bone marrow. It is thus recommended that all such cases should be reviewed by more than one observer. These issues are further compounded by pauci-cellularity of bone marrow aspirates.[23]

Presence of dysplasia whether in single or multiple lineages has an impact on prognosis if combined with unfavourable prognostic factors like age > 60 years or abnormal karyotypes. Study of prognostic impact of dysplastic features and other parameters such as age, cytogenetics, presence of auer rods, and lactate dehydrogenase level at diagnosis in de novo acute myeloid leukemia shows that dysplasia has not been found to be an independent prognostic parameter. One case of AML-M1 and 2 cases of AML-M4 showed marked dyserythropoiesis but dysplasia in other cell lines was not observed. However, the detection of

trilineage dysplasia correlates with unfavourable cytogenetics.[24]

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