Original Article

Clinical Manifestations of Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemias (AML) affect preferentially adults. Clinical manifestations are due to cytopenias and tissue infiltration. Manifestations vary with certain subtypes e.g. bleeding and infections are common with AML-M3, tissue infiltration is more often seen in AML-4 and M5, and bone marrow fibrosis is seen in AML-M7.

Objective: To study demographic features and clinical manifestations of acute myeloid leukemia.

Patients & Methods: A cross-sectional study was conducted at department of Pathology, Pakistan Institute of Medical sciences, Islamabad from July 2007 to July 2009. All the cases of AML (diagnosed on bone marrow biopsy) belonging to all age groups and both sexes were included in the study. Age at diagnosis, symptoms and clinical findings in AML and its various subtypes were noted. Results were entered on SPSS version 14 for statistical analysis.

Results: In a total of 82 cases of AML, 55% were males and 45% females, with mean age of 27.5 ± 19.9 years SD. The most common subtype was AML-M1 (33%) followed by M3 (22%) and M4 (18%), respectively. The common presenting symptoms were pallor, fever and bleeding. Hepatomegaly, splenomegaly, lymphadenopathy and gum hyperplasia were also frequent. Tissue infiltration was the commonest in AML-M5 and M4.

Conclusion: Acute myeloid leukemia is the malignancy of adults; it is more common in males and manifestations vary with its subtype.

Key words: Leukemia, clinical manifestations, AML, hematological malignancies

Introduction

Acute leukemias are highly malignant neoplasms and are responsible for a large number of cancer-related deaths.[1] Although the survival rates have improved remarkably in the younger age group, the prognosis in older patients is still poor.[2] Acute myeloid leukemia is characterized by hemopoietic insufficiency (with or without leukocytosis) and infiltration of bone marrow and other tissues by myeloid cells. It is further classified into 8 subtypes. AML occurs at any age but is more common in adults (comprising about 80% of acute leukemias).

Symptoms related to AML are caused by replacement of bone marrow and failure of normal hemopoiesis, 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. Fever is common and is the presenting feature in 15-20% patients. Bleeding can occur from nose, gums, gastrointestinal tract or urinary tract, or more commonly as petechial rash or easy bruisibility. The severity correlates with degree of thrombocytopenia or presence of disseminated intravascular coagulation (DIC), most commonly observed in AML-M3. Bone pains occur in less than 20% of patients.[3] Leukemic blast cells circulate and infiltrate other tissues. Extramedullary involvement is the most common in monocytic and myelomonocytic leukemias and usually involves tissues like liver, spleen lymph nodes, gums, skin and CNS. Palpable splenomegaly and hepatomegaly occur in about one third of patients.

Pustules or other major pyogenic infections of the skin and of minor cuts or wound common. With severe neutropenia after chemotherapy however, major bacterial, fungal or viral infections become frequent. Myeloid (granulocytic) sarcoma is an extra medullary tumor that occurs in 2 to 14% of cases of AML.[3] The tumors are usually localized; they often involve bone, periosteum, soft tissues, lymph nodes, or skin. Common sites are orbit and paranasal sinuses, but other sites may be involved. Testicular infiltration is less common in AML than in ALL, with an incidence of 1 to 8%.[4] Meningeal disease has been reported to develop in 5 to 20% of children and up to 16% of adults with AML.[3] The CNS disease is associated with young age (<2 years), hyperleukocytosis, and the AML-M0 variants.

The diagnosis of acute leukemia is based primarily on well-defined morphologic criteria and findings of cytochemical stains. Immunophenotyping is also very important particularly in characterizing morphologically poorly differentiated acute leukemias. Cytogenetics provide an important prognostic information and are becoming vitally important in classifying these leukemias (WHO Classification) and also determining the appropriate treatment protocol. Molecular studies are also helpful in

defining prognosis, response to treatment and identification of minimal residual disease.

A number of clinical and biologic factors affect the outcome and response to treatment in AML patients. The chance of cure for a specific patient depends on a number of prognostic factors.[5] In AML some differences in prognosis are seen among the different FAB categories. Cases of M5, M6, and M7 generally have a worse prognosis than those of M1-M4, and AML M0 has the worst prognosis. Cure rates for promyelocytic leukemia can be as high as 98%.[6] Conversely, evidence of maturation of leukemic cells, such as the presence of granules or auer rods, strong positivity of SBB and positive reactions for non-specific esterase, is associated with a more favorable prognosis. Other adverse prognostic factors include an age over 60 years, poor performance score before treatment, AML resulting from prior chemotherapy or antecedent MDS, and a white-cell count of more than 20,000 per cubic millimeter or an elevated serum lactate dehydrogenase level at presentation. Patients with t15; 17, t8; 21, t16; 16, and inv 16 have good prognosis. Cure rates in clinical trials have ranged from 20–45%.[7]

The objective of this study was to look into demographic features and clinical manifestations of acute myeloid leukemia and its various subtypes.

Patients & Methods

This was a cross-sectional study conducted at the Department of Pathology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, from July 2007- July 2009.

Inclusion Criteria: All freshly diagnosed cases of Acute Myeloid Leukemia from all age groups and both sexes were included in the study.

Exclusion Criteria: 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 other constitutional symptoms were entered in specially designed performa. Physical examination was also performed especially pertaining to lymphadenopathy, hepatomegaly, splenomegaly, purpuric or petechial rash and gum hyperplasia etc.

In every patient, about 2.5 ml blood sample was collected in EDTA containing tube. Complete blood picture was done on an automated hematology analyzer, Sysmex Kx-21. Peripheral blood smears were freshly made and stained by Wright stain and two slides were made for reticulocyte count by brilliant cresyl blue.

All the patients were subjected to bone marrow aspirations using disposable lumbar puncture needle size 16g. Bone marrow smears were stained by Wright stain. In all cases cytochemical stains (Sudan Black B, Non-specific esterase and PAS) were performed, according to requirement.

Statistical Analysis: All the findings (including clinical features, peripheral film and bone marrow findings) were entered on SPSS version 14 for final analysis.

Results

In a total of 82 patients of AML belonging to all age groups, 45 (55%) were males and 37(45%) were females with male to female ratio of 1.2:1. Age ranged from 2 months to 79 years with a mean age of 27.5 ± 19.92 SD years. Among them 26 (38%) were below the age of 15 years and 56 (68 %) were more than 15 years with adult to children ratio of 2.2:1.

Table1: Frequency of AML Subtypes (N= 82)	
Subtype	**N (%)**
AML-M1	27 (33)
AML-M2	12 (15)
AML-M3	18 (22)
AML-M4	15 (18)
AML-M5	06 (7.2)
AML-M6	02 (2.4)
AML-M7	01 (1.2)
AML-M0	01 (1.2)

`Table 2: Clinical Features in AML	
Clinical Feature	**N (%)**
Pallor	71 (86.6)
Bleeding	43 (52.4)
Fever	68 (82.9)
Weakness	31 (38)
Palpitation	02 (2.4)
Weight loss	08 (9.8)
Bone pains	15 (18.3)

The most common subtype (Table 1) was AML-M1 (33%) followed by AML-M3 (22%), AML-M4 (18%), AML-M2 (14.6%) and AML-M5 (7.3%). AML-M0, M6 and M7 were relatively infrequent.

Table 3: Physical Findings in AML Subtypes					
Physical finding	**AML-M1 N:27 N (%)**	**AMLM2 N:12 N (%)**	**AML-M3 N:18 N (%)**	**AML-M4 N:15 N (%)**	**AML-M5 N:06 N (%)**
Pallor	24 (89)	10 (83.3)	14 (77.8)	13 (86.7)	06(100)
Lymphadenopathy	06 (29.6)	04(32.3)	05 (28)	06 (40)	05 (83.3)
Hepatomegaly	16 (59.3)	04 (13.3)	05 (27.8)	07(46.7)	06(100)
Splenomegaly	14 (52)	05 (41.7)	05 (27.8)	07(46.7)	05 (83.3)
Gum Hyperplasia	0 (00)	0(00)	01(5.6)	03 (20)	03 (50)

The most common presenting symptoms were pallor, fever and bleeding seen in 87%, 83% and 52.4% patients, respectively (Table 2). Other symptoms which were observed less frequently were weight loss (9.8%), weakness (38%), dyspnea (12.2%), easy fatigability (29%) and palpitation (2.4%). Bone pains were noted in 18.3% patients.

Among the physical findings pallor was the most frequent (87%). Hepatomegaly, splenomegaly, lymphadenopathy and gum hyperplasia were observed in 48%, 45%, 38% and 9.8% cases respectively. Hepatosplenomegaly in majority of cases was mild to moderate type.

As shown in Table 3, hepatosplenomegaly was the commonest in AML-M5, M4 and M1. Gum hyperplasia was most frequent in AML-M4 and M5 (3 cases each). These findings show that tissue infiltration was most common in AML-M5 and M4 and least frequent in patients of AML-M3.

Discussion

AML 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. [8] In the present study among the total of 82 patients belonging to all age groups, male to female ratio was 1.2:1.The same frequency of gender distribution has also been reported in different international and local studies, e.g. 1.5:1. 1.2:1 and 1.7:1. [9-11] However one of the studies done by Frederick R. et al (to look for changes in biological features with age) shows an equal distribution of AML in both males and females. A study done by Kumar L et al on clinico-morphological features of AML shows male to female ratio of 2:1. [12]

AML is primarily a disease of adults. Overall incidence of AML increases with age. [13] Patients newly diagnosed with AML have a median age of 65 years. [14] In our study the mean age was quite low i.e. 27.5 ± 19.92 SD years. These results are comparable with another local study done at Agha Khan University hospital Karachi to see the frequency of AML subtypes in their population and they found that the mean age of their patients was 32 years (ranging between 6 months to 85 years). [9] In a study done by Hassan et al in 1993 on FAB subtypes and clinico-hematological features of AML the mean age was different for different FAB subtypes; For example they found that the mean age of M1, M2, M3 and M5 cases was between 25 and 29 years, whereas in M4 patients it was 45.6 years. [15] Almost similar observations were also made in our study. In a study done at Armed Forces Bone Marrow Transplant Centre, to evaluate outcome of treatment on patients of patients of denovo AML, the median age of patients was 21 years (ranging from 7 to 56 years).[11]

The median age for AML is quite high in West as compared to our studies. In one of the studies done in U.K. on AML patients from 26 hospitals in south and west region, the median age was 67 years. [16] In another study done in Spain on cytogenetic abnormalities of AML, median age was 61 years. (range was between 1 month-94 years) [17] Reports from Japan and Australia show a mean age of 51 and 52 years, respectively.[18] The reasons for the difference between age at presentation in subjects from the various regions are not clear. Whether this represents a true geographic/ethnic difference is difficult to ascertain. But higher mean age in the West is probably due to overall higher mean age in these countries as compared to East.

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. Bleeding however was a prominent symptom in AML-M3. Most common types of bleeding were epistaxis, gum bleeding and easy bruisibility. 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.

Other features included weakness, easy fatigability, dysnea, palpitation, bone pains and weight loss. Similar findings have been reported in different studies. [12,19-21] 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 (69 %), followed by in M5 (40 %), M2 (23.1 %), M4 (18.2 %) and M1 (16.6 %), respectively. [22] 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. [23] Hepatomegaly and splenomegaly were observed in 48% and 45% patients respectively in our study. Majority had mild to moderate hepatosplenomegaly. Lymph node enlargement was noted in 38% patients. Gum hyperplasia was seen inonly 10% cases and majority of them belonged to FAB types M4 and M5. Almost similar observations were made by Kumar et al in 2004 (42% patients and comparatively lesser number of patients having splenomegaly or lymphadenopathy, however gum hypertrophy was noted in 24% patients compared to 10% in our study. [12] Another interesting point which should be noted regarding this study is that majority of their patients with tissue infiltration belonged to AML-M4, M5 and M1 subtypes, the finding comparable to our results. Hoffman has reported the presence of splenomegaly in 50% of his cases. [24] In another study done by Ghosh et al, hepatosplenomegaly in 68 patients (26.2%) and lymphadenopathy was seen in 36% patients.[23] Two patients with acute myelomonocytic leukemia presented with extramedullary leukemia. Both these patients presented with orbital masses and belonged to the pediatric age group. We also had one patient with testicular swelling (he was a case of AML-M5) and the other one with bilateral proptosis. Similarly one of our patients presented with testicular swelling and when we

looked into the frequency of these findings in AML subtypes it was noticed that hepatosplenomegaly, lymphadenopathy and gum hyperplasia was most frequent in AML4, M5. Tissue infiltration is seen more with monocytic and myelomonocytic leukemia than with other subtypes of AML. Boils and mouth ulcers were seen in 6 patients. Geographic variations have been reported in the distribution of extramedullary leukemia and are more frequently reported from the African countries such as Uganda, Egypt and Turkey. Acute myeloblastic leukemia is the malignancy of adults and depending upon its subtype has variable manifestations.

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