International Journal of Pathology; 2005; 3(2): 71-75

Clinical Features and Hematological Investigations Pattern in Acute Promyelocytic Leukaemia Patients

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Background: Acute Promyelocytic Leukemia (AML-M3) patients, though amenable to treatment, present with early and sometimes severe bleeding manifestations. In our setup, for various reasons, patients are diagnosed rather late and therefore these bleeding manifestations are a limiting factor in the early and effective treatment of leukemia in such cases.
Objectives: To look into the clinical, peripheral blood and bone marrow features of AML-M3 patients in our setup.
Patients and Methods: A total of 40 consecutive cases of AML-M3 diagnosed on bone marrow biopsy over a period of 10 years were analyzed for clinico-morphological features.
Results: Majority of patients (75%) were <30 years of age. The male: female ratio was 3:2. The mean duration of symptoms was 4.2 weeks (Range 1-10 weeks). Commonest clinical features were fever, pallor and bleeding manifestations. The spleen and liver were variably enlarged in 25% and 45.5% of cases, respectively. The hemoglobin levels ranged from 3.1 to 12.8 g/dl with a mean of 6.6 g/dl. The WBC count ranged from 0.5 to 142 x 10^9/l with a mean of 28.3 x 10^9/l. Platelet counts ranged from 5-150 x 10^9/l with a mean of 28.8 x 10^9/l. Morphologically 36 patients had hypergranular and 4 had hypogranular promyelocytic leukemia.
Conclusion: The features identified in our study can help in early diagnosis of APL, which is known to be extremely important in effective management of patients.
Key Words: Acute Promyelocytic Leukemia; AML-M3

Introduction

Acute Promyelocytic Leukaemia (APL) is a distinctive sub-type of acute myeloid leukaemia (AML) that has distinct biologic and clinical features. According to the older French-American-British (FAB) classification of AML, based solely on morphology as determined by the degree of differentiation along different cell lines and the extent of cell maturation[1,2], APL is sub-typed as AML-M3. The new World Health Organization (WHO) classification of AML incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers and is more universally applicable and prognostically valid[3]. The WHO classification includes APL among the class of "*AML with characteristic genetic abnormalities*" with the characteristic APL abnormality being the reciprocal translocation t(15;17) (q22;q12). This unique structural chromosome rearrangement results in the formation of a hybrid promyelocytic leukaemia/retinoic acid receptor (PML/RAR) alpha fusion protein[4,5,6].

APL exists as 2 types, hypergranular or typical APL and microgranular (hypogranular) APL. APL comprises 5% to 8% of cases of AML and occurs predominately in adults in midlife[7]. Both typical and microgranular APL are commonly associated with disseminated intravascular coagulation (DIC) [8,9]. In microgranular APL, unlike typical APL, the leukocyte count is very high with a rapid doubling time[7]. Common morphologic features seen in typical APL include cytoplasm densely packed with large granules (bright pink, red, or purple in Romanowsky stains), bundles of auer rods within the cytoplasm (faggot cells), larger auer rods than in other types of AML, and strongly positive Sudan black/myeloperoxidase (MPO) reaction in all leukemic promyelocytes. Common morphologic features of microgranular APL include bilobed nuclear shape, apparent scarce or absent granules (submicroscopic azurophilic granules), small number of abnormal promyelocytes

with visible granules and/or bundles of auer rods (faggot cells), high leukocyte count in the peripheral blood, and strongly positive Sudan black/MPO reaction in all leukemic promyelocytes.

The severe bleeding diathesis associated with APL has a specific sensitivity to treatment with all-trans retinoic acid (ATRA), which acts as a differentiating agent[10-12]. High complete remission rates in APL may be obtained by combining ATRA treatment with chemotherapy[13].

Prognostic markers that may predict for inferior outcome in APL have been widely investigated, yet with the exception of older age and high initial WBC count, no features at diagnosis have been consistently associated with increased relapse risk in large multicenter studies[14-21].

The purpose of the present study was to document the clinical features and hematology investigation features of 40 cases of APL, diagnosed on the basis of FAB classification, and to try and identify the pattern of APL patients in our clinical practice. In the absence of laboratory investigations like immunophenotyping, karyotyping, identification of fusion proteins etc., early diagnosis of APL by identifying the typical features of presentation in our setup can lead to a good clinical outcome as there is a striking response to differentiating therapy with ATRA combined with chemotherapy[22-25].

Patients and Methods

This descriptive study includes all the patients of AML-M3 diagnosed at Rawalpindi Medical College, Rawalpindi from 1996 to 2001 and at Pakistan Institute of Medical Sciences, Islamabad from 2001 to 2005.

The diagnosis was based on morphology according to the French-American-British criteria. AML-M3 diagnosis was not further investigated for molecular or karyotypic abnormalities.

The clinical data recorded included age, sex, duration of illness, fever (low/moderate/high) intensity, bleeding (epistaxis, gum bleeding, petechiae, hematemesis, melaena etc.) and enlargement of liver, spleen &/or lymph nodes.

A 3-5 ml sample of peripheral blood was collected in EDTA containers and analyzed on automated hematology analyzer (Sysmex KX-21). The bone marrow aspirations were performed from posterior superior iliac spine in adults and the front of the upper part of tibia in children <2 years age. The blood and bone marrow smears were stained by Wright stain. The bone marrow smears were also stained by Sudan Black B and PAS stains.

Results

Amongst a total of 40 cases of AML-M3, 36 (90%) had hypergranular type and 4 (10%) had hypogranular variant with a hypergranular: hypogranular AML-M3 ratio of 9:1.

As shown in table 1, twenty four patients (60%) were males and 16 (40%) females with a male: female ratio of 1.5:1. Mean age was 22 years (range 1 to 90 years). Twenty nine patients were below the age of 30, 9 between 30 and 60 years, and only 2 above the age 60 but below 90 years.

Table 1: Age & Sex Distribution (n=40)

Parameters	No. of Patients	%
Age (years)		
Mean	22	
Range	1-90	
Age		
< 30 yrs	29	72.5
30-60 yrs	09	22.5
> 60 yrs	02	05
Sex		
Male	24	60
Female	16	40

The clinical features are documented in table 2. The duration of symptoms ranged from 1-10 weeks with a mean of 4.2 weeks. Twenty four patients presented with low-grade fever and 5 with moderate grade fever, while the rest gave no history of fever. Mild pallor was observed in 13 patients, moderate pallor in 20 and marked pallor in 6 patients. Bleeding marked by epistaxsis was found in 9 patients, gum bleeding in 15 patients, petechiae in 6 patients and hematemesis or melaena in 5 patients. One of the patients presented with unilateral exophthalmos. The spleen was enlarged mildly in 3 cases, moderately in 4 cases and grossly in 3 cases. Hepatomegaly was

detected mildly in 10 cases and moderately in 9 cases.

Table 2: Symptoms & Signs

	No. of Patients	% age
Symptoms duration (weeks)		
Median	4.2	
Range	1-10	
Fever		
Mild	24	60
Moderate	05	12.5
No fever	09	22
Pallor		
Mild	13	32.5
Moderate	20	50
Severe	06	15
No fever	01	2.5
Bleeding		
Epistaxis	09	22.5
Gum Bleeding	15	37.5
Petechiae	06	15
Hematemesis / Melaena	05	12.5
Splenomegaly		
Mild	03	7.5
Moderate	04	10
Gross	03	7.5
No splenomegaly	30	75
Hepatomegaly		
Mild	10	25
Moderate	09	22.5
No hepatomegaly	21	52.5
Lymph Nodes		
Cervical	03	7.5
Axillary	03	7.5
No lymphadenopathy	34	85

Cervical lymph nodes were palpable in 3 patients, axillary in 3 patients and both in 1 patient.

Table 3: Peripheral Blood Features

Parameters	Range (Mean)
Hemoglobin g/dl	3.1-12.8 (6.6)
RBC x 10^{12}/l	1.10-5.1(2.8)
MCV fl	80.5-109.1(93.7)
MCH pg	25.9-35.4(31.4)
MCHC (g/dl)	30.5-37.3 (33.5)
Retics %	0.2-0.8 (0.62)
WBC x 10^9/l	0.5-142 (28.3)
DLC (%)	
Lymphocyte	0-90 (28.3)
Neutrophils	0-70 (14.7)
Monocytes	0-10 (2.3)
Eosinophils	0-6 (0.35)
Promyelocytes	0-95 (35.95)
Myelocytes	0-8 (0.57)
Metamyelocyte	0-4 (0.18)
Platelets x 10^9/l	5-150 (28.8)

As shown in table 3, the hemoglobin levels ranged from 3.1 g/dl to 12.8 g/dl with a mean of 6.6 g/dl. The RBC count ranged from 1.10 to 5.1 x 10^{12}/l. with a mean of 2.8 x 10^{12}/l. The WBC count ranged from 0.5 to 142 x 10^9/l with a range of 28.3 x 10^9/l. Platelet counts ranged from 5-150 x 10^9/l with a mean of 28.8 x 10^9/l. Immature granulocytes were present in most of the cases including promyelocytes (range 0-95%, mean 35.95%), myelocytes (range 0-8%, mean 0.57%) and metamyelocytes (range 0-4%, mean 0.18%).

The bone marrow examination (table 4) revealed marked hypercellularity in 32 cases, one was hypocellular and 7 were moderately cellular. In all the cases, the three cell lines were depressed and the predominant feature was the presence of promyelocytes. And the majority of the cases showed

Table 4: Bone Marrow Features

	No. of Patients	% age
Cellularity		
Hypercellular	32	80
Hypocellular	1	2.5
Moderate	7	17.5
Erythropoiesis		
Cellularity		
Decreased	40	100
Type		
Normoblastic	22	55
Megaloblastic	18	45
Myelopoiesis		
Cellularity		
Moderate	4	10
Decreased	36	90
Maturation		
All cell series	2	5
Occ. Mature/maturing cells	38	95
Promyelocytes % age in BM		
50-60 %	1	2.5
60-70 %	4	10
70-80 %	5	12.5
80-90 %	15	37.5
> 90 %	13	32.5
Auer Rods		
Present	27	67.5
Megakaryopoiesis		
Cellularity		
Decreased	40	100
Platelets in BM smear		

Inadequate	40	100

the presence of more than 80% promyelocytes. Auer rods were observed in 27 cases.

Discussion

In this study we have attempted to try and identify the typical features of presentation of APL cases in our clinical practice. Delay in establishing the diagnosis of APL is associated with increase in risk of early hemorrhagic death. The absence of availability of diagnostic markers like immunophenotyping, karyotyping etc. even in most of Pakistan's tertiary care hospitals leaves us with little choice but to rely on history, clinical findings and hematology investigations to diagnose the APL cases at an early stage to prevent the occurrence of bleeding diathesis.

We report here a study of the initial presentation, clinical features and hematology investigations of our cases with a view to detect any peculiar pattern which may help in diagnosing such cases at an earlier stage. Unlike the other studies, where majority of cases at diagnosis are between 15 and 60 years of age, we found more patients in an earlier age groups (30 years or less), with a slightly increased male preponderance, whereas in the West, the males and the females are equally affected by APL[26]. Majority of our cases, as in other studies, were of the hypergranular variety[23,27,28].

The presenting features, as is usual, were fever and bleeding, however the percentage of patients presentation with fever was found to be more (> 60%) compared to the established range of 15-30%[29,30]. But the more commonly observed finding of hemorrhagic syndrome and mucocutaneous haemorrhage was the same in our cases too. However the frequency of cerebral hemorrhage which has been reported to be 20% was not observed in our study[28,31]. But this discrepancy may be due to lack of establishment of APL diagnosis in cases where cerebral haemorrhage has occurred as a presenting feature, cases which are likely to have a fatal outcome. Organomegaly is rare at presentation in APL[29,30,32]. Contrary to this general finding, organomegaly was found to be a frequent finding in our study. Liver was enlarged in a large number of cases, spleen to a lesser extent and lymph nodes were enlarged in a few cases.

Anaemia, leucopenia and thrombocytopenia are the usual presentation of APL[33]. However, in our study, although anaemia and thrombocytopenia

were present in most of the patients, leucocytosis rather than leucopenia was common. As leucocytosis is one of the few important risk factors identified for APL and is associated with a high incidence of bleeding diathesis, therefore it is very imperative that in our setup APL diagnosis is established early. This would help prevent bleeding diathesis, which would otherwise render treatment options ineffective in a disorder that has a very promising complete remission rate and disease free survival rate.

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