Acute Myeloid Leukemia-FAB Classification and its Correlation with Clinico-Haematological Features

Pages with reference to book, From 200 To 203

Khalid Hassan, Masood Qureshi, Shoaib Shafi (Departments of Medicine, Rawalpindi Medical College, Rawalpindi.)
Nadeem Ikram, M. Jamil Akhtar (Departments of Pathology, Rawalpindi Medical College, Rawalpindi.)

Abstract

The French-American and British (FAB) classification of 62 consecutive cases of acute myeloid leukemia was undertaken. AMLM2 was the commonest FAB type (32.26%). followed by M1 and M4 (22.58% each), M5 (8.6%) and M6 and M7 (1.61% each), respectively. One of the patients was diagnosed as AM 1-MO (not a FAB type). 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. AML-M2, M4 and M5 were commoner in males, M1 in females and M3 equal In both sexes. Feeling of weakness, easy fatiguability and pallor were invariably present in all FAR types. All the patients of M1 and MS. 85% of M2. 64% of M4 and 50% of M3 presented with fever. Bleeding manifestations were most frequent In M3 cases followed by M5, Ml, M4 and M2, respectively. Hepatomegaly and splenomegaly were relatively less prominent features in M3 os compared to other FAR types. Amongst the haematological parameters, anaemia was more severe In Ml, leucocytosis In M2 and thrombocytopenia in M3 cases as compared to other FAR types (JPMA 43:200, 1993).

Introduction

The French-American and British (FAB) classification of acute myeloid leukemia (AML) is based on the recognition of granulocytic (M1, M2 and M3), granulocytic-monocytic (M4), monocytic (M5a, M5b), erythroid (M6) and megakaryocytic (M7) types of cells[1-3]. This classification has been widely accepted due to its reproducibility and true morphological correlation. Although most acute myeloid leukemias can be recognised morphologically (on Romanowsky's stain), but for the diagnosis of FAB types, the help of cytochemical staining procedures should always be sought. Ml and M5a often require cytochemical evidence[4] and M7 can be diagnosed with the help of monoclonal antibodies and electron microscopy[5]. There are no major prognostic differences amongst FAB types[6]; however, some reports have shown a poorer prognosis with monocytic variants and a longer survival rate in M3 cases[7,8]. Swirsky et al[9] observed that irrespective of the morphologic types of leukemia, the age and clinical state of the patient are important predictors of response to therapy. Geehan et al[10] and Keating et al[11] also noted that certain clinical features, e.g., fever, renal and hepatic involvement and haemorrhage are adversc factors. A white cell count above $100x10^9$/l and marked thrombocytopenia (platelet count $<25x10^9$/l) are bad in-dicators for response to therapy[9,11-13] 'the present study was aimed at finding the relative frequency of various FAB types of AML and studying the clinico-baematological features of different types of AML.

Patients and Methods

All patients of acute myeloid leukemia (62 cases) diagnosed at the pathology department of Rawalpindi Medical College during a period of 5 years (1988-1992) were included. A detailed account of clinical features was noted in a proforma, especially emphasizing on age, sex, fever, feeling of weakness,

symptoms of anaemia, bleeding manifestations, bone tenderness, infection, lym¬phadenopathy and splenomegaly. Investigation in all cases of AML included haemoglobin estimation by cyanmet-haemoglobin method, total leucocyte count and platelet count by visual methods using improved Neubaur chamber and differential leucocyte count (DLC) after staining atleast 2 well made smears by May-Grunwald Giemsa Stain. Bone marrow aspiration was performed at the posterior superior iliac spine in adults and at upper part of tibia in children below 2 years of age. In every case, 6-8 marrow smears were made; two of them were stained by May-Grunwald Giemsa Stain and one smear each by Periodic Acid Schiff(PAS) Stain and Sudan Black Stain. In patients who showed a negative or diffuse positive staining pattern for PAS, one smear was also stained for Naphthyl Acetate Esterase (NAE). Esterase stain with fluoride inhibition could not be performed due to lack of funds. For all the three special stains, commercial kits (Sigma) were used. On the basis of cytologic features (May-Grunwald Giemsa stained smears), aided by cytochemical reactions (PAS, Sudan Black and esterases) all the patients were classified as AML-M1 to M7 according to criteria of FAB classification[1,2]. After classification, various types of AML patients were correlated with the clinical features and haematological parameters.

Results

In this study of 62 consecutive cases of AML (Table I),

Table I. Morphological types (M1-M7) in AML.

Types of AML	Number of patients	Percentage
*AML-MO	01	1.61
AML-M1	14	22.58
AML-M2	20	32.26
AML-M3	06	9.68
AML-M4	14	22.58
AML-M5	05	8.06
AML-M6	01	1.61
AML-M7	01	1.61

*One patient was labelled as AML-MO (not a FAB type).

M2 was the commonest type, followed by M1 and M4, M3 and M5 respectively. M6 and M7 were the least common (1.6% each). One of the patients (1.6%) who did not fit into any of the FAB types (Ml to M7) was labelled as MO, because his marrow was negative for all the cytochemical stains performed. AML-M1 was observed in 22.58% of patients, with an age range 16- 60 years (mean ±SD 25.4±16 years) as shown in Table II.

Table II. Age and sex distribution in FAB types of AML.

	FAB Type (Number of Patients)				
	AML-M1 (14)	AML-M2 (20)	AML-M3 (06)	AML-M4 (14)	AML-M5 (05)
Age range (years)	16-60	03-65	07-77	1 yr 9m-88	6m-55
Mean	25.3	29.2	26	45.6	25.5
±SD	16.0	17.1	-	26.3	-
Sex Male:Female ratio	3:4	3:1	1:1	4:3	4:1

It was slightly more common in females (male:female ratio 3:4). The commonest clinical features (Table III)

Table III. Clinical features of AML.

Clinical features	AML-M1 %	AML-M2 %	AML-M3 %	AML-M4 %	AML-M5 %
Fever	100	85	50	64	100
Feeling of weakness	100	100	100	100	100
Easy fatiguability	100	100	100	100	100
Pallor	100	100	100	100	100
Bleeding gums	21.4	25	66.1	28	60
Epistaxis	28.5	20	50	21	60
Ecchymoses	21.4	20	66.1	28	60
Melaena	14.4	05	16.7	7.1	-
Haemetemesis	21.4	05	16.7	-	-
Sub-conjunctival haemorrhage	-	05	-	-	-
Bone tenderness	36	30	50	43	40
Lymphadenopathy	36	-	30	-	28.40
Splenomegaly	71.4	75	33.4	64	80
Hepatomegaly	64.3	70	50	64	60

were fever, pallor, easy fatiguability and lethargy. Bone pains and/or tenderness were observed in 36%. Bleeding gums, epistaxis, ecchymosis, haemetemesis and melaena were observed in 28.5% patients. Lymph node enlargement (cervical 36%, axillary 28.6% and inguinal 14.3%) was much less frequent as compared to splenomegaly (71.4%) and hepatomegaly (64.3%). Anaemia and thrombocytopeniawere invariably present. Leucopenia was observed in 2 1.4%. Mean white cell count was 35.6x109/lI. Peripheral blood smear showed 02-97% of myeloblasts on differential count. On marrow smears erythroid and megakaryocytic depression were invariably observed. Myeloblasts ranged between 75 and 95% of marrow cells. Auer rods were seen in occasional cells in 57% of patients. The

marrowsmears were either negative or showed a faint diffuse positivity for PAS; Sudan black positivity was observed in less than 3% of leukemic cells. AML-M2 (32.3%) was commonest FAB type. Age ranged from 3 to 65 years, with mean±SD of 29.2±17.1 years. Males were affected three times more commonly as compared to females. Pallor, easy fatiguabiity and lethargy were the most frequent features, followed by fever, splenomegaly, bone tenderness and bleeding manifestations, respectively. Anaemia, neutropenia and thrombocytopenia were observed in all the patients. Total leucocyte count was either normal or decreased in 25% of cases. In the blood smears, the number of myeloblasts and promyelocytes ranged from 6-95% and 0-09% respectively. In marrow smears, erythroid and megakaryocytic depression, myeloblasts between 50 and 95% and Sudan positive cells between 05 to 10% were observed. Rare Auer rods were observed in 60% of cases. AML-M3 (9.68%): Five out of six patients of AML-M3 were below 25 years of age. Males and females were equally affected. The commonest clinical features were pallor, easy fatiguability, ecchymosis, bleeding from gums and epistaxis. Fever, hepatomegaly and bone tenderness were observed in 50% of cases. Haemoglobin level, white cell count and platelet count have been shown in Table IV.

Table I. Morphological types (M1-M7) in AML.

Types of AML	Number of patients	Percentage
*AML-MO	01	1.61
AML-M1	14	22.58
AML-M2	20	32.26
AML-M3	06	9.68
AML-M4	14	22.58
AML-M5	05	8.06
AML-M6	01	1.61
AML-M7	01	1.61

*One patient was labelled as AML-MO (not a FAB type).

In blood smears 22 to 93% of the cells were hypergranular promyelocytes. These cells constituted 60-90% of marrow cell population. In all the patients, numerous Auer rods were present in the leukemic cells. These cells were intensely Sudan positive. AML-M4 (22.58%): The age ranged from 1 year 9 months to 88 years. Mean age was 45.6 years. Male:female ratio was 4:3. The most frequent clinical features were constitutional symptoms and pallor, followed by fever, hepatosplenomegaly, bone tenderness and bleeding manifestations, in that order. All the patients manifested marked anaemia, neutropenia and thrombocytopenia. Leucopenia and normal leucocyte count were observed in 22% of cases. Blast cells constituted 11-90% of cells on blood smears. On the bone marrow smears, 50 to 95% of cells were blast cells; 25 to 55% of these cells manifested monocytoid configuration. The leukemic cells were Sudan black and esterase positive. Auer rods .were infrequent. AML-M5 (8.06%): Two out of 5 cases were below a year of age. Four patients were males and one female. All of them presented with fever, constitutional features and pallor. Other common features were splenomegaly, bleeding manifestations, hepatomegaly, bone tenderness and lymphadenopathy. Haematological features have been shown in Table IV. The bone marrow smears showed Sudan negative and esterase positive

monoblasts. In one of the patients, the diagnosis of AML-M7 was based on the following features: pancytopenia, a blood tap on “marrow aspiration", presence of large number of blast cells in marrow trephine imprints, a marked increase in the number of megakaryocytes, dense fibrosis as seen in trephine sections and negative cytochemical reactions. Since the number of AML-MO, M6 and M7 patients was very small these cases have not been further discussed in this paper.

Discussion

FAB classification of acute leukemias has now been adopted in most of haematology laboratories in Pakistan. Whereas a number of studies of acute lymphoblastic leukemia have been presented during past few years, only one study of acute non-lymphoblastic leukemias has been published in this country[14-17]. In the present study of 62 cases of AML, the distribution of various FAB types was partly comparable with the studies presented previously[15-19]. We observed AML-M2 as the commonest type, followed by M4 and M1, M3 and M5 respectively (Table I). Alvi et al[15] also presented similar findings; however, in their patients, AML-M3 was relatively more common (15.3%). In other similar study[20], M2 was much more frequent (63.5%) and M1 (7%) as well as M3 (2.5%) were relatively infrequent. In our patients, the mean age of M1, M2, M3 and M5 was between 25 and 29 years, whereas in M4 patients, it was 45.6 years. In all the FAB types, except M4, our patients were relatively younger as compared to, in two similar studies[6,18]. In Miguel’s cases, the mean age for all FAB types was between 37 and 60 years[6] and in Sultan’s series between 41 and 52 years[18]. In the present series, AML-M2, M4 and M5 were commoner in males, M1 in females and M3 equal in both sexes. In all FAB types, constitutional features and pallor were invariably present. All patients of Ml and M5 and 50% of M3 had fever. Muco-cutaneous bleeding manifestations were the most frequent in M3 (67%), followed by M5 (60%), M1 and M4 (28% each) and M2 (25%). Bone tenderness especially over the sternum could be elicited in 50% of M3, 43% of M4, 40% of M5, 36% of M1 and 30% of M2 patients. Lymphadenopathy and hepatosplenomegaly were slightly more frequent in M5, followed by M2, Ml and M4 cases, respectively (Table W). In a comparable study[6], lymphadenopathy was more common in M1 and hepatosplenomegaly was less frequent in all FAB types, as compared to our cases. In our patients of AML, the mean values of Hb in various FAB types were between 5.64 and 7.0 G/dl, as compared to between. 8.7 and 9.4 G/dl in series presented by Sultan et al[18]. Means of platelet counts in our patients of FAB types M1 to M5 were between $23x10^9$/l and $43.9x10^9$/I. These values were also much lower as compared to the values ($49x10^9$/l to $82x10^9$/l) presented in the Sultan’s series. The comparative evaluation of haematological parameters of various FAB types of AML in the present series revealed that anaemia was slightly more severe in M1, leucocytosis was more profound in M2 and thrombocytopenia most marked in M3 cases.

References

1. Bennett, 3M., Catovsky, D., Daniel, M.T. et al. Proposals for classification of the acute leukemia. Br.J. Haematol., 1976;33:451-58
2. Bennett, J.M., Catovsky, D., Daniel, M.T. et al. Proposed revised criteria for tbe classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. Ann. Intern .Med., 1985a;103:620-25.
3. Bennett, J.M., Catovsky, D.. Daniel, MT. et al. Criteria for the diagnosis of acute leukemia of megakaryocyte lineage. Ann.Intern. Med., 1985;103:460-62.
4. Hoffbrand, A.V. and Lewis, SM. Postgraduate haematology. 3rd ed. Heinemann Professional

Publishing Oxford, 1989; pp. 382-94.
5. Ruis-Arguelles, G.J., Lopez, MA., Mendizaloal, E.L. et aL Acute megakaryoblastic leukemia: a prospective study of its identification and treatment. Br.J.Haematol., 1986;62:55-63.
6. Miguel, J.F.S., Gonzalez, M., Canizo, M.C. et al. Surface makers analysis in acute myeloid leukemia and correlationwith FAB classification. Br.). HaematoL, 1986;64:547-60.
7. Mertelsman, R., Thaler, H.T., To, L, Gee, T.S. et al Morphological classification, response to therapyand survival in 263 adult patients with ANLL Blood, 1980;56:773-81.
8. Bennett, J.M. and Begg. C.B. Eastern Cooperative Group study of the cytochemistryof adult acute myeloid leukemia by correlation of subtypes with response and survival Cancer Res., 1981;41:4833-39.
9. Swirsky, F).M., Bastos, U.M.. Parish, S.E. et aL Features affecting outcome during remission induction of acute mycloid leukemia in 619 adult patients. Br.J. Haematol., 1986;64:435-53.
10. Geehan, E., Smith, T., Freireicb, EJ. Prognostic factors in acute leukemia. Semin. Oncol., 1976;3:271-82.
11. Keating M.J., meCaridie, K.B., Bodey, G.P. et at Improved prospects of long-term survival in adultswith acute rnyelogcnous leukemia. JAMA< 1982a;248:2481-86.
12. Keating, M.J., Smith, T.L., Gehan, E.A. et al. A prognostic factor analysis for use in development of predictive models for response in adult acute leukemia. Cancer. 1982b;50:45765.
13. Cassileth, P.A., Begg. C.B., Bennett, J.M. et al. A randomised study of the efficacy of consolidation therapy in adult ANLL Blood, 1984;63:843-47.
14. Zafar, M.N. FAB classification ofacute lymphoblastic leukemia (ALL) and its relevance to ALL inn Karachi children. J.Pak.Med. Assoc., 1985;35:233.36.
15, Alvi, E.A., Saleern, M., Ahmed, P. et al. A study of 100 cases of acute leukemia in Northern Pakistan with reference to French- American-British (FAB) Cooperative Group classification. PJP., 1990;1 (2):87-92.
16. Hassan, K., Bukhan, K.?., Zafar, A. et al. Acute leukemia in children. French-American-British (FAB) classification and its relation to clinical features. i.Pak.Med. Assoc., 1992;4229-31.
17. Zafar, M.N. and Zaidi, S.H.M. Acid phosphatase positive T. lymphoblastic leukemia (T-ALL) in Pakistani children. J.Pak.Med. Assoc., 1985;35:6-9.
18. Sultan. C., Deregnaucouri., J., Ko, Y.W. et al. Distribution of 250 cases of acute myeloid leukemia (AML) according to the FAB classification and response of therapy. Br.J. Haematol., 1981;47:545-51.
19. Van Rhenan, DJ., Verhulst, J.C.. Huijsens, P.C. et at. Maturation index: a contribution to quantitation in the FAB classification of acute leukemia. Br.J. Haematol., 1980;46:581- 86,
20. Whitekar, J.A., Withey. J., Powell, D.E.B. et al. Leukemia classification: a study of accuracy of diagnosis-456 patients. Br.J. Haematol., 1979;41:177-84.