RESEARCH ARTICLE

Clinical presentation of acute myeloid leukaemia — A decade-long institutional follow-up

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Abstract

Objective: To analyse a decade-long pattern of clinical presentation of acute myeloid leukaemia patients and compare it with contemporary data.

Methods: The retrospective cohort study was conducted at the National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, and comprised of medical record of acute myeloid leukaemia patients from March 2006 to October 2016. Data noted age at presentation, gender, medical history, physical examination, blood and bone marrow investigations such as, haemoglobin levels, blood cell count myeloperoxidase activity, periodic acid-Schiff and reticulin staining as well as final diagnosis. Comparison, where possible, was done with contemporary literature. SPSS 19 was used for data analysis

Results: Of the 626 subjects, 248(39.6%) were females and 378(60.4%) males. The overall mean age was 35.3±17.1 years. The most common age group was 15-40 years with 354(56.5%) patients. The most common subtype was acute myeloid leukaemia with maturation 183(33.6%). Myeloperoxidase activity was positive for the majority of the acute myeloid leukaemia patients. Periodic acid-Schiff test, done on only selected patients, was mostly negative. Reticulin staining was positive for 113(65.3%) patients. The most common presenting complaints were fever 266(71.9%) and weakness 168(45.4%). Mean haemoglobin and red blood cell count were 8.3 ± 2.4 g/dL and 2.9 ± 1.2 1012/L, respectively.

Conclusion: Acute myeloid leukaemia was found to be a highly variable disease that presented with non-specific signs and symptoms.

Keywords: AML presentation, AML epidemiology, AML in Pakistan, Myeloperoxidase, AML-M2. (JPMA 67: 1837; 2017)

Introduction

Acute myeloid leukaemia (AML) is a group of heterogeneous malignant disorders. It primarily results from aberrant differentiation that leads to uncontrolled proliferation of immature myeloid cells.[1] AML is more frequently observed in adults.[2]

AML patients may present with signs and symptoms related to pancytopenia, which include infections, fever, weakness, fatigue and haemorrhagic findings like petechiae, menorrhagia and epistaxis. This is because the proliferation of malignant cells gradually takes over the normal blood cell in bone marrow. Occasionally, there is sternal discomfort or tenderness and pain in lower extremities. There may be cutaneous or gingival infiltration by leukaemia cells. Physical examination may reveal pallor, lymph node enlargement, hepatomegaly and splenomegaly.[3]

AML classification is based on criteria defined in World Health Organisation's (WHO) or French-American-British (FAB) classifications.[1] In the WHO classification, genetic mutations, karyotyping abnormalities, different stages of maturation and blast cell subtypes are taken into account.[4] Thus, it points towards diverse underlying mechanisms in the development of AML. Therefore, more studies are required to report the common and rare presentations of AML at clinic as it will help in prompt diagnosis and timely management.

It is essential to specify AML subtype as investigations, treatment and prognosis may be different.[5] One good example is that of acute promyelocytic leukaemia (APL) which has very different management than other AML subtypes.[6,7] In APL, complete remission (CR) rate after chemotherapy is above 90% and the prognosis has greatly improved as manifested by a lower relapse rate, and longer disease-free survival (DFS) as well as overall survival (OS) rates.[6] However, different contemporary studies have reported differences in terms of various characteristics, such as, gender, age, presenting complaints, investigation profile and diagnosis.[2,8-12] The

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current study was conducted to report the clinical presentations of AML patients at the time of diagnosis to fill in any existing gaps in global clinical literature.

Patients and Methods

This retrospective cohort study was conducted at the National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD & BMT), Karachi, and comprised of medical records of AML patients from March 2006 to October 2016. Institutional ethics review board approved the study.

Data collected included age at presentation, gender, medical history, physical examination, blood and bone marrow investigations done as diagnostic workup for AML patients such as, haemoglobin levels, blood cell count myeloperoxidase (MPO) activity, periodic acid-Schiff (PAS) and reticulin staining as well as the final diagnosis. Patients were divided into four age groups of <15 years, 15-40 years, 41-60 years and >60 years.

Data was entered in Microsoft Excel. SPSS 19 was used for data analysis. All discrete data, such as number of patients in a category, were given as frequency and percentage. Continuous data, such as haemoglobin levels and other haematological parameters, were given as mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate. An attempt was made to compare our data with contemporary literature where appropriate.

Results

Of the 626 participants, 248(39.6%) were females and 378(60.4%) males with an overall mean age of 35.3±17.1 years while the median age was 35 years (IQR: 1-86 years). The most common age group was 15-40 years with 354(56.5%) patients, followed by 41-60 years with 168(26.8%). The number of patients in <15 and >60-year age groups was 53(8.5%) and 51(8.1%), respectively.

AML subtypes were available for 545(87.1%) patients. The most common AML subtype according to latest WHO classification was "AML with maturation" (M2) having 183(33.6%) patients, followed by "AML without maturation" (M1) with 141(25.9%). APL was the third-most frequent pathology with 62(11.4%) cases, followed by acute monocytic leukaemia 53(9.7%). Two (0.3%) cases of chronic myeloid leukaemia (CML) blast crisis were excluded.

MPO activity was reported for 336(53.7%) patients, out of which 316(94.1%) patients were found positive. PAS staining data was available only for 42(6.7%) patients, out of which 13(31%) patients were positive. Reticulin staining data was reported for 173(27.6%) patients, out of which it was positive for 113(65.3%) patients (Table-1; Figure-1).

Table-1: Baseline characteristics of the study population.

Parameter	Classification	N	%
Gender	Female	248	39.6
	Male	378	60.4
	Total	626	
Age Group	Mean age	35.3±17.1	-
	Median age	35 (IQR 1-86 years)	-
	Younger than 15 Years	53	8.5
	15-40 Years	354	56.5
	41-60 Years	168	26.8
	Older than 60 Years	51	8.1
	Total	626	
WHO Classification of AML	APL (M3) with a translocation of chromosomes 15 & 17	62	11.4
	AML with translocation of chromosomes 6 & 9	1	0.2
	AML with myelodysplasia-related changes	39	7.2
	AML related to previous chemotherapy or radiation	2	0.4
	AML with minimal differentiation (M0)	23	4.2
	AML without maturation (M1)	141	25.9
	AML with maturation (M2)	183	33.6
	Acute MyelomonocyticLeukaemia (M4)	53	9.7
	Acute MonocyticLeukaemia (M5)	12	2.2
	Acute Erythroid Leukaemia (M6)	14	2.6
	Acute MegakaryoblasticLeukaemia (M7)	4	0.7
	Acute Basophilic Leukaemia	1	0.2
	Acute Panmyelosis with fibrosis	8	1.5
	Undifferentiated and Biphenotypic Acute Leukaemias	2	0.4
	Total	545	
MPO Activity	Positive	316	94
	Negative	20	6
	Total	336	
PAS Staining	Positive	13	31
	Negative	29	69
	Total	42	
Reticulin Staining	Positive	113	65.3
	Negative	60	34.7
	Total	173	

WHO: World Health Organisation
AML: Acute myeloid leukaemia
APL: Acute promyelocytic leukaemia
MPO: Myeloperoxidase
PAS: Periodic acid-Schiff.

Most frequent clinical features at presentation included fever 266(71.9%), weakness 168(45.4%) and bleeding tendency 171(19.2%). A significant number of patients had presented with bodyaches, respiratory complaints and hepatosplenomegaly or other abdominal

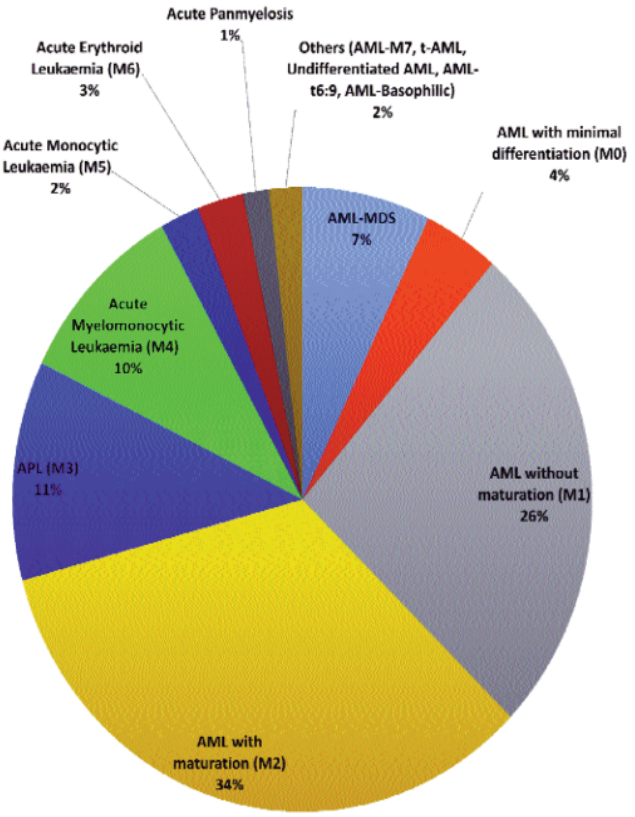

Figure-1: Distribution of AML Subtypes.

Table-2: Clinical presentation of the AML patients at the time of diagnosis.

Clinical Presentation at Diagnosis	N	%
Fever	266	71.9
Weakness	168	45.4
Bleeding tendency (from nose, mouth, rectum or bruising, menorrhagia etc.)	71	19.2
Body pain	47	12.7
Dyspnoea or cough	43	11.6
Hepatosplenomegaly	39	10.5
Pallor	35	9.5
Lymphadenopathy	29	7.8
Infections/oral ulcers	26	7
Weight loss	25	6.8
Abdominal pain	19	5.1
Miscellaneous (<5% each)	54	14.6
Diarrhea or constipation, Nausea or vomiting, Loss of appetite, Gum hypertrophy, Skin rash, Vertigo, Chest Pain, Periorbital edema, Anal fissure/ Perianal ulceration/ Haemorrhoids, Dysphagia/ Heart burn, Joint pain, Ascities, Proptosis, Ankle edema, Facial swelling, Sleep disturbances, Facial palsy, Black-out, Haemangioma on lip, Hiatus hernia, Hoarness of voice, Leg swelling and pain, Nasal growth, Stroke, Tooth-ache		
Total	370	100

AML: Acute myeloid leukaemia.

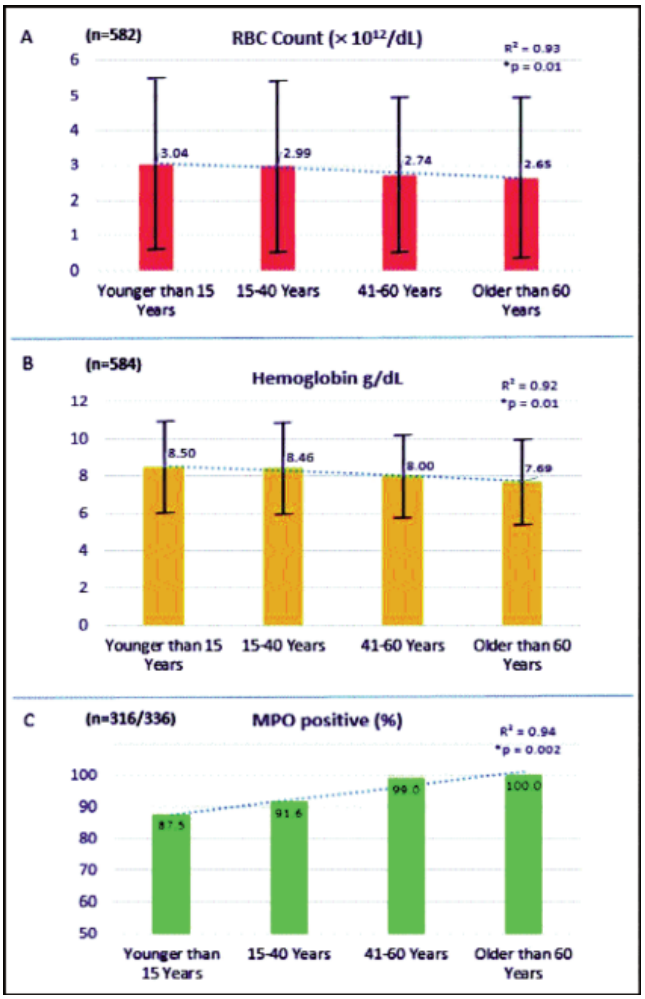

Figure-2: Significant trends between characteristics in AML patient. The values are Mean±SD in panels A and B, whereas percentage in panel C.

complaints (Table-2).

Normal blood cell counts were available for a majority of the patients, but due to extreme values (for example, leukocyte count) secondary to underlying pathology, we considered median levels in this case. Median haemoglobin levels was 8.1 g/dl (IQR: 2.1 - 17), whereas median counts for red blood cells (RBC), white blood cells (WBC), platelets and blasts were 2.9 1012/L (IQR: 0-23), 9.6 109/L (IQR: 2-234000), 36 109/L (IQR: 0-100000) and 48% (IQR: 1-100), respectively (Table-3). We carried out subgroup analysis to find any significant difference between blood counts, clinical presentation and other investigation results according to gender, age group and AML type. Pearson's correlation revealed that AML patients in older age groups tended to present with lower haemoglobin levels and RBC count compared to young patients (r= -0.106, p=0.01; and r= -0.103, p=0.01,

Table-3: Haemoglobin level and blood cell count in AML patients of our study as compared with other contemporary studies.

Parameters	Study	Haemoglobin g/dl	RBC Count (1012/l)	Total Leukocyte Count (109/l)	Platelet Count 109/l	Blast cells (%)
N	Our Study	586	584	585	582	362
Mean ± S.D		8.3 ± 2.4	2.9 ± 1.2	NR	NR	50.2 ± 31.6
Median		8.1	2.9	9.6	36	48
Range		2.1 - 17	0 - 23	2 - 234000	0 - 100000	1 - 100
Mean (Range)	Harani et al. 2005.[13]	8.4 (2.2 - 14.4)	NR	63.4 (0.6 - 97.4)	48.9 (1.0 - 70.0)	NR
	Wakui et al. 2008[10]	8.3 (3.8 - 17.2)	NR	13.7 (0.4 - 709)	52 (0 - 890)	56 (6 - 99)
	Asif and Hassan 2013[15]	7.4 (2 - 13.6)	NR	52.3 (1.3 - 272)	56.5 (3 - 392)	NR
	Ali et al. 2013[22]	NR	NR	30 (1.2 - 96)	64 (7 - 322)	48 (15 - 98)
	Sultan et al. 2016 (1)[8]					
	Sultan et al. 2016 (2)[9]	8.1 (3.7 - 13.6)	NR	43 (0.6 - 372)	62.3 (3.0 - 576)	NR

RBC: Red blood cell
AML: Acute myeloid leukaemia
SD: Standard deviation
NR: Not reported.

Table-4: A comparison of age, gender, subtypes and clinical presentation in AML patients from different studies.

Age Group	Female:Male	Most Frequent Presenting Complaint	Most Frequent AML Types	n	City/ Country	Study
NR	1:1.32	NR	AML-M4, AML-M2	146	Rawalpindi, Pakistan	Hassan et al. 1994[18]
NR	1:1.38	Fever, pallor	AML-M4, AML-M2	74	Karachi , Pakistan	Kakepoto et al. 2002[12]
NR	1:1.05	NR	AML-M2, AML-M1	300*	Durate, US	Arber et al. 2003[14]
NR	1:1.5	Hepatosplenomegaly	AML-M4, AML-M2	116	Karachi , Pakistan	Harani et al. 2005[13]
>56	1:1.2	NR	AML-M2, AML-M1, AML-M4	759	US	Appelbaum et al. 2006[11]
15-40	1:1.2	Pallor, Fever, Hepatosplenomegaly, lyphadenopathy	AML-M3, AML-M2	126	Diyala, Iraq	Al-Husseiny 2008[16]
NR	1:1.57	NR	AML-M2, AML-M4	809*	Japan	Wakui et al. 2008[10]
NR	1:1.27	NR	AML-M1, AML-M2	100	Lahore Pakistan	Ali et al. 2013[22]
15-40	NR	Fever, Pallor	AML-M1, AML-M3, AML-M4	NR	Islamabad, Pakistan	Asif and Hassan 2013[18]
15-30	1:1.5	Fever, weakness	AML-M1, AML-M2	125	Karachi , Pakistan	Sultan et al. 2016 (1)[8] Sultan et al. 2016 (2)[9]
41-60	1:1.18	Fever, pallor, weakness	AML-M2, AML-M1	107	Karachi , Pakistan	Chang et al. 2016[17]
21-40	1:1.53	NR	AML-M3, AML-M2	132		Singh et al. 2016[2]
15-40	1:1.52	Fever, weakness, bleeding tendency	AML-M2, AML-M1, AML-M4	626	Karachi , Pakistan	Our study

NR: Not reported, *=APL (AML-M3) not included
AML: Acute myeloid leukaemia.

respectively). Although the difference did not reach statistical significance, a clear downward trend could be noted as measured by Mantel-Haenszel test of trend (p=0.01). Such observation was not seen when gender or other factors were used to do similar subgroup analysis. Similarly, MPO activity being positive was more often seen in older age groups of patients with a significant positive trend (Mantel-Haenszel p=0.002). Other subgroup analyses yielded no significant differences (Figure-2).

Discussion

Our study is unique from this region, as it reports findings from a large group of patients who presented during a period of 11 years. We found extensive data in a large group of patients. Further, an attempt has been made to compare our data with contemporary literature published during the same period. This approach has revealed certain differences between different data sets. Our study included the largest number of patients, except that reported by Wakui et al. (Table-3).[10] Various aspects were compared between our findings and other reported studies. Female-to-male ratio is similar to those reported from different parts of Pakistan (Table-4).[8,9,12,13] A lower ratio is observed in a large study from Japan[10] while there

seems to be no difference in male-to-female ratio from the United States.[11,14] The mean age was 34 years for AML patients and a large number of patients (56.5%) fell into the age group of 15-40 years at presentation in clinic. The second-most common population of patient were from age group 41-60 years. Since AML is largely a disease of the adults, we found only 8.5% patients under 15 years of age. Our observations were consistent with most of the studies reporting age groups.[8,9,11,15,16]

As mentioned above, AML is a group of heterogeneous diseases which present with morphologically different subtypes.[1,4] Although some cytogenetic abnormalities have been identified in relation with AML, it is expected that in future various morphological presentations could be related to specific cytogenetic abnormality and/or altered gene expression. This will give clear explanation of underlying mechanisms involved in malignant transformation. The most common AML subtype was AML with maturation (M2), followed by AML without maturation (M1). Similar findings have been reported by studies from the United States,[11,14] India[5] and a recent study from Karachi.[17] Additionally, AML-M2 has been reported to be the most frequent subtype from Japan,[10] and as the second-most common subtype in many other countries.[2,12,13,16,18] Although we found APL as a frequent presentation, but it was not the most common presenting subtype as reported in studies from India and Iraq.[2,16]

AML patients present in clinic with a variety of non-specific and some specific signs and symptoms related to underlying pathology. In this study it was observed that most of the patients presented with fever and weakness. Such symptoms are highly non-specific and could be a source of delayed diagnosis.

MPO is the marker of myeloid lineage and its expression can help in determining need for treatment and bone marrow transplantation in AML patients.[19] Only 59% of total AML patients had MPO activity ordered, out of which 94.1% were positive for it. Interestingly, MPO activity was more likely to be positive in older group of patients. The significance of this finding is not clear at present.

Similarly, PAS staining (for cell surface glycoproteins)was performed for 42 AML patients and only 13 were found positive for PAS, which included 5 patients of AML-M1 and 3 of AML-M2. PAS test is characteristically positive in leukaemias from lymphoid series, but sometimes it is also positive in AML patients.[5] Additionally, matrix changes are also observed in AML. Reticulin staining is one of the matrix collagen testing,[20] and is associated with poor prognosis.[21] In our data, 173 patients were tested with reticulin staining and out of them 113(65.3%) were found positive. Among the positive cases, 51(45%) were AML-M2, 25(22%) were AML-M1 and 14(12.4%) were AML with myelodysplasia-related changes.

Haemoglobin levels and blood cell counts may be altered due to the fact that bone marrow is mostly populated by leukaemic blasts. Patients in our study presented with lower haemoglobin levels and RBC count. Others have also reported similar observations.[8-10,13,15,22] However, we observed that older age group patients have a tendency to present with lower haemoglobin and RBC count as compared to younger age groups. The significance of this finding is unclear at present.

The current study had some limitations. Firstly, it was a single-centre study. Secondly, complete record was not present for all the subjects. Similarly, not all patients had their investigations done, apparently due to financial constraints, because the healthcare in Pakistan is largely borne privately by the public, whereas the management of malignant disorders is highly expensive. A low gross domestic product (GDP) further augments such constraints.

Conclusion

AML was found to be a highly variable disease that presented mostly with non-specific and wide variety of signs and symptoms. The most common age to present was 15-40 years, most frequent subtype was M2 and most common features included infection, weakness and bleeding tendency. Haemoglobin levels, RBC counts and MPO activity tended to differ with age groups.

Disclaimer: The data was presented at HaemCon Conference, held in Lahore, Pakistan from February 16 to 18, 2017, and at Cell Sciences Conference, held in Dubai, United Arab Emirates (UAE) from April 6 to 8, 2017.

Conflict of Interest: None.

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