RESEARCH ARTICLE

Acute Promyelocytic Leukemia: a Single Center Study from Southern Pakistan

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Abstract

Background: Acute promyelocytic leukemia (APL) is a distinctive clinical, biological and molecular subtype of acute myeloid leukemia. However, data from Pakistan are scarce. Therefore we reviewed the demographic and clinical profile along with risk stratification of APL patients at our center. Materials and Methods: In this descriptive cross sectional study, 26 patients with acute promyelocytic leukemia were enrolled from January 2011 to June 2015. Data were analyzed with SPSS version 22. Results: The mean age was 31.8±1.68 years with a median of 32 years. The female to male ratio was 2:1.2. The majority of our patients had hypergranular variant (65.4%) rather than the microgranular type. The major complaints were bleeding (80.7%), fever (76.9%), generalized weakness (30.7%) and dyspnea (15.38%). Physical examination revealed petechial rashes as a predominant finding detected in 61.5% followed by pallor in 30.8%. The mean hemoglobin was 8.04±2.29 g/dl with the mean MCV of 84.7±7.72 fl. The mean total leukocyte count of 5.44±7.62x10^9/l; ANC of 1.08±2.98x10^9/l and mean platelets count were 38.84±5.38x10^9/l. According to risk stratification, 15.3% were in high, 65.4% in intermediate and 19.2% in low risk groups. Conclusions: Clinico-epidemiological features of APL in Pakistani patients appear comparable to published data. Haemorrhagic diathesis is the commonest presentation. Risk stratification revealed predominance of intermediate risk disease.

Keywords: Acute promyelocytic leukemia - clinico-epidemiological - risk stratification - Pakistan.

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Introduction

Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia (AML), first defined as a distinctive entity in 1957 by Hillestad (1957). The disease is recognized by characteristic morphology and is exemplified by a balanced reciprocal translocation between chromosomes 15 and 17 (Ziaei., 2004). It accounts for 10% of all cases of acute myeloid leukemia and is regarded as the most curable subtype of AML. (Bajpai et al., 2011; Mandegary et al., 2011). The peak incidence of APL is in young adults.

There are a multiple unique features of this disease includes; potentially life-threatening coagulopathy, characteristic t(15;17) translocation, resulting in the PML-RARα′ gene, unique sensitivity to all-trans-retinoic acid (ATRA), having potential for complete remission without chemotherapy and marrow aplasia and most curable (Bajpai et al., 2011; Chen et al., 2012; Imani-Saber and Ghafouri-Fard., 2014).

Most patients with APL present with pancytopenia; however 10-30% of patients present with leukocytosis (Devita et al., 2008; Dutta et al., 2008). Predominant clinical finding is easy bruising or bleeding secondary to thrombocytopenia or coagulopathy which needs urgent management. In around 40% of untreated patients, pulmonary and cerebral hemorrhages can occur.

Morphologically there are two variants of APL, commonest one is hypergranular variant while microgranular variant is accountable in 25% of cases but is more aggressive than the hypergranular type (Karim et al., 2014). The microgranular variant is also associated with a higher risk of early haemorrhagic death. APL patients are segregated into low-risk (WBC count ≤ 10×10^9/L, platelet count > 40×10^9/L), intermediate-risk (WBC count ≤ 10×10^9/L, platelets ≤ 40×10^9/L), and high-risk (WBC count > 10×10^9/L) groups, with distinctive outcomes (Sanz et al., 2000). APL should be considered as a medical emergency which requires early recognition and prompt treatment at earliest suspicion, even without confirmatory cytogenetic or molecular diagnosis.

Data on APL patients from Pakistan is limited. We have reviewed records of the patients diagnosed at our centre during the past 4.5 years. This report describes the demographical data, clinical features, laboratory findings and risk stratification in APL patients.

Materials and Methods

This is a retrospective descriptive study conducted at Liaquat National Hospital and Medical College, Karachi which is an over 700 bed tertiary care academic teaching institute. We retrieved the data of all patients with confirmed diagnoses of APL presented between January

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2011 and June 2015.

All patients were diagnosed with de novo APL. Demographical data include age, gender and medical history were recorded. Hematological parameters were determined by Cell Dyne (Abbott, Diagnostics). Bone marrow aspirate and trephine biopsy specimen were taken with Jamshidi needle. Bone marrow aspirations and biopsies were reviewed by consultant hematopathologists. Conventional G-band karyotype analysis (cytogenetic) was performed on bone marrow aspirate specimens. In negative cases diagnosis was confirmed by the presence of PML/RARα fusion gene by Fluorescence in situ hybridization (FISH), which was performed on interphase nuclei of bone marrow aspirate specimens.

Patients were stratified according to Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and PETHEMA studies (Sanz et al., 2000).

Patients were categorized into three risk groups as high, intermediate and low risk. Low-risk patients had leucocyte counts $\leq 10\times10^9$/L and platelets $> 40 \times 10^9$/L, intermediate-risk patients had leucocytes $\leq 10 \times 10^9$/L and platelets $< 40 \times 10^9$/L and high-risk patients had leucocytes $>10 \times 10^9$/L regardless of platelets counts.

Approval from the institutional ethical review committee for the study was obtained prior to study.

Data analysis

Data was compiled and analyzed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc, Chicago, IL, USA). The results were expressed as mean±SD for quantitative variables and qualitative variables are presented as frequency & percentages.

Results

During the study period, 26 patients were diagnosed as Acute promyelocytic leukemia.

Out of 26 patients, 10 were males (38.5%) and 16 were females (61.5%) with male to female ratio of 1.2:2. The mean age of patients was 31.84±1.68 (range 2-67) years with the median age of 32 years.

The major complaints were bleeding in 21 (80.7%) patients; fever in 20 (76.9%) patients; generalized weakness in 8 (30.7%) patients and dyspnea in 4 (15.38%) patients. None of our patient presented with thrombotic manifestation. Physical examination revealed petechial and purpural rashes as a predominant finding detected in 16 (61.53%) patients followed by pallor in 8 (30.76%) patients.

The mean hemoglobin was 8.04±2.29 (range 4.9-12.5) g/dl with the mean MCV of 84.68±7.72 fl. The total leukocyte count of 5.44±7.62 $x10^9$/l (range 0.5-31.3); Absolute neutrophilic count (ANC) of 1.08±2.98 $x10^9$/l (range 0.01-1.4) and platelets count were 38.84±5.38$x10^9$/l.

Based on morphology, majority of patients had hypergranular variant accountable in 17 (65.4%) patients; while 9 (34.6%) patients had microgranular type. The t(15;17) (q24.1;q21.1) translocation was detected in 21 (80.7%) patients. However, in 5 (19.2%) patients where the translocation could not be detected using conventional karyotyping technique, the diagnosis was established by detection of PML-RARA mutation by fluorescence in situ hybridization (FISH). One patient was negative for both.

According to Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and PETHEMA risk stratification, 4 (15.3%) patients were in high risk; 17 (65.38%) patients in intermediate risk, while 5 (19.23%) patients in low risk group.

Discussion

Acute promyelocytic leukemia was traditionally considered as an aggressive form of acute myeloid leukemia, characterized by arrest in differentiation at the promyelocyte stage, owing to a distinct chromosomal translocation t(15;17) resulting in gene rearrangement aberration. It is now the most curable of all subtypes as a result of intensive research into the molecular pathogenesis (Duffield et al., 2012).

We have described a series of 26 APL cases followed at our institution including their clinical, hematological and risk stratification profiles. Limited studies are available from Pakistan on APL.

It is persistently found that APL is the disease of younger age. The median age is approximately 30-40 years. Previously, a study conducted in Pakistan has reported a median age of 41 years, which is a bit high as compared with our findings. This difference might be the reflection of the fact that prior study was conducted exclusively on adult's patients (Karim et al., 2014). However large regional studies reported from China have shown the median age of 33 and 40 years respectively (Liang et al., 2008; Lou et al., 2015).

The principal APL epidemiological features so far described show no gender predilection in more studies (Karim et al., 2014). However we determined the female gender dominance, which was also seen in Malaysian APL patients (Ambayya et al., 2014). Similarly disease was pronounced in female gender in one large cohort of 1400 patients from USA (Park et al., 2011).

The clinical manifestations of APL are heterogeneous, patients are usually symptomatic. Patients often have hemorrhagic diathesis, fever, general malaise or thrombotic manifestations. Most of our patients had active bleeding as a predominant symptom (80.7%). This is more or less similar to studies reported from India (70%); Egypt (79%) and Italy (90%) (Avvisati et al., 1996; Bajpai., 2011; Khorshid et al., 2011).

Some series report the thrombotic manifestation of APL with a frequency as high as 2-10% (Chang et al., 2013; Mitrovic et al., 2015). We did not come across any such findings which is rather unusual. The incidence of thrombosis in APL is higher than in other subtypes of acute myeloid leukemia and risk of thrombosis has been associated with elevated WBC count ($>10x10^9$/l) and presence of FLT3-internal tandem duplication (Breen et al., 2012). The plausible explanation of no thrombotic manifestation is possibly due to less number of patients in high risk group (15.3%). Though we could not determined FLT-3 mutation in our series, but absence of thrombosis might predict low frequency of mutation in our patients.

Conventionally, diagnosis of APL is relied on its characteristic morphological features. It is then confirmed by immunophenotyping study, detection of t(15;17) and other chromosomal aberrations by karyotyping, or fluorescence in situ hybridization (FISH) and recently by reverse transcriptase polymerase chain reaction (RT-PCR).

The majority of patients had hypergranular variant in the present study (65.4%) while 34.6% patients had microgranular type. When compared with earlier reports, our results are in concurrence with studies reported from Spain and Italy, disclosed 29% and 20% microgranular variant respectively (Avvisati et al., 1996; Esteve et al., 2007). Similarly, larger PETHEMA trial conducted on 651 patients also disclosed; 28% of patients having hypogranular variant (Montesinos et al., 2011).

The t(15;17) (q24.1;q21.1) translocation was detected in 80.7% of our patients. Karim et al from Pakistan recently reported 73% of patients have shown specific t(15;17) (Karim et al., 2014). Analogous to our study, Spanish and Chinese studies have also reported 74% and 75.9% of patients had standard translocation t(15;17) (Liang et al., 2008; Montesinos et al., 2011).

The risk stratification is useful to predict the likelihood of disease outcome, treatment options, complications and most importantly to ascertain the disease prognosis. The majority (65.3%) of patients with APL in our study belonged to the intermediate-risk category, with WBC <10 $\times 10^9$/L at the time of diagnosis. While only 15.3% were in high risk group. In similarity, approximately 53% and 23% of patients were in the intermediate and high-risk groups respectively in the larger GIMEMA and PETHEMA trials (Sanz et al., 2000).

So in conclusion, clinico-epidemiological features are appearing comparable to published data. Hemorrhagic diathesis is the commonest presentation. Risk stratification revealed predominance of intermediate risk disease in Pakistani APL cases.

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