

Clinico hematological profile of acute promyelocytic leukemia

Abstract

Background: Acute promyelocytic leukemia (APL) is a unique subtype of acute leukemia's. It has distinct Cytogenetics, clinical features, and biologic characteristics. Acute promyelocytic leukemia (APL) is caused by an arrest of leukocyte differentiation at the promyelocytic stage. The discovery and elucidation of the molecular pathogenesis for APL has led to first and only targeted therapy for leukemia. It is classified as AML M3 by the French-American-British (FAB) system and acute promyelocytic leukemia (APL) with translocation between chromosomes 15 and 17, that is t(15;17) in the World Health Organization (WHO) classification system. A total of 55cases of APL were diagnosed in the 7year period. (JAN-2009 to DEC 2015) The majority patients presented with gum bleeding 86.4% with peripheral smear showing pancytopenia (54.5%). Prothrombin time was done on 24cases, out of which 14cases(58.3%) showed increased PT values. Immunophenotyping was done in 4cases showed positive for MPO, CD13, CD33, CD117 and negative for CD 34. Cytogenetics analysis was done in 35cases showed (15; 17) (q22; q12) PML RAR α .

Keywords: leukemia's, promyelocytes, MPO, CD13, CD33, CD117

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Abbreviations: APL, acute promyelocytic leukemia; FAB, french american british; WHO, world health organization; DIC, disseminated intra vascular coagulation; CR, complete remission

Introduction

Acute Promyelocytic leukemia (APL) or AML with t(15:17) (q22;q12) is an AML in which abnormal promyelocytes predominate.¹ Both hyper granular or typical APL and micro granular (hypo granular) types exist. Acute Promyelocytic leukemia (APL) is classified as an acute myelocytic leukemia sub class M3 (AML-M₃), using the FAB (French American British Classification) system.^{2,3} Acute Promyelocytic leukemia comprises 5-8% of AML. The disease can occur at any age but patients are predominantly adults in midlife. Typical and micro granular APL is frequently associated with Disseminated Intra Vascular Coagulation (DIC).⁴ In micro granular APL unlike typical APL leukocyte count's very high, with a rapid doubling time. It represents 6% of all cases of acute leukemia's or 13% of all cases of ANLL In past, prognosis of this diseases was so poor that complete remission (CR) could not be achieved with chemotherapy. These unique characteristics of this disease have recently attracted intense research interest. As in other types of leukemia where continuous cell lines are powerful research tools, studies using APL-derived cell lines have contributed a large body of relevant data in efforts to unravel the pathobiology and leukemogenesis of APL.⁵ In this study clinico haematological profile of acute promyelocytic leukemia will be analysed, as they have unique characteristics which differentiates them from other AML.⁶

Aim and objective

- To study the morphology and cytochemistry of Acute Promyelocytic Leukaemia.
- To correlate the clinical symptoms and signs with haematological features of APL.

Materials

Source of data

The cases will be selected from the samples received by the department of clinical pathology for Peripheral blood smear and bone-marrow aspiration and bone marrow biopsy.

- EDTA blood sample.
- EDTA Bone marrow blood sample.
- Bone marrow Biopsy Tissue specimen.
- Heparinized blood sample.

Methods

- Peripheral smear stained by Leishman's stain- Differential count, including the precursors and mature cells.
- Bone marrow aspiration stained by Leishman's stain- Differential count
- Bone marrow biopsy stained by Haematoxylin and Eosin stain
- Cytochemical staining- Peripheral smear and bone marrow with Sudan Black B
- Flow cytometry where available
- Clinical history and details medical record folders

Design of study

Prospective and retrospective study for 7yrs

- Retrospective : January-2009-August-2014
- Prospective : September 2014 to Dec 2015

Sample size: 55cases were analyzed in present study.

Inclusion criteria: All cases of Acute Promyelocytic Leukemia diagnosed by morphology will be included in this study.⁷

Exclusion criteria: Acute Promyelocytic leukemia on treatment will be excluded from the study.

Results

In present study 55 cases were analyzed of the age group 7-73yrs. The majority of the patients were in the age group 31-40 yrs, 34 % (19 cases).⁸⁻¹¹ In this study males were found to be slightly predominance than females (M: F-1.2:1). Among the symptoms, fever was the most common complaint. Pallor was the most common sign, followed by gum bleeding 86.4% (32 cases) and hepatomegaly 37.8% (14cases), splenomegaly 21.6%(8 cases).¹² The peripheral smear shows pancytopenia 54.50% and bicytopenia 21.6% (thrombocytopenia and leukopenia). Bone marrow Aspiration was done in all cases showed increased myeloid series, all cases showed predominantly abnormal promyelocytes and occasional blasts.¹³ Abnormal promyelocytes are large cells with bilobed nucleus, 1-2 nucleoli, and cytoplasmic granulation obscuring the details of the nucleus. Auer rods are seen in few promyelocytes. BM Biopsy shows hyper cellular marrow, normal marrow elements being replaced by sheets of promyelocytes these are large cells with clumped nucleus, some of them are bilobed and show moderate amount of cytoplasm. Erythroid precursor's shows normal maturation in 8 patients (21.6%). Immunophenotyping was done in 4cases showed positive for MPO, CD 13, CD 33, CD117 and negative for CD34 in all 4cases. Cytogenetics analysis done in 35cases showed positive for t(15; 17) (q22; q12) PML RAR α in all cases.¹⁴⁻¹⁶

Discussion

Acute Promyelocytic leukemia (APL) or AML with (t 15:17) (q22;q12) is an AML in which abnormal promyelocytes predominate.¹⁷⁻²¹ Both hyper granular or typical APL and micro granular (hypo granular) types exist. Acute Promyelocytic leukemia (APL) is classified as an acute myeloblastic leukemia sub class M₃ (AML-M₃), using the FAB (French American British Classification) system.²²⁻²⁹ Acute Promyelocytic leukemia comprises 5-8% of AML. The disease can occur at any age but patients are predominantly adults in midlife.³⁰⁻³² Typical and micro granular APL is frequently associated with Disseminated Intra Vascular Hemorrhage (DIC).^{33,34} In micro granular APL unlike typical APL leukocyte count's very high, with a rapid doubling time.³⁵⁻⁴¹ It represents 6% of all cases of acute leukemia's or 13% of all cases of ANLL In past, prognosis of this diseases was so poor that complete remission (CR) could not be achieved with chemotherapy.⁴²⁻⁴⁴ Subsequently, with the introduction of daunorubicin or idarubicin in the induction therapy, much improved remission rate and prolonged survival has been achieved. Also, the emergence of routine use of heparin during the induction therapy along with intensive care has made it possible to bring the disease under control.⁴⁵⁻⁵⁰ These unique characteristics of this disease have recently attracted intense research interest. As in other types of leukemia where continuous cell lines are powerful research tools, studies using APL-derived cell lines have contributed a large body of relevant data in efforts to unravel the pathobiology and leukemogenesis of APL.^{2,51-53} In this study clinico- haematological profile of acute Promyelocytic leukemia was analysed, as they have unique characteristics which differentiates them from other AML. The present study was done from the year 2009 to 2015. A total of 55 cases were studied.⁵⁴⁻⁵⁷

Age group

Patient's age ranged from 7years to 73years. The median age was

73yrs. The male to female ratio in the present study is 1.2:1. Slightly predominance of males was seen. Similar study done by Slater et al.⁵⁸ Showed male predominance (M: F 3.11:1).^{59,60} Another study done by Alan et al. shows that APML were more common in age group 40-49 (31 patients) and shows male predominance.⁶¹ In our study APML reported to be more common in the age between 31-40years (19cases). Another study done by Tallmas et al. Showed the median age of 39years (range 3-79).

Symptoms and signs

Fever (46.1%) was the most common complaint followed by bleeding and abdominal pain in the present study Pallor was the commonest sign which was more prominent in females (male 15.3% and female 35.8%). Pallor was followed by gum bleeding 86.4% (32cases) and hepatomegaly 37.8% (14cases), splenomegaly 21.6 % (8 cases). The peripheral smear shows pancytopenia 54.50% and bicytopenia 21.6%. A study done by Karimi et al.⁶¹ showed similar pattern of presentation, fever (74%) being the commonest followed by pallor (42%).⁶² Another study done by Chan et al.⁶³ Showed sixteen children (ages 2-17yrs) with APML. Bleeding diathesis was the predominant presenting symptom (>85%) associated with laboratory findings of DIC.⁶⁴ In the present study showed hemoglobin ranging from 6.0gm% to 12gm%, 21patients(56.75%) had anaemia, 15 patients(40..54%) had leukopenia and 21patients had thrombocytopenia(56.7%). One third of patients (13.5 %) had WBC count>10 \times 10³/L. In a study done by Chatterjee et al.⁶² analysed the clinico-pathological presentation of twenty APL patients confirmed by RQ-PCR. An unusual feature of gum hypertrophy was seen in four patients (20%). This observation is similar to a previous Indian study by Dutta et al. where the same clinical feature was observed in some of their patients.⁶⁵ It was shown that presence of gum hypertrophy seen commonly in acute myelomonocytic leukemia is also seen in Indian APL patients.

BMA & BM biopsy

In present study Bone marrow Aspiration was done in all cases showed increased myeloid series, all cases showed predominantly abnormal promyelocytes and occasional blasts. Abnormal promyelocytes are large cells with bilobed nucleus, 1-2 nucleoli, cytoplasmic granulation obscuring the details of the nucleus. Auer rods are seen in few promyelocytes. BM Biopsy shows hyper cellular marrow, normal marrow elements being replaced by sheets of promyelocytes these are large cells with clumped nucleus, some of them are bilobed and show moderate amount of cytoplasm. Erythroid precursors shows normal maturation in 8patients (21.6%).

Cytochemistry

Myelo Peroxidase (MPO) stain is specific for AML But because of its carcinogenic properties; it could not be done in all cases. SBB is used as an alternative to MPO. All the 55patients show positive for Sudan Black B cytochemical stain. In a study by Chatterjee et al.⁶² India, cytochemistry results showed positivity for MPO and CAE in all the APL cases (100%).⁶⁵ Interestingly 33.33% of cases also showed positivity for NSE. This finding is in concordance with previous published literature where NSE positivity in APL cases is between 13.5%- 60.7%.

Immunophenotyping

Immunophenotyping has become an important diagnostic tool in establishing the diagnosis and classification of acute leukemia. In this study Immunophenotyping done by Flow cytometry in 4 cases.

All cases showed MPO, CD 13, CD33, and CD 117, positivity. One study done by Chattarjee et al.⁶² flow cytometric analysis of eleven patients (micro granular, hyper granular) revealed characteristic findings of APL. All hyper granular variants revealed a high side scatter and antigenic expression of CD13, CD33 and MPO. CD117 was expressed in one hypo granular and two hyper granular variants. Weak CD34 expression was seen in two hypo granular variants. HLA-DR expression was not seen in any case. Weak CD15 was noted in three hyper granular variants.⁶⁵ Another study done by Nagendra et al.,⁶⁵ when morphologic and cytochemical classification of leukemia's fail, flow cytometric analysis may be performed to further classify the disease. APL has been known to have a characteristic immune phenotype: HLA-DR and CD13+ and/or CD33+. The blasts in 2 of 8 cases also expressed HLA-DR. Occasional cases of AML-M3v have been HLA-DR+; (Exner et al.) found 2 of 4 cases of AMLM3v positive for HLA-DR. Thus, HLA-DR positivity cannot always be used as an exclusionary criterion for APL.⁶³ One study done by Wojciech gorczyca et al. USA in their series of 97 cases, acute Promyelocytic leukemia (APL) with t(15;17)/PML-RARA had the following phenotype: CD11b-, CD11c-, CD13+, CD33+, CD45+, CD64+/-, CD117+, and HLA-DR-ve.⁶⁴

Cytogenetics

Currently chromosomal analysis forms an important component of the diagnostic, prognostic and biological studies of acute leukemia's. In its absence, the FAB classification based on morphology, cytochemistry and Immunophenotyping remains extremely useful in arriving at a correct diagnosis. In present study Cytogenetics analysis was done in all cases showed positive for translocation t (15; 17) (q22; q12).

Conclusion

In a study by Chatterjee et al.⁶² RQ-PCR done at the time of diagnosis revealed PML-RAR α transcript in twenty patients. Unusual feature was that in their study PML(L) RAR α isoform was found to be the predominant isoform (42.85%) followed by PML(S) RAR α isoform (38.09%). Whereas according to data published in India by Dutta et al.⁸ PML(S) RAR α isoform was found to be significantly high (72.7%).⁶⁵

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None.

Conflict of interest

The author declares no conflict of interest.

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