Original Article

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Clinicopathological Profile of Chronic Myelomonocytic Leukemia Cases: An Experience from A Tertiary Care Center

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ABSTRACT

Background: Chronic myelomonocytic leukemia (CMML) is a clonal hematological neoplasm with features of both myeloproliferation and myelodysplasia with an incidence 0.4 per lakh population. A number of prognostic risks scoring systems have attempted to predict survival and risk of CMML patients, like International Prognostic Scoring System (IPSS), the Spanish Score, the modified Bournemouth Score, the Dusseldorf Score and the MDAP Score. But no prognostic system has been widely accepted. More data from different regions are required to create a widely accepted working prognostic system for CMML. No case series on CMML has been published in literature from India in our knowledge. This article attempts to put to light the various clinicopathological parameters of CMML cases from India and the impact of these parameters on final outcome.

Methods: All admitted patients in a tertiary center in western India, with a diagnosis of either a chronic myeloproliferative disease or a myelodysplastic disease over a period of 3 years (2015-2018) were evaluated, out of which nine(n=9) cases fulfilled the diagnostic criteria of CMML. All patients underwent peripheral blood examination, bone marrow aspirate, bone marrow biopsy and cytogenetic studies.

Result: All patients (n=9) were between 50 and 80 years and most were males (n=8). Five patients presented with hepatosplenomegaly. Renal and liver function of one patient was deranged who had pleural effusion, ascites. Most patients (n=8) had total leukocyte count above 13000/cumm, while three had low platelet counts. Two out of three patients classified as CMML-II with increased blasts in peripheral blood and bone marrow had fatal outcomes. Patients whose karyotypes were available had normal karyotypes without any additional cytogenetic abnormalities. All were negative for JAK2 and BCR-ABL1.

Conclusion: The study concluded that altered biochemical tests (LDH, LFT), blast percentage, CMML II, relative lymphocytosis and transformation to AML were associated with poor outcome.

Keywords: *Chronic Myelomonocytic Leukemia, Survival, Ring Sideroblast, Myelodysplastic Syndrome, Myeloproliferative Syndrome,*

Introduction

Chronic myelomonocytic leukemia is a hematopoietic malignancy which has features of both myelodysplasia and myeloproliferation. CMML was earlier classified as a myelodysplastic syndrome by the French–American–British (FAB) group. Presently CMML is classified under MDS/MPN neoplasms in WHO classification of tumors of hematopoietic and lymphoid tissues.[1, 2]

Clinical and pathological features of CMML are varied and can range from a predominantly myelodysplastic picture with cytopenias and dysplastic changes, to mixed ones to a predominantly myeloproliferative neoplasm like picture with high total leukocyte count, hypercellularity of bone marrow, marrow fibrosis and organomegaly. CMML is a rare diagnosis with an yearly incidence of approximately 0.4 per lakh population. It is more common in elderly individuals above 80 years of age with a male to female ratio of 3:1. [1, 3]

Diagnostic criteria for chronic myelomonocytic leukemia as laid out by WHO includes persistent peripheral blood monocytosis ($\geq 1x10^9/L$) with monocytes accounting for ≥10% of the leukocytes; criteria for CML, primary myelofibrosis, polycythemia vera and essential thrombocythaemia are not met; Absence of rearrangement of PDGFRA, PDGFRB or FGFR1 and PCM1-JAK2; Blasts constitute <20% of the cells in the peripheral blood and bone marrow; Dysplasia involving ≥1myeloid lineages or if myelodysplasia is absent or minimal, and other criteria are met and an acquired, clonal cytogenetic or molecular genetic abnormality is present in hematopoietic cells or the monocytosis has persisted for more than 3 months and all other causes of monocytosis (e.g. malignancy, infection, and inflammation) have been excluded.[2]

CMML can be subdivided based on WBC counts into dysplastic (<13000/cumm) and proliferative (>13000/cumm). The former group presents mostly with constitutional symptoms while the latter with hematopoietic insufficiency. CMML cases are divided into three subcategories based on the percentage of blasts and promonocytes in the blood and bone marrow : CMML-0

(<2% blasts in the blood and <5% in the bone marrow; no Auer rods), CMML-1 (2-4% blasts in the blood or 5-9% in the bone marrow, and no Auer rods) and CMML-2 (5-19% blasts in the blood, 10-19% in the bone marrow or Auer rods are present).[4, 5]

Microscopically CMML shows monocytosis in peripheral blood along with dyspoietic features in neutrophils. Blasts and promonocytes (<20%) may also be present. Bone marrow is usually hypercellular with granulocytic proliferation and dyspoietic features. The tumor cells express CD33 and CD13, the myelomonocytic antigens. CD14 expression is decreased, which shows immaturity, along with aberrant markers like overexpression of CD56 and CD2 can be seen. Cytogenetic abnormalities may be found in up to 40% of CMML cases with gain of chromosome 8 and deletion 7q being the most common ones. About half of the patients show TET2 and ASXL1 mutations.[6-8]

Survival of CMML patients can range from few months to more than five years. Survival is dependent on various parameters, most important of which is the percentage of blasts in the peripheral blood and bone marrow. Karyotype, total leukocyte count and hematopoietic function are other survival determinates. Serum LDH levels, presence of splenomegaly, anemia, thrombocytopenia and lymphocytosis are the factors mentioned as being predictors of the course of disease. Acute myeloid leukemia arise in about a fourth of CMML patients, whom usually have poor clinical course.[3, 5, 9]

CMML with ring sideroblasts is rare and has an impact on overall survival, with CMML-RS having a better prognosis than CMML without RS. Many authors have suggested that CMML and Myelodysplastic syndrome with ring sideroblasts (MDS-RS) as being a continuum. Molecular Similarity between the two entities has been shown in some studies. As the prognosis is better in CMML-RS, classifying it under MDS-RS has also been suggested.[10, 11]

As the clinical course of CMML is highly variable, no fool proof prognostic scoring or system is available. No prognostic risk scoring system for CMML is widely accepted. Many systems which have tried to assess risk of CMML patients include International Prognostic Scoring System (IPSS), the Spanish Score, the modified Bournemouth Score, the Dusseldorf Score and the MDAP Score. A CMML-specific prognostic scoring system (CPSS) is probably the most accepted system for assessing the overall survival and evolution to acute myeloblastic leukemia (AML). More studies are required to add CMML specific data to further the accuracy of such prognostic systems. Ours is the first case series on CMML from India in our knowledge. Here we attempt to put to light the various clinicopathological parameters of CMML cases from India and the impact of these parameters on final outcome.[12]

Materials and Methods:

The descriptive study was conducted in a tertiary care center and teaching hospital in western India, India. All admitted patients in a tertiary center in western India, with a diagnosis of either a chronic myeloproliferative disease or a myelodysplastic disease over a period of 3 years (2015-2018) were evaluated, out of which nine cases fulfilled the diagnostic criteria of CMML.

Exclusion criteria

1. CMML arising in a patient with a previous diagnosis of MDS or myeloproliferative diagnosis.
2. Any case in which criteria for any MPN is fulfilled.
3. Any case in which myelodysplasia is absent.

Study Design

Medical records of patients who were admitted in hematology ward with a diagnosis of either a chronic myeloproliferative disease or a myelodysplastic disease over a period of 3 years were analyzed for age, clinical presentations, biochemical parameters and radiology. A total of nine (n=9) patients fulfilled the criteria of CMML. Peripheral blood, bone marrow aspiration, bone marrow biopsy and karyotyping were reported in the pathology department. Mutation studies were carried out in outside laboratory. All peripheral blood and bone marrow aspirate smears were stained with Wright's stain. The bone marrow biopsy was processed using Leica ASP 300S automated tissue processing system and stained with hematoxylin & eosin and reticulin stains. Immunohistochemical studies using CD34 marker was also performed on the bone marrow biopsies.

Analytical Statistics

Data was analyzed using proportions and student t-test. Each set of data was analyzed using Shapiro-Wilk test to assess normality and was further tested by student t-test for statistical significance.[13, 14]

Result

The present study was done by analyzing the medical records, peripheral smear, bone marrow aspirates and bone marrow biopsy slides of all the diagnosed cases of CMML (n=9) admitted in hematology ward in a tertiary care center in western India, Maharashtra.

Age and Sex

The age of the patients at the time of diagnosis ranged from 53 to 84 years, with a mean of 67.4 years. Most patients

belonged to more than 70 years age group. Age at the time of diagnosis did not show any relation with survival. Most (n=8) of the patients were males.

Relationship between Hepatosplenomegaly and Total leukocyte count (Table 1)
Hepatosplenomegaly was present in five out of nine patients and there was one fatality in either groups. Hepatosplenomegaly was present in only the proliferative group (TLC>13000/cumm) in this study.

Liver function test
Liver function parameters were deranged in two patients, both of whom had fatal outcomes. These patients had serum bilirubin levels ranging from 6.8 to 9.1 mg/dL, total proteins 4.5 to 5.4 g/L, albumin 2.7 to 3.3 g/L, AST between 60 to 69 units per liter and ALT between 66 to 84 units per liter. The association of LFT with outcome was statistically significant, $p<0.05$.

Serum lactate dehydrogenase (LDH)
Two patients had deranged LDH levels (range - 482 to 831U/L) and both patients had poor outcomes. The association of LDH with outcome was statistically significant, $p<0.05$.*(Table 2)*

Hemoglobin (Hb)
Hemoglobin levels ranged from 5.3g/dL to 12.4g/dL. Hb levels showed no statistically significant association with outcome.

Total leukocyte count (TLC)
Total counts ranged from 3780/cumm to 88300/cumm. TLC showed no statistically significant association with outcome in patients.

Percentage of lymphocytes in peripheral blood
Lymphocytes in peripheral blood ranged from 8 to 24 percentage of total leukocyte count. Two patients had lymphocyte count more than 15% and both had poor outcomes. The absolute lymphocyte counts of these patients were 908 and 4066/cumm. The percentage of lymphocytes in peripheral blood had statistically significant association with outcome, $p<0.05$.

Platelet count
Platelet counts ranged from 20000/cumm to 206000/cumm. Platelet counts showed no statistically significant association with outcome.

Monocyte percentage in peripheral blood (PB) and bone marrow aspirate (BMA)(Table 2)
Monocyte percentage in peripheral blood ranged from 11 to 44 percentage of total leukocyte count, while that in bone marrow aspirate ranged from 6 to 22 percentage of all nucleated cells. No statistically significant association was found between monocyte percentage in either peripheral blood or bone marrow and final outcome.

Pearl's stain (Figure 3)
Perl's stain on bone marrow aspirate showed more than 15% ring sideroblasts in one of the cases. The patient has not progressed further.

Subdivisions of CMML based on blast %
Three patients were classified as CMML-2, out of which two patients had fatal outcome. There were four patients in CMML-1 and two in CMML-0.

Bone marrow biopsy (Figure 4)
All cases had similar bone marrow biopsy pictures. All bone marrows were hypercellular for age and showed 80 to 100% cellularity. Myeloid preponderance was seen with increase in monocytes. Megakaryocytes were increased with dyspoietic features. There was an interstitial increase in CD34 positive cells (Figure 5) but were not seen in sheets or clusters.

Progression to Acute Myeloid Leukemia (AML)
One patient progressed to AML and succumbed to the disease within a month of diagnosis.

Karyotype
Karyotype of four patients out of seven were available. Other three had culture failure. All four had a karyotype of 46XY with no additional cytogenetic abnormalities.

Mutations
JAK2, MPL, CALR, BCR-ABL of all patients were evaluated and all patients were negative for these mutations.

Discussion

CMML is a clonal hematological neoplasm with features of both myeloproliferation and myelodysplasia. It is one of the rare hematopoietic neoplasm and no large series was available from India on literature search. Hence an attempt was made to compile and present the data of CMML cases diagnosed and managed in a tertiary care hospital. Our aim was to compare the clinicopathological profile of CMML cases (n=9) in our tertiary care setup in western India, with the final outcome.

The following findings in our study are consistent with current literature. All patients fulfilling the diagnostic criteria of CMML were above 50years, with median age at diagnosis in other studies being 65 to 75years. Deranged liver function tests and raised LDH are associated with poor outcome. Increased percentage of blasts in peripheral blood and lymphocytosis are associated with worse outcome. Acute leukemic transformation was seen in one out of nine patients and was associated with poor outcome.

Table 1: Total leukocyte count compared to hepatosplenomegaly.

	Total leukocyte count <13000/cumm	Total leukocyte count >13000/cumm	Final outcome
Hepatosplenomegaly present	Nil	05	01 fatal outcome
Hepatosplenomegaly absent	01	03	01 fatal outcome

Table 2: Monocyte percentage compared to final outcome.

	<10%	10-19%	20-29%	>30%
Monocyte % in peripheral blood	Nil	04	02	03
Outcome		One fatal outcome	One fatal outcome	
Monocyte % in bone marrow	06	03	Nil	Nil
Outcome		02 fatal outcomes		

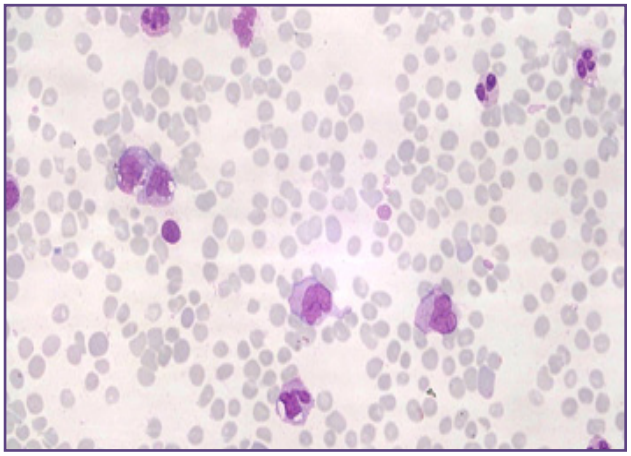

Fig. 1: Peripheral blood smear. Monocytosis with dysplastichypogranular neutrophils (Wright's stain; 400X).

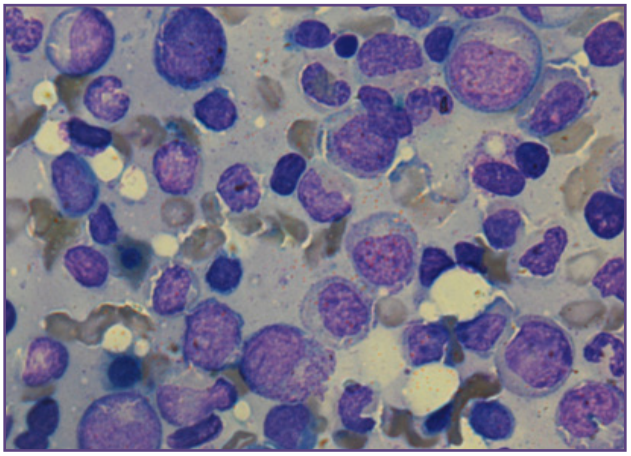

Fig. 2: Bone marrow aspirate. Myeloid preponderance (Wright's stain; 1000X).

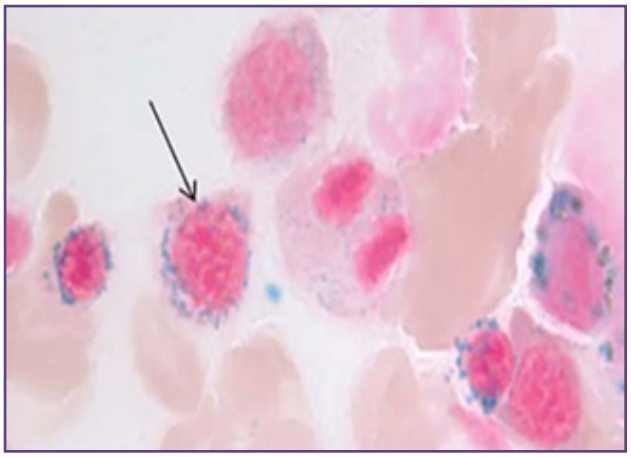

Fig. 3: Ring sideroblastsin CMML-RS (Pearl's stain; 1000X).

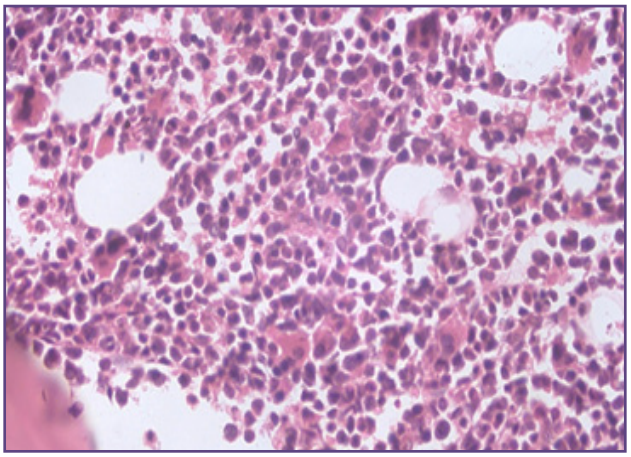

Fig. 4: Bone marrow biopsy. Hypercellular marrow with myeloid preponderance. Many hypolobateddyspoietic megakaryocytes and micromegaryocytes seen (Hematoxylin and Eosin, 100x).

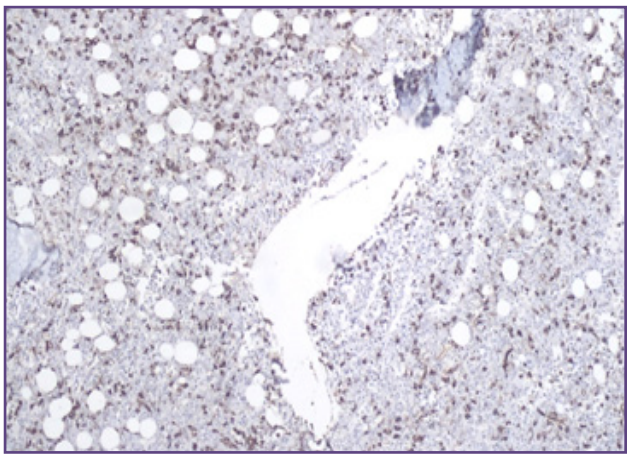

Fig. 5: Bone marrow biopsy showing interstitial increase of CD34 positive cells in one of the CMML-2 case. (CD34 immunohistochemistry, 40x).

Subdivision of CMML to 0, 1 and 2 stands to logic as CMML2 is associated with worse prognosis. Presence of ring sideroblasts in bone marrow aspirate is linked with a good outcome. [4, 11, 15-17] The following findings are not in agreement with the current literature, though this study is limited by the small sample size. Most CMML cases presenting in this hospital are men. Hepatosplenomegaly, hemoglobin concentration, total leukocyte count and platelet counts had mixed relationship to outcome. Monocyte percentage in PBS and BMA had no relation to final outcome. No chromosomal abnormalities were detected as opposed to studies showing up to 27% CMML cases having chromosomal abnormalities.[4, 15-17]

The presence of ring sideroblasts in bone marrow in CMML is a rare finding, but it has prognostic significance. This finding further supports the idea that, MDS-RS and CMML may be actually continuum of disease progression. [10, 11]

Conclusion

The spectrum of signs and symptoms of CMML patients is wide, so are the hematological findings. The prognostic factors of CMML are still not completely understood. In this study, the factors which were associated with poor outcome are altered biochemical tests (LDH, LFT), blast percentage, CMML II, relative lymphocytosis and transformation to AML. CMML with ring sideroblasts is associated with a better outcome.

Abbreviations

CMML-Chronic myelomonocytic leukemia, LDH-Serum lactate dehydrogenase, LFT-Liver Function Test, FAB-The French–American–British, MDS/MPN-myelodysplastic/myeloproliferative neoplasm, PB-peripheral blood, BMA-Bone marrow aspirate, AML-Acute Myeloid Leukemia, Hb-Hemoglobin, TLC-Total leukocyte count, AST-aspartate aminotransferase, ALT-alanine aminotransferase, CMML-RS - Chronic myelomonocytic leukemia with ring sideroblasts, MDS-RS - Myelodysplastic syndrome with ring sideroblasts

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