

PLASMA CELL LEUKEMIA: A COMPREHENSIVE ANALYSIS OF CLINICAL & PATHOLOGICAL FEATURES OF 7 CASES

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ABSTRACT

Background: Plasma cell leukemia (PCL) is a rare, yet aggressive plasma cell (PC) neoplasm, variant of multiple myeloma (MM), characterized by high levels of PCs circulating in the peripheral blood. PCL can either originate de novo (primary PCL) or as a secondary leukemic transformation of MM (secondary PCL) and is characterized by circulating PCs $>2 \times 10^9/L$ in peripheral blood and a peripheral blood plasmacytosis $>20\%$.

Aims & Objective: Present study was undertaken to analyze the main clinical & pathological features of PCL. For diagnostic purpose the morphological appearances and confirmation by immunophenotyping are emphasized rather than more sophisticated testing methods that may not be widely available.

Material and Methods: A descriptive study was carried out in the department of Pathology, in a tertiary care teaching hospital, Ahmedabad, India during year 2009-2013. We investigated the important clinical characteristics, pathological, biochemical & radiological features, immunophenotype, & prognostic factors of 7 patients of PCL.

Results: Common clinical features at diagnosis were anaemia, renal insufficiency, bone pain, splenomegaly or hepatomegaly. Anaemia, leucocytosis, thrombocytopenia & plasmacytosis were seen in peripheral blood. Plasma cell marker - CD 38 & CD 138 were expressed in all cases. Serum $\beta 2$ -microglobulin, serum LDH were increased & serum albumin was decreased in all 7 cases & were associated with poor prognosis. The median survival time from diagnosis was 9 months.

Conclusion: Plasma cells have characteristic morphological features which can be easily identified on peripheral blood & bone marrow examination. CD 38 & CD 138 are excellent plasma cell markers. Increased serum $\beta 2$ -microglobulin & serum LDH & decreased serum albumin are potent poor prognosis factors. PCL is aggressive neoplasm with poor response to chemotherapy & low median survival time from diagnosis.

Key-Words: Plasma Cell Leukemia; Multiple Myeloma; Lytic Lesions; Immunophenotyping; Plasmacytosis

Introduction

Plasma cell leukemia (PCL) is a rare, yet aggressive plasma cell (PC) neoplasm, variant of multiple myeloma (MM), characterized by high levels of PCs circulating in the peripheral blood.^[1] Diagnostic criteria for plasma cell leukemia are^[2]: (1) Plasma cells $>2 \times 10^9/L$ in peripheral blood; (2) Plasma cells $>20\%$ of blood leukocytes in peripheral blood; (3) Primary plasma cell leukaemia (pPCL): presents as de novo leukaemia; and (4) Secondary plasma cell leukemia (sPCL): progression from a pre-existing multiple myeloma.

Altogether 60% of all PCL is pPCL.^[3] Secondary PCL occurs as a progression of disease in 1 to 4% of all cases of MM, although it is now suspected to be a more common complication of patients exhibiting greater longevity.^[4] There appears to be a 3:2 male to female sex distribution in both primary and secondary PCL.^[5] The median age of diagnosis of pPCL is 55, a decade younger than the average age of MM diagnosis.^[5] The median time to leukemic transformation for patients with MM who evolve to sPCL is 21 months.^[5]

Up to 15% of patients will have hepatomegaly, splenomegaly or lymphadenopathy due to extramedullary deposits of plasma cells.^[4] Osteolytic lesions are more common in sPCL as they are also more common in pre-existing MM (sPCL 53% vs. pPCL 18%).^[5] Because of extensive involvement of the bone marrow patients with PCL have a higher prevalence of anaemia and thrombocytopenia.^[5-7] Patients with pPCL present without a MM prodrome are characterized by higher prevalence of renal insufficiency and elevated $\beta 2$ -microglobulin as opposed to newly diagnosed MM. Patients with sPCL are also frequently afflicted with renal insufficiency.^[5] Laboratory parameters of disease aggressiveness such as an elevated serum LDH or $\beta 2$ -microglobulin are common in PCL cases.^[5,7,8] The most common proteins are of the IgG subtype (33%) followed by IgA (20%), IgD (3%) and IgE (1%). Notably 35% of patients do not produce a heavy chain (light chain only disease) and less than 10% will be non-secretors.^[5]

Blood and bone marrow examination shows- Rouleux formation is most striking feature on PB smear examination .The morphological features of PCs can differ depending

upon their maturity. Mature PCs are oval with abundant basophilic cytoplasm. The nucleus is round and eccentrically located and the chromatin arranged in pyramidal blocks against the nuclear membrane, giving the characteristic “cartwheel” appearance. Immature PCs have dispersed nuclear chromatin, prominent nucleoli and high nuclear to cytoplasmic ratio. The findings on bone marrow aspiration and biopsy are similar to those seen in MM without PCL and demonstrate an increased number of monoclonal PCs^[9] The pattern of infiltration is mostly diffuse in all cases and this infiltration is able to disrupt normal hematopoiesis.

Immunophenotypic characteristics shows CD38 and CD138 antigen expression are excellent PC markers and does not differ between MM and PCL, while CD2, CD3 and CD16 are consistently negative. The frequency of CD10+, CD13+ and CD15+ is similar in both groups. Negative expression of CD56 has been associated with extramedullary MM.^[7,8,10] Acquisition of the CD28 antigen on PCs appears to correlate with an increased proliferative rate and disease progression.^[11]

Differential diagnosis include B-cell chronic lymphocytic leukemia, hairy cell leukemia and marginal zone lymphomas with circulating lymphocytes. Rarely PCL needs to be differentiated from reactive polyclonal plasmacytosis related to infectious or autoimmune disorders. The majority of cases will be easily distinguished from other forms of leukemia and lymphoma by morphology with confirmation by flow cytometry or immunohistochemistry. Reactive polyclonal plasmacytosis can be excluded based upon absence of kappa or lambda light chain restriction.

PCL is extremely aggressive associated with short survival; with treatment of only 7 to 11 months, with up to 28% of patients dying within the first month after diagnosis in different studies.^[6,5,12]

In general, patients are treated with aggressive induction therapy followed by HCT (haematopoietic stem cell transplantation) in those who are appropriate candidates for this approach. Chemotherapy alone is the principal option for those ineligible for HCT. Multi-agent infusional chemotherapy (e.g. vincristine, doxorubicin, plus dexamethasone) results in a superior, yet still poor median overall survival of approximately 15 to 18 months.^[5,7]

Materials and Methods

A descriptive study was carried out in department of pathology, in a tertiary care teaching hospital, Ahmedabad, India during year 2009-2013. 7 cases of PCL were thoroughly investigated. Detailed clinical history was taken

& physical examination was done to assess organomegaly & lymphadenopathy. Radiological examination was done to look for osteolytic lesions. Peripheral blood was collected for complete blood count & differential counting as well as peripheral smear examination. Smears were stained with Wright Giemsa stain. ESR (erythrocyte sedimentation rate) done by Westergren’s method & results obtained at the end of one hour. Bone marrow aspiration & bone marrow biopsy were done for morphological examination. Immunophenotyping was done to assess for plasma cell markers - CD 38 & CD 138. Biochemical investigations such as serum β 2-microglobulin, serum LDH & serum albumin were also performed along with blood urea nitrogen (BUN) & serum creatinine. Survival time was noted after chemotherapy.

Results

Seven cases of plasma cell leukemia (PCL) admitted to our hospital from 2009 to 2013 are reported. The following features were observed in PCL: (1) The age was younger in pPCL with a median age of 53.2 years, as compared to sPCL with median age of 68.1 years. (2) M:F ratio was 2.5 :1 (5 male & 2 female cases) (3) Onset was abrupt in pPCL. (4) Low-grade fever, anorexia, nausea, dyspnoea & fatigability were usual symptoms (5) On examination, there was pallor reported in all patients (6) 25% patients (1/4 cases) of pPCL & 0% patients (0 cases) of sPCL had liver enlargement, 25% patients (1/4 cases) of pPCL & 33.33% patients (1/3 cases) of sPCL had splenomegaly and 50% patients (2/4 cases) of pPCL & 66.66% patients (2/3 cases) of sPCL had sternum tenderness. (7) Infection and haemorrhage contributed significantly to morbidity in 4 patients. DIC had also been reported in one case. (8) All patients showed marked anemia with an average hemoglobin of 8.7 g/L in pPCL & 8.2g/L in sPCL. (9) Leucocytosis with median WBC count in peripheral blood was $23.4 \times 10^9/L$ in pPCL & $19.8 \times 10^9/L$ in sPCL (10) Thrombocytopenia with median platelet count $97 \times 10^9/L$ occurs in pPCL & $88 \times 10^9/L$ in sPCL. (11) Rouleaux formation was usually evident on the peripheral blood smear examination; which was seen in all seven of our cases. Plasma cells with their characteristic morphological features were seen in all smears stained with Wright Giemsa stain. Binucleate forms of plasma cells were also seen. (Figure 1) (12) The bone marrow aspiration & biopsy revealed hypercellularity with partial to almost complete replacement by plasma cells and plasmablasts. (Figure 2 & 3). Plasma cell number in the marrow was markedly increased with an average of 70% in pPCL & 56% in sPCL, of which the blast cells and immature forms were predominant.

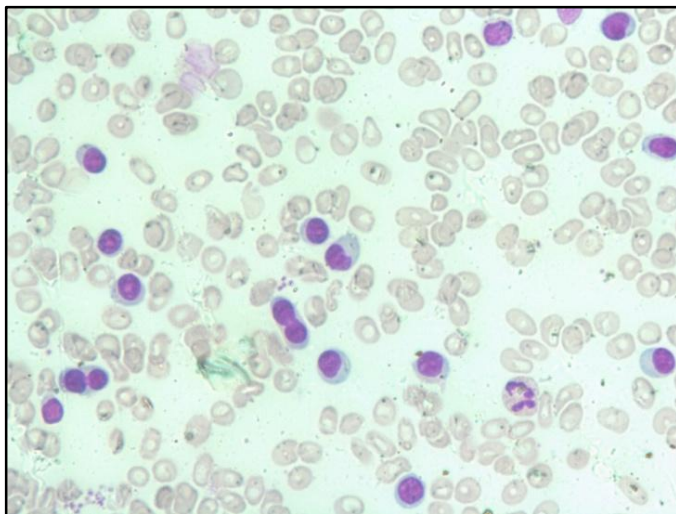


Figure-1: Peripheral Blood Smear (Wright Giemsa Stain): Plasma cells with round to oval eccentric nuclei & basophilic cytoplasm. Binucleate forms also seen.

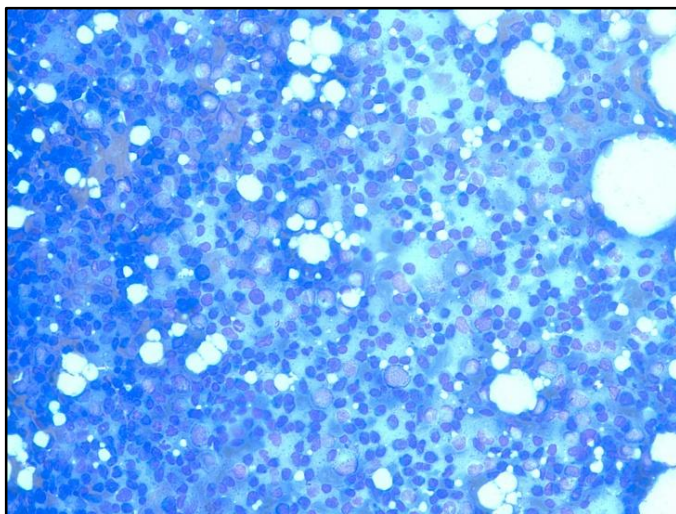


Figure-2: Bone Marrow Aspiration (Wright Giemsa Stain): Diffuse infiltration by plasma cells with characteristic morphological features

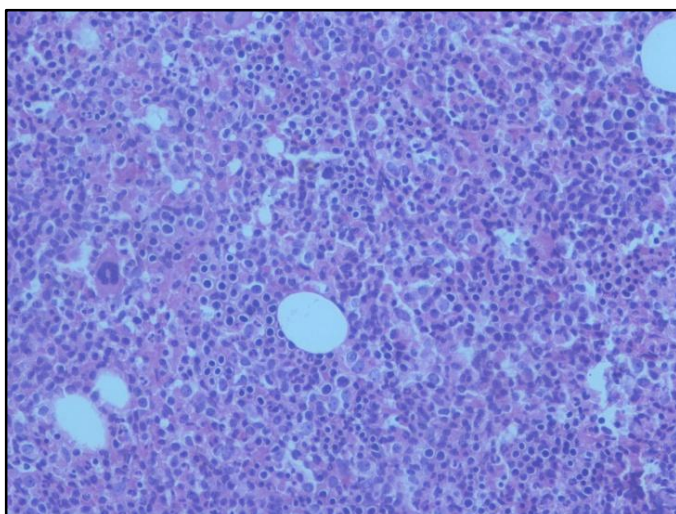


Figure-3: Bone Marrow Biopsy (H&E stain): Diffuse infiltration by plasma cells & plasma blasts

(13) X-ray skull revealed few punched out osteolytic lesions. Osteolytic lesions were seen in 25% patients (1/4 cases) of

pPCL & 66.66% patients (2/3 cases) of sPCL (14) serum β 2-microglobulin, serum LDH were increased & serum albumin was decreased in all 7 cases & were associated with poor prognosis. (15) The elevated blood urea nitrogen (BUN) & serum creatinine with average of 65 mg% 5.4 mg% respectively in pPCL in 75% patients (3/4 cases) & sPCL in 66.66% patients (2/3 cases) suggestive of renal insufficiency. (16) An elevated ESR erythrocyte sedimentation rate is a very common finding as seen in all 7 of our cases with mean of 78 mm at the end of one hour by Westergren's method. (17) Immunophenotypic findings show expression of CD 38 & CD 138 in all 7 cases. (18) The response to chemotherapy was poor, a mean survival of 9 months.

Discussion

Plasma cell leukemia (PCL) is a rare & aggressive neoplasm of plasma cells with short survival period. Biology of disease can be better understood by studying main clinical & pathological features of PCL. Morphology of plasma cell in blood & bone marrow is characteristic so blood & bone marrow examination was performed as initial investigation. Immunophenotyping yield excellent results so it was taken as confirmatory investigation.

A large case study of 80 cases of Plasma cell leukemia was done by Tiedemann RE, Gonzalez-Paz N, Kyle RA, et al. [5] Genetic aberrations and survival in plasma cell leukemia, for important clinical & pathological features. We compared our study with study of Tiedemann et al. We compared main clinical and biological differences between primary PCL (pPCL) and secondary PCL (sPCL) of both studies. We analyze 7 cases of PCL in present study with median age for pPCL was 53.2 years i.e. a decade younger than sPCL which was 68.1 years. It is comparable to previous study of Tiedemann et al in which it is 54.5 years in pPCL & 65.7 years in sPCL. In present study cases of splenomegaly were 25% & 33.33% in pPCL & sPCL respectively while in previous study they were 18% & 8% respectively. Cases of hepatomegaly in present study were 25% & 0% for pPCL & sPCL respectively while they were 32% & 11% in previous study. Osteolytic lesions were seen radiographically in 25% & 66.66% in pPCL & sPCL respectively in our study & in study of Tiedemann et al. They were seen in 35% & 53% respectively. The main pathological features such as peripheral blood Haemoglobin (g/dL), White blood cell count ($\times 10^9/L$), Platelet count ($\times 10^9/L$), peripheral blood plasmacytosis(%), peripheral blood plasmacytosis ($\times 10^9/L$) & Bone Marrow plasmacytosis were compared with previous study of Tiedemann et al. In present study median Hemoglobin level was 8.7 g/dL & 8.2 g/dL in pPCL

& sPCL respectively while it was 9.4 g/dL & 9.1 g/dL in previous study. WBC series show leucocytosis with median white blood cell count of $23.4 \times 10^9/L$ & $19.8 \times 10^9/L$ in pPCL & sPCL respectively in present study. Previous study also show leucocytosis with median white blood cell count of $21.5 \times 10^9/L$ & $15.7 \times 10^9/L$ in pPCL & sPCL respectively. Both pPCL & sPCL show thrombocytopenia with median platelet count of $97 \times 10^9/L$ & $88 \times 10^9/L$ respectively in present study & $98 \times 10^9/L$ & $53 \times 10^9/L$ respectively in previous study. Plasmacytosis is the diagnostic feature of plasma cell leukemia & is seen in both pPCL & sPCL in peripheral blood as well as bone marrow. Median peripheral blood Plasmacytosis (%) is 54 % & 48% in pPCL & sPCL respectively in present study which is comparable to median peripheral blood Plasmacytosis (%) of 46 % & 52% in past study. Median peripheral blood Plasmacytosis is $7.8 \times 10^9/L$ in pPCL & $6.2 \times 10^9/L$ in sPCL. Previous study show peripheral blood Plasmacytosis of $7.2 \times 10^9/L$ in pPCL & $6.3 \times 10^9/L$ in sPCL. There is partial to complete replacement of bone marrow with median marrow plasmacytosis of 70% & 56% in in pPCL & sPCL in present study while it is 78% & 63% in previous study. Main clinical & pathological features were comparable to study of Tiedemann et al.

Conclusion

Plasma cells have characteristic morphological features which can be easily identified on peripheral blood & bone marrow examination. CD 38 & CD 138 are excellent plasma cell marker. Increased serum $\beta 2$ -microglobulin & serum LDH & decreased serum albumin are potent poor prognosis factor. PCL is aggressive neoplasm. Primary plasma cell leukaemia has a rapid course with short survival whereas the secondary form may be associated with a more indolent clinical course and survival is variable. Our observation indicates poor response to chemotherapy and poor

prognosis of disease & low median survival time from diagnosis is seen in both types.

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