Am J Blood Res 2022;12(6):190-195
www.AJBlood.us /ISSN:2160-1992/AJBR0145689

Original Article

Clinicopathological and laboratory parameters of plasma cell leukemia among Indian population

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Received August 2, 2022; Accepted November 29, 2022; Epub December 15, 2022; Published December 30, 2022

Abstract: Background: Plasma cell leukemia (PCL) is a rare and aggressive plasma cell neoplasm distinguished by extensive clonal expansion of plasma cells in the bone marrow (BM) and peripheral blood (PB). PCL is divided into two subtypes: primary (pPCL) originates *de novo* without preceding multiple myeloma, while secondary (sPCL) comprises a leukemic modification that occurs as a late manifestation from previous multiple myeloma (MM). pPCL and sPCL are clinically and biologically two different entities. The molecular mechanisms of the development of PCL, either primary or secondary, remain poorly understood. We aim to present 5 years of data on clinical profiles and treatment outcomes of pPCL and sPCL patients treated at our cancer hospital in India and to find a predictive parameter of the development of PCL in cases of MM. Methods: In this study, we retrospectively reviewed and evaluated the clinicopathological features, laboratory parameters, immunophenotypic profile, and patient outcomes of 17 PCL cases diagnosed among 180 plasma cell dyscrasia patients during the study period to establish a correlation between pPCL & sPCL for diagnosis and management of PCL. Results: A total of 17 PCL patients were diagnosed among 180 plasma cell dyscrasia patients during the study period. Among PCL patients, 9 cases had pPCL (52.94% of all PCL patients), and 8 cases had sPCL (47.06% of all PCL patients). Peculiar differences were seen between the two PCL types. Both types of PCL had a younger age at the time of diagnosis, having elevated BM plasma cell infiltration percentage, frequent anemia, thrombocytopenia, elevated beta-2-microglobulin (B2M) levels, raised LDH levels, and positive M-protein in both serum and urine. In addition, SFLC assay and Immunofixation assay showed higher κ and lower λ in pPCL compared with sPCL ($P<0.05$). Higher Renal insufficiency was also observed in pPCL compared to sPCL ($P=0.335$). The survival and response to treatment of PCL patients remain considerably poor, sPCL exhibit shorter overall survival (OS) than pPCL with (median 1.75 months vs. 7 months respectively, *P=0.1682*). Plasma cell leukemia (PCL) needs to be diagnosed early and requires prompt initiation of treatment before patients get complications. Conclusion: Our study characterizes the clinical and laboratory features of pPCL and sPCL and may aid physicians in prognosticating the course of disease of their patients. However, future multicentre studies are the need of the hour to develop accurate diagnostic criteria and establish the efficacy of therapeutic regimens.

Keywords: Plasma cell leukemia (PCL), leukemia, multiple myeloma

Introduction

Plasma cell leukemia (PCL) is a rare hematological malignancy distinguished by an extensive clonal expansion of plasma cells (PCs) in the bone marrow and peripheral blood, accounting for 2-4% of all multiple myeloma cases according to the 2017 WHO classification [1-3]. PCL is distinguished by the presence of ≥20% of circulating plasma cells and an absolute count of $\geq 2\times10^9$/L clonal plasma cells in peripheral blood [4, 5]. Circulating plasma cells persist in the peripheral blood despite the absence of the bone marrow microenvironment as a set of molecular abnormalities and signaling through chemokine receptors facilitates tumor development by inhibiting apoptosis of tumor cells and aiding in immune escape [6]. PCL is classified as primary (pPCL) when it develops de novo in patients without prior manifestations of multiple myeloma and accounts for 60-70% of PCL cases, while secondary PCL (sPCL) evolves in patients with pre-existing multiple myeloma and is responsible for 30-40% of

PCL cases [7]. pPCL and sPCL are clinically and biologically two distinct clinical entities. However, the biological mechanisms and the responsible molecular events implicated in developing the two forms of PCL remain to be elucidated [7-11]. Since sPCL is a leukemic evolution of MM, there are no significant differences in the clinical profiles of MM and sPCL. On contrary, the clinical presentation of pPCL is more aggressive than that of observed in MM, with distinct cytogenetic aberrations, different molecular phenotype and bone marrow (BM) microenvironmental characteristics, elevated plasma cell proliferation, and clinical features such as impaired renal function, higher prevalence of lymphadenopathy, thrombocytopenias, leukocytosis, hypercalcemia, extramedullary plasmacytomas hepatosplenomegaly, pleural effusion, extramedullary plasmacytomas, more pronounced anemias, raised lactate dehydrogenase (LDH) and beta-2-microglobulin (B2M) levels [15]. It exhibits an aggressive clinical course with an unsatisfactory response to traditional therapy and has a dismal overall survival (OS) due to the destruction of red blood cells, influences extramedullary organs, and bone marrow failure [12-14]. The 5-year survival rate of PCL does not exceed 10%. In response to treatment, the prognosis of PCL has been reported to be very poor, with a median survival of (7-13 months) for pPCL, and (2-7 months) for sPCL [15]. Therefore early, accurate diagnosis is essential for the appropriate management of PCL, so that one can offer a combination of chemotherapy and autologous hematopoietic stem cell transplant (HSCT) followed by multidrug maintenance treatment employing novel agents which may prolong survival. Because of the rarity of the disease, PCL has not been thoroughly investigated in an Indian population. Therefore our present study aims to evaluate the clinicopathological features, laboratory parameters, immunophenotypic profile, and patient outcomes of all the cases of plasma cell leukemia.

Material and methods

Patients

The study was commenced after obtaining relevant ethical clearances from our Institute Ethical Committee. Approximately 160-180 new plasma cell dyscrasia cases at our institution are diagnosed yearly. Out of these, 17 PCL cases were included based on the presence of both >20% clonal plasma cells in PB and a circulating plasma cell count higher than 2×10^9/L. The rest of the patients with plasma cell dyscrasia (multiple myeloma, light chain disease, etc.) were excluded from the study.

Methodology

We retrospectively reviewed and analyzed all 17 cases of PCL from 2016 to 2021. We explored the case files from medical records and retrieved laboratory data from the electronic health records of our hospital. Patients who fulfilled the diagnostic criteria for PCL from the onset of the disease to the last follow-up or until death were retrospectively analyzed. Subclassification of pPCL and sPCL was established on the presence or absence of preceding MM. An excel sheet consisted of patients' clinical details and their lab investigations like bone marrow aspiration with biopsy, lactate dehydrogenase (LDH) assay, β2-microglobulin estimation, light chain assay, and electrophoresis with immunofixation in both serum and urine samples. In addition, the following data of all the cases were collected: date of pPCL or sPCL diagnosis, age at diagnosis, race, gender, the date of the last follow-up, the existence of plasmacytomas at diagnosis, plasma cells in PB and BM, overall survival (OS), hematological parameters (hemoglobin concentration, leukocytes count, and platelet count), serum biochemistry (LDH level, B2-microglobulin, and M-protein in serum and urine). All these results were summarized and compared to the existing published investigations on PCL.

Statistical analysis

Descriptive statistics such as median/range was calculated for all the variables. Differences and clinical and laboratory characteristics correlations between patients with pPCL and sPCL were tested using Pearson's chi-square test and the Mann-Whitney U test. The Kaplan-Meier method was utilized to calculate survival curves. Fisher exact test was used to compare categorical and continuous variables, to predict the risk of developing pPCL and sPCL using SPSS version 20.

Results

There were 17 PCL patients diagnosed and treated during the study period. pPCL was diagnosed in 9 patients (52.94% of all PCL patients),

Table 1. Clinical characteristics and laboratory characteristics of all pPCL and sPCL patients

Variable	pPCL N, Median (min, max)	sPCL N, Median (min, max)	*p*-value
Age	9, 54 (39, 71)	8, 53.5 (39, 67)	0.5937
Hemoglobin (Hb) g/L	9, 7.8 (3.5, 11.5)	8, 6.85 (4.8, 13.8)	0.5964
Platelet Count (PLT)/cmm	9, 80000 (15000, 256000)	8, 66000 (16000, 106000)	0.2479
Leukocyte Count (TLC)/cmm	9, 10500 (2600, 41300)	8, 9200 (3400, 13700)	0.5637
(BM PC)%	9, 85 (25, 90)	8, 90 (40, 98)	0.2858
(LDH) mg/L	4, 223.5 (155, 250)	6, 425 (137, 933)	0.0881
B2M mg/L	7, 12.4 (1.16, 12.6)	5, 12.6 (3.6, 12.6)	0.8006
DLC-PC%	8, 20 (5, 90)	7, 20 (4, 43)	0.7703
κ	4, 54.2 (25, 60750)	6, 19.85 (9.7, 167)	0.2008
λ	4, 18.25 (8.69, 3960)	6, 327 (3.5, 5864)	0.5224
κ/λ	4, 3.37 (0.006, 6990)	6, 0.18 (0.003, 47.7)	0.6242
IgG	6, 725 (346, 6090)	1, 1517 (1517, 1517)	No value due to lesser no of sample
IgM	5, 26 (16, 53)	1, 15 (16, 53)	No value due to lesser no of sample
IgA	5, 47 (23, 77)	1, 586 (586, 586)	No value due to lesser no of sample
S. M band	3, 0.9 (0.7, 4.5)	5, 0.8 (0.2, 6.2)	0.8815
OS (months)	7, 7 (3, 66)	6, 1.75 (0.25, 15)	0.1682

Table 2. Clinical characteristics and laboratory characteristics of all pPCL and sPCL patients

Variable	pPCL N (Percentage)	sPCL N (Percentage)	Total N (Percentage)	*P* value
Female	4 (44.4%)	3 (37.5%)	7 (41.1%)	1.0
Male	5 (55.5%)	5 (62.5%)	10 (58.8%)	
Total	9 (100%)	8 (100%)	17 (100%)	
s+u+	7 (77.78%)	6 (85.71%)	13 (81.25%)	0.475
s-u+	2 (22.22%)	0 (0%)	2 (12.50%)	
s-u-	0 (0%)	1 (14.29%)	1 (6.25%)	
κ	1 (11.11%)	1 (14.29%)	2 (12.5%)	0.878
λ	2 (22.2%)	3 (42.86%)	5 (31.25%)	
IgG κ	5 (55.56%)	2 (28.57%)	7 (43.75%)	
IgG λ	1 (11.11%)	1 (14.29%)	2 (12.50%)	
Total	9 (100%)	7 (100%)	16 (100%)	
Renal Disease Urea/Creatinine (Abnormal)	7 (77.78%)	4 (50%)	11 (64.71%)	0.335
Renal Disease Urea/Creatinine (Normal)	2 (22.22%)	4 (50%)	6 (35.29%)	
Total	9	8	17	

while sPCL was diagnosed in 8 patients (47.06% of all PCL patients). The baseline clinical characteristics and laboratory characteristics of all pPCL and sPCL patients are presented in (**Tables 1** and **2**).

Clinical features

Clinical features of pPCL and sPCL cases were compared. The median age of 9 pPCL cases was 54 years old (39-71) with a male-to-female ratio of 1.25:1, while the median age of 8 sPCL cases was 53.5 years old (39-67) with a male-to-female ratio of 1.66:1 (**Table 1**).

Laboratory features

In pPCL cases, the median hemoglobin (Hb) concentration was 7.8 g/L (3.5-11.5 g/L), with a median platelet count of 80000/cmm (15000-256000/cmm), and the total median leukocyte count was 10500/cmm (2600-41300/cmm). Bone marrow examination exhibited a median proportion of circulating plasma cells of 85% (25 to 90%) (**Figure 1**). The sPCL cases had a mean hemoglobin level of 6.8 gm% (4.8-13.8 gm%) with a median platelet count of 66000 (16000-106000/cmm), and the total median leukocyte count was 9200/cmm

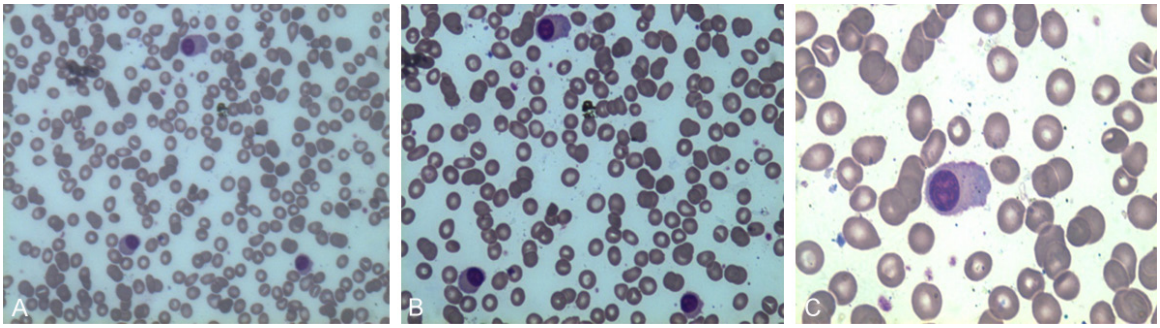

Figure 1. Bone marrow examination of PCL cases. A. Peripheral blood smear showing plasma cells in Giemsa stain (20×). B. Peripheral blood smear showing plasma cells in Giemsa stain (20×) in 40×. C. Peripheral blood smear showing plasma cells in Giemsa stain (20×) in oil immersion lens (100×).

(range, 3400-13700/cmm). Bone marrow examination showed a median proportion of circulating plasma cells of 90% (40 to 98%), respectively. On serum chemistry examination, in pPCL cases, median LDH level was 223.5 mg/L (155-250 mg/L), with a median beta-2-microglobulin was 12.4 mg/L (1.16-12.6 mg/L). In sPCL cases, the median LDH level was 425 mg/L (137-933 mg/L), with a median beta-2-microglobulin was 12.6 mg/L (3.6-12.6 mg/L) respectively [**Table 1**]. Serum/Urine protein electrophoresis data was available for 9 pPCL patients, of which 7 (77.78%) were positive for M-protein while 6 out of 7 sPCL patients (85.71%) were positive for M-protein. Immunofixation in 16 cases revealed that 5 out of 9 (55.56%) pPCL patients revealed IgG κ light chain, and 1 case (11.11%) showed IgG λ light chain. However, 2 out of 7 (28.57%) sPCL patients revealed IgG κ light chain, and 1 case (14.29%) showed IgG λ light chain. The SFLC assay showed κ 54.2 mg/L (range, 25-60750 mg/L), λ 18.25 mg/L (range, 8.69-3960 mg/L), and a κ/λ ratio 3.37 (range, 0.006-6990 mg/L) in pPCL while κ 19.85 mg/L (range, 9.7-167 mg/L), λ 327 mg/L (range, 3.5-5864 mg/L), and a κ/λ ratio 0.18 (range, 0.003-47.7 mg/L) in sPCL. Renal insufficiency was seen in 7 (77.78%) pPCL patients compared with sPCL 4 (50%) at diagnosis, respectively (**Table 2**).

Survival and treatment

The median overall survival of pPCL and sPCL was 7 months and 1.75 months, respectively (**Table 2**). Response to treatment of sPCL cases due to its lower prevalence and limited therapeutic management.

Discussion

PCL is an aggressive form of monoclonal gammopathy with an inferior prognosis and a higher likelihood of lethal outcomes despite therapeutic advancement over the years. Detailed information concerning its prevalence, clinical manifestations, and pathological characteristics is developing systematically [16]. There is growing evidence that PCL is an aggressive and distinct clinicopathological entity with a different molecular (genetic and gene-expression profile) makeup and phenotypic and cytogenetic abnormalities compared to multiple myeloma. PCL frequently presents with elevated LDH and β2-microglobulin levels, consistent with a higher proliferation rate and significant tumor burden at the time of diagnosis [17, 18]. The surveillance, Epidemiology, and End Results database (SEER) published in 2009 investigated the characteristics and survival of 291 PCL patients treated with traditional chemotherapy and inferred lower overall survival (OS) [19]. Our study analyzed clinical features, laboratory parameters, and patient outcomes of both pPCL & sPCL patients. Our study had a much higher prevalence of pPCLs (52.94%) compared to sPCLs (47.06%). The male prevalence seen among our pPCL cohort (M:F ratio of 1.25:1) is consistent with existing literature [11]. sPCL exhibited more severe clinical features as compared to pPCL, such as massive bone marrow infiltration and a higher frequency of anemia and thrombocytopenia. LDH and β2-microglobulin were significantly more elevated in sPCL patients compared to pPCL patients, a finding similar to other published studies [15, 20-22]. Moreover, SFLC and Immunofixation

assays revealed a higher proportion of IgG κ light chain and low IgG λ light chain in pPCL and sPCL; this is in sharp contrast to the other published studies where a higher λ light chain restriction than κ light chain restriction was observed [23]. Further, a significant number of sPCL patients had a positive M protein on protein electrophoresis compared to patients with pPCL in both serum and urine. However, rates of renal insufficiency were higher in pPCL patients than in sPCL. The prognosis for sPCL was unfavorable, with a lower median OS as compared with pPCL cases consistent with previously published data [15, 20, 22]. The main limitations of our study were the unavailability of cytogenetics/FISH profile data for several PCL cases. A smaller cohort size limits the definitive conclusion of our study. Furthermore, given the lower incidence and prevalence of PCL, the clinical characterization of PCL is mainly based on different retrospective investigations. The disease course, clinical manifestation, and disease biology of PCL and MM are different. Hence, distinguishing between pPCL and MM at diagnosis is critical to provide adequate curative therapy. The significant results of our investigation must be tested in a larger patient cohort to unmask any effective mechanism of pathogenesis.

Conclusion

Our study characterizes the clinical and laboratory features of pPCL and sPCL and may aid physicians in prognosticating the course of their patients. In this pilot study, we can affirm that LDH may perform a crucial role in the prediction of sPCL in cases of MM. sPCL has a poor prognosis and a low response rate to traditional therapy compared to pPCL. PCL is a rare lymphoid malignancy that requires early diagnosis and rapid treatment initiation before patients get complications. The survival and response to therapy of PCL patients remain poor, particularly for sPCL patients, due to their lower prevalence and limited therapeutic management. The clinical and immunologic manifestation of patients with PCL holds minimal implications on prognosis. Our study's critical findings must be experimented with a more extensive patient cohort and validated by molecular and cytogenetic examinations to unveil potential impacts on pathogenesis. Multi-center studies should be performed to develop distinct criteria for the initial diagnosis and rapid treatment of this disorder. However, future multicenter studies are the need of the hour to develop accurate diagnostic criteria and establish the efficacy of therapeutic regimens. Thus, new drugs must be explored with distinct mechanisms of action. Our study predicts the development and identifies primary and secondary PCL in cases of plasma cell dyscrasia which can improve the prognosis of this devastating disease.

Disclosure of conflict of interest

None.

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