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ORIGINAL ARTICLE

Plasma Cell Leukemia: Case Series From a Tertiary Center with Review of Literature

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Abstract Plasma cell leukemia is an unusual manifestation of multiple myeloma, reported to occur in 2% of newly diagnosed patients. It may either present at the time of diagnosis (primary) or evolve as a late feature in the course of multiple myeloma (secondary). Most clinical signs of myeloma are observed in plasma cell leukemia, although osteolytic lesions and bone pain are less frequent and lymphadenopathy, organomegaly and renal failure are more often present. The immunophenotype of plasma cell leukemia differs typically from that of myeloma by lack of aberrant CD56 expression. An abnormal karyotype is more frequently found in plasma cell leukemia and there is higher incidence of unfavourable cytogenetics. Plasma cell leukemia is an aggressive disease, characterized by a fulminant course and a short survival. We are reporting cases of this rare condition which presented at our center over 3 years along with review of literature.

Keywords Primary plasma cell leukemia · Secondary multiple myeloma · Multiple myeloma

Introduction

Monoclonal gammopathies comprise a wide range of entities characterized by the proliferation of a clonal population of immunoglobulin secreting, heavy-chain class-switched, terminally differentiated B cells (plasma cells). When the number of circulating plasma cells is significant, the term plasma cell leukemia (PCL) is used. PCL is considered the leukemic variant of multiple myeloma (MM). The diagnosis is based on the presence of clonal plasma cells in the peripheral blood exceeding 2×10^9/l or is 20% of the leukocyte differential count [1]. In addition to peripheral blood and bone marrow, the neoplastic plasma cells may be found in extramedullary tissues, such as spleen and liver and in pleural effusions, peritoneal and cerebrospinal fluid.

There are two forms of PCL: (i) Primary PCL—occurs in patients without preceding MM or monoclonal gammopathy of unknown significance (MGUS), these patients present with peripheral plasma cells at the time of diagnosis; (ii) Secondary PCL—arises as a late manifestation in patients with MM [2].

The incidence of PCL ranges between 2 and 4% of all myelomas [3, 4]. About 60% PCL are primary and the remaining 40% are secondary, part of the terminal phase of MM, which occurs in about 1% of myelomas [5].

Clinically, patients with primary PCL have a greater incidence of hepatosplenomegaly and lymphadenopathy, and fewer lytic bone lesions.

Laboratory investigations show involvement of bone marrow along with circulating plasma cells; additionally, patients with primary PCL have higher platelets counts and smaller M components compared to patients with secondary PCL. The cytologic characteristics of the leukemic plasma cells span much of the morphologic spectrum found in other myelomas but often, many of the plasma cells are small with relatively little cytoplasm and may resemble plasmacytoid lymphocytes [6]. Compared to IgG or IgA myeloma, a higher proportion of light chain only, IgD, or

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IgE myeloma presents as PCL [2]. Cytogenetic aberrations are detected more frequently in PCL than in MM, the overall pattern of cytogenetic changes is very similar to the pattern observed in MM. Numerical changes and/or structural aberrations have been described, hypodiploidy is more common in PCL than in myeloma. Apart from chromosome 9, gains also involve chromosomes 3, 5, 7, 11, 15, and 19, whereas losses also involve chromosome X and Y [7, 8].

PCL is usually progressive; secondary PCL rarely responds to chemotherapy because patients have already received alkylating agents and became resistant to them; in the primary form, responses have been observed with melphalan and prednisolone; the response rate seems to be higher with combination therapy than with single alkylating agents. Maximum survival benefit is with high dose chemotherapy with autologous bone marrow or stem cell support, especially in younger patients. The overall survival is short being a few months.

Because of the low frequency of PCL, most of the literature is either as case reports or a few reviews [2, 5, 9, 10]. Here we are reporting cases of PCL diagnosed from 2004 to 2007 at our center with their clinical and laboratory features. We are reporting these cases because of the rarity of the condition.

Materials and Methods

We retrospectively reviewed all cases of plasma cell dyscrasias (PCD), which were registered in Hematology department, Sanjay Gandhi Post Graduate Institute of Medical Science, from January 2004 to December 2007. There were 5 cases of PCL among 200 consecutive cases of MM. The criteria for diagnosis of PCL required greater than 2×10^9/l blood plasma cells. The diagnosis of MM was based on criteria from the World Health Organisation [11].

In each patient, the most relevant clinical and laboratory characteristics documented at diagnosis were evaluated for biologic and disease prognostic significance. These included clinical features (age, sex, bone pain and lesions, hepatosplenomegaly, and plasmocytomas), hematologic parameters (hemoglobin level, white blood cell count, platelet count, and erythrocyte sedimentation rate), serum biochemical data (creatinine, urea, calcium, lactate dehydrogenase, and β2-microglobulin levels), electrophoretic characteristics (total protein, albumin, type of monoclonal component, and presence of urine immunoglobulin light chains), the percentage of bone marrow plasma cells, and the presence or absence of bone lesions. Patients were grouped into clinical stages according to the Durie and Salmon criteria [12].

Immunophenotypic Studies

Immunophenotypic characterization of peripheral plasma cells was performed as previously described by Gracia-Sanz et al. [13]. Monoclonal antibodies (MoAbs) tested included—CD38, CD5, CD19, CD20, CD23, CD10, CD25, CD103, FMC-7, kappa and lambda light chain. Irrelevant isotype-matched mouse Igs were used as negative controls. Analysis of cell reactivity with the different combinations of MoAbs was performed on a FAC Scan flow cytometer (Becton–Dickinson, San Jose, CA). Results were analyzed for at least 10,000 cells per test. An antigen was considered positive when at least 15% of the plasma cells displayed reactivity for this marker.

Result

Out of a total of 200 cases of PCD, 5 (2.5%) cases of PCL were identified. Amongst these, 4 cases (2%) were of primary PCL and 1 case (0.5%) was of secondary PCL arising in a follow up patient of MM. From our review clinical and laboratory features did not differ significantly between primary and secondary PCL.

Most relevant clinical and laboratory features are presented in Table 1.

There was an admixture of mature and immature forms of plasma cells. Mature plasma cells had round eccentric nucleus with cartwheel chromatin without nucleoli and abundant basophilic cytoplasm with perinuclear hof. Plasmablastic form of plasma cells were few but present in the peripheral blood in all the cases and showed dispersed nuclear chromatin, high nuclear–cytoplasmic ratio and prominent nucleoli.

Median age of presentation, gender distribution and bone lesion extension were similar in cases of PCL as that in MM, but these cases had high tumor mass and when compared with comparable patients without leukemia, displayed a higher incidence of stage 3 disease, thrombocytopenia, anemia, raised LDH levels and extramedullary involvement, most frequently affecting the spleen and liver (hepatosplenomegaly was attributable to myeloma after other causes were ruled out by appropriate studies). Incidence of adverse prognostic factors was higher in these cases compared to that of myeloma.

All 4 cases of primary PCL presented with advanced disease, 3 died within a week of presentation, one was unwilling for treatment and left on request. In only case of secondary PCL, which presented at our center, treatment was started with Arsenic trioxide, 4 cycles were instituted but before treatment could be completed he died because of multiorgan failure.

Table 1 Clinical and biologic data of our 5 cases of PCL

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5 (secondary PCL)
Age	57	49	66	59	77
Sex	Female	Male	Male	Female	Male
Extramedullary involvement	+	+	–	+	+
Hemoglobin <8.5 g/dL	+	+	+	+	+
Platelet $<100 \times 10^3$/cumm	+	+	+	–	+
Peripheral blood plasma cell count	94%	46%	33%	30%	92%
Bone marrow plasma cells >30%	+	+	+	+	+
S. LDH >460 IU/dL	+	+	ND	+	+
Albumin <3.5 g/dL	+	+	–	+	+
Creatinine >2 mg/dL	–	+	+	+	–
Type of monoclonal component	ND	IgG	ND	IgG	Non-secretory
Immunophenotype	Positive markers = CD38 and kappa light chain. Negative markers = CD5, CD19, CD20, CD23,CD10, CD25, CD103, FMC-7 and lambda light chain.	ND	ND	ND	Positive markers-CD38 and kappa light chain. Negative markers CD20 and lambda light chain.

S.LDH serum lactate dehydrogenasem, *ND* not done, *IgG* immunoglobulin G

Discussion

Plasma cell dyscrasias are a common group of disorders having the proliferation of a single clone of immunoglobin secreting cells as a common feature. The incidence of various PCD is as follows: (i) MGUS—60 to 70%; (ii) MM—15%; (iii) Amyloidosis—9%; (iv) B cell lymphoproliferative disorders: non-Hodgkin's lymphoma—5%, Waldenstrom's macroglobinuria—2%, Chronic lymphocytic leukemia—2%; (v) Solitary plasmacytoma 1%; and (iv) Plasma cell leukemia—Rare [14].

Because of the low frequency of PCL, most of the data has come from case reports or small series of cases [2, 5, 9, 10]. In almost all the series median age ranged between 53 and 57 years. However, Castello et al. [15] and Raj et al. [16] reported PCL in patients who were 30 and 21 years old respectively. In our patients the median age was 57 years, in accordance to that reported by others.

Primary PCL has a more aggressive course—high frequency of extramedullary involvement (liver, spleen, lymph nodes, extra osseous plasmacytomas etc.), thrombocytopenia, anemia, hypercalcemia and impaired renal function. A large study by Gracia-Sanz et al. [2] analyzing the clinic-biologic characteristics of 26 cases of PCL, together with the immunophenotype, DNA cell content, proliferative index, and numeric chromosomal aberrations of the neoplastic PC with 664 MM patients at diagnosis showed that the median age, sex ratio, and bone lesion extension were similar to MM, but PCL cases displayed a higher prevalence of clinical stage III disease and extramedullary involvement.

Patients with PCL in addition to having symptoms of typical myeloma have more frequent extra-osseous disease commonly involving the spleen, lymph nodes, liver and skin. Our 4 of the 5 patients had extra-medullary involvement, spleen and liver was involved in 3 of them and thyroid in 1. Other sites which may be involved are kidney, heart, pleura, testes, skeletal muscle and the CNS. In a recent report by Madhvan et al. [17] 53 year old patient with PCL presented with features of restrictive cardiomyopathy.

Radiographic bone lesions appear not to be more frequent in PCL compared to nonleukemic phase myeloma [18].

The cytologic characteristics of leukemic plasma cells in PCL span much of the morphologic spectrum found in MM [6, 19]. The bone marrow is usually infiltrated heavily with plasma cells showing the same morphological features as those in the peripheral blood [19, 20]. The cases of PCL

analyzed in this study also showed similar morphological features in peripheral blood and bone marrow.

Well differentiated plasma cells have a characteristic phenotype: Strong expression of CD38 and CD19 and weak expression of CD56. In contrast to normal plasma cells, myeloma cells are often immature and may have the plasmablastic appearance [21]. While the expression of CD19 is usually negative, myeloma cells express CD56 antigen strongly along with CD38 [22].

Plasma cells from PCL display a more immature phenotype than MM as assessed by expression of CD20 antigen, which is usually absent in MM [23]. In addition plasma cells from PCL frequently lack CD56 antigen, which has been considered important in anchoring plasma cells to bone marrow stroma [24, 25]. Immunophenotypic expression is similar in PCL as MM for CD38, CD138, CD2, CD3, CD6, CD10, CD13 and CD15. Immunophenotyping of plasma cells in our patients where it was carried out was compatible with these literature findings.

The phenotypic differences do not allow a complete discrimination between PCL and MM, but help to explain the differences in survival, since CD56 expression has been associated with good prognosis while CD20 expression has been associated with a shorter survival [2].

Cytogenetic aberrations are detected more frequently in PCL than in MM, the percentage of abnormal cases varies in different series but seems to be more than 50%. The overall pattern of cytogenetic changes is very similar to the pattern observed in MM, numerical changes and/or structural aberrations are seen. Monosomy 13 and trisomy 9 are the most frequent numerical abnormalities. Up to 90% may show chromosome 13 monosomy. Hypodiploidy is more common in PCL than in myeloma. Apart from chromosome 9, gains also involve chromosomes 3, 5, 7, 11, 15, and 19, whereas losses also involve chromosome X and Y; structural aberrations mainly involve chromosome 14, with 14q+ resulting from translocation t(11;14)(q13;q32) or other changes (e.g. Burkitt's translocations); chromosomes 16 (p or q), 1 (p or q), 19 (p or q), 6q, 17q, 2p and 7q might also be involved. Chromosomal changes are detectable by conventional cytogenetic techniques or by FISH; in addition, comparative genomic hybridization showed to be a useful tool in PCL, allowing assessment of regions showing copy number changes [26].

Chromosomal changes are detectable by conventional cytogenetic techniques or by FISH; in addition, comparative genomic hybridization is a useful tool in PCL, allowing assessment of regions showing copy number changes.

PCL is a rare aggressive variant of MM, characterized by a fulminant course and poor prognosis. Compared to MM, patients usually present with advanced disease, have more extra-medullary involvement, thrombocytopenia, anemia, raised LDH levels and impaired renal function. These findings can be explained not only by the presence at presentation of more extensive disease in PCL versus MM, but also by the presence of high proliferative ratio of neoplastic versus adverse cytogenetic data, which represents a unique array of adverse prognostic factors that explain the poor outcome described for patients with PCL. The survival of patients with PCL is therefore shorter then that of comparable patients with advanced myeloma, primarily because of early death due to irreversible disease complications. Clonal plasma cells from primary PCL display a higher proliferative capacity (S-phase cells) versus MM, thus explaining frequent association of high LDH and aggressive behavior in PCL [2]. Residual bone marrow function is poorer in PCL versus MM, as assessed by both the hemoglobin level and platelet count. This is because proliferation of normal bone marrow cells (residual cells in S-phase) is markedly blunted. Therefore degree of anemia and thrombocytopenia is much higher in PCL versus MM which is difficult to explain based only on the tumor burden.

The outcome of plasma cell leukemia treated with the first-line myeloma regimen melphalan, prednisolone is usually disappointing, with medial survival of two months. There have been clinical trials with various drug combinations for PCL. Few to mention are VAD regimen (vincristine, doxorubicin, dexamethasone), cyclophosphamide–etoposide regime etc. Maximum survival benefit was observed with high dose chemotherapy with autologous bone marrow or stem cell support, especially in younger patients.

Since the prognosis is so poor, intensification of high dose chemotherapy followed by allogenic/autologous stem cell rescue should be tried [27]. However, in un-affording patients induction with combination chemotherapy, followed by high dose chemotherapy is the current recommended approach for eligible patients [28]. PCL requires such aggressive management so as to provide any survival advantage.

Of our 4 patients with primary PCL, 3 died within a week of diagnosis and start of chemotherapy and 1 patient did not take treatment and was discharged on request. Patient who had developed secondary PCL after 7 years of diagnosis of MM, treatment was started with Arsenic trioxide, 4 cycles were instituted but before treatment could be completed he died because of multi-organ failure and disseminated intra-vascular coagulation.

The prognosis in patients with PCL is poor. Median survival is less than 1 year [4]. The longest survival reported is 28 months [5]. Secondary PCL represents a terminal event for a refractory/relapsed MM and is usually not responsive to any treatment modality.

Conclusion

Our observation and data from literature indicate that PCL both primary and secondary, it is a very poor prognosis disease. Constellation of adverse prognostic factors is already present at diagnosis.

Because PCL reflects far-advanced disease with life threatening complications treatment with single alkylating agent plus prednisolone is not appropriate. Immediate institution of intensive chemotherapy is required followed by allogenic/autologous stem-cell rescue, if age and clinical condition do not preclude these intensive approaches [14].

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