# Plasma Cell Leukemia: A Report of 5 Cases and Review of the Literature

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ABSTRACT

Plasma cells are occasionally observed in the peripheral blood of the patients with multiple myeloma. When the number of these circulating cells is significant, the term of plasma cell leukemia is used. We report 5 cases of plasma cell leukemia with poor prognosis with review of the literature.

Key Words: Multiple myeloma, Plasma cell leukemia, Chemotherapy.

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## INTRODUCTION

Plasma cell leukemia (PCL) is a rare form of plasma cell dyscrasia which is distinguished from multiple myeloma (MM) by the precense of more than 2 x $10^9$/L plasma cells in the peripheral blood, constituting at least 20% of the leukocytes[1,2]. The incidence of PCL ranges between 2-4% of all myelomas [1-3]. The primary form accounts for 60% of the cases whereas the secondary form occurs as a leukemic transformation in previously diagnosed myeloma patients in the remaining 40%[1,4]. The patients with primary PCL almost always have a high tumour mass and more frequently have thrombocytopenia, hypodiploid plasma cells, high LDH levels and extramedullary involvement[2]. The response to therapy in primary PCL is in the range of 37% to 47% in reported series with a median survival of 7-12 months[2-4]. Patients with secondary PCL are usually refractory to chemotherapy and have a median survival of less than 2 months[4].

Here we report 5 cases of PCL diagnosed between 1992-1999 in our hospital with their clinical and laboratory features.

## CASES

### CASE 1

A 67 years old woman presented with high fever, weakness and weight loss. Physical examination revealed hepatosplenomegaly and a blood count showed Hb: 9.2 g/dL, WBC count 15 x $10^9$/L including 85% plasma cells which show plasmablastic features with prominent nucleoli and basophilic cytoplasms, and platelets 87 x $10^9$/L. Other abnormal laboratory studies were: Serum creatinine 1.8 mg/dL, serum calcium 10.9 mg/dL, LDH: 2470 IU/L, a high sedimentation rate of 150 mm/h. Bone marrow examination revealed MM with immature plasma cells of 90%. Coagulation parameters indicated a probable ongoing disseminated intravascular coagulation (DIC) Prothrombin time (PT): 17 sec., activated partial thromboplastin time (aPTT): 53 sec., fibrinogen: 3.3 g/dL and 10 • FDP Ž 40. Serum protein electrophoresis and immunofixation showed a monoclonal component of IgG type (IgG: 7170 mg/dL, kappa light chain: 10500 mg/dL). Immunophenotyping of peripheral blood cells with flow-cytometer disclosed 80% CD38-positive plasma cells and the cells were negative for CD45, CD19 and CD56. Cytogenetic analysis revealed multiple karyotypic abnormalities: 10: 46-48, XX del (1) p (22), + der (7) del (7) (q32), del (12) p (11) + mar [cp]. VAD chemotherapy was started and on the 3rd day of her admission abdominal pain occurred in the patient. Abdominal ultrasonography revealed a localized fluid collection with 14 x 6 x 6 cm in diameters retroperitoneally at the level of renal arteries. On the same day the patient died because of retroperitoneal hemorrhage.

### CASE 2

A 65 years old woman presented with weakness, poor performance status, gingival bleeding and petechiae on the trunk and legs. In physical examination she had hepatosplenomegaly. Hb was 8 g/dL, WBC count 27 x $10^9$/L, platelets 119 x $10^9$/L, LDH 384 IU/L, calcium 11.7 mg/dL. Peripheral blood smear showed 65% plasma cells with varying maturity, PT 25 sec., aPTT 120 sec., fibrinogen 1.44 g/dL, FDP > 40. Bone marrow examination was compatible with multiple myeloma with plasma cells of 68%. Immunofixation showed IgG monoclonal protein (IgG: 8243 mg/dL). Immunophenotyping of peripheral blood cells disclosed CD38-positive, CD45, CD56 and CD19-negative plasma cells. The patient was put on VAD chemotherapy. Although VAD chemotherapy and fresh frozen plasma were started, the patient died because of DIC on the 10th day of her admission.

### CASE 3

A 60 years old female patient presented with low back pain. Computerized tomography of the spine revealed multiple lumbal lytic lesions and loss of height on L2 and L3 vertebras and collapse in C6. Protein electrophoresis disclosed no monoclonal gammopathy. Laboratory examination showed Hb: 11.1 g/dL, WBC: 5.4 x $10^9$/L, platelets: 218 x $10^9$/L, LDH: 642 IU/L, calcium: 12 mg/dL. Differential count of leukocytes in peripheral blood smear were within normal limits with no detectable plasma cells. Bone marrow aspiration was “dry tap”. Examination of bone marrow biopsy imprint showed plasma cells of 16% with immature dysplastic morphology and increased lymphocytes of 32% in which some of them carry plasmacytoid features (Figure 1). The diagnosis of nonsecretory myeloma was established and the patient was put on melphelan and prednisolone chemotherapy and local radiotherapy to the spine. Three months later the patient was admitted to the hospital with fever and fatique. Laboratory results showed Hb: 8.5 g/dL, WBC count of 40 x $10^9$/L, platelets: 70 x $10^9$/L. Periperal blood smear examination disclosed plasma cells of intermediate maturity with narrow and basophilic cytoplasm and nuclei with 2-3 nucleoli. Flow-cytometric analysis of peripheral blood showed CD38-positive, CD45, CD56 and CD19 negative plasma cells. Repeated protein electrophoresis again was negative for M protein. The patient was put on VAD chemotherapy and she died of sepsis on the 4th week of her admission.

### CASE 4

A 78 years old male patient was admitted to hospital with the chief complaint of back pain of 1,5 months duration. Physical examination showed sensoriomotor loss of left lower extremity. Magnetic resonance imaging of lomber vertebrae disclosed the heigth loss of L2 vertebra and partial stenosis of spinal canal. His blood count showed Hb: 9.5 g/dL, WBC: 12 x $10^9$/L, platelets: 42 x $10^9$/L, calcium: 11.7 mg/dL. Erythrocyte sedimantation rate was 161 mm/h. His peripheral blood smear showed 28% immature plasma cells. Immunophenotyping of gated plasma cells disclosed po-

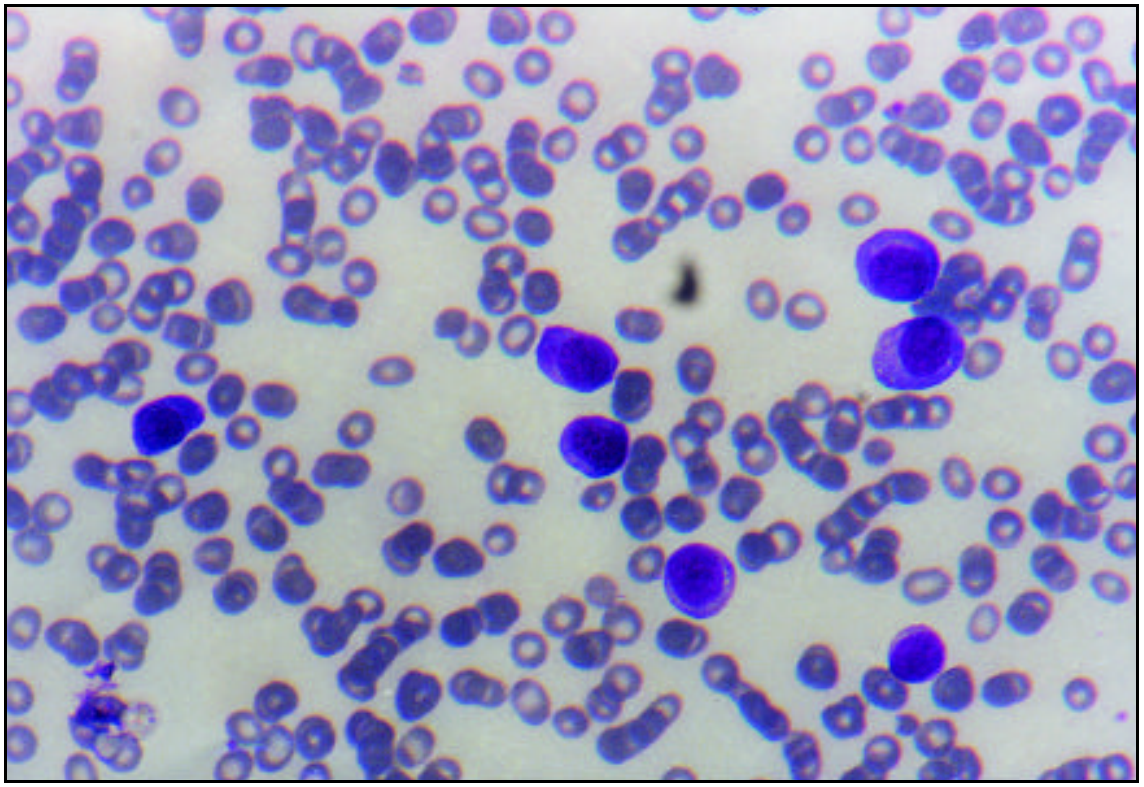

**Figure 1.** Plasma cells with lymphocytoid morphology in peripheral smear of case 3 (Wright, x 100).

sitivity for CD38, and negativity for CD45, CD56 and CD19. Bone marrow aspiration revealed 85% immature dysplastic plasma cells with exantric and ortocentric nuclei and with basophilic cytoplasm. Bone marrow biopsy showed diffuse monoclonal plasma cell infiltration with lambda-positive staining. Skeletal survey showed widespread lytic lesions and osteoporosis. In serum immunofixation there was IgA monoclonal protein (IgA > 824). There was no karyotypic abnormality in cytogenetic study. After administration of three courses of VAD chemotherapy, the laboratory examinations were as follows: No plasma cells in peripheral blood, 5% immature plasma cells in bone marrow and IgA > 740 mg/dL. After the fourth course of VAD, pneumonia developed and the patient was hospitalized. Three weeks later findings of 70% of plasma cells in peripheral blood and in bone marrow smears were compatible with PCL. The patient is currently out of our follow-up since he has refused further chemotherapy.

### CASE 5

A 66 years old male patient presented with hepatosplenomegaly, acute renal failure and pneumonia. His blood count was Hb: 8.6 g/dL, WBC: 6.5 x $10^9$/L with 40% plasma cells and platelets: 117 x $10^9$/L. Blood urea nitrogen was 111 mg/dL, creatinine 12 mg/dL, calcium 12.3 mg/dL, erythrocyte sedimentation rate was 117 mm/h. Immunfixation revealed IgG M protein (IgG 6070 mg/dL). In bone marrow aspiration there were 85% plasma cells with blastic morphology. Skeletal survey disclosed no lytic lesions. Immunophenotyping of plasma cells revealed CD38 positivity, CD45, CD56 and CD19 negativity. After two courses of VAD chemotherapy the patient died of sepsis.

## DISCUSSION

Although plasma cells are occasionally observed in the peripheral blood of patients with myeloma, the term PCL is only used when the number of these circulating cells is significant[3]. Because of the low frequency of PCL, most clinical data are collected from case reports and few reviews[1-4].

As it can be noticed from the review of our PCL cases, four of them were primary whereas one was secondary who was previously diagnosed as nonsecretory MM. Primary PCL has a more agressive clinical course than MM, with a higher frequency of extramedullary involvement (liver, spleen, lymph nodes, extraosseos plasmacytomas), anemia, thrombocytopenia, hypercalcemia and renal insufficiency. Three of our patients had hepatosplenomegaly, all patients had anemia and thrombocytopenia with varying degrees. While all patients had hypercalcemia, only one patient presented with acute renal failure. All patients had high LDH levels compatible with high tumour burden.

Lytic bone lesions appeared in two of our patients. Three patients with primary PCL demonstrated no lytic lesions in their skeletal survey. In primary PCL the presence of lytic bone lesions seems to be lower than those usually observed in MM[1]. Two of our patients had findings of DIC at their presentation and despite administration of chemotherapy and fresh frozen plasma, coagulation abnormalities did not improve. In MM prolongation of thrombin time has been reported to be due to antibodies to thrombin and impaired fibrin polimerization by paraproteins[5,6]. Defective fibrinolysis due to inhibition of plasmin and thrombotic complications could also occur[7,8].

In our three patients paraprotein type was IgG and in one patient IgA. In the remaining one with secondary PCL no M protein was detected. In the reported series the frequency of nonsecretory PCL is between 4-12.5% which seems to be higher than MM[9].

Well differantiated 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[10]. While the expression of CD19 is usually negative, myeloma cells express CD56 antigen strongly along with CD38[11]. Plasma cells from PCL frequently lack CD56 antigen which has been considered to have an important role in anchoring plasma cells to the bone marrow stroma[12]. Immunophenotyping of plasma cells in our patients were compatible with these literature findings. In the third patient who was diagnosed as nonsecretory myeloma and transformed to secondary PCL, the morphologic appearance of leukemic cells were more resembling lymphocytes rather than plasma cells and immunophenotyping with flow-cytometry helped us in confirming the diagnosis.

Because of the low proliferative activity of plasma cells, karyotypic analysis in myeloma has been difficult to perform. Only one patient of our cases demonstrated an abnormal karyotype including chromosome 1 and chromosome 7. In a recent review, chromosome 1 abnormality was detected by 57% with fluorescent in situ hybridization (FISH) study[1]. Some authors noted that a putative tumour supressor gene, located on chromosome 1p may be associated with development of myeloma[13].

The response to the therapy in PCL is extremely poor[1-4]. There is no doubt that treatment with a single alkylating agent plus prednisone is not appropriate for patients with PCL[2]. Combination chemotherapy with VAD, cyclophosphomide and etoposide or other alternating regimens seems to be a better treatment modality. Although all of our patients recieved VAD chemotherapy, none of them responded to this regimen.

Because of the poor prognosis of PCL, intensive chemotherapy and subsequent consolidation with autologous or allogeneic stem cell transplantation could be a better approach especially in younger patients who are in good clinical conditions[14].

PCL is a fulminant form of MM with poor prognosis and requires treatment options different than myeloma.

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