Case Report

A Case of Rare Subtype of Multiple Myeloma: Secondary Plasma Cell Leukemia

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Abstract

Description
Plasma cell leukemia is a rare, aggressive form of multiple myeloma with the presence of circulating plasma cells in the peripheral blood. There are two types of plasma cell leukemia, primary and secondary, depending on if there was previous evidence of multiple myeloma. The diagnostic criterion of plasma cell leukemia is based on a percentage (>20%) or an absolute number of (≥2 x 10⁹/L) plasma cells in the peripheral circulation. We present the clinical course of a rare case of secondary plasma cell leukemia in a patient from the time of initial diagnosis of multiple myeloma, its remission period of about 5 years, and its final progression into refractory secondary plasma cell leukemia. This case report details the patient’s presenting symptoms, pertinent laboratory and diagnostic imaging findings, and histopathology of peripheral blood and bone marrow. This case report presents a chronological comparison of key laboratory findings that manifest the progression of multiple myeloma into secondary plasma cell leukemia. It also offers a brief review of the literature for the diagnosis and treatment of plasma cell leukemia.

Keywords
plasma cell leukemia/diagnosis; plasma cell leukemia/therapy; multiple myeloma; serum protein electrophoresis; SPEP

Introduction
The first case of plasma cell leukemia (PCL) was identified more than a century ago by Gluzinski and Reichenstein.1 There are two types of PCL, primary and secondary. Primary PCL (PPCL) is diagnosed when there was no previous evidence of multiple myeloma (MM). The diagnosis of secondary PCL (SPCL) is made when previously MM was present, and it advanced to a relapsed refractory form.1 In the remainder of this text, the term PCL generally applies to both PPCL and SPCL.

PCL resembles acute leukemia more than MM. In PCL, there is more systemic infiltration of the organs and less bone as compared to MM.2 The incidence of PCL is between 2–4% of patients with MM.1 Among all cases of PCL, 60–70% are primary, and 30–40% are secondary.1 Secondary conversion to plasma cell leukemia occurs in 1–4% cases of MM.3 In the United States, the incidence of PCL is 0.02–0.03 cases per 100,000 population, accounting for less than 0.2% of all leukemia cases between 1997–2002.3 The prognosis of PPCL is poor, with a median survival of 7–11 months.2,3 Survival is even shorter for SPCL with a median survival of 2–7 months.3,4 There appears to be a 3:2 male to female sex distribution in both PPCL and SPCL.3 Induction chemotherapy should be started without delay to minimize the risk of early death.1,5 PPCL is almost 100% responsive to chemotherapy and, due to its aggressiveness, exhibits early relapse.2 SPCL has only a 50% response to treatment and culminates in premature death within months.2 Commonly used chemotherapy for PCL includes treatment with bortezomib-based regimens followed by autologous or allogeneic stem cell transplantation in patients who are appropriate candidates.1,4–6 The best survival data for PCL is in patients who received salvage autologous stem cell transplantation (ASCT) following an
aggressive chemotherapeutic regimen. The unfavorable prognostic factors in PCL are the same as that of MM, but their prevalence is significantly higher. These risk factors include elevated β2-microglobulin, low serum albumin, hypercalcemia, elevated serum lactate-dehydrogenase, poor performance status and advanced age.

Case Presentation

Our patient was a 70-year-old male with a past medical history of hypertension, multiple myeloma and prostate cancer status post external beam radiation treatment. His prostate cancer was in remission. About 5 years before the current presentation, he was diagnosed with IgA Kappa MM. His initial diagnosis of MM was confirmed with elevated IgA levels, elevated Kappa light chains, high Kappa/Lambda light chain ratio with no monoclonal M-spike in SPEP. (Tables 1 and 2)

Bone marrow flow cytometry revealed 6% monotypic plasma cells of Kappa type consistent with plasma cell dyscrasia with no evidence for abnormal myeloid maturation or increased blast population. (Table 3)

The skeletal survey didn’t reveal any lytic lesions. Upon initial diagnosis of MM, he received cyclic treatments using bortezomib, lenalidomide, elotuzumab and zoledronic acid at standard dosage. He developed moderate peripheral neuropathy from bortezomib, and subsequent treatments with bortezomib were held. Overall, he had a good response to all these treatments and remained symptoms and disease-free for about 5 years since his initial diagnosis of MM.

In his current clinical presentation, the patient exhibited symptoms of worsening progression of back pain, abdominal pain and generalized weakness over several weeks. The patient’s family stated that he had increasing cognitive decline, frailty and irritability. A complete blood

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**Table 1.** Serum Immunofixation and Serum Protein Electrophoresis.

|                      | Initial (MM diagnosed) | SPCL Progression (5 years post MM diagnosis) |
|----------------------|------------------------|---------------------------------------------|
| Immunoglobulin G:    | 383 (L)                | 241 (L)                                     |
| Immunoglobulin A:    | 1294 (H)               | 4802 (H)                                    |
| Immunoglobulin M:    | 22 (L)                 | 10 (L)                                      |
| Protein, total:      | 6.9                    | 9.5 (H)                                     |
| Albumin:             | 4.1                    | 3.0 (L)                                     |
| Alpha-1 globulin:    | 0.3                    | 0.2                                         |
| Alpha-2 globulin:    | 1.4 (H)                | 0.6                                         |
| Beta globulin:       | 0.8                    | 5.3 (H)                                     |
| Gamma globulin:      | 0.4 (L)                | 0.4 (L)                                     |
| Globulin, Total:     | 2.8                    | 6.5 (H)                                     |
| A/G ratio:           | 1.5                    | 0.5 (L)                                     |
| M-spike              | Not observed           | Observed in the beta region                 |

**Table 2.** Serum Free Light Chain Assay.

|                      | Initial (MM diagnosed) | SPCL Progression (5 years post MM diagnosis) |
|----------------------|------------------------|---------------------------------------------|
| Free Kappa:          | 31.26 (H)              | 1547.5 (H)                                  |
| Free Lambda:         | 6.30                   | 2.4 (L)                                     |
| Kappa/Lambda ratio:  | 4.96 (H)               | 644.79 (H)                                  |
| Comment              | IgA monoclonal protein with Kappa light chain sensitivity | IgA monoclonal protein with Kappa light chain sensitivity |
count revealed marked anemia with hemoglobin <7.0 g/dL and thrombocytopenia with platelets <50,000/uL, both of these counts had significantly declined from his baseline levels over the previous 5 years. Bone marrow biopsy revealed 90% plasma cells, and immunohistochemical stain with CD34 revealed a normal number of blasts. (Figure 1) A CD138 confirmed the vast majority of plasma cells.⁹

Cytogenetic analysis demonstrated a deletion of the short arm of chromosome 1. We compared several of his key laboratory and imaging findings from his initial diagnosis of MM to current presentation: serum immunofixation, serum-free light chains essay, SPEP, flow cytometry and skeletal survey. The comparison revealed that his serum IgA levels had increased about three-fold, SPEP revealed M-spike present in the beta region that was not present during the initial MM diagnosis. (Table 1, Figure 2)

His serum Kappa light chain levels increased by about 50 times, Kappa/Lamba light chain ratio increased by about 130 times. (Table 2) Flow cytometry of peripheral blood confirmed circulating monoclonal plasma cells population comprising of 89% leukocytes, consistent with plasma cell leukemia or peripheralized myeloma. (Table 3, Figure 3) The skeletal survey revealed multiple lesions in the axial and appendicular skeleton. (Table 3)

After the diagnosis of SPCL, in a period of about 4 months, he was hospitalized multiple times for symptomatic anemia and neutropenic infections associated with marked pancytopenia. During these hospital admissions, he was treated for opportunistic infections of the lung and urinary tract related to febrile neutropenia. He also required frequent red blood cell and platelet transfusions. Since the onset of progression to SPCL, his platelet count stayed in the range of 9,000–47,000/uL despite regular platelet transfusions. (Table 4) His treatments with elotuzumab were restarted, and he exhibited no improvements in symptom progression.⁷

| Flow Cytometry | Bone marrow flow revealed 6% monotypic plasma cells of Kappa type consistent with plasma cell dyscrasia. There was no evidence of abnormal myeloid maturation or increased blast population. No evidence of B-cell or T-cell lymphoproliferative disorder was present. | Peripheral smear flow cytometry revealed circulating monoclonal plasma cell population 89% of leukocytes, consistent with plasma cell leukemia/ peripheralized myeloma. |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Skeletal Survey | No lytic lesions were seen.                                                                                                                                | Multiple lesions were noted in the axial and appendicular skeleton.                                                                                       |

Table 3. Flow Cytometry and Skeletal Survey.

Initial (MM diagnosed) | SPCL Progression (5 years post MM diagnosis)
---|---
Flow Cytometry | Peripheral smear flow cytometry revealed circulating monoclonal plasma cell population 89% of leukocytes, consistent with plasma cell leukemia/ peripheralized myeloma.
Skeletal Survey | Multiple lesions were noted in the axial and appendicular skeleton.

Figure 1. Bone marrow biopsy of a patient showing a diffuse infiltrate of atypical plasma cells lacking blastic features.⁹
During his last hospitalization, the patient had presented with symptoms of severe respiratory distress and septic shock. He was placed on mechanical ventilator support due to complications from Pseudomonas pneumonia and treated with IV antibiotics. His blood cultures were positive for Candida tropicalis and Pseudomonas. His pancytopenia became worse with absolute neutrophil count less than 400/μL and platelet count remaining below 10,000/μL, despite frequent platelet transfusions. (Table 4)

His bone marrow output continued to remain severely depressed, and he did not respond well to bone marrow colony-stimulating factors such as filgrastim. He failed multiple extubation attempts from mechanical ventilation, and his clinical status deteriorated rapidly, eventually leading to his demise. In summary, the patient had progressed from MM to SPCL in nearly five years since the diagnosis of MM and then rapidly progressed to his death in about 4 months since the diagnosis of SPCL.

**Figure 2.** (A) SPEP Initial (MM Diagnosed). M-spike is not present. (B) SPEP at the time of SPCL diagnosis (five years post MM diagnosis). M-spike is present in the beta region.

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**Figure 3.** Peripheral blood flow cytometry, representative dot plot(s). This study was done at the time of SPCL diagnosis.
Plasma cell malignancies include four entities: classic MM, extramedullary plasmacytoma without MM, solitary plasmacytoma of bone and PCL.10 PCL represents between 2–4% of all plasma cell malignancies, and 0.3% of acute leukemias.2,10 The median time to leukemic transformation for patients with MM who evolve to SPCL is 21 months.3 In the case of our patient, this transformation was clinically observed after 58 months since the initial diagnosis of MM. Both PPCL and SPCL patients present with renal insufficiency, as was the case with our patient.2 (Table 4) Osteolytic lesions are more common in the case of SPCL as compared to PPCL.2,3 Our patient had osteolytic lesions noted in the skull and the ribs. (Table 4) The bone marrow cytogenetic analysis was remarkable for the presence of 1p deletion. The deletion of 1p is associated with worse overall and progression-free survival for patients with MM.3

The cut off for diagnosis of PCL to initiate timely treatments and improve survival outcomes.1 Both CD38 and CD138 are expressed in MM and PCL.1,2 The principal immunophenotypic difference between PPCL and MM is that PPCL tumor cells are less often positive for CD27, CD56, CD71, CD117 and HLA-DR, but more often express CD20, CD44, CD45, CD19 and CD23.2 PCL usually expresses CD20 and has negative CD56 expression.2,10 CD56 is associated with anchoring plasma cells to bone marrow.2,12 CD28 is more frequently expressed in SPCL.1 Genomic and clinical differences between PCL and MM have been recognized. P53 and DIS3 mutations are more common in PPCL and MM, whereas NRAS, KRAS, BRAF mutations are less frequent in PPCL than in MM and SPCL.6 Both MM and PPCL have the following translocations that include chromosome 14: t(11;14), t(14;16) and t(4;14).6 The t(4;14) mutation predicts sensitivity to treatment with BCL-2 inhibitor venetoclax, whereas t(11;14) and t(14;16) are associated with high-risk MM.6 Furthermore, hypodiploidy, 13q deletions, 1p deletions and 1q gains could define an advanced stage of plasma cell disease characterized by poor prognosis and resistance to therapy.2 The treatment options for PPCL with conventional regimens of VAD (vincristine, doxorubicin,
dexamethasone) in a combination of alkylating agents with corticosteroids is found to be inferior compared to novel agents.\textsuperscript{2,8,13,14} The novel agents include proteasome inhibitors (bortezomib) and immunomodulatory agents (lenalidomide).\textsuperscript{2,8,13,14}

In PPCL, favorable outcomes of increased overall and progression-free survival over 12 months are reported with combination regimens, including bortezomib, lenalidomide and dexamethasone.\textsuperscript{2,7,8} Stem cell transplant (SCT) can be considered depending on the patient’s age and functional status and other clinical parameters.\textsuperscript{2} For patients less than the age of 50, allogeneic SCT (AlloSCT), and for patients over the age of 50, autologous SCT (ASCT) offer improved treatment outcomes.\textsuperscript{2} Patients receiving ASCT had improved overall survival of 34 versus 11 months over those receiving only chemotherapy.\textsuperscript{2} AlloSCT is potentially curative but is associated with high transplant-related mortality.\textsuperscript{2} In one study, overall 3-year survival in ASCT was better than AlloSCT, 64\% versus 39\%, respectively.\textsuperscript{2,6}

Regarding SPCL treatment, there are limited case statistics due to the rarity of the disease. In a case series of nine SPCL patients, who received the treatment combination of lenalidomide, bortezomib and dexamethasone, had an overall response rate of 44\% and median overall survival of only 5.13 months.\textsuperscript{3} A recent case series further investigated the treatment of SPCL with bortezomib and lenalidomide-containing regimen achieving progression-free survival of more than 27 months in 2 of 9 patients.\textsuperscript{6} In a multicenter retrospective study of 72 SPCL patients, in a median followup of 16.3 months of those patients who received any treatment for SPCL, had a median overall survival rate of 4.2 months and a 1-year overall survival rate of 19\%.\textsuperscript{4} In SPCL, the overall response rate was substantially higher in patients who received salvage ASCT than those who did not receive ASCT (93\% versus 36\%, respectively, \(p < 0.001\)).\textsuperscript{4} In SPCL patients AlloSCT is not indicated.\textsuperscript{7} In SPCL, platelet count less than 100,000/uL is an independent risk factor of poorer prognosis in SPCL. In our patient, at the time of SPCL diagnosis, we observed several orders of magnitude increase in free light chain counts and ratios with marked differences in gamma globulin counts from baseline values noted at the time of MM diagnosis. These laboratory data could potentially serve as crucial early indicators for the progression of MM into SPCL. Despite the current armamentarium for the treatment SPCL, this disease has high mortality and poor overall survival with rapid succession to death within months of diagnosis. Hence, research for novel agents with higher efficacy is warranted towards improved treatment outcomes for this difficult and challenging disease process.

**Conclusion**

PPCL is a rare disease, and SPCL is even more unique. PCL is very aggressive with poor survival statistics. Upon initial diagnosis of PCL, high dose induction chemotherapy should be started without delay, followed by autologous or allogeneic stem cell transplantation, depending on the patient’s age and other factors as applicable. Platelet counts lower than 100,000/uL are an independent risk factor of poorer prognosis in SPCL. In our patient, at the time of SPCL diagnosis, we observed several orders of magnitude increase in free light chain counts and ratios with marked differences in gamma globulin counts from baseline values noted at the time of MM diagnosis. These laboratory data could potentially serve as crucial early indicators for the progression of MM into SPCL. Despite the current armamentarium for the treatment SPCL, this disease has high mortality and poor overall survival with rapid succession to death within months of diagnosis. Hence, research for novel agents with higher efficacy is warranted towards improved treatment outcomes for this difficult and challenging disease process.

**Conflicts of Interest**

The authors declare they have no conflicts of interest.

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