

The Quiet Intruder: An Insidious Presentation of Primary Plasma Cell Leukemia and a Literature Review on Current Treatment Strategies

Deeksha Grover^{1*}, Rao Moravineni¹, Oluchi Idenyi¹, Daniel Assaf¹, Vishwanath Anil¹,
Madhu Bhargavi Chandra¹

Abstract

Introduction: Primary plasma cell leukemia (pPCL) is a rare and aggressive plasma cell dyscrasia, defined by $\geq 5\%$ circulating plasma cells, with poor prognosis and rapid progression. **Case Presentation:** A 66-year-old African–American female with no prior medical history presented with one week of fatigue, dehydration, and polydipsia. Laboratory evaluation revealed leukocytosis, severe thrombocytopenia, acute kidney injury (creatinine 4.03 mg/dL), and hypercalcemia (13.0 mg/dL) with suppressed PTH. Imaging showed intra-abdominal lymphadenopathy without hepatosplenomegaly. Myeloma workup demonstrated markedly elevated kappa free light chains (>3000 mg/L), abnormal kappa/lambda ratio (>197), and IgG kappa monoclonal protein. Peripheral smear showed 18% circulating plasma cells. Bone marrow biopsy revealed 45% clonal plasma cells with kappa restriction. Pleural fluid cytology confirmed malignant plasma cells, indicating extramedullary involvement. Cytogenetics showed chromosome 1p abnormality. A diagnosis of pPCL was made. The patient received carfilzomib-based quadruplet therapy and was referred for stem cell transplantation. Her course was complicated by tumor-lysis syndrome and renal failure. **Discussion:** pPCL is characterized by aggressive disease biology, high tumor burden, and frequent extramedullary involvement. Compared to multiple myeloma, patients often present with cytopenias and end-organ damage, though atypical presentations may occur, as in this case with isolated fatigue. Treatment strategies are evolving and include proteasome inhibitor-based induction regimens, anti-CD38 monoclonal antibodies, and early consideration for stem cell transplantation. Despite advances, outcomes remain poor, and there is no standardized treatment approach due to the rarity of the disease and exclusion from most clinical trials. **Conclusion:** pPCL can present subtly despite aggressive disease. Early recognition and prompt treatment are essential, and further research is needed to guide management.

Keywords: Plasma cell leukemia, multiple myeloma, hypercalcemia, monoclonal gammopathy, proteasome inhibitors

*Author for Correspondence

Deeksha Grover

E-mail: Dr.deeksha.grover@gmail.com

¹MD, Department of Internal Medicine, Wellstar Spalding Regional Hospital, Griffin, GA 30224, United States

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INTRODUCTION

Multiple myeloma is a malignancy of the plasma cells, which are critical for antibody production. Plasma cells multiply uncontrollably, leading to overcrowding in the bone marrow and disrupting normal blood cell production. MM is a relatively uncommon cancer accounting for approximately 1 to 2 percent of all cancers and slightly more than 17 percent of hematologic malignancies [1].

Plasma cell leukemia (PCL) is a rare and more aggressive form of multiple myeloma. It is defined by the presence of greater than/equal to 5% plasma

cells in the peripheral blood. PCL can present de novo as primary PCL or evolve from pre-existing multiple myeloma as secondary PCL. The reported incidence of PCL in the United States and Europe is approximately 4 cases per 10,000,000 persons per year [2]. We present a rare, insidious presentation of primary PCL in an elderly AA female

CASE PRESENTATION

A 66-year-old African American female with no significant past medical history presented to our ER with complaints of fatigue that started one week ago. She reported dehydration and excessive thirst over the last week. She endorsed no other pertinent complaints. The white blood cell (WBC) count was elevated at 18.42 k.

Platelet count was critically low at 31 k. Differential counts showed 26.7% neutrophils, 35.0% lymphocytes, 32.2% 5.0% immature granulocytes. Serum creatinine was critically high at 4.03. The total calcium level was critically high at 13.0. PTH was appropriately low at 13 ng/dl. She was admitted under the impression of Hypercalcemia secondary to possible malignancy. CT chest abdomen pelvis without IV contrast showed enlarged lymph nodes in the upper abdomen, abutting the superior margin of the pancreas posteriorly and anteriorly. There was no hepatosplenomegaly.

Her myeloma profile pointed us towards the diagnosis. Her Kappa Light Chain Free levels greater than 3,000.00, a Kappa/Lambda Free Light Chain Ratio greater than 197.37, serum electrophoresis showed spikes of Paraprotein in beta and gamma region and a serum immunofixation interpretation indicating IgG kappa monoclonal protein. X-ray skeletal survey showed no lytic lesions. Peripheral blood film showed many of the atypical mononuclear cells to be atypical plasma cells (18%). These were medium to large, eccentric round to oval nuclei with coarsely clumped chromatin, and abundant basophilic cytoplasm. Bone marrow was extensively infiltrated by atypical plasma cells on core biopsy with flow cytometry showing 45% plasma cells with bright CD38, CD138, and cytoplasmic Kappa expression and negative for CD19, CD20, CD117, CD56, and Lambda. Immunohistochemical stain for CD138 highlighted numerous plasma cells with lambda restriction. Flow cytometry showed that the plasma cells were monoclonal with kappa light chain restriction. The patient also had right pleural effusion. Examination of the pleural effusion showed numerous atypical plasma cells. Immunohistochemical staining on the pleural fluid cell block showed these plasma cells to be positive for CD138 and kappa. They were negative for lambda light chains. FISH panel showed gain of Chromosome 1p. These findings confirm a diagnosis of primary plasma cell leukemia with extramedullary involvement. The patient was transferred to a different facility for HCT. She received 6 doses of multi agent therapy quad regimen including Carfilzomib, Isatuximab, Lenalidomide, and Dexamethasone. Patient had multiple hospitalizations for tumor lysis syndrome and developed renal failure. Patient had multiple hospitalizations for tumor lysis syndrome and developed renal failure.

DISCUSSION

Primary Plasma Cell Leukemia (PPCL) is a rare and aggressive form of plasma cell neoplasm characterized by the presence of a significant number of malignant plasma cells in the peripheral blood. According to the revised diagnostic criteria established by the International Myeloma Working Group in 2021, PPCL is diagnosed when there are at least 5% circulating plasma cells (CPCs) in a peripheral blood smear, which is a change from the previous threshold of 20% [3].

Primary plasma cell leukemia arises de novo and is characterized by the absence of a prior history of multiple myeloma, while secondary plasma cell leukemia typically develops as a progression from an existing plasma cell disorder such as multiple myeloma or other related conditions.

American SEER database between 1973 and 2009, PCL accounted for approximately 0.6% of the MM cases, which translates to about 1200 patients a year in the USA. This incidence is bound to increase with the decrease in threshold of circulating plasma cells to diagnose PCL [4].

PPCL is characterized by a more aggressive clinical course, often leading to a rapid deterioration of the patient's condition. Patients with PPCL tend to present with higher levels of circulating malignant plasma cells and more severe organ dysfunction at diagnosis compared to those with secondary plasma cell leukemia [5].

PCL presents, like multiple myeloma, with bone pain and pathological fractures. Leukocytosis, Thrombocytopenia and anemia is frequently seen. Our patient had the sole chief complaint of fatigue which made this diagnosis even more astonishing.

Chemotherapy is often the first line of treatment for patients with Primary Plasma Cell Leukemia, induction therapy mainly consisting of bortezomib-based regimens [6–11].

A common induction regimen includes cisplatin, doxorubicin, cyclophosphamide, and etoposide (PACE). Per this recent analysis of overall response rate after induction therapy with PACE was reported to be 75% for patients who proceeded to stem cell transplant [9]. PACE was not given 1st line in this case due to renal insufficiency; the benefit is short lived with not an impressive progression free survival. There is promising data about carfilzomib-based regimens. The EMN12/HOVON-129 study utilized a combination of carfilzomib, lenalidomide, and dexamethasone (KRd) for induction, showing improved progression-free survival [12].

An induction approach involves the use of chimeric antigen receptor T-cell (CART) therapy combined with autologous stem cell transplantation (ASCT), demonstrating high efficacy in achieving stringent complete responses with a favorable safety profile. 100% of patients achieved at least a very good partial response (VGPR) or better one month after the first CART infusion [13–16]. However, the long-term benefit of CART is unclear, with a predisposition to neurotoxicity and cytokine release syndromes.

Immunotherapy-based regimens are not widely used for pPCL, however, Anti-CD38 monoclonal antibody-based regimens are being investigated for plasma cell dyscrasias.

SCT can significantly impact patient outcomes and is considered standard of care. Patients who underwent stem cell transplantation showed significantly improved overall survival, with median survival reaching 46 months compared to 9 months for non-transplant patients [9, 17].

Autologous SCT has shown promise, particularly in transplant-eligible patients, as it may lead to prolonged remission periods when combined with maintenance therapy post-transplantation [18]. Allo-SCT, particularly haploidentical transplantation, has emerged as a viable option for patients lacking HLA-matched donors [19]. However, allo-SCT upfront has been associated with poorer overall survival compared to ASCT, indicating the need for careful patient selection and timing [20].

In cases where patients were non-transplant eligible, maintenance therapy with bortezomib has been effective in sustaining remission. A retrospective study indicated a 90% overall response rate in pPCL patients receiving bortezomib-based regimens, with a median overall survival of 23.3 months [21, 22].

For refractory cases, a combination of venetoclax, daratumumab, and dexamethasone has shown promise, particularly in a subset of patients with translocation t(11;14) and bi-allelic TP53 inactivation [23].

pPCL remains rare and is nearly always an exclusion criterion for clinical trials. We don't have conclusive studies comparing different types of chemotherapy regimens available for pPCL and a lack of standardised treatment protocol.

This rare case of pPCL posed significant therapeutic challenges, highlighting the need for tailored treatment strategies and further research to improve clinical outcomes in this exclusionary patient population.

CONCLUSION

PPCL is a rare and aggressive plasma cell disorder with a poor prognosis, requiring early diagnosis and tailored treatment strategies. Advances in multi-agent chemotherapy, stem cell transplantation, and emerging immunotherapies offer hope for improving patient outcomes.

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