

Case Report

Plasma Cell Leukemia Presenting with Spontaneous Tumor Lysis Syndrome: Report of a Rare Case and Literature Review

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Abstract

Plasma cell leukemia (PCL) is a rare but aggressive plasma cell neoplasm. It is defined by more than 20% plasma cells in the peripheral blood or an absolute plasma cell count of more than $2 \times 10^9/L$. We describe an interesting case of PCL in a 46-year-old African American female who presented with rib pain, fatigue, anemia, acute renal failure, leukocytosis with 85% plasma cells and spontaneous tumor lysis syndrome (TLS). TLS was managed with intravenous hydration and antihyperuricemic therapy. Despite an initial favorable response after induction chemotherapy, the patient's disease progressed and she expired from infection and multi-organ failure eight months later. A detailed report of this case and a review of the management of TLS, plasma cell leukemia diagnosis and treatments are presented here.

Keywords: Plasma cell leukemia; Renal failure; Tumor lysis syndrome

Abbreviations

PCL: Plasma Cell Leukemia; TLS: Tumor Lysis Syndrome; MM: Multiple Myeloma; ORR: Overall Response Rate; OS: Overall Survival; ASCT: Autologous Hematopoietic Cell Transplantation

Introduction

Plasma cell leukemia (PCL) is a rare but aggressive lymphoproliferative disorder with a poor prognosis. It accounts for 2-3% of all plasma cell neoplasms. PCL is defined by more than 20% plasma cells in the peripheral blood or an absolute plasma cell count of more than $2 \times 10^9/L$ [1]. PCL usually has a more aggressive clinical presentation than multiple myeloma (MM), including a higher incidence of diffuse bone marrow involvement, hepatomegaly, splenomegaly, lymphadenopathy, leptomeningeal infiltration, and extramedullary soft tissue plasmacytomas [1]. Here we report a case of PCL whose clinical course represented the rare and aggressive aspects of this disease.

Case Presentation

A 46-year-old African American female presented with two months history of worsening right-sided rib pain, shortness of breath and fatigue. Her past medical history included hypertension and a four pack-year smoking history. Family history was unremarkable for solid or hematological malignancies. Examination revealed pallor, chest wall tenderness, tachycardia and bilateral lower extremity edema. Her initial laboratory results showed anemia, marked leukocytosis, thrombocytopenia, azotemia, hyperuricemia and hypercalcemia. Urinalysis showed 2+ proteinuria and amorphous crystals. Table 1 summarizes the relevant laboratory findings.

With hyperuricemia, hyperphosphatemia and acute kidney failure, tumor lysis syndrome (TLS) was highly suspected. Immediately the patient was given intravenous normal saline for aggressive hydration,

forced diuresis with furosemide and one dose of rasburicase (6 mg IV) for hyperuricemia. Calcitonin and one dose of pamidronate were also administered to treat hypercalcemia.

The peripheral blood smear revealed leukocytosis with lymphocyte-like plasma cells (Figure 1). Flow cytometry analysis of peripheral blood showed 85% plasma cells that were positive for CD138, CD38, dim positive for CD45, negative for CD19 and CD56, and with kappa light chain restriction (Figure 2). A diagnosis of PCL was made. We failed to obtain bone marrow aspiration as specimen was a dry tap. The bone marrow core biopsy confirmed the diagnosis of PCL with massive (90%) bone marrow involvement. Serum protein electrophoresis did not show significant M-band. The serum free kappa light chain level was elevated at 338 mg/dL (normal 0.35-2.49 mg/dL) with an increased free kappa/lambda ratio of 751 (normal 0.27 to 1.80). A skeletal survey revealed numerous lytic lesions.

The patient's hyperuricemia, hyperphosphatemia and

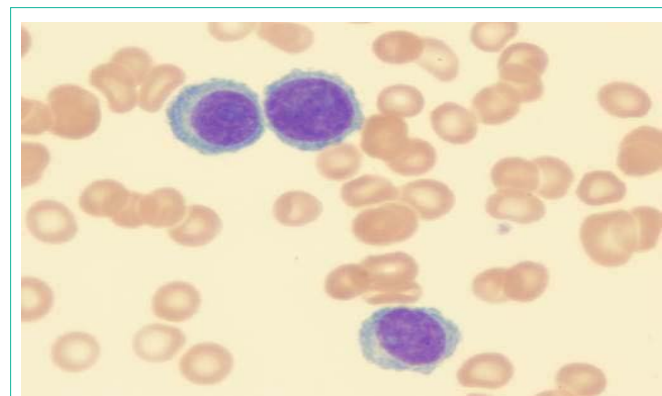


Figure 1: Peripheral blood smear showing plasma cells with eccentric nuclei, perinuclear halos with basophilic cytoplasm.

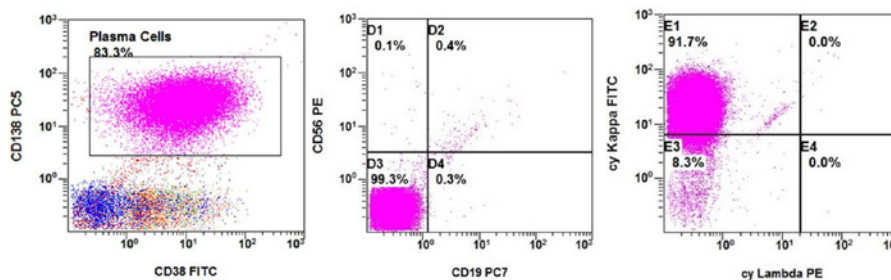


Figure 2: Flow cytometry analysis of peripheral blood.

Table 1: Laboratory tests results before and after spontaneous TLS development.

Laboratory tests	2 months prior to admission	On admission	Reference range
Hemoglobin(g/dL)	14.1	7.3	12-15
Platelet count(cells/mm ³)	116,000	17,000	150,000 – 400,000
Total WBC(cells/mm ³)	5,200	125,200	4,000-10,000
Serum creatinine (mg/dL)	0.66	2.78	0.6-1.4
Serum BUN(mg/dL)	12	47	8-22
Potassium (mEq/L)	4.2	4.2	3.5-5.2
Phosphorus(mg/dL)	NA	5.9	2.3-4.3
Uric acid(mg/dL)	NA	12.5	1.5-6.0
Calcium (mg/dL)	9.2	13.6	8.4-10.4
β_2 -microglobulin(mg/L)	NA	25.95	0.00-1.9

NA: Not Available

hypercalcemia improved significantly with initial treatments (Figure 3A). Chemotherapy was initiated on day 4 with systemic bortezomib, cyclophosphamide and dexamethasone. Leukocytosis resolved by day 15. The patient’s creatinine level had decreased initially with TLS treatments and then with initiation of chemotherapy the creatinine gradually rose as well as uric acid level (Figure 3B). Allopurinol 200 mg daily was started to decrease uric acid formation. Postrenal obstruction was ruled out by image studies. Renal biopsy was contraindicated due to a high bleeding risk from thrombocytopenia. Given the strikingly high free light chain level, the likelihood of light chain nephropathy was great. Plasmapheresis was initiated on day 7 and renal function significantly improved after five sessions without the need for hemodialysis (Figure 3B).

After four cycles of chemotherapy, her free light chain kappa/lambda ratio completely normalized and a repeat bone marrow biopsy showed 5-8% plasma cell involvement. According to International Myeloma Work Group response criteria, she had achieved partial remission [1]. Unfortunately, she later developed complications including pathological fracture which delayed the planned autologous bone marrow transplantation. Her disease progressed and she expired from infection and multi-organ failure eight months after her diagnosis.

Discussion

PCL is a pathologic entity distinct from multiple myeloma with aggressive features and a poor prognosis. Here we described a case of PCL with the unusual presentation of spontaneous TLS.

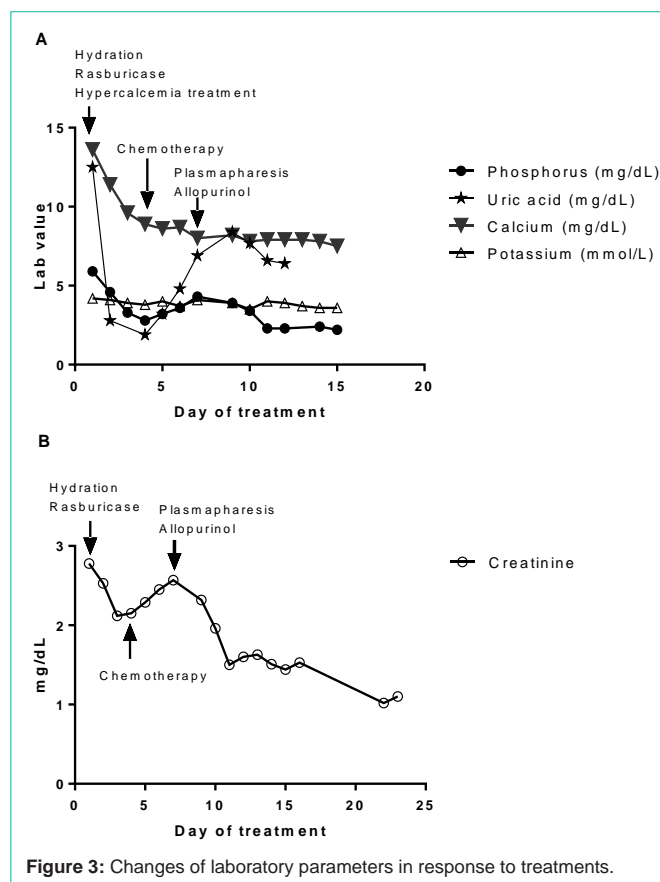


Figure 3: Changes of laboratory parameters in response to treatments.

TLS is an oncologic emergency comprised of metabolic disturbances resulting from either spontaneous or cytotoxic therapy-induced tumor cell death. The lysis of a large number of tumor cells releases intracellular contents, including nucleic acids, proteins, and electrolytes, into the systemic circulation which leads to the development of hyperuricemia, hyperphosphatemia, hyperkalemia and secondary hypocalcemia. This may cause multi-organ dysfunction including acute renal failure, cardiac arrhythmia and seizure [2]. TLS is most often seen after initiation of chemotherapy. In the absence of therapy, spontaneous TLS can occur, although it is rare, mostly in patients with acute leukemia and highly aggressive non-Hodgkin’s lymphoma. According to the Cairo and Bishop Classification system, in the absence of cytotoxic therapy or other triggering factors, this patient met the criteria for clinical TLS as she presented with laboratory derangements of hyperuricemia, hyperphosphatemia and

acute renal failure [1]. To our knowledge, this is the first report of spontaneous TLS occurring in PCL.

TLS is extremely rare in plasma cell neoplasms due to the low proliferation rate of plasma cells. However, in the setting of extremely high tumor burden, TLS can occur. TLS has been reported in MM patients who were treated with bortezomib [3-9], carfilzomib [10,11], thalidomide [7,12-15], corticosteroid alone [16], or spontaneously [17]. TLS occurrence in PCL has been described only in one case after initiation of bortezomib treatment [18]. The definition of high tumor burden which potentially increases risks of TLS in plasma neoplasm is not clear in the literature. It is believed to be correlated with increased β -2 microglobulin, elevated lactate dehydrogenase, high percentage bone marrow involvement, immature morphology and advanced bone lytic lesions. It has been proposed that light chain nephropathy may be associated with a higher risk of TLS, a scenario similar to our patient [15]. PCL is the most aggressive form of plasma cell neoplasm with a high tumor burden and a high prevalence of organ involvement at presentation [19]. Our patient's characteristics reflects the aggressive nature of this disease, represented by her extreme peripheral plasmacytosis, advanced bone lytic lesions and massive bone marrow infiltration, all of which predisposed her to a high risk of TLS.

Acute renal failure, as seen in our patient, was a sequela of multiple factors, including uric acid and calcium phosphate crystallization, superimposed upon light chain nephropathy. Adequate hydration, diuresis as well as reducing uric acid level with the use of rasburicase particularly are essential to preserve or improve renal function [2]. Hyperphosphatemia can be less remarkable in spontaneous TLS than in chemotherapy-induced TLS, and presumably results in a lesser degree of secondary hypocalcemia [20]. This phenomenon may be due to actively growing malignant cells rapidly take up extracellular phosphate released from dying cells, causing a neutral net phosphate flux [20]. The hypercalcemia observed here may represent a net outcome between PCL causing hypercalcemia and TLS causing secondary hypocalcaemia. Hypercalcemia and normocalcemia in TLS have been previously reported [17,21]. Although evidence for utilizing plasmapheresis in light chain nephropathy is limited to uncontrolled retrospective case series, it is a reasonable therapy for individuals with extremely high free light chain level (above 200 mg/dL).

Due to the rarity of PCL, there have been no large prospective randomized trials of treatments. Recommendations are largely based on case reports, small retrospective series and data extrapolated from the treatment of MM. Historically, outcomes in PCL are dismal, with a median survival of 6 to 12 months [22]. This early mortality is likely due to the typical initial aggressive presentation with complications as well as the lack of effective therapy to achieve sustained response.

Case series and retrospective studies reported that regimens containing bortezomib, a proteasome inhibitor, had better disease control with an overall response rate (ORR) ranging from 69% to 89.9% and an overall survival (OS) ranging from 12-24 months [22-25]. Lenalidomide, an immunomodulatory drug, showed an ORR of 74% and a median OS of 28 months in a very small phase II prospective trial [26]. Several retrospective studies of high-dose chemotherapy followed by autologous hematopoietic cell transplantation (ASCT)

demonstrated prolonged OS and ASCT may be of value, although no definite conclusion can be drawn due to the lack of randomized prospective studies [19,27,28].

Conclusion

Our report raises the need for clinical awareness of spontaneous TLS in PCL. Although uncommonly encountered, TLS should not be overlooked as it is associated with significant mortality. Laboratory parameters need to be closely monitored. Improvement in PCL outcomes requires focusing on two aspects: reducing early mortality and achieving sustained long term disease control. Early recognition of PCL and management of its complications are essential first steps. Induction chemotherapy should be initiated immediately to achieve rapid cytoreduction and minimize the risks contributing to early death. Strategies to improve long term survival include incorporating novel therapies with induction, consolidation and post-graft maintenance treatment stages. Prospective randomized trials investigating these approaches are necessary.

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