Case Report

Plasma cell leukemia

Shaylika Chauhan[1], Priya Jaisinghani[2], Jaivir Rathore[3], Hassan Tariq[4], Yesenia Galan[1], Arjun Madhavan[5], Haris Rana[5], Douglas Frenia[5]

Departments of [1]Internal Medicine and [5]Pulmonary Medicine, Saint Peter's University Hospital, Rutgers Robert Wood Johnson Medical School, [2]Department of Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, [3]Department of Neurology, College of Medicine, University of Illinois, Chicago, Illinois, [4]Department of Neurology, Marshall University, WV, USA

Abstract

We present a rare case report of a patient diagnosed with primary plasma cell leukemia (PCL) who presented with atypical signs and symptoms which acutely evolved into life-threatening multi-organ failure. This case raises questions regarding the latest diagnostic guidelines and therapeutic options in the management of acute PCL and reinforces the need for prompt treatment after diagnosis.

Keywords: Atypical symptoms, multi-organ failure, multiple myeloma, plasma cell leukemia, primary plasma cell leukemia, prompt diagnosis, targeted therapy

Introduction

Plasma cell leukemia (PCL) is a rare and aggressive subtype of multiple myeloma (MM) known to have a poor prognosis. It is characterized by a predominantly monoclonal population of plasma cells in the peripheral blood, specifically more than 20% of total white blood cell or $>2 \times 10^9$/L.[1] Most of the genetic lesions which progressively accumulate during the transformation from monoclonal gammopathy of undetermined significance to overt MM are frequently present at diagnosis in primary PCL (pPCL). Such changes cause modifications in the expression of adhesion molecules, chemokine receptors, and surface antigens which favor the inhibition of apoptosis and immune escape of neoplastic cell lines leading to the aggressive phenotype of pPCL with respect to MM.[2] PCL is classified as either primary or secondary. In pPCL, the plasma cell population is of *de novo* origin and is an initial manifestation of the disease at the time of diagnosis, while in secondary PCL (sPCL) the plasma cell population is a secondary leukemic transformation of progressive MM, usually occurring in the terminal phase. pPCL and sPCL constitute 50%–70% and 30%–50% of all PCLs.[1]

pPCL constitutes approximately 50%–70% of all PCL cases. pCPL manifests similarly to MM but may present with nonspecific and atypical symptoms as described in our case report. The prognosis of PCL is poor with the median survival ranging from 6 to 11 months with up to 28 percent dying within the 1st month after diagnosis.[3-6] The percentage of leukemic plasma cells in the peripheral blood is not a true indicator of disease severity, and peripheral blood plasma cell counts of as low as 27% can evolve into a fulminant life-threatening situations. Metastatic plasma cell infiltration and massive proteinemia can lead to multi-organ failure. The most important prognostic factor in pPCL remains response to treatment as patients presenting with disease that is resistant to initial therapy have the poorest outcome.[1] Prompt diagnosis and treatment with supportive and targeted therapy (plasmapheresis, bortezomib-doxorubicin, steroids, transfusions, and hemodialysis) can be lifesaving.

Case Report

A 51-year-old Hispanic female presented to the ER with a complaint of acute abdominal pain with worsening generalized

Address for correspondence: Dr. Shaylika Chauhan, Rutgers Robert Wood Johnson Medical School, Saint Peter's University Hospital, New Brunswick, New Jersey, USA. E-mail: drshaylikachauhan@gmail.com

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_310_17

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Chauhan S, Jaisinghani P, Rathore J, Tariq H, Galan Y, Madhavan A, *et al*. Plasma cell leukemia. J Family Med Prim Care 2018;7:461-5.

rash [Figure 1]. She also reported associated shortness of breath, fever with chills and diarrhea for the past few weeks. Laboratory analysis indicated acute renal failure, coagulopathy, transaminitis, and electrolyte imbalances. Without a clear reason attributed to her lactic acidosis, she was taken for emergent exploratory laparoscopy. No signs of bowel ischemia were revealed.

Her complete blood count revealed acute hemolytic anemia, marked thrombocytopenia, and leukocytosis. The peripheral blood smear showed 27% circulating atypical plasma cells, which were confirmed from flow cytometry to be immunophenotypically aberrant. Computed tomography scan of her abdomen showed diffuse abdominal and pelvic lymphadenopathy. Her serum protein electrophoresis (SPEP) revealed marked polyclonal hypergammaglobulinemia with mild monoclonal proteinemia. Liver, skin, and bone marrow biopsies supported a diagnosis of pPCL, although marrow cytogenetic studies were normal. Lymph node biopsy could not be performed due to her critical condition. Her condition deteriorated and she eventually developed renal failure despite plasma exchange. Furthermore, her clinical course was complicated by disseminated intravascular coagulation, asystole cardiac arrest, and respiratory failure. Chemotherapy using dexamethasone, bortezomib-doxorubicin was initiated, but she remained critically ill.

Discussion

In 1906, the first case of pPCL was reported by Professor A. Gluzinski and Dr. M. Reichenstein. Then in 1974, Noel P and Kyle RA established the first diagnostic criteria for PCL: presence of absolute plasma cell count more than 2×10^9/L and >20% of total white blood count. These criteria are still been followed as WHO criterion for the diagnosis of PCL. It is a rare but most aggressive type of plasma cell dyscrasia. The prognosis of PCL is poor, with median survival with chemotherapy is 2–8 months, and it reduces, if its secondary type, to less than a month of diagnosis.

The exact incidence of pPCL is believed to be less than 1 case/million.[7] From the surveillance, epidemiology and end results (SEER) database it is evident that there are no significant differences based on gender, age, or race when compared with patients with MM. PCL occurs in all races and all geographic locations. As with MM, PCL is more common in African Americans and blacks from Africa than in whites.[7] pPCL patients have a younger age at presentation when compared to MM or sPCL patients, and their performance status is usually worse and faster declining.[1] pPCL presents at a slightly younger age with median ages at diagnosis of 55 compared to patients with sPCL at 66.

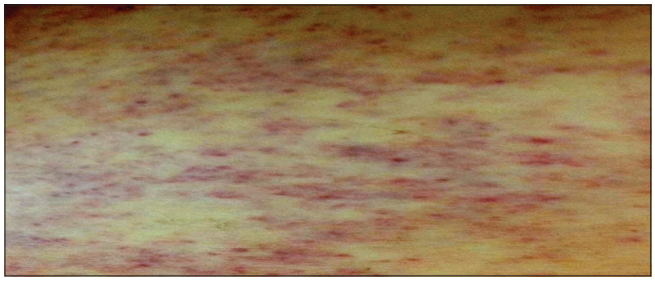

Figure 1: Diffuse morbilliform rash

pCPL manifests similarly to MM often presenting as bone pain, anemia, renal dysfunction, hypercalcemia and lytic bone lesion lymphadenopathy, hepatosplenomegaly, with possible pulmonary findings related to pleural effusions, and neurological deficits related to central nervous system involvement. On blood analysis, anemia, leukocytosis, and thrombocytopenia will be evident. In addition, PCL patients may show an increased level of lactic dehydrogenase (LDH) and beta 2 microglobulin.[1] Immunophenotypically, plasma cells in PCL show the following pattern CD38+, CD138+, CD79a+, cytoplasmic Ig+, CD20−/+, CD19−, CD45−, CD 56−, and surface Ig−. PCL should be considered in patients with MM who present with or develop circulating plasma cells on a conventional leukocyte differential count or peripheral smear, elevated LDH, hepatosplenomegaly, or effusions. The diagnostic evaluation of a patient with suspected PCL is identical to MM. It includes a review of the peripheral blood smear, bone marrow aspiration and biopsy, SPEP with immunofixation, protein electrophoresis of an aliquot from a 24-h urine collection (urine protein electrophoresis), and peripheral blood plasma cell assessment by flow cytometry.

The most important prognostic factor in pPCL remains response to treatment as patients presenting with disease that is resistant to initial therapy have the poorest outcome.[1] The current treatment plan follows steps involved in the management of MM. Induction therapy includes various bortezomib-based regimens such as VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide, and etoposide), VDT (bortezomib, thalidomide, and dexamethasone), VRD (bortezomib, lenalidomide, and dexamethasone), VCD (bortezomib, cyclophosphamide, and dexamethasone), VAD (bortezomib, doxorubicin, and dexamethasone), or VMP (bortezomib, melphalan, and prednisone).

With the widespread use of high-dose therapy with autologous hematopoietic cell transplantation (rescue) and the availability of novel agents, survival time has slightly increased. The SEER demonstrated this in 445 patients with pPCL which reported median overall survival times of 5, 6, 4, and 12 months for those patients diagnosed during 1973–1995, 1996–2000, 2001–2005, and 2006–2009, respectively.[8] Therefore, SEER was able to detect a doubling in cohorts from 2006 onwards after the introduction The median overall survival time for the entire pPCL cohort was 6 months, and it was 1, 2, and 5 years for 56%, 31%, and 5%, respectively. It should be taken into account that the SEER database does not contain specific information about the use of treatment types and various time periods; thus, it only represents an indirect surrogate for the potential use of novel agents.[2] In another study, a national survey of 38 cases of pPCL over a period of 12 years, published in Acta Haematologica, Iruchishima, etc., there was no difference in

the overall response rate to conventional or novel therapies, but significantly higher rates of complete response and very good partial response when with novel response (50% vs. 16% $P = 0.029$).[2] Different results have been reported from other studies. On such study was a retrospective study with 27 pPCL patients treated with total therapy trials including thalidomide or thalidomide and bortezomib. Overall, the median overall survival time was 1.8 years with no significant difference when bortezomib was added.[2]

Although the best induction regimen for PCL is not known, older treatments for MM such as VAD have had poor survival outcome in patients. Recently, lenalidomide and bortezomib-based regimens have demonstrated activity and are more widely used. In a multicenter retrospective study involving 42 patients with pPCL or sPCL [Figures 2-5], bortezomib-based therapies were associated with 69% response rates, 1–3-month median survival time [Figure 6].[9] Although there is great variability in treatment plans, typically individuals <65 years in good performance status are treated with aggressive induction therapies such as VDT-PACE. In younger patients, leukemia/lymphoma-like more intensive regimens include hyperfractionated cyclophosphamide, vincristine, doxorubicin, and etoposide +/−bortezomib/thalidomide. In older patients or unfit patients, a combination of lenalidomide or dexamethasone may be a valuable alternative option. It can also be used in patients with the slower evolution of disease of those with signs of neuropathy in whom the use of bortezomib would be contraindicated.[1]

Induction therapies are followed by stem cell transplantation unless there is a contraindication. In patients eligible for stem cell transplantation and other alkylating agents such as melphalan, they should be initially avoided to allow adequate collections of CD34+ peripheral blood stem cells reaching a threshold of at least 5×10^6 CD34+ PBSC/kg using cyclophosphamide plus G-CSF and adding a mobilizing agent plerixafor.[1]

Surveillance, epidemiology, and end result database

Recently, new high throughput technologies such as single nucleotide polymorphism array, gene expression profiling, miRNA-expression profiling and whole genome sequencing have facilitated identification of clear genomic diverse array with respect heterogeneity amongst pPCL patients with regard to response to therapy and clinical outcomes. The candidate

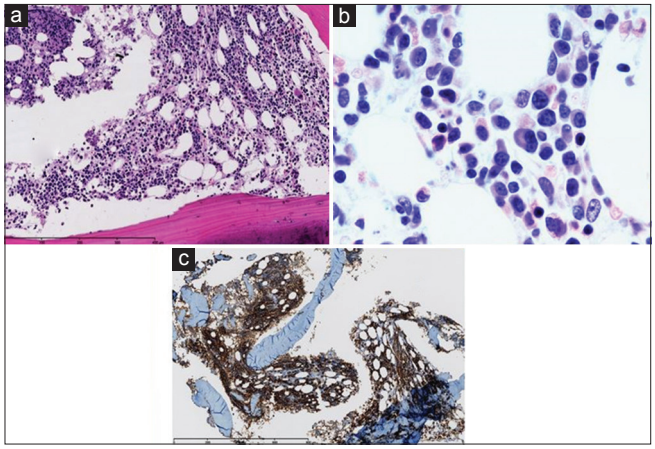

Figure 2: (a) Increased atypical plasma cells (central nucleus, binucleation, and nucleoli). H and E strained section of bone marrow biopsy, ×40). (b) Increase plasma cells and decreased trilineage hematopoiesis. H and E stained section of bone marrow biopsy, ×40). (c) Increase plasma cells highlighted by CD138 immunohistochemical, ×10)

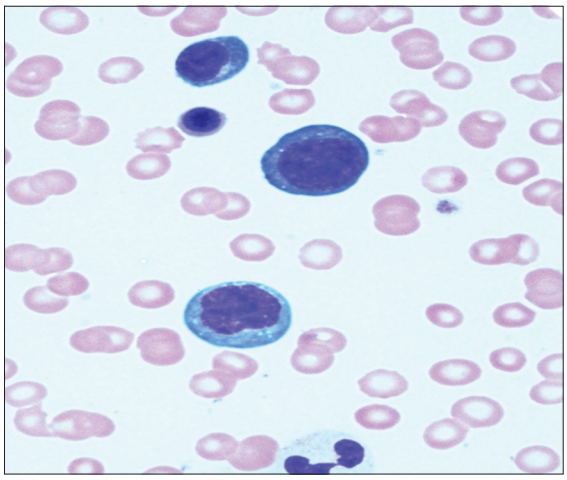

Figure 4: Circulating atypical plasma cells with high nuclear: cytoplasmic ratio, loss of clock-face chromatin and variable sizes rouleaux formation is appreciated in the background. Wright Giemsa stained peripheral blood smear (×100)

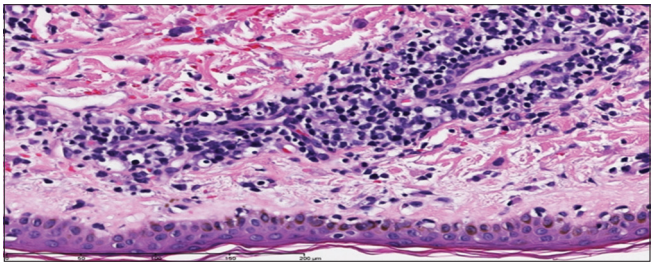

Figure 3: Skin with increased atypical plasma cells (leukemia cutis) (H and E, ×10)

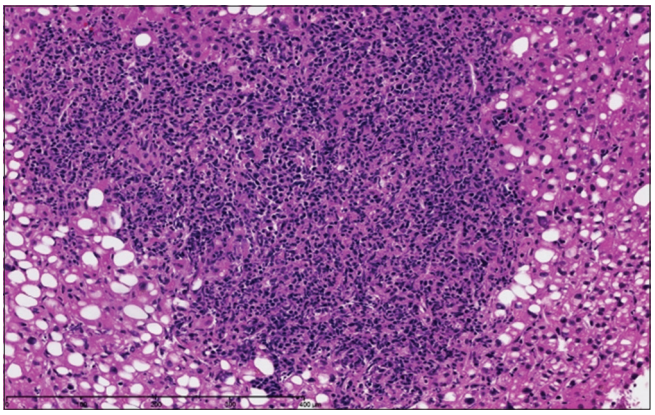

Figure 5: Increased nodular and sinusoidal infiltrate with atypical plasma cells. H and E stained section of liver (×10)

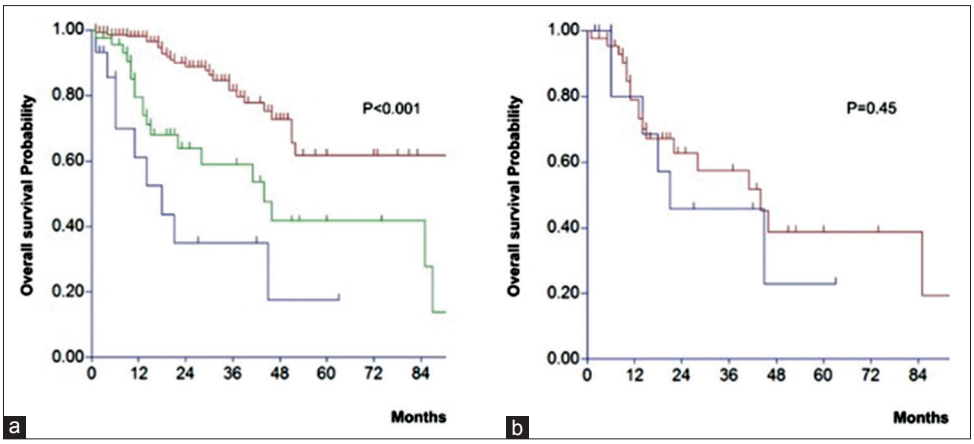

Figure 6: Probability of overall survival in months

genes identified in these pathways might also be useful as feasible targets for innovative therapeutic approaches. The possibility of stratifying treatments for pPCL according to genetic risk factors associated with adverse events is an attractive prospect.[2]

Strengths/limitations of the study

Due to the rarity of this diagnosis, prospective studies have not been feasible. Most of the information about PCL has been extrapolated from the case reports, case series, and retrospective reports. More case reports and research will provide us better insight into etiopathology, therapy, and overall management. Most importantly, more research may also help us to generate new guidelines for early diagnosis. One another factor for early deaths can be pinned to unavailability of curative management.

Next generation IMIDs (pomalidomide) and PI (carfilzomib and ixazomib), monoclonal antibodies (elotuzumab and daratumumab) and histone-deacetylase (parabinostat) or kinesin spindle (ARRY-520) inhibitors represent different possibilities of multi-target mechanisms of action within different phases of treatment-induction, transplant, consolidation, and maintenance. Ideally, the approach to treatment should be to control the initial disease aggressiveness, limit molecular heterogeneity, and eradicate minimal residual disease to avoid relapse.

Conclusion

Treatment of PCL should start immediately once the diagnosis is confirmed. Induction treatment should begin immediately after diagnosis is confirmed, and the best strategies to improve long-term survival are high-dose chemotherapy followed by autologous transplantation of stem cells or allogeneic transplantation in younger patients. Due to aggressive nature and high mortality rate associated with PCL, we need to conduct multicenter prospective randomized studies to gain more insight on causes and to update the guidelines for early diagnosis and effective management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Musto P, Simeon V, Todoerti K, Neri A. Primary plasma cell leukemia: Identity card 2016. Curr Treat Options Oncol 2016;17:19.
2. Musto P. Novel agents for the treatment of primary plasma-cell leukemia: Lights and shadows. Acta Haematol 2016;135:110-2.
3. Tiedemann RE, Gonzalez-Paz N, Kyle RA, Santana-Davila R, Price-Troska T, Van Wier SA, *et al.* Genetic aberrations and survival in plasma cell leukemia. Leukemia 2008;22:1044-52.
4. Ramsingh G, Mehan P, Luo J, Vij R, Morgensztern D. Primary plasma cell leukemia: A surveillance, epidemiology, and end results database analysis between 1973 and 2004. Cancer 2009;115:5734-9.
5. Noel P, Kyle RA. Plasma cell leukemia: An evaluation of response to therapy. Am J Med 1987;83:1062-8.
6. Avet-Loiseau H, Daviet A, Brigaudeau C, Callet-Bauchu E, Terré C, Lafage-Pochitaloff M, *et al.* Cytogenetic, interphase, and multicolor fluorescence *in situ* hybridization analyses in primary plasma cell leukemia: A study of 40 patients at diagnosis, on behalf of the Intergroupe Francophone du Myélome and the Groupe Français de Cytogénétique Hématologique. Blood 2001;97:822-5.
7. Dadu T, Rangan A, Handoo A, Bhargava M. Primary non-secretory plasma cell leukemia with atypical

morphology – A case report. Indian J Hematol Blood Transfus 2009;25:81-3.

8. Gonsalves WI, Rajkumar SV, Go RS, Dispenzieri A, Gupta V, Singh PP, *et al.* Trends in survival of patients with primary plasma cell leukemia: A population-based analysis. Blood 2014;124:907-12.

9. Katodritou E, Terpos E, Kelaidi C, Kotsopoulou M, Delimpasi S, Kyrtsonis MC, *et al.* Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: Analysis of the Greek myeloma study group. Am J Hematol 2014;89:145-50.