ejpmr, 2022, 9(9), 44-49

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

PRIMARY PLASMA CELL LEUKAEMIA

***Abotaleb Alia A. MD**

Consultant Hematology, Division of Hematology-Oncology, Department of Medicine, King Fahd Armed Forces Hospital, Saudi Arabia.

***Corresponding Author: *Abotaleb Alia A. MD**

Consultant Hematology, Division of Hematology-Oncology, Department of Medicine, King Fahd Armed Forces Hospital, Saudi Arabia.

***Article* Received on 12/07/2022** **Article Revised on 02/08/2022** **Article Accepted on 23/08/2022**

ABSTRACT

Background: Plasma cell leukemia (PCL) is a rare and aggressive form of plasma cell disorder characterized by the presence of circulating plasma cells. It is classified as either primary PCL (pPCL) or as secondary PCL (sPCL). Intensive chemotherapy regimens and bortezomib-based regimens are recommended followed by high-dose therapy with autologous stem-cell transplantation (HDT/ASCT) if feasible. Because the incidence of PCL is relatively low and fulminant presentation, we are reporting this case. **Case Summery:** A 52-year-old Saudi woman with a history of hypertension, diabetes mellitus, dyslipidemia and morbid obesity presented with symptoms of anemia and recurrent community acquired pneumonia.Laboratory evaluation showed normocytic anemia, leukocytosis with 46% atypical lymphocytes, and normal platelets. Peripheral smear and flow cytometry confirmed PCL with 30% plasma cells. Bone marrow biopsy demonstrated 50% plasma cells (38+, 138+, 117+, 10-, 19-, 20-, 56-) and hypercellularity. Fish on bone marrow showed p53 in 40% of cells, deletion 13q in 30% of cells, duplication 1q and deletion 1p.VCD therapy was started then upgraded to VD-PACE regimen to be followed by autologous bone marrow transplantation but unfourtionatly deteriorated and died due to septic shock and multi-organ failure. **Conclusion:** PCL is the most aggressive variant of monoclonal gammopathy that carry a poor prognosis despite of all available treatment modalities. From what described in the literatures and by looking to our case, pPCL sometimes is difficult to be differentiated from sPCL, so we need more biological and immunohistochemistry tools in addition to more molecular studies to help in distinguish between these two forms. Multi-center studies and clinical trials should be conducted to develop accurate criteria for the early diagnosis and prompt treatment of this disease.

KEYWORDS: Case report, multiple myeloma, plasma cell leukemia, VD-PACE, VCD, ASCT.

INTRODUCTION

Plasma cell leukemia (PCL) is one of the most aggressive and rarest forms of plasma cell disorder characterized by the presence of 2×10^9/μL peripheral blood clonal plasma cells or > 20% plasma cells in the peripheral blood by Kyle's criteria. It is accounting for 0.6%-4% of all plasma cell neoplasms and is reported to occur in <1 in a million. PCL is classified as primary(pPCL) when it presents "de novo" in patients with no evidence of previous multiple myeloma (MM) and as secondary(sPCL) when it is occurring in patient with previous diagnosis of MM.[1-7] In this case, we describe the clinicopathologic, immunophenotypic and cytogenetic finding of our case report which diagnosed as pPCL at king Fahad military hospital, Jeddah, Saudi Arabia. and we compared with other reported cases.

CASE PRESENTATION

A 52 -years-old Saudi women known to have hypertension, diabetes mellites, dyslipidemia and morbid obesity. The patient had been well until 1year before this admission when recurrent infections began to occur.

Six months before admission, episodes of fever, shortness of breath and hemoptysis developed. The patient was admitted to our hospital on two occasions for community-acquired pneumonia. Laboratory evaluation revealed progressive reduction in her hemoglobin level with persistence of lymphocytosis, monocytosis and plasma cells in peripheral blood in addition to high total protein. Blood levels of electrolytes, glucose, amylase, lipase, were normal, as were results of renal-function tests, the prothrombin time, the international normalized ratio, and the partial-thromboplastin time; other laboratory test results are shown in (**Table 1**)

On this admission, her vitals were stable, physical examination revealed a pallid woman of large body habitus (BMI 45), and the remainder of physical examination was unremarkable. Laboratory results revealed WBC16x 10^9/μL (reference range, 3.3-10.8), Hb 6.53g/dL (reference range, 12-16), PLT 162x10/L(reference range,150-500), lymphocyte 7.4x10/L (reference range, 1.5-4), serum creatinine was 161.2umol/L (reference range, 28-174), LDH 246U/L

(reference range, 110-220 IU/L), calcium 2.11mmol/L (reference range, 2.11-2.57), serum total protein 107g/L (reference range, 66-83), albumin 28g/L (reference range, 37-50). Normal blood level of ferritin, vitamin B12, folate, electrolytes, glucose, and lactic acid were normal, as were results of liver-function tests and the prothrombin time, the international normalized ratio, and the partial-thromboplastin time.

Antibodies against HIV, HBV, and HCV were negative. Patient managed accordingly and referred to hematology when multiple myeloma workup and additional diagnostic tests were performed; other laboratory test results are shown in (**Table 1**)

Bone marrow biopsy and aspirate highlights 50% myeloma cell infiltrated (**Figure 1A and 1B**), with kappa restricted monoclonal plasmacytosis (38+, 138+, 117+, 10-, 19-, 20-, 56-) and 100% cellular. Peripheral smear showed more than 25% of plasma cells (**Figure 1C**), and flow cytometry of peripheral blood confirmed PCL with 30% plasma cells CD138+, CD38 with partial expression of CD117 and Kappa restricted (Figure 2).

Serum β2- Microglobulin 11.5mg/L (reference range, 0.6-2.4), erythrocyte sedimentation rate (ESR) 57mm/hr. Serum protein electrophoresis(SPE) and Immunofixation (IF): showed paraprotein in the gamma globulins, IgG 60.8g/L (reference range, 7.0-16.0), IgA 0.11g/L(reference range, 0.7-4.00), IgM 0.05g/L (reference range, 0.4-2.30), serum monoclonal IgG kappa, serum free kappa light chains 487.8mg/L (reference range, 3.3-19.40), free lambda light chain 2.8mg/L (reference range, 5.7-26.3), kappa/lambda ratio 174.2 (reference range, 0.26-26.3). Urine kappa free light chain 808.89mg/L (reference range, 4.9-32.7), urine lambda free light chain 5.4mg/L (reference range, 1.0-5.0), free K/L ratio 149.8 (reference range, 1-33).

Fish on bone marrow showed feature of high-risk disease positive p53 in 40% of cells, deletion 13q in 30% of cells, duplication 1q and deletion 1p in 35%, and negative IGH rearrangement. Cytogenetic was normal. Low dose whole body CT revealed no evidence of lytic lesion or sclerotic lesion to suggest multiple myeloma, scanning lung window show mild right pleural effusion with no suspicious lung nodule, scanning abdomen show evidence of hepatosplenomegaly, multiple small para-aortic lymph nodes and no ascites.

Patient was diagnosed with primary plasma cell leukemia (pPCL) and started on VCD (bortezomib, cyclophosphamide, prednisone) protocol and planned to be referred to transplant center after 2 cycles.

Treatment and outcome

Treatment with bortezomib- based chemotherapy VCD (bortezomib 1.5mg/m^2 iv once daily on days 1, 8, 15, and 22; cyclophosphamide 300mg/m^2 iv once daily on days 1, 8, 15, 22; and dexamethasone 40mg iv once daily on days 1,8,15,22) was initiated for two cycles, along with supportive therapies.

During first cycle of VCD patient showed an improvement in hematological and biochemical parameters in which circulating plasma cell reduced to 18% on day8 and no circulating plasma cell on day 30, SPE and IF: showed IgG 32.27.8g/L (reference range, 7.0-16.0), IgA 0.08g/L (reference range, 0.7-4.00), IgM 0.06g/L (reference range, 0.4-2.30), strong serum monoclonal band IgG kappa, serum free kappa light chains 253mg/L (reference range, 3.3-19.40), lambda light chain 2.07mg/L (reference range, 1.0-5.0), kappa/lambda ratio 122.5 (reference range, 0.26-26.3).

During the second cycle of chemotherapy her renal function is deteriorated with persistence need for transfusions. Thus, we started the second -line treatment with VD-PACE regimen (dexamethasone 40mg po daily on days 1-4; bortezomib 1.0mg/m^2 SC on days 1,4,8,11; Cisplatin 10mg/m^2/day iv on days 1-4; etoposide 40mg/m^2/day iv on days 1-4; cyclophosphamide 400mg/m^2/day iv on days 1-4; doxorubicin 10mg/m^2/day iv on days 1-4) but cisplatin was omitted due to renal impairment.

Later the patient condition rapidly deteriorated and ultimately died from neutropenic septic shock and multi-organ failure, 4 months after diagnosis of pPCL.

FINAL DIAGNOSIS

Primary Plasma Cell Leukemia (pPCL).

Table 1: Laboratory data[2]

Variables	Reference Range, Adult[1]	First admission	Second admission	This admission
Hemoglobin (g/dL)	12-16	6.4	6.20	6.5
Hematocrit (%)	36-46	21.3	23.40	21
MCV	80-100	87	87	98
Platelets (x10^9)	150-500	189	110	162
White blood cell (x10^9/L)	3.3-10.8	26.8	10.6	16
Differential count (x10^9/L)				
Neutrophils	2-7.5	10.4	3.09	4.23
Lymphocyte	1.5-4	13.9	6.90	7.4
Monocytes	0.2-0.8	1.87	2.48	4.17
Eosinophils	0-0.4	0.53	0.074	0.055

Basophils	0-0.2	0	0.003	0.004
Peripheral blood film		Lymphocytosis with monocytosis, occasional plasma cells with left shift. Normocytic anemia with hypochromia and Rouleau in red cells seen		More than 25% of plasma cells
Total protein (g/L)	66-83	101	108	107
Albumin (g/L)	37-50	33	32	28
Calcium (mmol/L)	2.11-2.57	NA	2.65	2.1
Lactate dehydrogenase (U/L)	125-220	551	…..	246
Creatinine (umol/L)	50-98	83.1	138	161
Uric Acid (umol/L)	150-350	….	….	320

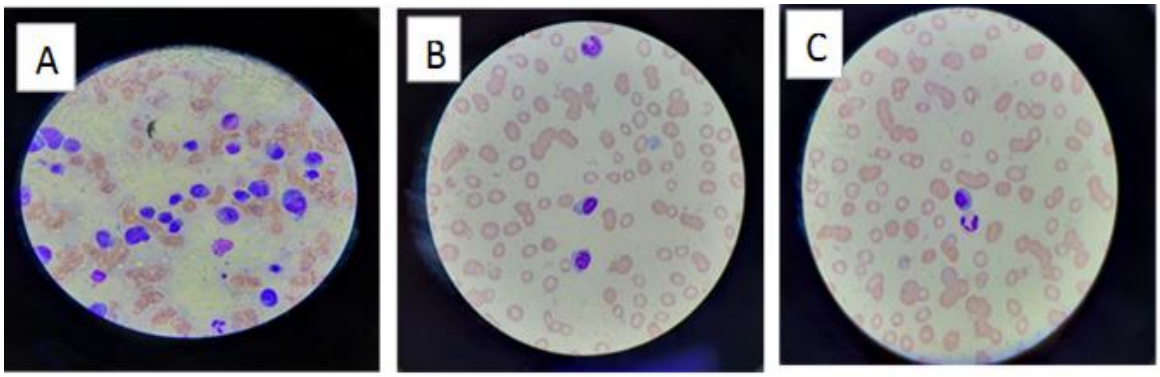

Figure 1: Bone Marrow–Biopsy Specimen, Bone Marrow Aspirate, and Peripheral-Blood Specimen.

Hematoxylin and eosin staining of a biopsy of the bone marrow biopsy (Panel A) and Wright-Giemsa staining of the bone marrow aspirate smear (Panel A) shows that bone marrow is 100% cellular, with marked increase in pleomorphic plasma cells at~50%. Wright's staining of peripheral- blood smear (Panel B and C), shows leukocytosis, plasma cells ~25% and hyper segmented neutrophils; Normocytic anemia with Marked Rouleaux in Red Cells; Platelet count appears decreased on blood film with occasional giant platelets, which consistent with plasma cell leukemia.

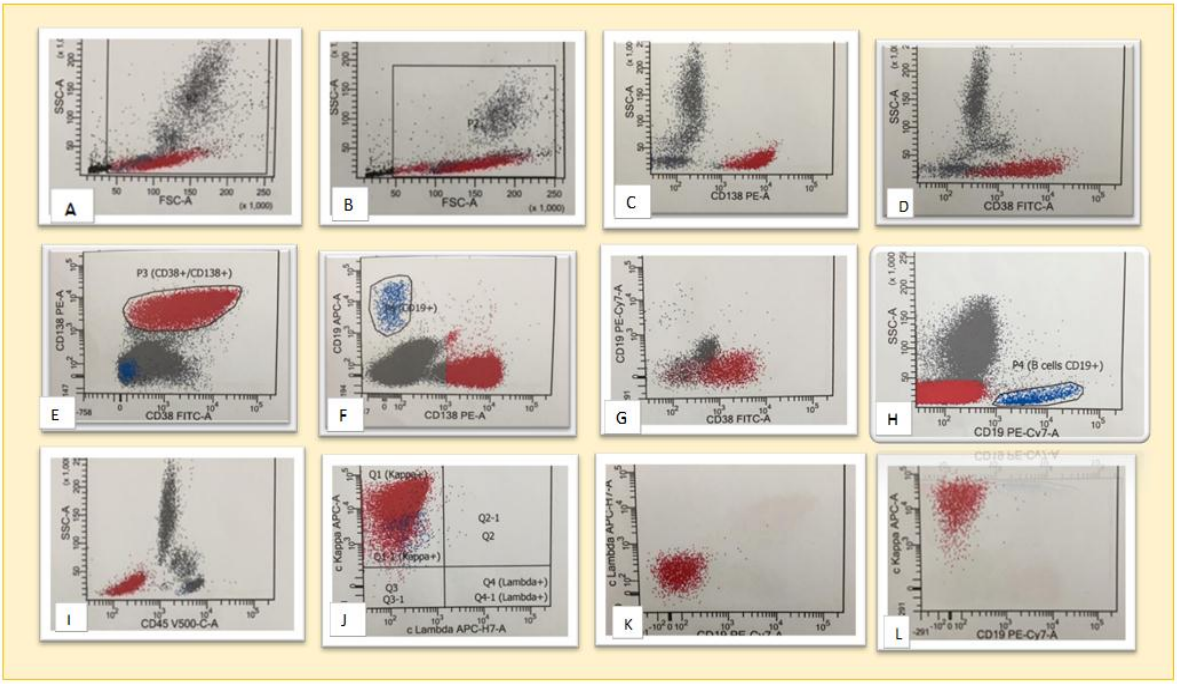

Figure 2: Flow cytometry of a peripheral blood sample detects a population of neoplastic plasma cell 27% of analyzed events (Panel A and B).The plasma cell co-express CD38, CD138 (Panel C through F) with dim CD45 (Pane I) and are Kappa restricted (Panel J through L). (Panel G and H) shows negative CD19.

DISCUSSION

Plasma cell leukemia (PCL) is established by the presence of > 20% circulating plasma cells or an absolute plasma cell count > 2×10^9/L on peripheral smear. It is a very uncommon and represent the most aggressive form of monoclonal gammopathy which has a poor prognosis and a rapidly fatal outcome. Complications usually lead to death within the first few months of diagnosis. Outcome is thought to be poor because of the absence of effective treatment for this condition.[1-8] PCL is classified as "primary" (pPCL), or "secondary" (sPCL) (occurring in patients with MM).

From our case we noticed that patient has circulating plasma cell in peripheral blood since the first admission but missed because it did not reach the diagnostic criteria for PCL, so I think that the diagnostic criteria of PCL should be revised to avoid underdiagnosis of the cases and to allow early detections and treatment.

lower peripheral blood plasma cell counts (i.e., ≥5% peripheral blood plasma cells and/or an absolute number ≥0.5×10^9/L) has been suggested by the International Myeloma Working Group (IMWG).[5]

From reviewing the literature, patients with (pPCL) are usually younger (aged 50-59 years) and has a predisposition to develop malignant plasma cells, which circulate in peripheral blood and lead to extra-medullary spread involving the liver, spleen, lymph nodes, pleura, peritoneum, and less often the bone, resulting in lytic lesions like our case. The extra-medullary spread is explained by negative CD56, a cell adhesion molecule which anchors plasma cells to the bone marrow stroma in contrast to MM, where most of the plasma cell population is found in bone marrow.[2-5,8] Hypercalcemia, low platelet count, and destruction of erythrocytes is found in both diseases, but it is more pronounced in PCL than in MM.

Plasma cell markers, which can be identified in PCL on immunophenotyping, include CD38 and CD138, which were both present in our patient. Flow cytometry should be performed on peripheral blood to confirm the presence of plasma cells that typically have immunophenotypes of CD138+, CD38+, CD19–, and CD45+/–.[2-5] Our finding of negative expression of CD10, CD19, CD20, CD56 was consistent with previously published cases and literature findings.

Again, our finding of fish which showed p53 in 40% of cells, deletion 13q to 30% of cells, duplication 1q and deletion 1p were consistent with pPCL and previously published cases Most pPCL patients have abnormal karyotypes at the time of diagnosis and usually hypodiploid or diploid cells which is associated with poor prognosis.[5] Chromosome 13 deletion and monosomy are the most frequent features Deletion of 17p13.1, causing allelic loss of *TP53*, has been detected in almost 50% of pPCL and in 75% of secondary forms in one report.[2-7]

Managing patients with PCL requires an intensive risk-adapted approach. Induction therapy with novel triplet therapy using immunomodulators and proteasome inhibitors such as VRd (bortezomib, lenalidomide, and dexamethasone) or KRd (carfilzomib, lenalidomide, and dexamethasone), is usually a satisfactory choice. In some patients with pPCL who have an aggressive form of disease, more aggressive combination regimen, such as VDT-PACE (bortezomib, dexamethasone, thalidomide or lenalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) or HyperCVAD (high dose cyclophosphamide, vincristine, adriamycin and thalidomide or lenalidomide) should be used, because cyclophosphamide and doxorubicin are particularly effective in proliferative disease. For elderly patients who may not be able to tolerate such an intense regimen, CyBorD (cyclophosphamide, bortezomib, and dexamethasone) or PAD (bortezomib, doxorubicin, and dexamethasone) can be used as a milder alternative.[2,10-14]

After induction therapy, autologous stem cell transplant (ASCT) is recommended (for transplant-eligible pPCL patients) to achieve prolonged disease control.[2,10-15]

Median survival has been estimated to be around 6-7 months with conventional chemotherapy. With autologous or allogeneic stem cell transplantation, survival has shown improvement to around three years. Less than 10% patients survive for more than five years.[2-5]

The presence of p53 deletion in a high level, 13q deletions, karyotypic complexity, hypodiploidy and 1q gains could define an advance stage on PCL disease progression characterized by therapy resistance and a dismal prognosis like our case.[2,3]

To the best of our knowledge, there have been approximately hundreds of pPCL reported cases, but no prospectively randomized controlled trials performed; thus, the biological, clinical, and prognostic features of this disease have remained unclear and there is no consensus regarding how to treat it.[2,6,7,8,15]

CONCLUSION

PCL is the most aggressive variant of monoclonal gammopathy and is a rare form of clonal plasma cell dyscrasia that carry a poor prognosis despite of all available treatment modalities. From what described in the literatures and by looking to our case, pPCL sometimes is difficult to be differentiated from sPCL, so we need more biological and immunohistochemistry tools in addition to more molecular studies to help in distinguish between these two forms. Despite of bortezomib- based chemotherapy regimen is one of the most recommended treatment of PCL, still our case did not respond, and this keep PCL is an aggressive disease with poor outcome. Multi-center studies and clinical

trials should be conducted to develop accurate criteria for the early diagnosis and prompt treatment of this disease.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived.

AUTHOR CONTRIBUTIONS

Authors contributed to the writing and the follow up of the case and read and agreed to the final version of this manuscript.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

REFERENCES

1. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol, 2003 Jun; 121(5): 749-57. PMID: 12780789.
2. Jelinek T, Kryukov F, Rihova L, Hajek R. Plasma cell leukemia: from biology to treatment. Eur J Haematol, 2015 Jul; 95(1): 16-26. doi: 10.1111/ejh.12533. Epub 2015 Mar 16. PMID: 25778450.
3. Albarracin F, Fonseca R. Plasma cell leukemia. Blood Rev, 2011 May; 25(3): 107-12. doi: 10.1016/j.blre.2011.01.005. Epub 2011 Feb 3. PMID: 21295388; PMCID: PMC3907188.
4. Jain AG, Faisal-Uddin M, Khan AK, Wazir M, Shen Q, Manoucheri M. Plasma cell leukemia - one in a million: A case report. World J Clin Oncol, 2019 Mar 24; 10(3): 161-165. doi: 10.5306/wjco.v10.i3.161. PMID: 30949445; PMCID: PMC6441660.
5. Fernández de Larrea C, Kyle RA, Durie BG, Ludwig H, Usmani S, Vesole DH, Hajek R, San Miguel JF, Sezer O, Sonneveld P, Kumar SK, Mahindra A, Comenzo R, Palumbo A, Mazumber A, Anderson KC, Richardson PG, Badros AZ, Caers J, Cavo M, LeLeu X, Dimopoulos MA, Chim CS, Schots R, Noeul A, Fantl D, Mellqvist UH, Landgren O, Chanan-Khan A, Moreau P, Fonseca R, Merlini G, Lahuerta JJ, Bladé J, Orlowski RZ, Shah JJ; International Myeloma Working Group. Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. Leukemia, 2013 Apr; 27(4): 780-91. doi: 10.1038/leu.2012.336. Epub 2012 Nov 21. PMID: 23288300; PMCID: PMC4112539.
6. Tiedemann RE, Gonzalez-Paz N, Kyle RA, Santana-Davila R, Price-Troska T, Van Wier SA, Chng WJ, Ketterling RP, Gertz MA, Henderson K, Greipp PR, Dispenzieri A, Lacy MQ, Rajkumar SV, Bergsagel PL, Stewart AK, Fonseca R. Genetic aberrations, and survival in plasma cell leukemia. Leukemia, 2008 May; 22(5): 1044-52. doi: 10.1038/leu.2008.4. Epub 2008 Jan 24. PMID: 18216867; PMCID: PMC3893817.
7. Ngu S, Asti D, Valecha G, Thumallapally N, Pant M, Bershadskiy A. Primary plasma cell leukemia: A case report and review of the literature. Clin Case Rep, 2019 Jul 30; 7(9): 1702-1708. doi: 10.1002/ccr3.2339. PMID: 31534731; PMCID: PMC6745387.
8. Singh S, Rath A, Yadav S. Primary Plasma Cell Leukaemia: Case report and review of the literature. Sultan Qaboos Univ Med J, 2018 Aug; 18(3): e397-e401. doi: 10.18295/squmj.2018.18.03.024. Epub 2018 Dec 19. PMID: 30607287; PMCID: PMC6307653.
9. Naseem S, Kaur S, Gupta R, Kashyap R, Nityanand S. Plasma cell leukemia: case series from a tertiary center with review of literature. Indian J Hematol Blood Transfus, 2012 Mar; 28(1): 10-4. doi: 10.1007/s12288-011-0097-8. Epub 2011 Jul 21. PMID: 23449039; PMCID: PMC3311967.
10. D'Arena G, Valentini CG, Pietrantuono G, Guariglia R, Martorelli MC, Mansueto G, Villani O, Onofrillo D, Falcone A, Specchia G, Semenzato G, Di Renzo N, Mastrullo L, Venditti A, Ferrara F, Palumbo A, Pagano L, Musto P. Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: a retrospective study from GIMEMA Multiple Myeloma Working Party. Ann Oncol, 2012 Jun; 23(6): 1499-502. doi: 10.1093/annonc/mdr480. Epub 2011 Oct 29. PMID: 22039089.
11. Avet-Loiseau H, Roussel M, Campion L, Leleu X, Marit G, Jardel H, Dib M, Decaux O, Lamy T, Tiab M, Cony-Makhoul P, Banos A, Lepeu G, Lifermann F, Macro M, Kolb B, Hulin C, Caillot D, Traulle C, Mathiot C, Royer B. Cytogenetic and therapeutic characterization of primary plasma cell leukemia: the IFM experience. Leukemia, 2012 Jan; 26(1): 158-9. doi: 10.1038/leu.2011.176. Epub 2011 Jul 29. PMID: 21799511.
12. Niels W. C. J. van de Donk,1,2 Henk M. Lokhorst,2 Kenneth C. Anderson,1 and Paul G. Richardson1. How I treat plasma cell leukemia.Blood First Edition paper, July 26, 2012; DOI 10.1182/blood-2012-05-408682.
13. Kim SJ, Kim J, Cho Y, Seo BK, Kim BS. Combination chemotherapy with bortezomib, cyclophosphamide and dexamethasone may be effective for plasma cell leukemia. Jpn J Clin Oncol, 2007 May; 37(5): 382-4. doi: 10.1093/jjco/hym037. Epub 2007 May 30. PMID: 17538191.
14. Katodritou E, Verrou E, Gastari V, Hadjiaggelidou C, Terpos E, Zervas K. Response of primary plasma cell leukemia to the combination of bortezomib and dexamethasone: do specific cytogenetic and immunophenotypic characteristics influence treatment outcome? Leuk Res, 2008 Jul; 32(7):

1153-6. doi: 10.1016/j.leukres.2007.11.010. Epub 2008 Feb 20. PMID: 18083228.

15. Jimenez-Zepeda VH, Dominguez-Martinez VJ. Plasma cell leukemia: a highly aggressive monoclonal gammopathy with a very poor prognosis. Int J Hematol, 2009 Apr; 89(3): 259-268. doi: 10.1007/s12185-009-0288-3. Epub 2009 Mar 27. PMID: 19326058.