

## Case report

# Plasma cell leukemia with t(11;14)(q13;q32) simulating lymphoplasmacytic lymphoma – a diagnostic challenge solved by flow cytometry



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## ARTICLE INFO

### Article history:

Received 6 September 2016

Accepted 10 October 2016

Available online 22 December 2016

## Introduction

Plasma cell leukemia (PCL) is a rare and aggressive manifestation of malignant plasma cell proliferation and corresponds to 2–4% of multiple myeloma (MM) cases.<sup>1,2</sup> The World Health Organization (WHO) defines PCL by the presence of high levels (at least  $2 \times 10^9/L$ ) of clonal plasma cells in the peripheral blood (PB) or at least 20% of the leukocyte differential count.<sup>1</sup> Primary PCL (pPCL) corresponds to 60% of the cases and presents as leukemia at diagnosis, usually with tissue infiltration, organomegaly and lymphadenopathy and a lower frequency of bone lesions (15–40% cases) than multiple myeloma.<sup>2</sup> Secondary PCL is the terminal phase of MM and corresponds to the remaining 40% of PCL cases; it usually has a poor response to standard MM treatment.<sup>2,3</sup> The diagnosis of plasma cell neoplasms is easily suggested by the characteristic plasma cell

morphology, both in MM and in PCL. The great contribution of immunophenotyping by flow cytometry (FC) in such disorders depends on differentiating normal from neoplastic plasma cells.<sup>4,5</sup> However, in rare cases of MM with atypical morphology the differential diagnosis with other lymphoproliferative disorders may be a challenge. Here, we present a case of pPCL in which the diagnosis of lymphoplasmacytic lymphoma (LPL) was initially suggested by morphology of peripheral blood (PB) and bone marrow (BM) cells (aspirate and biopsy) with the final diagnosis of pPCL being established by FC.

## Case report

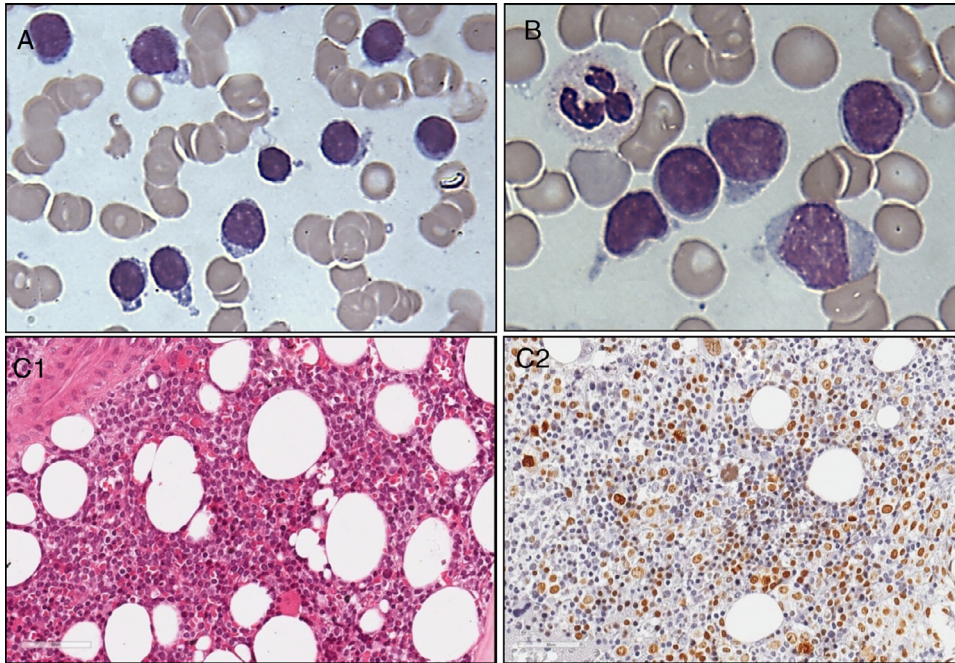
A 77-year-old female patient consulted in the Rheumatology Service of the Hospital São Paulo for osteoporosis and was referred to the Hematology Clinic to investigate

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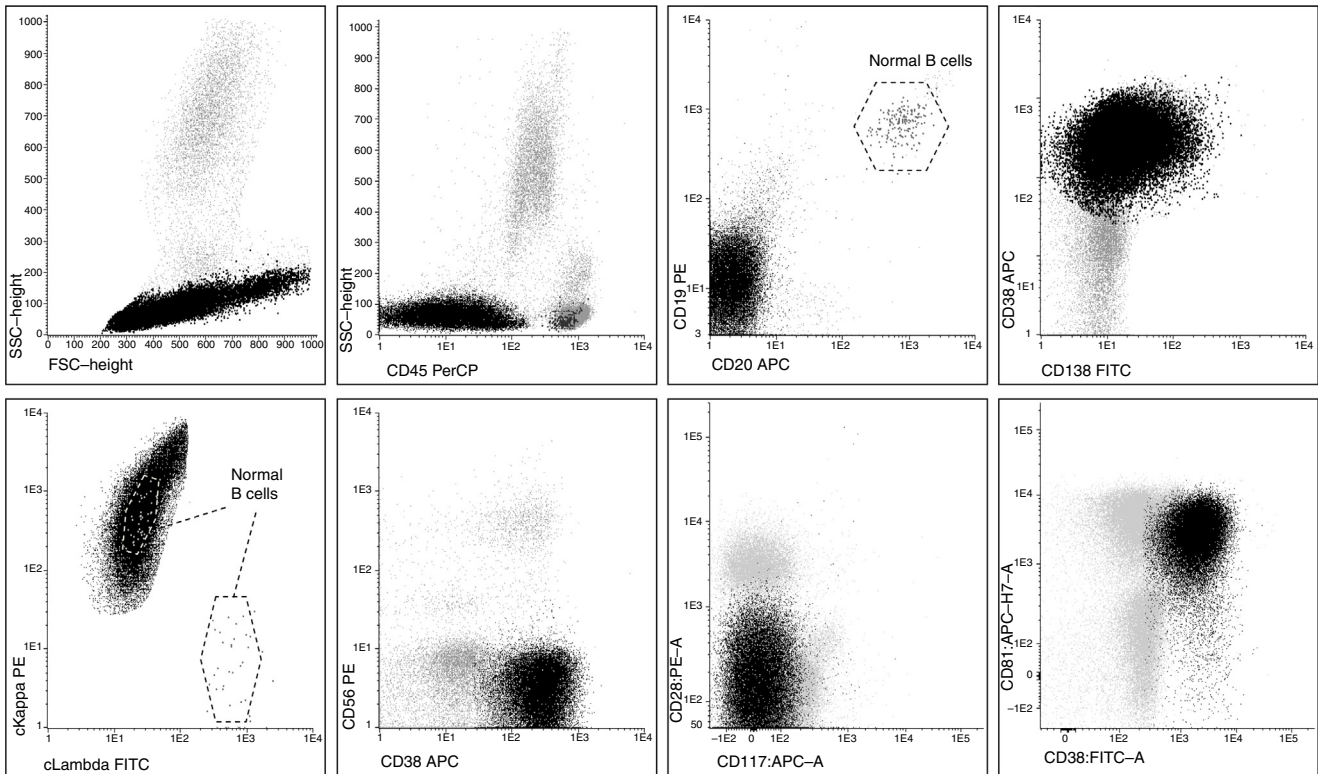
E-mail address: [yamamoto@unifesp.br](mailto:yamamoto@unifesp.br) (M. Yamamoto).

<http://dx.doi.org/10.1016/j.bjhh.2016.10.001>

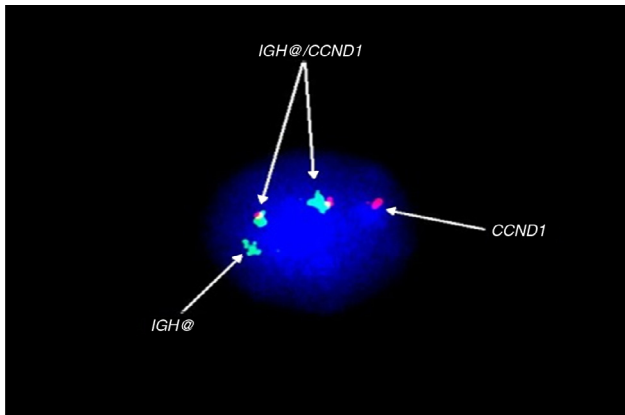
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**Figure 1 - Neoplastic cell morphology in peripheral blood (A) and bone marrow aspirate films (B) showing small- to medium-sized lymphoplasmacytic lymphocytes (May Grunwald Giemsa stain, 1000x). Bone marrow biopsy (C) replaced by medium-sized lymphocytes (C1; Hematoxylin and eosin stain, 400x) and immunohistochemistry expression of Ki67 of tumor cells (C2; immunoperoxidase, 400x).**



**Figure 2 - Flow cytometry dot plots of the circulating plasma cells (in black dots) showing small- to large-sized clonal plasma cells expressing (forward/side scatter of light) CD45<sup>-</sup>, CD19/CD20<sup>-</sup>, CD38<sup>++</sup>/CD138<sup>+</sup> heterogeneous and cκ<sup>+</sup>/λ<sup>-</sup>. Neoplastic cells also expressed CD81 but were negative for CD56, CD28 and CD117. Normal B cells (in dashed lines) are CD45<sup>+</sup>, CD19/CD20<sup>+</sup> and polyclonal (κ<sup>+</sup> and λ<sup>+</sup> populations).**



**Figure 3 – FISH using probes for the CCND1 gene (red) and IGH gene (green), and red and green fusion, corresponding to IGH-CCND1 rearrangement.**

anemia. At physical examination, she was in good general condition without palpable lymph nodes, or liver or spleen enlargement. The complete blood count showed: Hemoglobin = 10.1 g/dL; Hematocrit = 32.4%; white blood cell count  $8.6 \times 10^9/L$  (neutrophils: 37%; lymphocytes: 58%) and platelet count  $140 \times 10^9/L$ . Morphological analysis of the PB smear showed small- to moderate-sized lymphoplasmacytoid lymphocytes (75% of the lymphocytes) with basophilic cytoplasm and 1 to 2 nucleoli (Figure 1A). BM aspirate showed 90% of lymphocytes with the same characteristics and 5.6% of typical plasma cells (Figure 1B). BM biopsy showed hypercellular marrow with 80% of young, small- to medium-sized lymphoid cells (Figure 1C). BM immunohistochemistry was inconclusive: tumor cells were negative for all of the following antigens: CD45, CD3, CD5, CD10, CD20, CD23, CD30, CD79a, CD138, PAX 5, CD1A, CD56, TdT, kappa, lambda and cyclin D1, but the Ki67 was positive in about 40% of cells. The other laboratorial tests showed total serum proteins of 10.2 g/dL, albumin of 3.83 g/dL and monoclonal peak in the gamma globulin region (4.4 g/dL) that was identified as IgG by immunofixation; normal total serum Ca (10.8 mg/dL) with ionic Ca 1.45 mM/L (normal 1.15–1.32 mM/L) and increased beta-2 microglobulin (4.7 mg/L). Lytic lesions were seen on skull X-ray. Immunophenotyping by FC of BM cells showed the presence of clonal plasma cells (40%) expressing CD38, CD138<sup>dim</sup>, cykappa, smkappa,  $\beta$ -2 microglobulin and CD81, and were negative for CD45, CD56, CD19, cylambda, CD28 and CD117, suggesting a plasma cell malignancy despite the morphologic features of LPL (Figure 2). Small B lymphocytes (1.17%) expressed the normal B cell phenotype (CD 45<sup>++</sup>, CD 19<sup>+</sup>, CD20<sup>++</sup>, CD79b<sup>+</sup>, CD24<sup>+</sup>, FMC-7<sup>-</sup>, smKappa<sup>+</sup>/smLambda<sup>+</sup> ratio of 2:1, and negative for the CD5, CD10, CD11c, CD23, CD200, CD38, CD43 antigens). The final diagnosis was PCL, IgG kappa. A fluorescent in situ hybridization (FISH) study was positive for cyclin D1 (PRAD1, CCND1)/IGH rearrangement, showing the presence of t(11;14)(q13;q32) (Figure 3). Considering the age of the patient (>70 years old) and transplant ineligibility, the treatment option was melphalan, thalidomide and dexamethasone. However, the patient evolved with worsening of performance status and gastric discomfort and she

decided to stop the thalidomide. Due to the worsening of her clinical condition, it was decided to use only dexamethasone (40 mg/week) and close monitoring of her clinical condition. After three months, the patient suffered a pathological femur fracture and eventually died of pulmonary sepsis.

## Discussion

pPCL is a rare disease that affects younger individuals; it has a subacute onset and patients have a poorer performance status (ISS 3 in about 60% of cases) at diagnosis than those with MM.<sup>1,2,6</sup> There is a high incidence of anemia and thrombocytopenia due to the suppression of normal hematopoiesis in the BM which is usually greatly infiltrated.<sup>2,4,6</sup> Moreover, pPCL has a higher incidence of extramedullary involvement that appears to be a result of a lower expression of cell adhesion molecules, such as CD56, facilitating the release of leukemic plasma cells from the BM microenvironment.<sup>4,5</sup> Our patient had no evidence of extramedullary disease at diagnosis, but she presented mild anemia and was under treatment for osteoporosis. Her BM biopsy showed extensive involvement by lymphoplasmacytoid cells that had the same characteristics as in the PB, which sometimes makes the differential diagnosis between LPL and PCL difficult by morphological analysis alone. Immunohistochemistry was inconclusive as, unexpectedly, the expression of CD138 was negative in neoplastic cells. The reasons for this may be due to down-regulation of the antigen or the sample preparation process. In this particular case, FC had a key role in establishing the correct diagnosis.<sup>4,5,7,8</sup> Normal plasma cells are CD19<sup>+</sup>/CD45<sup>+</sup>/CD38<sup>bright</sup>/CD56<sup>-</sup> while neoplastic plasma cells are usually CD19<sup>-</sup>/CD45<sup>-</sup>/CD38<sup>+</sup>/CD56<sup>+</sup>.<sup>5,8</sup> However, as seen in the present case, PCL cells show a low expression of the cell adhesion molecule CD56 suggesting a worse prognosis; this was associated with the presence of neoplastic cells in the PB.<sup>4,9</sup> LPL is morphologically characterized by the presence of small plasmacytoid lymphocytes and some plasma cells in which the immunophenotype usually resembles the normal lymphocytes and plasma cells except for clonal restriction and CD25<sup>+/-</sup> and CD138<sup>+/-</sup> expression. This differs from the immunophenotype profile of neoplastic plasma cells found in this case.<sup>1,7,8,10</sup>

Furthermore, FC can also give additional information related to the prognosis in plasma cell neoplasms. The expressions of B2 microglobulin and CD81, both positive in the current case, and the absence of CD45 are related to an adverse prognosis.<sup>5,11</sup> Expression of CD28 represents an aggressive phenotype associated with tumor expansion and shorter disease free survival.<sup>5</sup> In our patient, the malignant cells expressed an unfavorable immunophenotypic profile except for the absence of CD28. Plasma cells, either normal or malignant, usually express CD138, but malignant plasma cells may have dim expression of this marker, which may be due to down-regulation of this antigen. Importantly, the cytogenetic alteration detected in this case is described in approximately 20% of all plasma cell neoplasms.<sup>2,3</sup> The presence of t(11;14)(q13;q32) reflects the juxtaposition of the proto-oncogene cyclin D1 (CCND1) at 11q13 with the immunoglobulin heavy chain (IGH) gene) at 14q32 and is associated with a longer

overall survival.<sup>2,12</sup> However, the expected overexpression of cyclin D1 was not identified in the BM biopsy specimen, probably due to antigen retrieval problems after the decalcification of the sample. Additionally, the presence of this abnormality in plasma cell neoplasms is usually associated with the atypical morphologic appearance of LPL reported in 50% of the cases.<sup>6</sup> Furthermore, lack of expressions of CD56 and CD117 have been associated to plasma cell malignancies in patients with t(11;14), as previously described.<sup>9</sup> Of interest, the MYD88 L265P somatic mutation, present in >90% of patients with LPL/Waldenström's macroglobulinemia and also in non-IgM LPL, is useful to differentiate these disorders from MM, including IgM secreting myeloma, and some other B-cell malignancies.<sup>13</sup> This study was not carried out in the present case because the diagnosis of PCL was quickly concluded by FC. In conclusion, the present clinical case illustrates the rare presentation of PCL with atypical morphology and highlights the importance of FC in the differential diagnosis between PCL and LPL. Additionally t(11;14)(q13;q32) by FISH, increased the information not only about the diagnosis but about the prognosis.

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### Conflict of interest

The authors declare no conflict of interest.

### REFERENCES

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- Mckenna RW, Kyle RA, Kuehl WM, Grogan TM, Harris NL, Coupland RW. Plasma cell neoplasms. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. fourth edition Lion: IARC; 2008. p. 200-13.
- Fernández de Larrea C, Kyle RA, Durie BG, Ludwig H, Usmani S, Vesole DH, et al. Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. *Leukemia*. 2013;27(4):780-91.
- 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(5):1044-52.
- García-Sanz R, Orfao A, González M, Tabernero MD, Bladé J, Moro MJ, et al. Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. *Blood*. 1999;93(3):1032-7.
- Raja KR, Kovarova L, Hajek R. Review of phenotypic markers used in flow cytometric analysis of MGUS and MM, and applicability of flow cytometry in other plasma cell disorders. *Br J Haematol*. 2010;149(3):334-51.
- Fonseca R, Blood EA, Oken MM, Kyle RA, Dewald GW, Bailey RJ, et al. Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients. *Blood*. 2002;99(10):3735-41.
- Rawstron AC, Orfao A, Beksac M, Bezdicikova L, Brooimans RA, Bumbea H, et al. Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders. *Haematologica*. 2008;93(3):431-8.
- Bataille R, Jégo G, Robillard N, Barillé-Nion S, Harousseau JL, Moreau P, et al. The phenotype of normal, reactive and malignant plasma cells. Identification of many and multiple myelomas and of new targets for myeloma therapy. *Haematologica*. 2006;91(9):1234-40.
- Mateo G, Montalbán MA, Vidriales MB, Lahuerta JJ, Mateos MV, Gutiérrez N, et al. Prognostic value of immunophenotyping in multiple myeloma: a study by the PETHEMA/GEM cooperative study groups on patients uniformly treated with high-dose therapy. *J Clin Oncol*. 2008;26(16):2737-44.
- Konoplev S, Medeiros LJ, Bueso-Ramos CE, Jorgensen JL, Lin P. Immunophenotypic profile of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia. *Am J Clin Pathol*. 2005;124(3):414-20.
- Paiva B, Gutiérrez NC, Chen X, Vidriales MB, Montalbán M, Rosiñol L, et al. Clinical significance of CD81 expression by clonal plasma cells in high-risk smoldering and symptomatic multiple myeloma patients. *Leukemia*. 2012;26(8):1862-9.
- Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2016;91(7):719-34.
- Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N Engl J Med*. 2012;367(9):826-33.