



Case Report

Hairy cell leukemia variant: the importance of differential diagnosis



Renata Cristina Messores Rudolf-Oliveira, Mayara Marin Pirolli,
Fernanda Santos de Souza, Juliana Michels, Maria Cláudia Santos-Silva*

Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil

ARTICLE INFO

Article history:

Received 25 August 2014

Accepted 4 October 2014

Available online 11 February 2015

Introduction

Hairy cell leukemia is a rare disease comprising about 2% of lymphoid neoplasms.¹ This neoplasm can be confused with other hematologic diseases. Therefore, a differential diagnosis must be performed between classic hairy cell leukemia, hairy cell leukemia variant, and splenic marginal zone lymphoma (SMZL).² According to the World Health Organization (2008), hairy cell leukemia variant was classified as a provisional entity because it has clinical and pathological features that differ from classic hairy cell leukemia.³ Among these aspects are morphological and immunophenotypic variations and resistance to conventional treatment.¹ Furthermore, patients with hairy cell leukemia are treated with nucleoside analogs but these drugs have a reduced response in hairy cell leukemia variant and are even ineffective in some cases.^{3,4} An alternative for these patients is the association of nucleoside analogs with the monoclonal antibody rituximab (anti-CD20).⁵ Thus, due to differential treatment, the aim of this study was to report a case of hairy cell leukemia variant and cover some aspects related to the differential diagnosis between the classic and variant forms of the disease and SMZL. This study was

approved by the Research Ethics Committee of the Universidade Federal de Santa Catarina (#913/2010).

Case report

The case of a 74-year-old male patient is reported. The presence of splenomegaly was observed since 2011, with areas of infarction in the splenic periphery evidenced by cholangiography and computed tomography. In 2012, due to the persistence of splenomegaly, a complete blood count and immunophenotyping by flow cytometry were requested. At this time, there was no lymphadenopathy. The blood count showed alterations in red blood cells (poikilocytosis, acanthocytes and squizocytes), anemia (hemoglobin 10.1 g/dL), thrombocytopenia ($100 \times 10^3/\text{mL}$), and mild leukocytosis ($11.03 \times 10^3/\text{mL}$). A white blood cell differential revealed the following: 2.86×10^3 neutrophils/mL (25.9%), 4.67×10^3 lymphocytes/mL (42.3%), 1.16×10^3 monocytes/mL (10.5%), 1.73×10^3 eosinophils/mL (15.7%), 0.07×10^3 basophils/mL (0.6%) and 0.55×10^3 lymphocytes/mL (5.0%) with cytoplasmic projections (Figure 1). Immunophenotyping of peripheral blood (Figure 2) showed 23.2% of B lymphocytes

* Corresponding author at: Divisão de Análises Clínicas, Hospital Universitário Professor Polydoro Ernani de São Thiago, Universidade Federal de Santa Catarina (UFSC), Campus Universitário, s/n°, Trindade, 88036-800 Florianópolis, SC, Brazil.

E-mail address: maria.claudia.silva@ufsc.br (M.C. Santos-Silva).

<http://dx.doi.org/10.1016/j.bjhh.2015.01.003>

1516-8484/© 2015 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved.

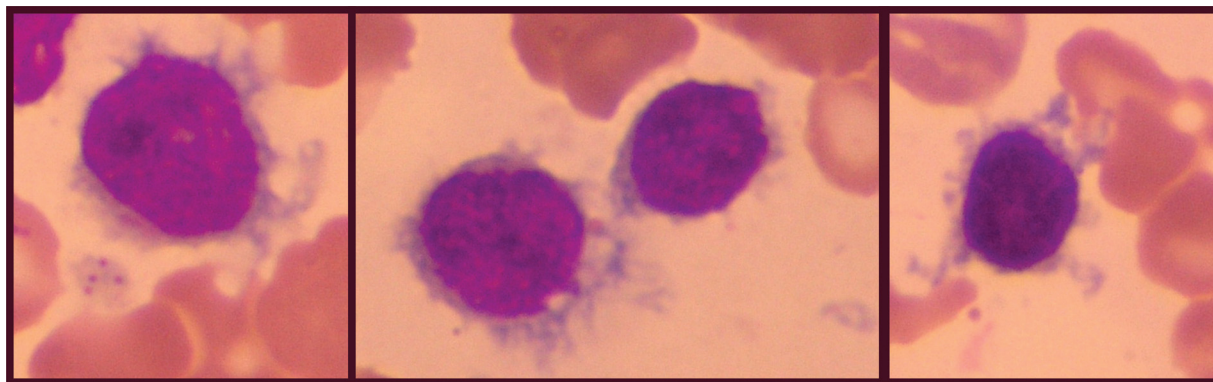


Figure 1 – Small/intermediate-sized cells with moderate pale-gray cytoplasm, round/oval nuclei with smooth nuclear borders, stippled chromatin, occasional nucleoli, cells have circumferential hair-like and short, blunt cytoplasmic projections.

(CD19⁺), monoclonal (sIg Kappa⁺), CD103⁺, CD11c⁺, CD20⁺⁺, CD22⁺, IgM^{+/++} FMC7⁺⁺, CD79b⁺⁺, BCL2⁺ and no expression of sIg Lambda, CD3, CD4, CD5, CD8, CD10, CD23, CD24, CD25, CD27, CD38, CD43, and CD123. Assessment of sIgD, sIgG, and sIgA expression on the pathological lymphocytes was not performed. The bone marrow was not evaluated and staging was not performed during diagnosis. The treatment was four intravenous doses of rituximab 600 mg. After the first dose, the patient was discharged and the response was monitored in the outpatient clinic. At the end of the treatment, the patient returned to the hospital and underwent a bone marrow aspiration for immunophenotyping, myelogram, and immunohistochemistry. Immunophenotyping showed 1.1% of B lymphoid cells with a similar phenotype to that found

at diagnosis (Figure 2). The myelogram showed hypercellularity for the age, normal myeloid:erythroid ratio, as well as normality for all other myelogram parameters. Immunohistochemistry revealed aggregates of small lymphocytes CD20⁺ and DBA44^{-/+} and the result of TRAP staining was indeterminate. Currently, the patient is being treated in the outpatient clinic and undergoes periodic laboratory tests to monitor the disease.

Discussion

Classic hairy cell leukemia, hairy cell leukemia variant, and SMZL share some common features, including malignant

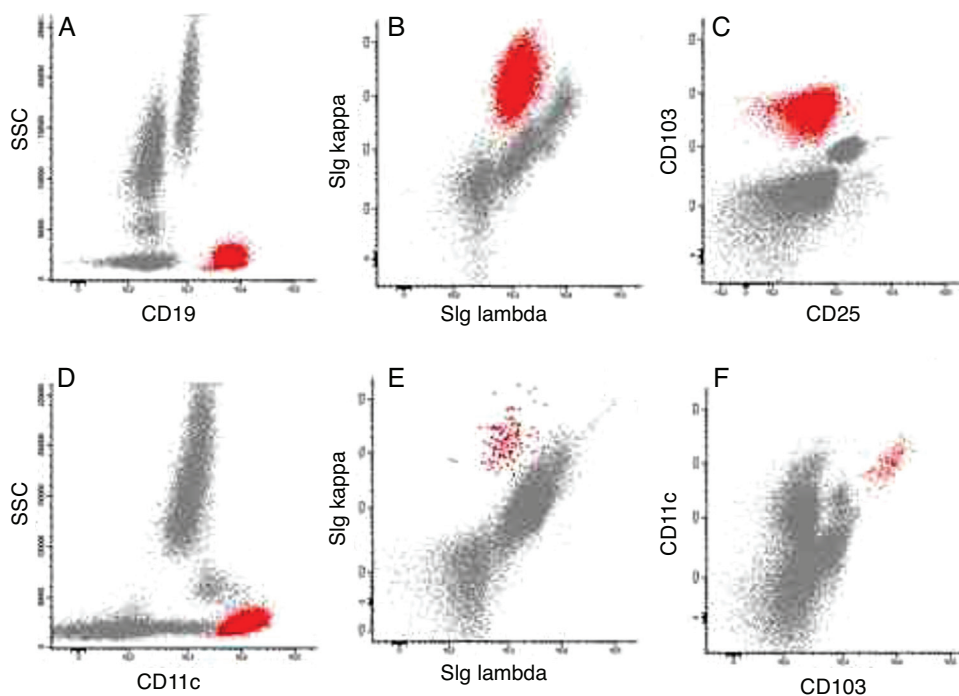


Figure 2 – Representative dot plots of peripheral blood immunophenotyping. (A) Pathological cells (red) CD19⁺ at diagnosis; (B) pathological cells (red) sIg Kappa⁺ and sIg Lambda⁻ at diagnosis; (C) pathological cells (red) CD103⁺ and CD25⁻ at diagnosis; (D) pathological cells (red) CD11c⁺ at diagnosis; (E) pathological cells (red) sIg Kappa⁺ and sIg Lambda⁻ in minimal residual disease; (F) pathological cells (red) CD103⁺ and CD11c⁺ in minimal residual disease.

Table 1 – Comparison between classic hairy cell leukemia, hairy cell leukemia variant, and SMZL.

	Classic hairy cell leukemia	Hairy cell leukemia variant	Splenic marginal zone lymphoma
Age	Midlife	Over 50 years	Over 50 years
Gender prevalence	Males	No difference	No difference
Granulocytopenia and monocytopenia	Present	Usually absent	Usually absent
Morphology	Bone marrow and peripheral blood: small- or medium-sized cells; presence of oval or bean-shaped nucleus; homogeneous, less aggregated chromatin; absent or inconspicuous nucleoli; cytoplasm is abundant, basophilic without granules or villous projections	Bone marrow cells: similar to the classic hairy cell leukemia cells. Peripheral blood: small cells; round or oval nucleus; nucleus:cytoplasm ratio is greater; evident nucleolus; moderately basophilic, villous cytoplasm	Bone marrow and peripheral blood: small- and medium-sized cells; slightly basophilic cytoplasm; moderately condensed chromatin and indistinct nucleoli; polar cytoplasmic projections (villi) may appear
Spleen	Infiltration of the red pulp	Infiltration of the red pulp	Infiltration of the white pulp
Bone marrow	Dry tap	Easy aspiration	Easy aspiration
TRAP	Positive	Negative	Negative
Annexin A1	Positive	Negative	Negative
Immunophenotype	CD25 ⁺ , CD103 ⁺ , CD11c ⁺ , CD19 ⁺ , CD20 ⁺ , CD22 ⁺ , CD79a ⁺ , FMC7 ⁺ , sIg ⁺ , Kappa predominance, CD10 variable, CD79b ⁻ , CD5 ⁻ , CD23 ⁻	CD25 ⁻ CD103 variable, CD19 ⁺ , CD20 ⁺ , CD22 ⁺ , CD11c ⁺ , IgG ⁺ , IgA ⁺ , FMC7 ⁺	CD25 variable, CD103, CD19 ⁺ , CD20 ⁺ , CD22 ⁺ , CD79a ⁺ , IgM ⁺ , IgD ⁺ , CD5 ⁻ , CD10 ⁻ , CD23 ⁻ , CD43 ⁻ , cyclin D1 ⁻

lymphocytic infiltration in bone marrow and peripheral blood, splenomegaly, and B lymphocytes with a similar immunophenotype.⁵ Unlike classic hairy cell leukemia, the variant form affects older individuals.¹

Anemia and/or thrombocytopenia and leukocytosis are common at diagnosis of hairy cell leukemia variant, while pancytopenia, granulocytopenia, and monocytopenia are more common in classic hairy cell leukemia. The patient in this study presented with anemia, thrombocytopenia, and mild leukocytosis due to monocytosis, eosinophilia and the presence of pathological lymphocytes.

Immunophenotyping by flow cytometry contributes to differential diagnosis, although it must also be associated with immunohistochemistry and clinical data (Table 1). Classic hairy cell leukemia cells are always positive for CD25 and CD103 and hairy cell leukemia variant cells are always negative for CD25 and occasionally positive for CD103. In SMZL, on the other hand, CD103 is negative and CD25 may be positive or negative.^{3,5} Classic hairy cell leukemia and the variant form are also differentiated by the expression of CD123, which is positive in the classic form and negative in the variant form.⁶ Evaluation of immunoglobulin heavy chain isotype expression is another way to possibly differentiate hairy cell leukemia variant from SMZL. An unusual feature of hairy cell leukemia variant, not typically observed in other B-cell lymphoproliferative disorders, is the expression of pre-switched IgM/IgD and post-switched IgG/IgA immunoglobulins by the same cells in approximately 40% of cases. In contrast, SMZL cells characteristically express IgM with IgD and lack IgG or IgA.⁷ Unfortunately in this case the IgG, IgA and IgD immunoglobulins were not available for evaluation. Thus, the results of immunophenotypic analysis of peripheral blood here were consistent with hairy cell leukemia variant.

In immunohistochemistry, DBA44 provides strong staining for lymphocytes with cytoplasmic projections in tissues; however, it may also be present in normal B cells.³ Moreover, cells from hairy cell leukemia variant patients rarely show TRAP reactivity (unlike the classic form).¹ In the patient of this study, TRAP staining remained indeterminate; hence, it did not help in the diagnosis. The morphology and phenotype confirmed the diagnosis of hairy cell leukemia variant.

When the patient returned to the hospital of the Universidade Federal de Santa Catarina (HU-UFSC) at the end of treatment, the myelogram was hypercellular for his age, but this alteration has no clinical relevance to his condition. The presence of 1.1% of cells with a phenotype similar to that found at diagnosis, as evidenced by immunophenotyping of a bone marrow aspirate, indicates the presence of minimal residual disease (MRD). MRD is present in many patients treated for hairy cell leukemia; however, these patients may have long-term survival. Treatment with Rituximab is used to achieve complete remission, although the response is dependent on how much bone marrow is involved and on the characteristics of the individual.⁸

Conclusion

Hairy cell leukemia variant is a chronic lymphoproliferative disorder whose characteristics resemble the classic form and SMZL, making differential diagnosis essential for therapeutic follow-up, as hairy cell leukemia variant has a decreased response to drugs prescribed for the classic form. Immunophenotyping is a key tool for diagnosis, as some markers are different between these neoplasms. Therefore, immunophenotyping, clinical, morphological, and immunohistochemical manifestations must be considered in the differential diagnosis.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Hsieh YC, Chang ST, Chuang SS, Lu CL, Tsao CJ, Li GN, et al. Hairy cell leukemia and variant in Taiwan: report of a variant case and literature review. *Int J Clin Exp Pathol.* 2011;1(4): 183-9.
2. Fino P, Fioramonti P, Onesti MG, Passaretti D, Scuderi N. Skin metastasis in patient with hairy cell leukemia: case report and review of literature. *In Vivo.* 2012;2(26):311-4.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Geneva: WHO Press; 2008.
4. Palomera L, Domingo JM, Sola C, Azaceta G, Calvo MT, Gutierrez M. Cladribine (2-chlorodeoxyadenosine) therapy in hairy cell leukemia variant. A report of three cases. *Haematologica.* 2002;87(1):107-8.
5. Robak T. Hairy-cell leukemia variant: recent view on diagnosis, biology and treatment. *Cancer Treat Rev.* 2011;37(1): 3-10.
6. Venkataraman G, Aguhar C, Kreitman RJ, Yuan CM, Stetler-Stevenson M. Characteristic CD103 and CD123 expression pattern defines hairy cell leukemia: usefulness of CD123 and CD103 in the diagnosis of mature B-cell lymphoproliferative disorders. *Am J Clin Pathol.* 2011;136(4):625-30.
7. Cessna MH, Hartung L, Tripp S, Perkins SL, Bahler DW. Hairy cell leukemia variant: fact or fiction. *Am J Clin Pathol.* 2005;123(1):132-8.
8. Grever MR, Lozanski G. Modern strategies for hairy cell leukemia. *J Clin Oncol.* 2011;5(29):583-90.