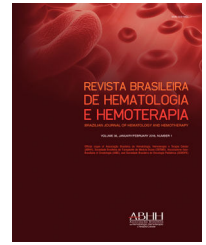




Revista Brasileira de Hematologia e Hemoterapia Brazilian Journal of Hematology and Hemotherapy

www.rbhh.org



Case Report

Concomitant chronic myeloid leukemia and monoclonal B cell lymphocytosis – a very rare condition



Sara Duarte^{a,b,*}, Sónia Campelo Pereira^a, Élio Rodrigues^a, Amélia Pereira^a

^a Internal Medicine Service, District Hospital of Figueira da Foz, EPE, Figueira da Foz, Portugal

^b Clinical Hematology Department, University Hospital Center of Coimbra, Coimbra, Portugal

ARTICLE INFO

Article history:

Received 3 November 2016

Accepted 13 February 2017

Available online 11 March 2017

Introduction

Chronic lymphocytic leukemia (CLL) is the commonest leukemia in adults. It is defined, according to the latest guidelines, as $>5 \times 10^3/\mu\text{L}$ circulating B lymphocytes (BL) expressing a typical cell surface marker signature (CD5⁺, CD10⁻, CD19⁺ and CD20^{dim}, surface immunoglobulin^{dim}, CD23⁺, CD43^{+/-} and cyclin D1⁻).¹ If lymph node enlargement and/or hepatosplenomegaly is present in a patient with $<5 \times 10^3/\mu\text{L}$ monoclonal circulating BL, the diagnosis of small lymphocytic lymphoma (SLL) is reached and treatment may be required.² The identification of CLL-like cells in healthy people due to increasingly more sensitive immunophenotyping methods led to the definition in the 2008 World Health Organization (WHO) classification of lymphoid neoplasms of monoclonal B cell lymphocytosis (MBL) as up to $5 \times 10^3/\mu\text{L}$ monoclonal BL in peripheral blood (PB), phenotypically similar to CLL cells, but without cytopenias or palpable lymphadenopathies. MBL is subdivided into two subgroups, “low-count” MBL ($<0.5 \times 10^3/\mu\text{L}$), with a residual chance to boost into CLL/SLL and “high-count” MBL, which share phenotypic and molecular/genetic features with Rai staging system 0 CLL and

require routine follow-up. It has been shown that CLL is always preceded by MBL, however, despite its prevalence of 12% in the healthy population, MBL progresses to overt CLL/SLL in only 1–2% of cases yearly.¹

Chronic myeloid leukemia (CML) is a myeloproliferative disease characteristically expressing the aberrant Philadelphia chromosome, a product of the translocation of the *Abelson murine leukemia 1 (ABL1)* gene from chromosome 9 to the *breakpoint cluster region (BCR)* gene on chromosome 22 – t(9;22)(q3.4;q1.1). This results in the BCR-ABL1 fusion gene that codes for an oncoprotein that constitutively triggers tyrosine kinase activity. The incidence of CML is gradually rising due to the high efficiency of tyrosine-kinase inhibitors used to treat and prolong the life expectancy of patients.

Rarely, CML and CLL or CLL-related neoplasms coexist in the same patient. To date, only a few dozens of cases of simultaneous CML and CLL have been reported and only in a minority of patients, they are diagnosed concomitantly.³ In addition, only one case of simultaneous CML and MBL has been reported, where CML followed MBL.⁴

Herein we describe a rare case of simultaneous diagnosis of CML and “high-count” MBL. After completing six years of treatment using imatinib, our patient developed pancytopenia

* Corresponding author at: Internal Medicine Service, District Hospital of Figueira da Foz, EPE, Gala, 3094-001 Figueira da Foz, Portugal.
E-mail address: sarafruarte@gmail.com (S. Duarte).

<http://dx.doi.org/10.1016/j.bjhh.2017.02.004>

1516-8484/© 2017 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

and multiple adenopathies, strongly suggesting disease progression to SLL. We additionally demonstrate that myeloid and lymphoid neoplastic cells originate from distinct progenitors.

Case report

We report on an 82-year-old man with cardiovascular disease and obstructive sleep apnea, who was seen in the emergency room (ER) in April 2008 for leukocytosis in his routine blood tests and complaints of fatigue, osteoarticular pain, sweats and anxiety for several weeks. On physical examination, he had a BMI of 30.0 kg/m², and presented with a sad facies and depression. Lung and heart auscultations were normal. A thorough examination of the head, ears and neck excluded enlargement of regional lymph nodes. No organomegalies were found on abdominal palpation. Infectious and acute inflammatory conditions were excluded. He had no history of exposition to myelotoxic drugs or radiation.

A complete blood count (CBC) confirmed leukocytosis of $26.6 \times 10^3/\mu\text{L}$, with neutrophilia ($14.44 \times 10^9/\text{L}$), lymphocytosis ($4.73 \times 10^9/\text{L}$), a platelet count of $282 \times 10^9/\text{L}$ and hemoglobin of 13.7 g/dL. Serum chemistry showed unaltered renal and hepatic parameters however, lactate dehydrogenase was elevated at 636 U/L. A peripheral blood smear revealed leukocytosis with immature granulocytes (2% of myelocytes, 4% of metamyelocytes and 11% of band cells). Additionally, bone marrow (BM) aspiration identified hypercellularity, <1% of blasts and myeloid hyperplasia with predominance of immature cells, rare orthochromatic erythroblasts with Howell-Jolly bodies and a ratio of myeloid to erythroid precursors of 4:1. Strikingly, phenotypic analysis of the BM showed 5% of lymphocytes, of which 90% were monoclonal, small sized B lymphocytes co-expressing CD5, CD43, CD38 and CD20 at low levels. CD23 was heterogeneously expressed. The B-cell clone was negative for Zap-70, CD79b, FMC7, CD10 and the Kappa immunoglobulin light chain. Thirty percent of the clone was positive for CD11c. Apoptosis regulator Bcl2 was expressed at normal levels, while lambda chains were little expressed. A BM biopsy was inconclusive. Computerized tomography (CT) excluded generalized lymphadenopathies and hepatosplenomegaly.

Altogether, the analyses above suggested the diagnosis of "high-count" MBL.

In agreement with the observation of circulating immature myeloid cells but at odds with the immunophenotypic study, cytogenetic analysis revealed the presence of the t(9;22)(q3.4;q1.1) translocation in all metaphases analyzed and reverse transcriptase polymerase chain reaction (RT-PCR) showed BCR-ABL1 transcripts, establishing, concurrent CML in addition to the MBL diagnosis.

We lost contact with the patient for 14 months at which time he was readmitted to the ER due to active bleeding subsequent to a dental implant procedure. On this occasion, the CBC showed an escalation of leukocytosis to $170.0 \times 10^3/\mu\text{L}$, with neutrophilia shifted to the left ($109.65 \times 10^9/\text{L}$), lymphocytosis ($14.28 \times 10^3/\mu\text{L}$) and thrombocytosis ($532.0 \times 10^9/\text{L}$). Hemoglobin had dropped to 12.1 g/dL. A second PB phenotypic study was pursued revealing 1.7% of B cells with a CLL phenotype. Moreover, 91% of neutrophils (60% of these in mat-

uration) were detected and a slight increase of CD34⁺ cells (0.12%).

The definitive diagnosis of concomitant "high-count" MBL and CML was reached.

The patient completed six days of cytoreduction with hydroxyurea (1g per day) and the absolute leukocyte count dropped to $16.3 \times 10^3/\mu\text{L}$ ($10.81 \times 10^9/\text{L}$ neutrophils and $3.19 \times 10^3/\mu\text{L}$ lymphocytes). Treatment with imatinib (400 mg per day) was initiated one month later. Complete hematological and molecular responses were achieved with six months of treatment (ratio of BCR-ABL1 to ABL1 0.04% by RT-PCR) and sustained for 5.5 years of follow up.

During the first semester of 2015, the patient developed leukopenia while lymphocytes boosted to over 70% of all white blood cells, platelets reached counts between 84.0 and $140.0 \times 10^9/\text{L}$ and hemoglobin levels dropped from 9.9 g/dL in November 2014 to 8.5 g/dL in June 2015. A supraclavicular adenomegaly was detected on physical examination. Nevertheless, the patient was asymptomatic. Reevaluation of BM aspirate showed 90% of clonal B cells, positive for lambda immunoglobulin light chain and a characteristic phenotype of B-CLL. PB immunophenotypic analysis showed 15% of B lymphocytes of which 99% had the phenotype CD19⁺, CD20^{low}, CD5⁺, CD38^{het}, CD23⁺, CD200⁺, CD43⁺, CD10⁻, CD79b⁻ and expressed lambda chain. Cytogenetic studies of PB for trisomy 12, del11q23, BCR/ABL1 fusion gene, del17p13.1 (p53) and del13q14.3 molecular abnormalities on fluorescence-activated cell sorting purified CLL-like lymphocytes and monoclonal blasts were all negative, demonstrating that characteristic genomic abnormalities for CLL were absent in this patient and that the BCR/ABL1 translocation occurred exclusively in CML cells. Thoraco-abdomino-pelvic CT revealed lymph node enlargement (>1.5 cm) of subcarinal, para-aortic, axillary bilaterally, lower cervical and abdominal (celiac and hepatic) lymph nodes. Liver and spleen presented with normal dimensions. Nevertheless, the ratio of BCR-ABL1/ABL1 was $\leq 0.0011\%$. All together, the above events strongly suggest an expansion of the MBL condition to SLL, stage III of Lugano modification of Ann Harbor staging system for primary nodal lymphomas² besides a complete molecular response of CML with imatinib. In addition, results show that CML and MBL clones have distinct origins.

Imatinib treatment has been suspended while the patient's clinical condition is re-staged and a new treatment strategy is being appraised.

Discussion

Previous studies have suggested that patients with Philadelphia negative myeloproliferative neoplasms (Ph⁻ MPN) are at higher risk of developing B cell lymphoid neoplasms than the general population. This notion was substantiated by a recent report demonstrating that MBL occurs more frequently in Ph⁻ MPN compared to a control group.⁵ Altogether, these studies may indicate a shared pathophysiology between the Ph⁻ MPN and lymphoid malignancies. Contrastingly, Ph⁺ CML and CLL/SLL or MBL in the same patient is a very rare condition and even rarer is their simultaneous diagnosis. When sequentially diagnosed, these mature BL neoplasms more often precede

CML.^{3,4} Leukemogenic effects of chemotherapy drugs used to treat CLL as well as immunodeficiency associated to CLL have been suggested as plausible causes for the development of CML following CLL diagnosis.⁶ Nevertheless, secondary solid tumors are much more likely to occur in CLL patients than hematological malignancies. Simultaneous MBL and CML has only been reported once, where CML onset followed MBL diagnosis.⁴ Contrastingly, CML often evolves to a blast crisis and secondary neoplasms are not commonly found in these patients.⁷ Nevertheless, the above arguments have no place in cases of concomitant occurrence of CML and mature BL neoplasms, as herein reported.

Though only occasionally found, it is of great interest to the field and clinically important to understand the causes and molecular mechanisms underlying the concomitant occurrence of hematological malignancies. It is generally accepted that myeloid and lymphoid neoplasms emerge and progress independently, however studies unequivocally demonstrating a biclonal origin of the two lymphoid and myeloid clones are still lacking. D'Arena et al. have, for the first time, sorted myeloid and lymphoid cells apart to show that each cell type carries characteristic and mutually exclusive genomic aberrations (BCR-ABL and del17q11, respectively), demonstrating therefore, that CLL and CML cells have distinct origins.⁸ Similarly, in our study, we ran cytogenetics on separated circulating lymphocytes and proved that B cell and myeloid neoplasm populations originate from distinct progenitors. Thus, to date, evidence is lacking for a common and unique stem cell capable of originating both leukemic lymphoid and myeloid clones.

Finally, as previously mentioned, MBL is a precursor of virtually all cases of CLL and the diagnosis of the latter is established when $>5.0 \times 10^3/\mu\text{L}$ monoclonal BL are detected in PB. However, clinical data supporting this arbitrary laboratory cut-off value is lacking. Nevertheless, it is powerful enough to stratify patients between having the diagnosis of MBL, a benign condition despite its potential to progress to malignancy, against patients with CLL/SLL. In fact, 1-2% of "high-count" MBL patients progress to overt CLL/SLL per year.¹ In our case, although a lymph node biopsy is required for definitive diagnosis, analytical and imaging data strongly suggest the progression of MBL to SLL six years after the diagnosis of concomitant MBL and CML. It is legitimate to hypothesize that imatinib may be responsible for this transformation. However, most adverse effects of tyrosine-kinase inhibitors such as imatinib, used as first-line treatment drugs for CML, result in low-grade toxicities and generally occur at an early phase of the treatment. Furthermore, although studies have suggested an interaction between imatinib and DNA repair mechanisms and its potential to inhibit T-lymphocytes and dendritic cells,⁹ as of today, there is no irrefutable evidence that tyrosine-kinase inhibitors induce secondary malignancies. In contrast, BCR-ABL1 expressing cells secrete several cytokines, including interleukin-3, which may lead to increased production of immature B cells that, in turn, may result in the development of CLL.¹⁰

Conclusion

Our study is a very important contribution to the sparse number of cases of simultaneous diagnoses of myeloproliferative

and lymphoproliferative neoplasms found in the literature, particularly concomitant occurrence of Ph⁺ CML and MBL; this is the first case ever reported in Portugal. We also demonstrate that clonal lymphoid and myeloid cells originate from distinct progenitors. Further work is necessary to understand the molecular pathogenesis underlying this condition and discover a common and efficient therapy to treat patients who progress to simultaneous myeloid and lymphoid malignancies.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors acknowledge Dr. Artur Paiva.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-90.
2. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-68.
3. Rahman K, George S, Mangal S, Mehta A. Simultaneous occurrence of chronic myeloid leukemia and chronic lymphocytic leukemia: report of an unusual case. *Indian J Pathol Microbiol*. 2013;56(4):453-6.
4. Laurenti L, Tarnani M, Nichele I, Ciolli S, Cortelezzi A, Forconi F. The coexistence of chronic lymphocytic leukemia and myeloproliferative neoplasms: a retrospective multicentric GIMEMA experience. *Am J Hematol*. 2011;86(12):1007-12.
5. Miltiades P, Lamprianidou E, Kerzeli IK, Nakou E, Papamichos SI, Spanoudakis E, et al. Three-fold higher frequency of circulating chronic lymphocytic leukemia-like B-cell clones in patients with Ph-Myeloproliferative neoplasms. *Leuk Res*. 2015; pii:S0145-2126(15)30357-X.
6. Friman V, Winqvist O, Blimark C, Langerbeins P, Chapel H, Dhalla F. Secondary immunodeficiency in lymphoproliferative malignancies. *Hematol Oncol*. 2016;34(3):121-32.
7. Miranda MB, Lauseker M, Kraus MP, Proetel U, Hanfstein B, Fabarius A, et al. Secondary malignancies in chronic myeloid leukemia patients after imatinib-based treatment: long-term observation in CML Study IV. *Leukemia*. 2016;30(6):1255-62.
8. D'Arena G, Gemei M, D'Auria F, Deaglio S, Statuto T, Bianchino G, et al. Chronic lymphocytic leukemia after chronic myeloid leukemia in the same patient: two different genomic events and a common treatment? *J Clin Oncol*. 2012;30(32):e327-30.
9. Appel S, Rupf A, Weck MM, Schoor O, Brümmendorf TH, Weinschenk T, et al. Effects of imatinib on monocyte-derived dendritic cells are mediated by inhibition of nuclear factor-kappaB and Akt signaling pathways. *Clin Cancer Res*. 2005;11(5):1928-40.
10. Peters DG, Klucher KM, Perlingeiro RC, Dessain SK, Koh EY, Daley GQ. Autocrine and paracrine effects of an ES-cell derived, BCR/ABL-transformed hematopoietic cell line that induces leukemia in mice. *Oncogene*. 2001;20(21):2636-46.