Case Report

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

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Introduction

Chronic lymphocytic leukemia (CLL) is the commonest leukemia in adults. It is defined, according to the latest guidelines, as >5 × 10^9/μL circulating B lymphocytes (BL) expressing a typical cell surface marker signature (CD5+, CD10−, CD19+ and CD20dim, surface immunoglobulin dim, CD23−, CD43+/− and cyclin D1−) 1. If lymph node enlargement and/or hepatosplenomegaly is present in a patient with <5 × 10^9/μL 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 × 10^9/μL 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 × 10^9/μL), 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 characterized by expressing the aberrant Philadelphia chromosome, a product of the translocation of the Abelson murine leukemia 1 (ABL1) gene from chromosome 9 to the break point cluster region (BCR) gene on chromosome 22 – (t(9;22)(q34;q11). 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 CML-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...
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 exposure to myelotoxic drugs or radiation.

A complete blood count (CBC) confirmed leukocytosis of 26.6 × 10⁹/μL, with neutrophilia (14.44 × 10⁹/L), lymphocytosis (4.73 × 10⁹/L), a platelet count of 282 × 10⁹/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 orthochromat 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)(q34;q11.2) 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 × 10⁹/μL, with neutrophilia shifted to the left (109.65 × 10⁹/L), lymphocytosis (14.28 × 10⁹/μL) and thrombocytosis (532.0 × 10⁹/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 maturation) 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 cytotherapy with hydroxyurea (1g per day) and the absolute leukocyte count dropped to 16.3 × 10⁹/μL (10.81 × 10⁹/L neutrophils and 3.19 × 10⁹/μL 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 × 10⁹/L and hemoglobin levels dropped from 9.9 g/dL in November 2014 to 8.5 g/dL in June 2015. A supravacular 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<sup>low</sup>, CD5<sup>+</sup>, CD38<sup>neg</sup>, CD23<sup>+</sup>, CD200<sup>+</sup>, CD43<sup>+</sup>, CD10<sup>−</sup>, CD79<sup>−</sup> 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 ≤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 lymphomas 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. Altogether, these studies may indicate a shared pathophysiology between the Ph⁻ MPN and lymphoid malignancies. Contrasting, 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 CML as well as immunodeficiency associated to CLL have been suggested as plausible causes for the development of CML following CML 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.\(^4\) Contrasting, 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 that, CLL and CML cells have distinct origins.\(^3\) 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 \(>5.0 \times 10^3/\muL\) 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,\(^3,4\) 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.

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REFERENCES