

Sequential Coexistence of Small Lymphocytic Lymphoma as a Second Primary Tumor and BCR:: ABL1-Positive Chronic Myeloid Leukemia: A Case Report

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ABSTRACT

Introduction: The simultaneous or sequential occurrence of hematologic malignancies derived from divergent cellular lineages (myeloid and lymphoid) represents an extremely rare clinical and immunobiological phenomenon. The emergence of small lymphocytic lymphoma / chronic lymphocytic leukemia (SLL/CLL) as a metachronous second primary tumor during maintenance therapy and close surveillance of chronic myeloid leukemia (CML) poses a true challenge for differential pathological diagnosis and targeted therapeutic strategies. **Objective:** To report the diagnostic process, immunohistochemical characterization, and interdisciplinary clinical management of a patient who developed SLL after achieving a deep molecular response for CML under tyrosine kinase inhibitor (TKI) therapy. **Case and Methods:** A 47-year-old male with an established diagnosis of chronic phase CML with BCR::ABL1 p210 fusion transcript, treated with dasatinib (100 mg daily), achieved a Major Molecular Response. During his 3-year evolutionary surveillance, he developed left supraclavicular and right cervical lymphadenopathies. Neck ultrasound demonstrated rounded nodes with a loss of the corticomedullary relationship. An excisional biopsy of the right cervical lymph node was performed, revealing infiltration by mature monoclonal B lymphoid cells with a CD20+, CD43+, BCL2+, MUM1+ profile, and a Ki67 index of 15%, confirming SLL. During follow-up, the patient developed a pericardial effusion that required the scheduled temporary suspension of the TKI. **Conclusions:** Sequential myeloid/lymphoid coexistence requires meticulous differentiation between a clonal evolution of a common pluripotential stem cell versus two biologically independent malignancies. Management must be guided by the stratification of IWCLL criteria, individualizing the need for chemoimmunotherapy versus the continuation of TKI therapy.

KEYWORDS: Lymphoma, Small Lymphocytic; Leukemia, Myelogenous, Chronic, BCR-ABL Positive; Neoplasias, Multiple Primary; Protein Kinase Inhibitors; Diagnosis, Differential.

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I. INTRODUCTION

The simultaneous or successive occurrence of multiple primary hematologic malignancies with dissimilar morphological and immunophysiological characteristics constitutes a low-frequency scenario in global oncohematological practice. Historically, medical classification systems considered lymphoid and myeloid lineages as compartmentalized and mutually exclusive

entities in their malignant transformation processes. However, the increase in overall survival of patients with chronic myeloproliferative neoplasms has allowed documenting the emergence of metachronous second primary tumors of B-lymphoid lineage, opening a debate on molecular mechanisms and host susceptibility.¹

Within this spectrum, the coexistence of Chronic Myeloid Leukemia (CML) and Small Lymphocytic Lymphoma (SLL)

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or its leukemic counterpart, Chronic Lymphocytic Leukemia (CLL), represents a window of great scientific interest. CML is a myeloproliferative neoplasm molecularly defined by the presence of the Philadelphia chromosome, a product of the reciprocal translocation t(9;22)(q34.1;q11.2), which generates the BCR::ABL1 fusion gene with constitutive tyrosine kinase activity. For its part, SLL is an indolent mature B-cell non-Hodgkin lymphoma that shares the same immunophenotypic profile as CLL but manifests predominantly in nodal tissues without absolute lymphocytosis in peripheral blood.²

From the standpoint of oncogenesis and current hematological taxonomy endorsed by the World Health Organization (WHO), it is essential to precisely discriminate the biological nature of this association. Three theoretical scenarios attempt to explain the coexistence of both disorders: first, the presentation of true concomitant neoplasms that develop synchronously (simultaneous diagnosis) or metachronously (sequential) from two completely independent progenitor clones. Second, the hypothesis of a clonal evolution or divergence derived from a mutated common pluripotential hematopoietic stem cell is postulated. Finally, the possibility of an iatrogenic second primary tumor induced by previous chemotherapeutic agents must be evaluated.³

The clinical relevance of this phenomenon lies not only in its diagnostic rarity but also in the prognostic impact and therapeutic dilemmas it generates for the treating physician. The presence of persistent or newly appearing lymphadenopathies in a patient with a diagnosis of CML can be erroneously interpreted at first glance as a sign of disease progression toward an accelerated phase or an extramedullary blastic crisis of lymphoid lineage. An error in this pathological distinction can lead to the inappropriate initiation of intensive chemotherapy regimens for acute leukemia, omitting the diagnosis of a coexisting indolent lymphoma that might only require an active surveillance strategy or targeted immunotherapy of low toxicity.⁴

The advent of tyrosine kinase inhibitors (TKIs) at the beginning of the 21st century radically revolutionized the prognosis of CML, transforming a medium-term lethal disease into a chronic condition with a life expectancy close to that of the general population. This substantial increase in the exposure and survival time of patients chronically treated with drugs such as imatinib, dasatinib, or nilotinib has brought with it the documentation of long-term adverse effects and the observation of second primary tumors. Continuous medical surveillance and prolonged analytical screening studies facilitate the detection of lymphoid neoplasms that in earlier times did not manifest clinically due to the early death of the patients.⁵

The morphological characterization of SLL requires a multidisciplinary approach where excisional lymph node biopsy and immunohistochemistry study represent the gold

standard. The classic profile of SLL includes the coexpression of B-lymphoid lineage markers such as CD19 and CD20 along with the T-cell marker CD5 and the B-activation marker CD23, demonstrating kappa or lambda light chain restriction. The absence of germinal center markers such as CD10 helps differentiate this entity from other aggressive or follicular B-cell lymphomas. Likewise, the quantification of the cellular proliferation index using the Ki67 antibody is essential to predict the biological behavior of the lymphoid disease.⁶

The design of an optimal therapeutic plan for a patient with a coexisting diagnosis of CML and SLL raises critical questions: which tumor clone should be prioritized for treatment? Is it feasible to combine targeted therapies against both lineages without exacerbating bone marrow myelosuppression? In most reported scenarios, if the CML is controlled under an adequate molecular response and the lymphoid component does not meet the criteria for active progression dictated by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL), it is preferred to maintain TKI therapy and subject the patient to close observation of the lymphoma. However, when the lymphoma becomes symptomatic or generates massive volumetric compromise, the initiation of monoclonal antibodies or inhibitors of the B-cell receptor (BCR) signaling pathway such as ibrutinib or venetoclax should be evaluated.⁷

Finally, the detailed analysis of these clinical cases is indispensable to nourish global databases and refine oncohematological clinical practice guidelines. The collection of evidence regarding drug interactions, cumulative risk of severe cytopenias, and susceptibility to opportunistic infections is of high value for the medical community. This case report aims to break down the diagnostic tools, cellular interactions, and vicissitudes of treatment in a CML patient who developed an SLL as a second primary, providing a structured review of the available scientific literature.⁸

II. CASE REPORT

The patient is a 47-year-old male from Puebla, Mexico, with no significant family history of hematological malignancies. The patient's initial clinical management dates back three years, when he attended the Hematology service referred due to a clinical presentation characterized by severe asthenia, adynamia, unquantified involuntary weight loss, and a marked hyperleukocytosis in the routine complete blood count. Complementary molecular studies performed on bone marrow and peripheral blood confirmed at that time the presence of the BCR::ABL1 p210 fusion transcript, formally establishing the diagnosis of Chronic Myeloid Leukemia (CML) in Chronic Phase.

Based on the risk stratification of international guidelines, definitive first-line treatment was started with the second-generation tyrosine kinase inhibitor (TKI), dasatinib, at a

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standardized oral dose of 100 mg every 24 hours. The patient demonstrated excellent pharmacological tolerance and an optimal biological response, achieving Major Molecular Response (MMR) criteria in less than one year from the initiation of the drug. The patient remained on a strict maintenance regimen and close outpatient surveillance by the Hematology service, documenting quantitative BCR::ABL1 transcript loads that were undetectable or below the molecular safety limit.

During one of the protocol control visits carried out in February 2026, the patient reported the appearance of multiple painless lumps located in the lateral region of the neck, with insidious but progressive growth over the last three months, denying the presence of fever, profuse night sweats, or additional weight loss. Upon detailed physical examination, the presence of palpable lymphadenopathies of firm, elastic, mobile consistency and not adhered to deep planes was noted, located specifically in the left supraclavicular region and in the right middle and lower cervical chain. No clinically detectable visceromegalies were evident at that time.

Given the etiological suspicion of a probable extramedullary relapse, CML progression, or the development of a second neoplasm, the patient was sent to undergo a high-resolution ultrasound study of the neck and thyroid on February 14, 2026. The sonographic report detailed a thyroid gland of normal size, margins, and echogenicity, with no evidence of intrathyroidal nodules, with an isthmus that measured 2.6 mm in anteroposterior diameter. The parotid and submaxillary salivary glands appeared homogeneous and symmetrical bilaterally.

The twins and pathological finding of the ultrasound lay in the characterization of the cervical lymphoid tissue: in the right neck, multiple abnormal-appearing lymph nodes were documented at the level of nodal chains II, III, and IV, highlighting round-shaped structures with circumscribed margins, complete loss of normal corticomedullary differentiation, heterogeneous cortical echotexture, and a total absence of physiological fatty hilum, associating predominantly peripheral vascularity on Doppler analysis. Identical findings were described in the left neck at nodal level II. The study concluded the presence of abnormal bilateral cervical lymphadenopathies, suggesting an excisional biopsy.

Based on the imaging recommendation, an excisional biopsy of the right level III cervical lymph node was chosen to guarantee an adequate evaluation of the tissue architecture, submitting the surgical specimen to the Pathology service on February 18, 2026. The macroscopic description reported a nodular tissue fragment with a lobulated surface, whitish-yellow in color, measuring 2.9 x 1.6 cm, of soft consistency and homogeneous solid appearance upon cutting. Histological findings with routine staining revealed a complete distortion of the lymph node architecture at the

expense of a diffuse proliferation of medium-sized lymphoid cells with paracortical distribution, in the mantle zone, and in the interfollicular space. These cells were round, with oval nuclei and prominent nucleoli, scanty cytoplasm, and indistinct cell membranes, with a centrocyte-like morphological appearance, showing only residual non-confluent follicular centers, with no evidence of necrosis or granulomas.

The immunohistochemistry panel demonstrated the following results: intense and diffuse reactivity for the B-lineage marker CD20, positivity for the co-marker CD43, and positivity for BCL2 and MUM1. The germinal center marker CD10 was strictly negative, while the CD3 antibody showed only a reactive pattern corresponding to residual accompanying T lymphocytes. The cellular proliferation index evaluated by Ki67 was 15%. The definitive diagnosis of diffuse pattern nodal lymphoma was issued, compatible by histology and immunophenotype with Small Lymphocytic Lymphoma (SLL) / Chronic Lymphocytic Leukemia. Subsequent systemic staging studies did not demonstrate lymphoid disease activity at any other nodal or extranodal level. During his post-biopsy clinical evolution, the patient developed an acute non-purulent pericardial effusion, categorized as an adverse effect secondary to long-term dasatinib therapy, which required the scheduled temporary suspension of the tyrosine kinase inhibitor and close symptomatic management by cardiology.

In order to comprehensively evaluate the systemic extension of the Small Lymphocytic Lymphoma (SLL) and to determine the evolutionary status of both malignancies following the established management schemes, a high-resolution follow-up tomographic study was performed. This Computed Tomography (CT) scan of the head, neck, chest, abdomen, and pelvis, in unenhanced and contrast-enhanced phases with multiplanar reconstructions, provided critical anatomical evidence regarding the patient's progress in his current follow-up period. The study was formally interpreted and dictated by the radiology specialist.

III. METHODS

The methodological design of this study corresponds to a descriptive, retrospective, analytical clinical case report study associated with a structured review of the available medical literature on multiple hematologic malignancies. The study universe consisted of the clinical records, outpatient evolution notes, imaging reports, and histopathological files of the oncohematological patient integrated into the institutional database. The collection of primary clinical data was performed through the review of the electronic clinical record, abstracting demographic variables, oncological history, debut symptoms, antineoplastic drug dosages, and quantitative molecular response curves.

The imaging evaluation methodology was based on high-resolution real-time cervical ultrasonography, executed on

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February 14, 2026, using a conventional multifrequency linear transducer connected to color Doppler ultrasound equipment. The central thyroid compartments, isthmus, major salivary glands, and bilateral nodal chains organized from level I to level VI were systematically explored. Metric variables evaluated included the longitudinal, transverse, and anteroposterior diameter of the thyroid lobes and identified pathological lymphadenopathies, calculating glandular volumes using standard ellipsoidal formulas with color Doppler analysis to map vascular flows of the suspicious nodes.

The methodological processing of the lymphoid tissue sample began with an architectural surgical excisional biopsy of the right level III cervical lymph node on February 18, 2026. The tissue specimen was immediately fixed in 10% buffered formalin solution at room temperature for a standard period of 24 hours to preserve cellular architecture. Subsequently, the 2.9 x 1.6 cm nodular tissue fragment was dehydrated in ascending alcohols, cleared in xylene, and embedded in solid paraffin blocks, performing histological sections of 3 to 4 microns using a high-precision microtome for subsequent staining with Hematoxylin and Eosin technique.

For definitive immunophenotypic characterization and cellular differentiation of the lymphoid clone, an automated immunohistochemistry protocol was implemented on sections of the paraffin block. The methodological panel of primary monoclonal antibodies included directed evaluation of CD20 (pan-B marker), CD3 (pan-T marker), CD43 (lymphoid aberrant coexpression marker), CD10 (germinal center marker), MUM1 (advanced plasmacytoid differentiation marker), and BCL2 (apoptosis inhibition marker). Antigen retrieval was performed by induction heat in citrate buffer at physiological pH.

Quantification of the tumor cellular replication rate was determined by analyzing the Ki67 proliferation index. The counting method consisted of microscopic evaluation by an oncological pathologist, quantifying the percentage of cellular nuclei with positive brown nuclear staining out of a total of 1000 tumor cells distributed in the fields of highest proliferative activity under high magnification. Classification criteria were based on the current WHO Classification of Hematopoietic and Lymphoid Tumors guidelines.

Monitoring CML molecular response was executed serially using the quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) technique from messenger RNA samples extracted from the patient's peripheral blood. Genetic amplification focused on quantifying the copy number of the BCR::ABL1 p210 fusion transcript, expressing final results in percentage according to the standardized International Scale. Methodological thresholds to define Major Molecular Response were established at transcript levels $\leq 0.1\%$, while Deep Molecular Response was categorized at levels $\leq 0.01\%$.

The scientific literature search for the integrated bibliographic review was carried out in PubMed/MEDLINE, Embase, Scielo, and Scopus biomedical databases using MeSH/DeCS descriptor terms combined with Boolean operators. Selection was limited to original articles, case reports, and systematic reviews published within the last 5 years. Methodological inclusion criteria encompassed those articles explicitly describing the chronological sequence of diagnosis, detailed immunohistochemical profiles, documented cytogenetic mutations, applied therapeutic schemes, and long-term clinical outcome.

IV. RESULTS

The results of the initial clinical evaluation demonstrated the long-term biological success of treatment for Chronic Myeloid Leukemia, showing that the malignant myeloid clone harboring the BCR::ABL1 p210 translocation remained under deep and stable molecular suppression. Serial quantitative molecular analyses by RT-qPCR confirmed that the patient persisted in a sustained Major Molecular Response phase, with fusion transcript expression levels below the international critical limit of 0.1% IS during the 3 years of follow-up with dasatinib at a dose of 100 mg daily. Complete blood counts did not reveal data of leukocytosis, thrombocytosis, or circulating blasts that would suggest TKI failure.

The results of the neck ultrasound examination performed on February 14, 2026, provided specific metric data on the thyroid gland and the pathological bilateral cervical nodal structures. The right lobe recorded a longitudinal diameter of 50.15 mm, a transverse diameter of 12.0 mm, and an anteroposterior diameter of 19.60 mm, with a calculated total volume of 6.1 cc. The left lobe yielded a longitudinal diameter of 33.02 mm, a transverse diameter of 19.21 mm, and an anteroposterior diameter of 13.30 mm, with a calculated volume of 4.4 cc, totaling a normal overall thyroid volume of 10.5 cc without the presence of detectable focal nodes.

The pathological finding on the neck ultrasound was the demonstration of multiple clusters of bilateral cervical lymphadenopathies with imaging criteria of structural alteration. The lymph nodes located in the right nodal chain at levels II, III, and IV, as well as in level II of the left neck, showed a rounded morphology and well-circumscribed margins, with a complete loss of the physiological corticomedullary relationship and a total absence of the normal fatty hilum. The echotexture of the nodal cortex was reported as heterogeneous, and Doppler analysis demonstrated the presence of peripheral high-resistance neovascular flow.

The results of the macroscopic evaluation of the surgical specimen submitted to oncological pathology documented a whitish-yellow lobulated nodular tissue fragment measuring 2.9 x 1.6 cm, with a solid, homogeneous surface and soft

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consistency upon cutting. Microscopic histological analysis stained with H&E demonstrated the effacement of the internal architecture of the lymph node, secondary to a massive infiltration of mature morphology medium-sized lymphoid cells. The cellular proliferation was uniformly distributed, occupying paracortical zones, the interfollicular space, and expanding the mantle zone, exhibiting round or oval nuclei, single prominent nucleoli, and scanty amphophilic cytoplasm, with the appearance of centrocytes. Non-confluent atrophic residual follicular centers were identified, with no evidence of necrosis or granulomatous inflammation.

The results of the immunohistochemical profile confirmed the presence of a mature B-lineage clonal lymphoid cell population with a characteristic phenotype of Small Lymphocytic Lymphoma. The neoplastic cells demonstrated an intense cytoplasmic immunoreactivity for the CD20 antibody and diffuse positivity for the CD43 marker. Likewise, positive immunohistochemical coexpression was documented for BCL2 and MUM1 proteins. In contrast, results for the CD10 antibody were strictly negative, ruling out a germinal center origin. The CD3 antibody was negative in the dominant tumor population, staining only residual infiltrating non-neoplastic reactive T lymphocytes.

The result of the cell kinetic analysis using the Ki67 antibody yielded a low-to-moderate cell proliferation index of 15%, confirming the indolent biological nature of the chronic lymphoproliferative component and ruling out a high-grade transformation or aggressive lymphoma. Complementary post-surgical clinical staging studies confirmed the absence of other mediastinal, retroperitoneal, or inguinal lymphadenopathies, as well as the absence of gross liver or spleen infiltration, staging the SLL as a disease confined to the evaluated cervical compartment.

In the evolutionary results of the patient after the diagnosis of lymphoma, clinical data of a moderate acute pericardial effusion were documented, without immediate hemodynamic compromise or cardiac tamponade. This event required the scheduled, controlled temporary interruption of dasatinib administration (100 mg daily). Following TKI discontinuation, clinical results demonstrated complete resolution of the pericardial effusion and stabilization of the patient's symptomatic picture, maintaining complete blood count values within normal ranges and persistence of CML molecular remission, with the decision to keep the patient under an active surveillance regimen for SLL.

Follow-up computed tomography (CT) scan results conclusively demonstrated that the patient is in a solid phase of clinical consolidation and remission, with no imaging evidence of malignant tumor activity or progression from either Chronic Myeloid Leukemia or Small Lymphocytic Lymphoma.

In the lymph node regions of the neck, axillae, and groins, nodes displayed normal morphology and size with a preserved fatty hilum, confirming the complete resolution of previous pathological lymphadenopathies. No mediastinal or hilar lymph node aggregates or mass-occupying lesions were observed. The lung parenchyma and bone structures showed no zones of infiltration or lytic/blastic lesions.

In the abdominal and pelvic compartments, the absence of organ involvement or compromise by either tumor lineage was confirmed; the liver and spleen maintained completely normal dimensions, morphology, and attenuation coefficients, ruling out infiltrative hepatomegaly or splenomegaly.

The only relevant finding was located in the cardiac compartment, where an increased amount of fluid in the pericardial space was identified, most clearly visualized along the diaphragmatic wall, registering a thickness of 15 mm with an attenuation of 18 HU, compatible with a mild-to-moderate pericardial effusion secondary to tyrosine kinase inhibitor therapy (**Figure 1** and **Figure 2**).



Figure 1. Axial chest CT scan showing a mild-to-moderate pericardial effusion with a maximal fluid thickness of 15 mm along the posterior-diaphragmatic wall and an attenuation coefficient of 18 HU (arrow), secondary to tyrosine kinase inhibitor therapy.



Figure 2. Coronal abdominal CT scan reconstruction showing a normal-sized liver and spleen with a perfectly homogeneous parenchyma and proper contrast enhancement, confirming complete remission and the absolute absence of infiltrative hepatosplenomegaly.

V. DISCUSSION

The sequential or metachronous coexistence of a chronic myeloproliferative neoplasm such as Chronic Myeloid Leukemia (CML) and a chronic lymphoproliferative neoplasm of mature B cells such as Small Lymphocytic Lymphoma (SLL) represents a phenomenon of extraordinary epidemiological and immunobiological rarity in modern hematology. In the provided international medical literature, the vast majority of cases that associate myeloid and lymphoid disorders correspond to synchronous simultaneous diagnoses or to late clonal evolution toward a lymphoid blastic crisis in advanced CML. The emergence of an SLL as a metachronous second primary tumor, in a patient who is under a sustained major molecular response and biological remission of his CML with targeted therapy, constitutes an exceptional scenario that challenges traditional theories of hematological oncogenesis.¹

From the perspective of the underlying molecular mechanisms, the central scientific debate revolves around determining whether both neoplasms originate from two completely independent clones that coexist by chance or whether they derive from a clonal evolutionary divergence of a mutated common pluripotential hematopoietic stem cell. The common clone hypothesis suggests that an ancestral hematopoietic progenitor acquires a latent predisposing genomic instability; subsequently, a daughter cell of the myeloid line acquires the t(9;22) translocation expressing the BCR::ABL1 fusion gene, while another cell of the lymphoid line undergoes independent aberrant rearrangements of SLL.

In our patient, the preservation of the molecular remission of CML coinciding with the nodal volumetric progression of SLL provides indirect clinical evidence favoring the theory of two biologically independent neoplastic clones with disconnected replication kinetics.³

The role of long-term treatment with tyrosine kinase inhibitors (TKIs) in the genesis of second primary tumors is an area of intense critical research in the molecular era. First- and second-generation drugs such as imatinib, dasatinib, and nilotinib have demonstrated an excellent safety profile, but their implication in the long-term modulation of the bone marrow and nodal immune microenvironment remains under scrutiny. It has been postulated that the constitutive inhibition of accessory endothelial kinases by certain TKIs could induce a state of attenuated or dysfunctional cellular immunovigilance, decreasing the capacity of cytotoxic T lymphocytes and NK cells to recognize and clear emerging aberrant lymphoid clones. However, evidence suggests that the appearance of lymphoid second primaries in these patients reflects a bias of close and prolonged medical surveillance, allowing the diagnosis of indolent lymphomas that otherwise would have remained clinically silent.⁴

The clinical presentation of this patient highlights the diagnostic pitfalls that the hematologist must systematically evade in practice. Faced with the appearance of newly established cervical and supraclavicular lymphadenopathies in a subject with a history of CML, the first mandatory diagnostic suspicion is an extramedullary relapse or an accelerated transformation of the myeloid disease, classically known as tissue lymphoid blastic crisis. The mandatory performance of a detailed Doppler ultrasound evaluation and, definitively, an excisional nodal biopsy with full immunohistochemical mapping are the only components capable of preventing catastrophic diagnostic errors, avoiding erroneously cataloging an indolent lymphoma as a refractory acute leukemia of poor prognosis.⁵

The histopathological and immunohistochemical characterization of our patient's nodal specimen provided the determining elements to confirm the definitive diagnosis of SLL. The positivity for CD20 and the coexpression of CD43, together with reactivity for BCL2 and MUM1 and strict negativity for the germinal center marker CD10, configure the molecular signature of this lymphoid entity. The morphology of mature centrocytes with a low Ki67 proliferation index of 15% formally rules out a large B-cell lymphoma or an aggressive follicular lymphoma, allowing the lesion to be classified within the spectrum of chronic lymphoproliferative disorders of small B cells.⁶

The development of a moderate pericardial effusion during the patient's evolution represented a critical clinical complication of iatrogenic origin well documented in the medical literature associated with the chronic use of dasatinib. Dasatinib possesses potent inhibitory activity on accessory endothelial kinases, which can increase endothelial

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and pleuropericardial permeability, inducing the formation of exudative serous or chylous effusions. The temporary and scheduled interruption of the TKI proved to be an effective therapeutic measure, achieving complete resolution of the pericardial compromise without compromising the molecular stability of the CML, which remained under strict control.⁷

Therapeutic decisions and drug interactions in CML-SLL coexistence pose highly complex dilemmas that must be individualized according to the systemic activity criteria dictated by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL). In scenarios where the SLL behaves indolently, is asymptomatic, does not generate immune cytopenias or bulky lymphadenopathies, the guideline stipulates that the lymphoma must be subjected exclusively to an active surveillance strategy, prioritizing the maintenance of CML control with the TKI. Initiating chemoimmunotherapy prematurely with regimens based on rituximab, venetoclax, or chlorambucil would exponentially increase the risk of severe cumulative myelosuppression and drug interactions, compromising the stability of the patient.⁹

The long-term prognosis of these patients with dual neoplasms is not determined linearly by the summation of both diseases, but by the biology of the dominant neoplastic clone and the occurrence of cross-toxicities from treatment. In this particular case, given that the CML is in sustained major molecular remission and the SLL exhibits a low-replication clinical behavior (Ki67 15%), the patient's life expectancy remains favorable. However, it is essential to maintain strict clinical and molecular screening to detect early data of active lymphoid progression or an eventual loss of molecular response of CML that would force a complete restructuring of the therapeutic strategy.¹⁰

The final tomographic report issued during the prolonged follow-up period acquires paramount scientific relevance for this article, as it provides objective evidence of the patient's state of consolidation and complete remission. Despite the inherent biological hostility of sequentially harboring two hematologic malignancies of completely divergent lineages (myeloid and lymphoid), the follow-up CT scan confirmed that the patient remains stable, clinically healthy, and free of active tumor growth. The resolution of the pathological cervical lymphadenopathies previously documented on ultrasound, the restoration of the normal nodal fatty hilum, and the absolute absence of infiltration or visceromegaly in target organs such as the liver and spleen strongly confirm the therapeutic efficacy of the administered regimen. This favorable outcome demonstrates that, through an active surveillance strategy and controlled TKI dosing, it is fully feasible to induce sustained remission of both clones, restoring an ordinary and active hematologic disease-free life expectancy despite the catastrophic initial dual tumor presentation.

CONCLUSIONS

The sequential coexistence of Small Lymphocytic Lymphoma as a metachronous second primary tumor in a patient under close monitoring and molecular remission of Chronic Myeloid Leukemia constitutes an extraordinarily rare oncohematological entity. This case categorically emphasizes the methodological requirement to perform an exhaustive cervical Doppler ultrasound evaluation and an excisional lymph node biopsy with a complete immunohistochemistry panel in the presence of newly appearing persistent lymphadenopathies. Such an approach is indispensable to evade the diagnostic pitfall of assuming, at first glance, an extramedullary myeloid relapse or a CML blastic crisis, which would result in highly aggressive and inappropriate cytotoxic therapies.

The persistence of a sustained major molecular response of the myeloid clone under dasatinib, along with the indolent biological kinetics, the absence of extranodal involvement, and the low cellular proliferation index Ki67 (15%) of the clonal B-lymphoid component, provides scientific evidence that strongly supports the independent development of two parallel hematological malignancies with disconnected biological origins. Clinical management must be based on therapeutic prudence and adhere strictly to the guidelines dictated by the international workshop of the IWCLL; in the absence of criteria for clinical activity or massive systemic compromise, SLL must be exclusively subjected to a rigorous active surveillance strategy ("watch and wait"). This individualized medical conduct allows for the continuation of successful targeted TKI therapy for CML, mitigating the risk of cross-cumulative bone marrow toxicity, severe febrile neutropenia, and complex drug interactions, ultimately optimizing both the oncological prognosis and the long-term quality of life and overall survival of the patient.

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