CASE REPORT

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The occurrence of chronic lymphocytic leukemia after chronic phase of chronic myeloid leukemia: case report and literature review

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Abstract

The occurrence of chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) in the same patient is a rare event. In published literature, CML diagnosis follows CLL diagnosis or both leukemias are diagnosed simultaneously or rarely, CLL diagnosis follows CML diagnosis. We report the case of one patient with renal adenocarcinoma who was diagnosed with CLL 60 months after CML diagnosis. At that time, the patient was in complete cytogenetic response (CCyR) and major molecular response (MMR) of CML clone according to *European LeukemiaNet* (ELN) recommendations and presented clinical and hematological signs of progressive CLL clone. After 24 months of regular monitoring, the patient presented signs of CLL clone expansion. The FISH (fluorescence *in situ* hybridization) analysis for CLL prognostic factors, performed before treatment, was positive for tumor protein p53 (TP53) and 13q14.3 mutations. The Li–Fraumeni syndrome (LFS) was considered but TP53 mutation was considered acquired and patient's reduced overall, progression free and disease free survival might sustained that hypothesis. Imatinib (IM) was stopped and patient received chemotherapy until obtained a stable partial response. Twelve months after last cycle of chemotherapy, the patient received second line treatment due CLL clone progression signs but died due to neutropenia related complications. This article is the first Romanian report of CLL occurrence after CML diagnosis and as far as we know the fourth case report of such association in published literature.

Keywords: chronic myeloid leukemia, chronic lymphocytic leukemia, tyrosine kinase inhibitors, *BCR-ABL1*, Philadelphia chromosome, TP53 mutation.

Introduction

Chronic myeloid leukemia (CML) is, according to 2008 WHO (*World Health Organization*) classification, a myeloproliferative neoplasm and it becomes symptomatic when a pluripotent hematopoietic stem cell acquires a Philadelphia chromosome that carries the *BCR-ABL1* (break cluster region – Abelson gene) fusion gene, conferring a proliferative advantage to normal hematopoietic cells and allowing Philadelphia positive clone to gradually displace normal hematopoiesis. CML is characterized by a unique cytogenetic abnormality known as translocation (9;22)(q34;q11) or Philadelphia chromosome involving fusion *BCR* gene on chromosome 22 and *ABL* gene on chromosome 9. As a result, this fusion gene determines permanent activation BCR-ABL tyrosine kinase leading to uncontrolled proliferation of myeloid cells.

Chronic lymphocytic leukemia (CLL) is an indolent neoplasm arising from the accumulation of monoclonal CD5-positive B-cells with low proliferation rate and is the most common form of leukemia in the Western world adult population.

The occurrence of CML and CLL in the same patient has been described as single cases [1–8]. Laurenti *et al.* [9] reported the largest series of patients with a coexistence of CLL and other myeloproliferative neoplasms including CML, as a result of a retrospective multicentric Italian study. These authors identified eight patients with concomitance of CLL and CML; however, in some cases, they occurred simultaneously.

Aim

In published literature, there are only three case reports in which CLL clone was detected at 20, 36 and 74 months after the diagnosis of chronic phase of CML. In most cases, patients had concomitant CML and CLL or CML developed several years after chemo- or radiotherapy for CLL. Our paper is the first Romanian report of CLL occurrence after CML diagnosis and as far as we know the fourth case report of such association in published literature.

Case report

In this article, we report the case of a 54-year-old patient who underwent nephrectomy for renal tumor. The histopathology exam with immunohistochemical tests was

suggestive for basophilic subtype of papillary tubular adenocarcinoma.

Six months later, routine blood count showed leukocytosis with left deviation of differential count and normal platelet and red cell parameters.

The bone marrow biopsy (BMB) revealed hypercellular marrow with marked hyperplasia of granulocytic and megakaryocytic series, with left deviation (Figure 1).

FISH (fluorescence *in situ* hybridization) exam for *BCR* (22q11.23)/*ABL* (9q34) used Dual Color ON *BCR/ABL* translocation probe, BCR was marked with green (G) and ABL with red (R). Expected signals patterns: negative 2R 2G (normal) and positive (standard): 1R 1G 2F (presence of *BCR/ABL* translocation). The exam analyzed interphase nuclei not metaphases. BCR/ABL rearrangement because of translocation BCR/ABL was positive in 71% of analyzed nuclei. Conclusion: Nuc ish (ABL1x3), (BCRx3), (ABL con BCRx2) [71/100].

A fresh bone marrow (BM) sample was obtained and standard cytogenetic technique was performed. The bone marrow sample was processed using overnight and synchronized cultures and conventional cytogenetic procedures with GTG banding. At least 20 metaphases were analyzed and the karyotype was described according to *International System for Human Cytogenetic Nomenclature* (ISCN) recommendations [10]. Cytogenetic exam was positive for Philadelphia chromosome in 95% of analyzed metaphases (Figure 2).

Qualitative and quantitative real-time PCR (polymerase chain reaction) analyses were performed using LightCycler™ platform. The result was expressed on an international scale (IS) and it was used a conversion factor (CF) according to the *European LeukemiaNet* (ELN) recommendations [11]. The results showed *BCR/ABL* transcript b2a2 type and the level of transcript [*BCR-ABL1* × CF (0.8461)] was 60%.

The patient was diagnosed as chronic phase of CML and received Hydroxycarbamide (Hydroxyurea – Hu), which lead to normal blood count parameters followed six months later by 400 mg daily of Imatinib (IM). Complete cytogenetic remission (CCyR) was achieved at 12 months and major molecular response (MMR) was achieved at 18 months according ELN recommendations [12]. The periodic follow-up showed maintenance of CCyR and MMR according to ELN recommendations [12].

At month 60 after CML diagnosis, routine blood count showed normal leukocytes count with absolute lymphocytosis and normal platelet and red cell parameters.

The bone marrow exam (bone marrow aspirate and BMB) revealed hypercellular bone marrow due to 45–50% infiltration with small-sized mature lymphoid cells. Immunohistochemical staining showed that these cells were positive for CD20 (CD – cluster of differentiation), with aberrant expression of CD5 (pan T-cells marker) and CD23 (dendritic cells marker) small B-cells. These results were suggestive for B-cell clone CLL (Figures 3 and 4).

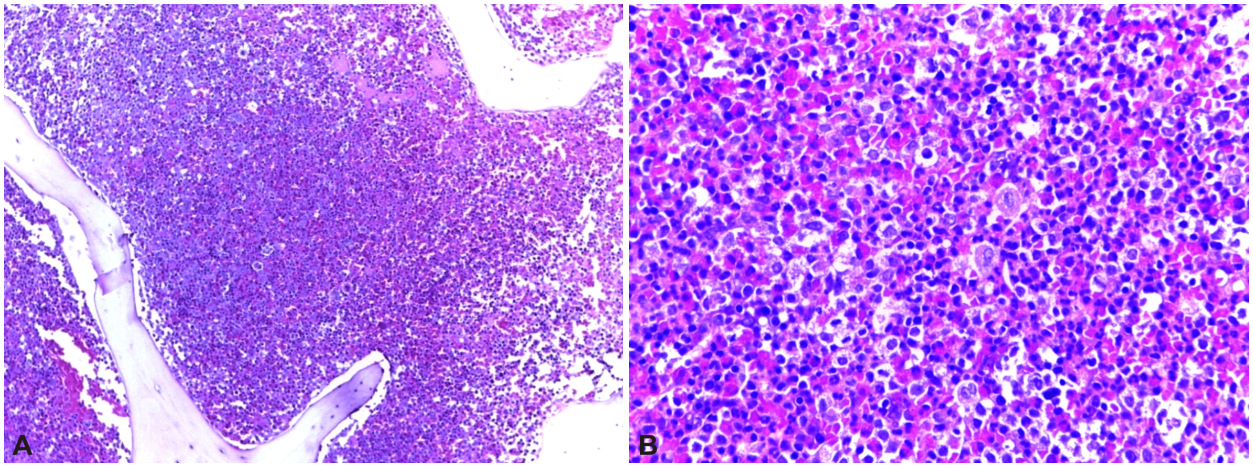

Figure 1 – ***BMB suggestive for CML: (A) Compact hypercellular marrow [Hematoxylin–Eosin (HE) staining, ×100]; (B) Myeloid and megakaryocytic hyperplasia with left deviation (HE staining, ×400).***

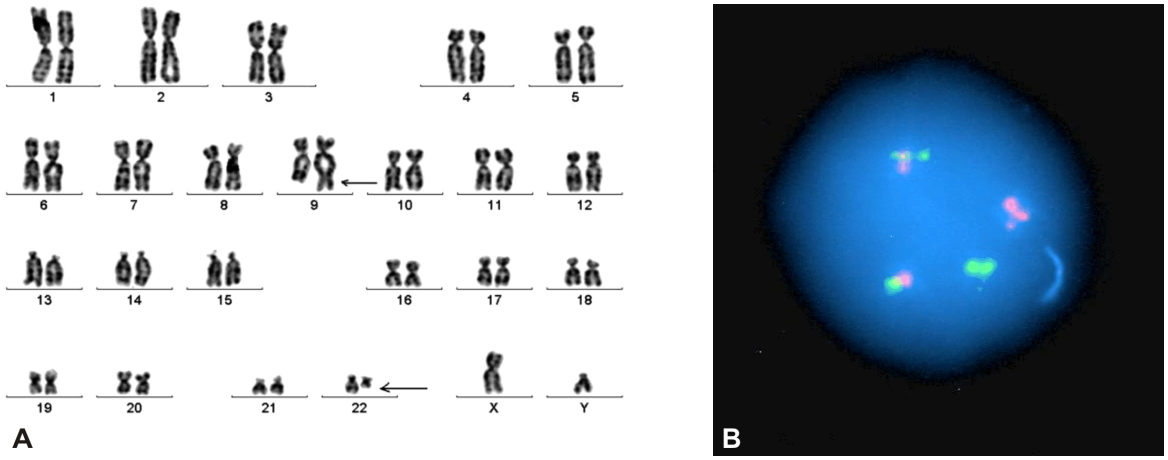

Figure 2 – ***(A) The karyotype according to ISCN recommendations [46, XY, t(9;22)(q34;q11)] and (B) Nuc ish (ABL1x3), (BCRx3), (ABL con BCRx2).***

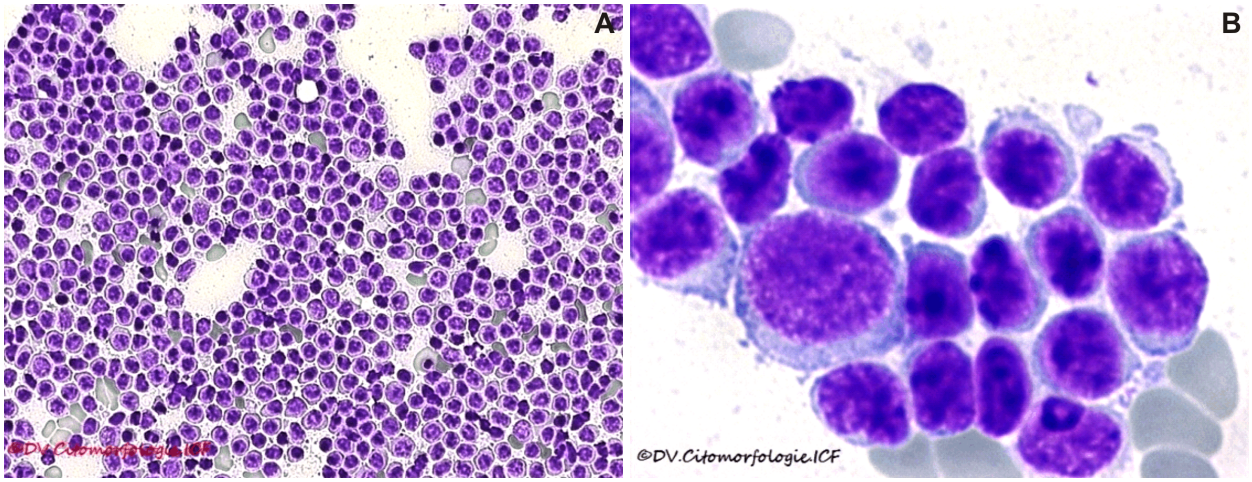

Figure 3 – ***Morphology of bone marrow aspirate of CLL: marrow infiltration with slightly polymorphous mature lymphocytes. (A) May–Grünwald–Giemsa (MGG) staining, ×200; (B) MGG staining, ×1000 (oil immersion).***

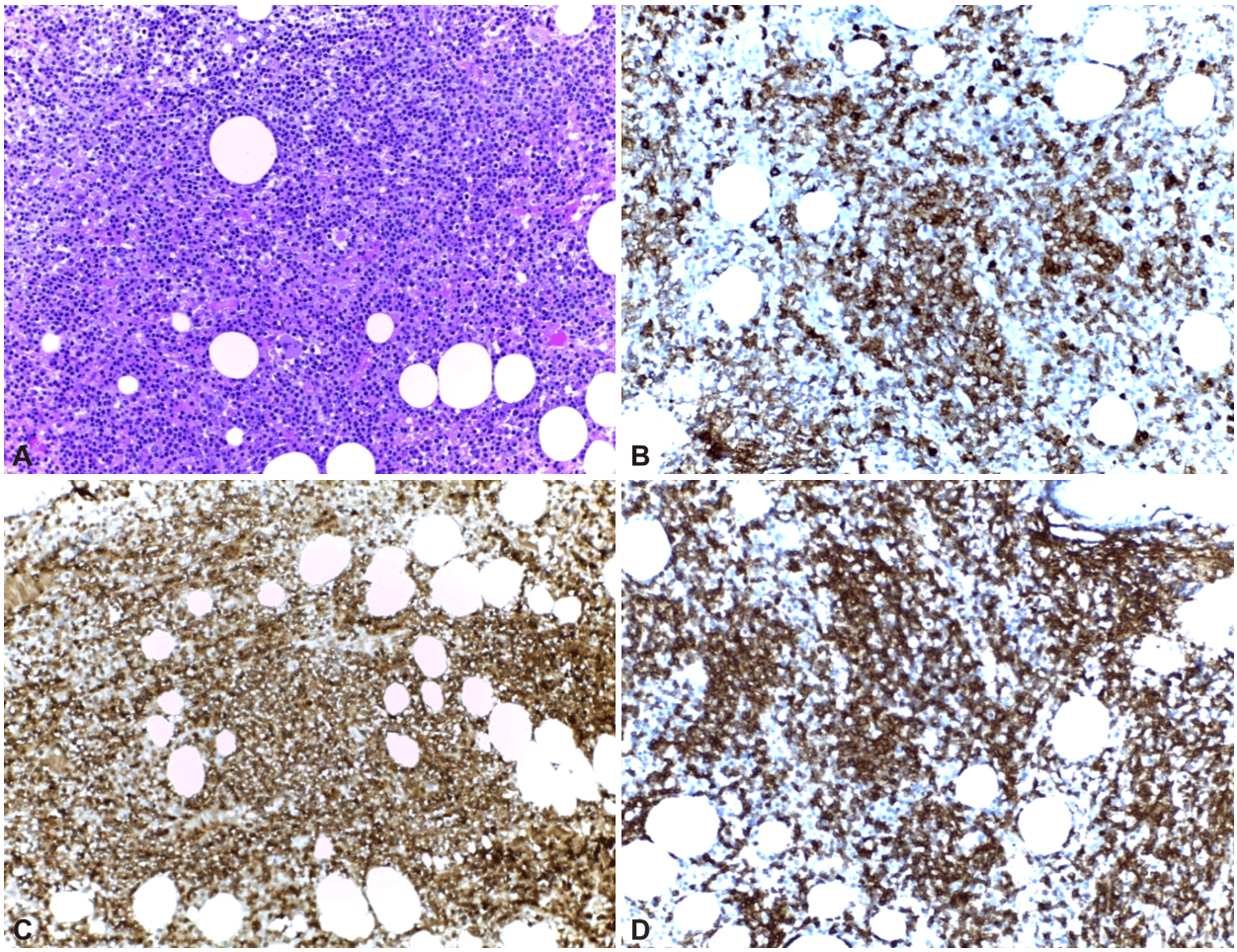

Figure 4 – ***BMB of CLL: (A) Involvement of bone marrow by small-sized mature lymphoid cells in an interstitial and a nodular pattern (HE staining, ×200); Immunohistochemistry (IHC) tests positive for CD20 (B), CD5 (C), and for CD23 (D) (IHC staining, ×200).***

The peripheral blood immunophenotype exam analyzed 7000 events using FACSCalibur™ flow-cytometry technique and CellQuest software and showed a monoclonal B-cell population (59%) positive for CD5, CD23, CD20, CD22, CD43, CD11c, IgG (kappa) and negative for CD79b, CD38, and FMC7 (Figure 5).

At month 24 after the CLL diagnosis, the patient maintained CCyR and MR4.5 (4.5 molecular response) [*BCR-ABL1* × CF (0.8461) = 0.002%] according to ELN recommendations but presented progressive generalized lymphadenopathies, splenomegaly, anemia, thrombocytopenia and massive lymphoid bone marrow infiltration up to 90%, suggestive for CLL clone progression.

Peripheral blood FISH exam for CLL prognostic factors was performed and analyzed 100 interphase nuclei. Two colors for specific loci were used: 13q14.3 (red) and 13qter (green); D11Z1 (green) and ATM (red); TP53 (red) and D17Z1 (green); D6Z1 (green) and MYB (red);

D12Z3 (red) in interphase nuclei. The interphase 100 nuclei showed positivity for 13q14.3 in 90% {nuc ish (D13S319x1) [90/100]}; negativity for ATM {nuc ish (ATMx2) [100]}; positivity for TP53 in 80% {nuc ish (TP53x1) [80/100]}; negativity for MYB {nuc ish (MYBx2) [100]}, negativity for trisomy 12 {nuc ish (D12Z3x2) [100]}. FISH analysis showed nuc ish (ATM, MYB, D12Z3)x2 [100], (D13S319x1) [90/100] (TP53x1) [80/100].

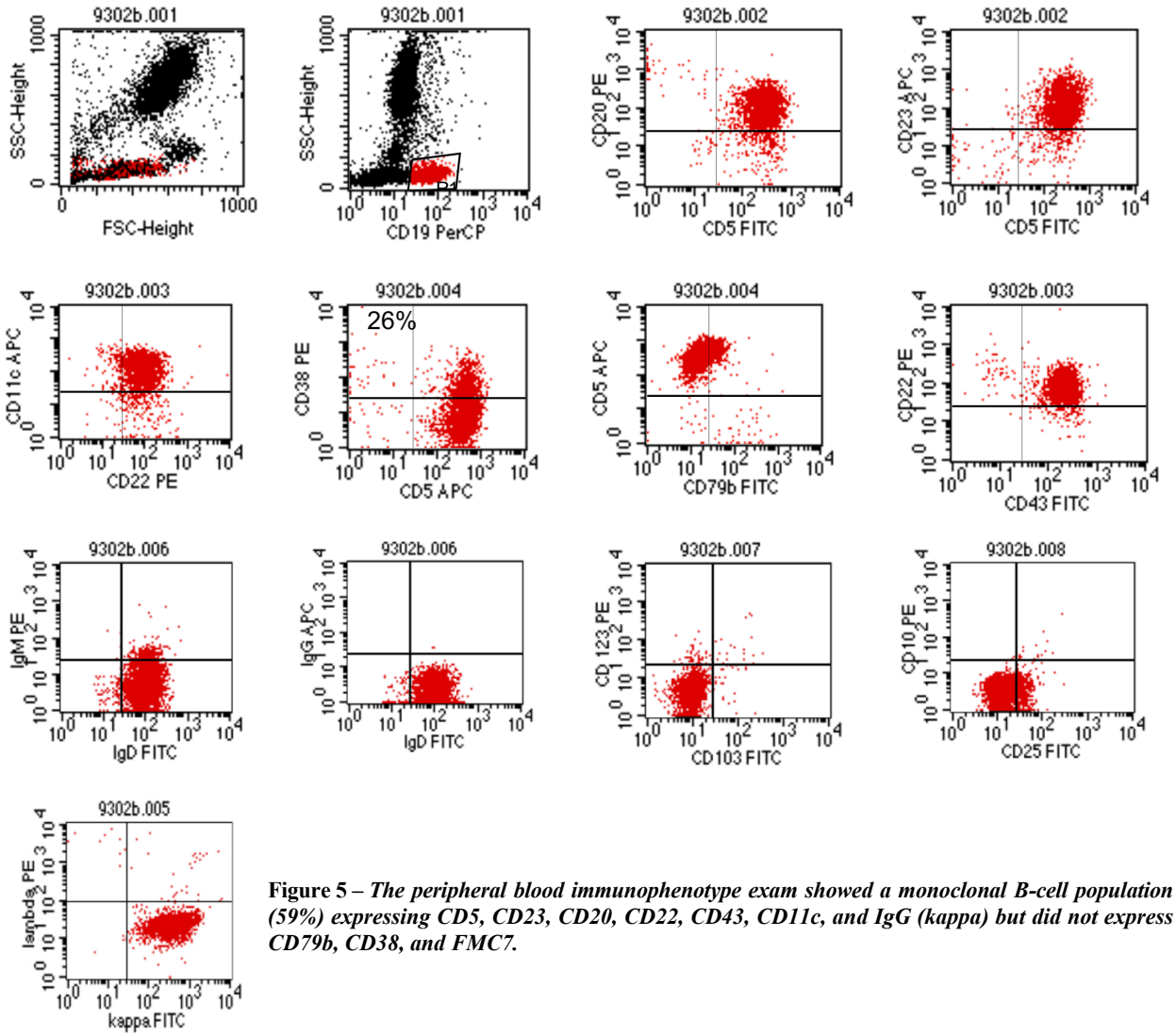

Figure 5 – ***The peripheral blood immunophenotype exam showed a monoclonal B-cell population (59%) expressing CD5, CD23, CD20, CD22, CD43, CD11c, and IgG (kappa) but did not express CD79b, CD38, and FMC7.***

At that time, Imatinib (IM) was stopped due to silent CML clone and patient received Rituximab-based chemotherapy (five cycles) until obtained a stable partial response.

At month 12 after last cycle of chemotherapy, the patient presented signs of CLL progression and received second line chemotherapy but died due to neutropenia related complications. At that time, there were no cytogenetic and molecular markers of CML clone.

Discussion

We report the case of one patient without any family history of cancer who was treated by nephrectomy for adenocarcinoma and six months later was diagnosed as chronic phase of chromosome Philadelphia positive CML with excellent response to first generation tyrosine-kinase inhibitor (TKI). At month 54 of TKI treatment, with patient in CCyR and MR4.5, CLL's clinical and biological signs developed. At month 24 after CLL diagnosis, the patient received treatment due to disease progression and due to silent CML clone, Imatinib treatment was stopped. At month 12 after last cycle of chemotherapy, the patient presented signs of CLL progression and received second line chemotherapy. The patient died due severe neutropenia complications at 96 months after CML diagnosis and 36 months after CLL diagnosis. At the time of death, there were no cytogenetic and molecular markers of CML clone.

In published literature, there are three case reports in which CLL clone was detected at 20, 36 and 74 months after the diagnosis of chronic phase of CML [4, 13, 14]. In most cases, patients had concomitant CML and CLL [1–3, 15–17] or CML developed several years after chemo- or radiotherapy for CLL [18–26] (Table 1).

In this setting, two hematological diseases occurring in the same patient, there are several hypotheses to be considered: the same clone origin, Li–Fraumeni syndrome (LFS), leukemogenesis triggered by failure of bone marrow microenvironment or long-term exposure to TKIs.

Is there a common hematopoietic stem cell for CML and CLL? This is an unsustainable hypothesis since there is data demonstrating the cellular origin of CML in a myeloid hematopoietic stem cell while CLL arises from naïve B-cell that already left bone marrow compartment.

In our case, there were no cytogenetic and molecular markers of an active CML clone at the time of CLL diagnosis, which makes it difficult to demonstrate that the two diseases have a common hematopoietic stem cell origin and it sustains published data of different clone origin.

Table 1 – ***Published articles with CML and CLL patients***

Articles	Age [years]	Gender	Interval [months]	Treatment
Simultaneous CML and CLL				
Leoni *et al.* (1987) [15]	55	M	simultaneous	–
Maher *et al.* (1993) [16]	69	M	simultaneous	Chl, Hu
Crescenzi *et al.* (2002) [1]	64	M	simultaneous	Hu
Vilpo *et al.* (1979) [17]	58	M	simultaneous	none
Esteve *et al.* (1997) [2]	71	F	simultaneous	Hu
Mansat-De Mas *et al.* (2003) [3]	68	M	simultaneous	Hu, IFN-*α*
CML after diagnosis of CLL				
Khojasteh *et al.* (1981) [18]	55	M	61	Chl
Faguet *et al.* (1983) [19]	83	M	2	Bus, Chl
Teichmann *et al.* (1986) [20]	47	M	72	Chl, Vin, Bleo
Whang-Peng *et al.* (1974) [21]	62	M	36	Chl
	74	M	24	none
Schreiber *et al.* (1984) [22]	55	M	84	Chl
Hashimi *et al.* (1986) [23]	82	F	60	none
Nanjangud *et al.* (1996) [24]	43	M	73	TBI
Mossafa *et al.* (2001) [25]	76	F	12	none
Ramanarayanan *et al.* (2006) [26]	52	F	29	Fludarabine
CLL after the diagnosis of CML				
Salim *et al.* (2002) [13]	54	F	36	Hu, IFN-*α*, IM
Gargallo *et al.* (2005) [4]	88	F	20	Chl, Hu
Bhagavathi *et al.* (2008) [14]	71	M	74	IM

CML: Chronic myeloid leukemia; CLL: Chronic lymphocytic leukemia; M: Male; F: Female; Chl: Chlorambucil; Hu: Hydroxyurea (Hydroxycarbamide); IFN-*α*: Interferon-alpha; Bus: Busulfan; Vin: Vinblastine; Bleo: Bleomycin; TBI: Total body irradiation; IM: Imatinib.

Esteve *et al.* reported the simultaneous diagnosis of CML and CLL in a patient who received Hu and 18 months later, was diagnosed with acute lymphoblastic leukemia. Initially, complete remission was achieved after induction treatment but the patient lost response during consolidation treatment and died five months later due to progression [2].

Mansat-De Mas *et al.* used FISH and molecular techniques to demonstrate that CD19-positive cells shows no *BCR/ABL* rearrangement but CD19-negative cells expressed the fusion gene demonstrating that monoclonal transformation of B-lymphocytes occurs in a subset of Philadelphia negative cells [3].

Salim *et al.* reported CLL diagnosis few years after CML diagnosis. The authors demonstrated that CLL clone arisen from a Philadelphia chromosome negative clone [13].

Chang *et al.* reported CLL diagnosis six months after CML diagnosis in a patient who received Hu until normal blood count parameters followed by IM. The occurrence of both diseases has been demonstrated by bone marrow, flow cytometry, cytogenetic and molecular exams. The authors used fluorescence activated sorting method of purified CLL cells (CD5+/CD19+) and analyzed them by interphase FISH with two color to detect translocations *BCR/ABL1*. CLL patients may present genomic aberrations especially 13q, 11q23, 12 and 17p, FISH technique was used but no abnormalities were detected. The conclusion was that there are two different clone proliferations: a population of B-cells clone, which did not expressed the *BCR/ABL1* fusion gene and another CML clone which expressed BCR/ABL1 fusion gene [27].

Gargallo *et al.* reported B-cell CLL diagnosis 20 months after CML diagnosis. The patient received Hu and 20 months later, blood count reveals leukocytosis and absolute lymphocytosis. The authors demonstrated by cytogenetic, FISH and molecular exams that the two diseases have emerged from different clones. B-cell CLL clone was represented by CD5 and CD19-positive mature lymphocytes with rearrangements in heavy chain immunoglobulin and FISH exam detected the presence of deletion 13q14, one of the most common aberrations associated with the disease. CML clone revealed immature morphology, Philadelphia chromosome positivity at cytogenetic exam and p210 transcript of *BCR/ABL* at molecular exam. Thus, it was demonstrated CLL clone arisen from a pluripotent progenitor cell different from CML clone. Although it is known that irregular immune response in CLL contributes to increased risk of second malignancies, the natural evolution of CML is to blast phase and few cases were reported in which second hematological or non-hematological neoplasm developed. The authors' conclusion was that during chronic phase of CML, a negative Philadelphia chromosome B-cells population arises from a different pluripotent stem cell and it proliferates into CLL [4].

Bhagavathi *et al.* reported B-cell CLL diagnosis 72 months after CML diagnosis. The patient received IM and was in MMR at the time of CLL diagnosis. The CLL clone was demonstrated by flow cytometry and cytogenetic exams. No further investigations were made to demonstrate if the two diseases had different progenitor stem cells [14].

Laurenti *et al.* reported the largest number of patients with a coexistence of CLL and other myeloproliferative neoplasms including CML, polycythemia vera, essential thrombocythemia or primary myelofibrosis as a result of a retrospective multicentre Italian study of 46 cases. The authors identified eight patients with concomitance of CLL and CML. The pattern of onset of the two neoplasms was heterogeneous. In majority of cases, CML diagnosis followed CLL diagnosis but in some cases, they occurred simultaneously [9].

Another hypothesis to be considered is whether this association represents malfunctions of bone marrow microenvironment that triggers leukemagenesis or if the two events occur randomly in the same individual. The occurrence CLL and CML may be favored by interaction between lymphoid and myeloid lines [28]. It appears that

the transformed BCR-ABL cells produce several cytokines especially interleukin-3 (IL-3). IL-3 increases the production of immature B-cells from CD34-positive CD38-negative progenitor cells [29]. This mechanism may contribute to the development of CLL in patients previously diagnosed with CML. It is an interesting hypothesis, but it requires more data.

LFS is a hereditary cancer predisposition syndrome reported by Frederick Li and Joseph Fraumeni who observed that wide range of cancers found in affected families, the inherited higher risk of developing cancer among generations and the relatively early age of the cancer diagnosis with nearly half of affected individuals having a cancer diagnosis before age 30. The most common types of cancer found in families with LFS include osteosarcoma, soft-tissue sarcoma, acute leukemia, breast cancer, brain cancer and adrenal cortical tumors. An increased risk for melanoma, Wilms' tumor, cancers of the stomach, colon, pancreas, esophagus, lung, and gonad have also been reported. LFS is most commonly caused by a mutation (alteration) in a gene called *TP53*, which is the genetic blueprint for a protein called p53. The mutation takes away the gene's ability to function correctly. Approximately 70% of families with LFS will have a mutation in the *TP53* gene. Mutations in another gene, called *CHEK2*, have been found in some families with LFS. It is not known if the cancer risks are the same in families that have *TP53* mutations and *CHEK2* mutations. Classic LFS is diagnosed when a person has all of the following criteria: a sarcoma diagnosed before age 45; a first-degree relative with any cancer before age 45; a first-degree relative or second-degree relative with any cancer before age 45 or a sarcoma at any age. In our case, the FISH exam showed *TP53* and 13q14.3 mutations. LFS was considered but it is inherited in an autosomal dominant pattern and in most cases, an affected person has a parent and other family members with cancers, which is one characteristic of the condition. *TP53* mutation was considered acquired and short overall, progression free and disease free survival might explain that hypothesis.

In published literature, there are reports of CML patients, which developed a second cancer during first and second generation TKI. An important study was conducted by *MD Anderson Cancer Centre*, which analyzed the records of 1445 patients with CML/myeloproliferative neoplasm or other hematological malignancies treated with TKIs to investigate frequency and characteristics of second malignancies. After a median follow-up of 107 months (range: 13–362 months) after CML/myeloproliferative neoplasm diagnosis, 66 (4.6%) patients developed 80 second cancers, including skin (31%), prostate (15%), melanoma (13%), digestive system (10%), kidney (4%), thyroid (4%), breast (3%), chronic lymphocytic leukemia (3%), hepatobiliary (3%) and other cancers (14%). The risk of second cancer was lower than expected (observed-to-expected ratio, 0.6; 95% confidence interval, 0.44–0.81). Second cancers occur in a small percentage of patients receiving therapy with TKIs for hematological malignancies, mostly CML. At the moment, no evidence suggests that exposure to TKIs increases the risk of developing second cancers [30].

Conclusions

The occurrence of CLL and CML is a rare event and the widely accepted hypothesis is that the two leukemias arise from two separate events but it does not exclude entirely the implication of TKIs in developing another cancer. Analyzed in the context of the underlying lifetime risk of developing cancer by the general population and in patients who survive cancer, no evidence at the moment suggests that exposure to TKIs is carcinogenic. Continued long-term monitoring of these patients and reporting of any patients who develop second cancers are warranted to further define any possible longer-term risks. This article is the first Romanian report of CLL occurrence after CML diagnosis and as far as we know the fourth case report of such association in published literature.

Conflict of interests

The authors indicated no potential conflicts of interest.

Author contribution

All authors have equal contribution.

Acknowledgments

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References

[1] Crescenzi B, Sacchi S, Marasca R, Temperani P, La Starza R, Matteucci C, Bonacorsi G, Romoli S, Martelli MF, Mecucci C, Emilia G. Distinct genomic events in the myeloid and lymphoid lineages in simultaneous presentation of chronic myeloid leukemia and B-chronic lymphocytic leukemia. Leukemia, 2002, 16(5):955–956.

[2] Esteve J, Cervantes F, Rives S, Rozman M, Zarco MA, Montesettat E. Simultaneous occurrence of B-cell chronic lymphocytic leukemia and chronic myeloid leukemia with further evolution to lymphoid blast crisis. Hematologica, 1997, 82(5):596–599.

[3] Mansat-De Mas V, Rigal-Huguet F, Cassar G, Kuhlein E, Laurent G, Dastugue N. Chronic myeloid leukemia associated with B-cell chronic lymphocytic leukemia: evidence of two separate clones as shown by combined cell-sorting and fluorescence *in situ* hybridisation. Leuk Lymphoma, 2003, 44(5):867–869.

[4] Gargallo P, Cacchione R, Chena C, Dupont J, Garay G, Riveros D, Larripa I, Slavutsky I. Chronic lymphocytic leukemia developing in a patient with chronic myeloid leukemia: evidence of distinct lineage-associated genomic events. Cancer Genet Cytogenet, 2005, 161(1):74–77.

[5] Gozzetti A, Bocchia M, Crupi R, Calabrese S, Pirrotta MT, Raspadori D, Defina M, Algeri R, Lauria F. Concomitant chronic myeloid leukemia and chronic lymphocytic leukemia: a different clonal origin shown by molecular cytogenetics. Cancer Genet Cytogenet, 2008, 180(1):83–84.

[6] Buda-Okreglak EM, Cordaro DV. Simultaneous chronic myeloid leukemia and chronic lymphocytic leukemia. Blood, 2011, 177(20):5279.

[7] D'Arena G, Gemei M, Luciano L, D'Auria F, Deaglio S, Statuto T, Bianchino G, Grieco V, Mansueto G, Guariglia R, Pietrantuono G, Martorelli MC, Villani O, Del Vecchio L, Musto P. 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–e330.

[8] Yoon JY, Kumar R, Aloyz R, Johnston JB. Response of concomitant chronic myelogenous leukemia and chronic lymphocytic leukemia to imatinib mesylate. Leuk Res, 2011, 35(9):e179–e180.

[9] Laurenti L, Tarnani M, Nichele I, Ciolli S, Cortelezzi A, Forconi F, Rossi D, Mauro FR, D'Arena G, Del Poeta G, Montanaro M, Morabito F, Musolino C, Callea V, Falchi L, Tedeschi A, Ambrosetti A, Gaidano G, Leone G, Foà R. The coexistence of chronic lymphocytic leukemia and myeloproliferative neoplasms: a retrospective multicentric GIMEMA experience. Am J Hematol, 2011, 86(12):1007–1012.
[10] Shaffer LG, Slovak ML, Campbell JL (eds). An International System for Human Cytogenetic Nomenclature. Cytogenetic and Genome Research, Karger, Basel (Switzerland), 2009.
[11] Müller MC, Cross NC, Erben P, Schenk T, Hanfstein B, Ernst T, Hehlmann R, Branford S, Saglio G, Hochhaus A. Harmonization of molecular monitoring of CML therapy in Europe. Leukemia, 2009, 23(11):1957–1963.
[12] Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Martinelli G, Mayer J, Müller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Saußele S, Schiffer C, Silver R, Simonsson B, Steegmann JL, Goldman JM, Hehlmann R. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood, 2013, 122(6):872–884.
[13] Salim R, Wang L, Lin K, Clark RE. Chronic lymphocytic leukemia developing in the course of chronic myeloid leukemia. Leuk Lymphoma, 2002, 43(11):2225–2227.
[14] Bhagavathi S, Borromeo V, Desai H, Crisan D. Case report and literature review: a rare patient with chronic myeloid leukemia and chronic lymphocytic leukemia. Ann Clin Lab Sci, 2008, 38(4):405–409.
[15] Leoni F, Ferrini PR, Castoldi GL, Pata M, del Prete GF, Tomasi P. Simultaneous occurrence of chronic granulocytic leukemia and chronic lymphocytic leukemia. Haematologica, 1987, 72(3):253–256.
[16] Maher VE, Gill L, Towners PL, Wallace JE, Savas L, Woda BA, Ansell JE. Simultaneous chronic lymphocytic leukemia and chronic myelogenous leukemia. Evidence of a separate stem cell origin. Cancer, 1993, 71(6):1993–1997.
[17] Vilpo JA, Klemi P, Lassila O, Schröder J, de la Chapelle A. Transformation in chronic granulocytic leukaemia. Different blast cell clones in different anatomical sites. Acta Haematol, 1979, 62(5–6):247–250.
[18] Khojasteh A, Perry MC, Taylor HM. Chronic myelocytic leukemia developing as a second cancer in a patient with chronic lymphocytic leukemia. CA Cancer J Clin, 1981, 31(3):172–176.
[19] Faguet GB, Little T, Agee JF, Garver FA. Chronic lymphocytic leukemia evolving into chronic myelocytic leukemia. Cancer, 1983, 52(9):1647–1652.
[20] Teichmann JV, Sieber G, Ludwig WD, Karow J, Ruehl H. Chronic myelocytic leukemia as a second neoplasia in the course of chronic lymphocytic leukemia. Case report and review of the literature. Leuk Res, 1986, 10(4):361–368.
[21] Whang-Peng J, Gralnick HR, Johnson RE, Lee EC, Lear A. Chronic granulocytic leukemia (CGL) during the course of chronic lymphocytic leukemia (CLL): correlation of blood, marrow, and spleen morphology and cytogenetics. Blood, 1974, 43(3):333–339.
[22] Schreiber ZA, Axelrod MR, Abebe LS. Coexistence of chronic myelogenous leukemia and chronic lymphocytic leukemia. Cancer, 1984, 54(4):697–701.
[23] Hashimi L, Al-Katib A, Mertelsmann R, Mohamed AN, Koziner B. Cytofluorometric detection of chronic myelocytic leukemia supervening in a patient with chronic lymphocytic leukemia. Am J Med, 1986, 80(2):269–275.
[24] Nanjangud GJ, Saikia TK, Chopra H, Kadam PR, Advani SH. Development of Ph positive chronic myeloid leukemia in a patient with chronic lymphocytic leukemia treated with total body irradiation: a rare association. Leuk Lymphoma, 1996, 22(3–4):355–359.
[25] Mossafa H, Fourcade C, Pulic M, Jary L, Cheze S, Szpiro-Tapia S, Troussard X. Chronic lymphocytic leukemia associated with myelodysplastic syndrome and/or chronic myeloid leukemia: evidence for independent clonal chromosomal evolution. Leuk Lymphoma, 2001, 41(3–4):337–341.
[26] Ramanarayanan J, Dunford LM, Baer MR, Sait SN, Lawrence W, McCarthy PL. Chronic myeloid leukemia after treatment of lymphoid malignancies: response to imatinib mesylate and favorable outcomes in three patients. Leuk Res, 2006, 30(6): 701–705.
[27] Chang H, Sutherland R, Nayar R, Li D, Kamel-Reid S, Mile MA, Messner H, Lipton J. Chronic lymphocytic leukemia in the course of chronic myelocytic leukemia: evidence of independent clonal origin as shown by interphase fluorescence *in situ* hybridization and fluorescence-activated cell sorting. Cancer Genet Cytogenet, 2004, 152(2):146–148.
[28] Peters DG, Klucher KM, Perlingeiro RC, Dessain SK, Koh EY, Daley GQ. Autocrine and paracrine effects of an ES-derived, BCR/ABL-transformed hematopoietic cell line that induces leukemia in mice. Oncogene, 2001, 20(21):2636–2646.
[29] Crooks GM, Hao QL, Peterson D, Barsky LW, Bockstoce D. IL-3 increases production of B lymphoid progenitors from human CD34+CD38- cells. J Immunol, 2000, 165(5):2382–2389.
[30] Verma D, Kantarjian H, Strom SS, Rios MB, Jabbour E, Quintas-Cardama A, Verstovsek S, Ravandi F, O'Brien S, Cortes J. Malignancies occurring during therapy with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML) and other hematologic malignancies. Blood, 2011, 118(16): 4353–4358.

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