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An unusual case of chronic lymphocytic leukemia with trisomy 12 and t (14;18) and a favorable response to ibrutinib

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia. Chromosomal abnormalities are reported to play important roles in CLL pathogenesis and evolution, including deletions of 11q, 13q, 17p, and trisomy12, that are frequently observed and have a known prognostic value. Furthermore, the mutational status of the *IGHV* gene was reported as an independent prognostic marker in CLL impacting the choice of therapy. We herein, report an unusual presentation of a Lebanese CLL patient with two cytogenetic abnormalities: trisomy 12 and t(14;18)(q32;q21), along with an unmutated *IGHV*, displaying a favorable response to ibrutinib with a maintained complete remission.

Background

Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia in developed countries [1]. It shows a higher occurrence in elderly individuals, mostly males, with a median age at diagnosis around 72 years, and a sex ratio, of 1.7M:1F [2, 3]. Up to 80% of CLL cases present with recurrent genomic abnormalities, including cytogenetic rearrangements such as deletions in chromosomes 11q, 13q, 17p, trisomy 12, and/or mutations in *TP53, NOTCH1, SF3B1* or *BIRC3*, genes; each conferring distinct prognostic implications and subsequent treatment protocols [4]. Chromosomal reciprocal translocations on the other hand, are uncommon in CLL, described in less than 5% of all reported cases [5].

Over the past few years, mutational status of the immunoglobulin heavy chain variable region (*IGHV*) gene was outlined as an independent prognostic marker in CLL patients, conferring poor survival and resistance to chemoimmunotherapy, when unmutated [6]. The t(14;18)(q32;q21) translocation involving the immunoglobulin heavy chain (*IGH*) locus and B-cell CLL/lymphoma 2 (*BCL2*) gene is a characteristic finding in follicular lymphomas reported in around 90% of cases, while described in only 1% to 2% of CLL cases [7].

In this report, we present an atypical CLL case with rare co-occurrence of 2 chromosomal abnormalities: t(14;18)(q32;q21) and trisomy 12, and a favorable response to ibrutinib treatment

Case report

A 53-year-old woman, with over 20 years of history of smoking and dyslipidemia, was admitted to our hospital, for routine blood tests analyses prior to a hysterectomy procedure in November 2018. The patient had no other remarkable personal or familial medical history. Her blood test showed mild anemia with hemoglobin (Hb) level of 11 g/dl and, white blood count (WBC) of 9,900/μL with 45% lymphocytes [absolute lymphocyte count (ALC) of 4,500/μL].

In July 2019, a follow up blood test analysis, showed lymphocytosis with 36,000 WBC consisting of 86% lymphocytes (ALC of 36,000/μL), along with a Hb of 10.9 g/dl, platelets count of 250,000/μL, as well as high LDH (342 U/L; normal range: 120-245 U/L) and Beta-2 microglobulin (3.6 μg/mL; normal range: 1.1-2.5μg/mL).

Flow cytometry analysis on peripheral blood showed that 65% of cells were positive for CD5, CD19, CD20, CD22, CD23, CD43, HLADR and Lambda S; which is compatible with B-CLL. On physical examination, a few cervical lymph nodes were palpable. CT Scan revealed the presence of multiple cervical and axillary lymph nodes between 8 and 10 mm in size, with moderate diffuse splenomegaly of 13 cm in longitudinal diameter. Fluorescence in situ hybridization (FISH) panel for CLL and *IGHV* mutational status assessment were requested.

Meanwhile, and prior to obtaining the molecular results, the patient presented to the clinic with fatigue and pallor. New blood tests were

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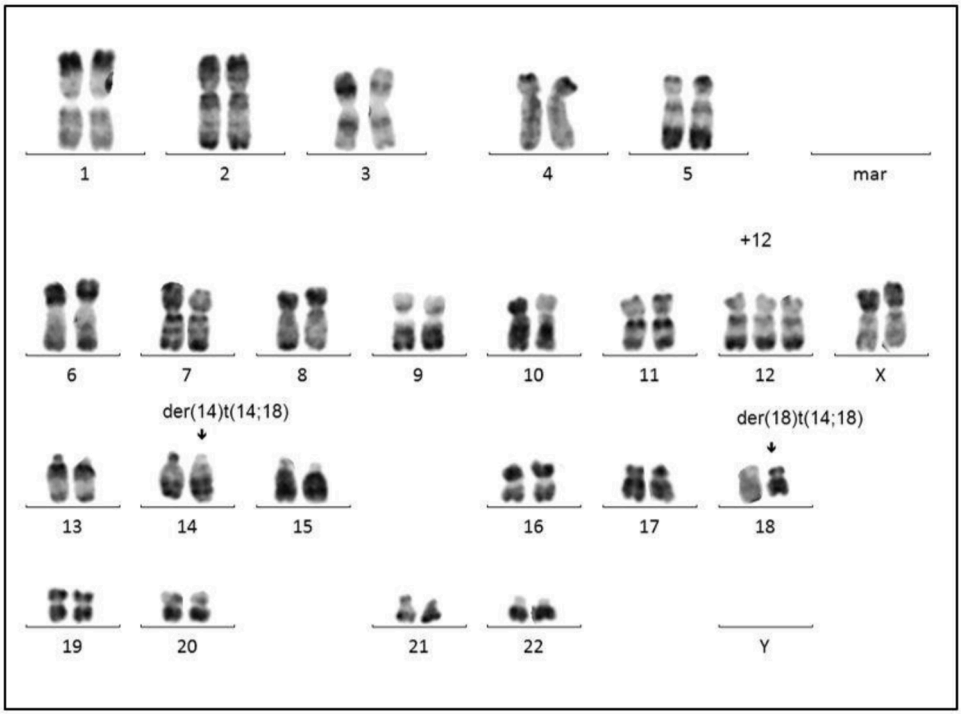

Figure 1. Abnormal karyotype showing an extra chromosome 12 and a translocation t(14;18)(q32;q21)

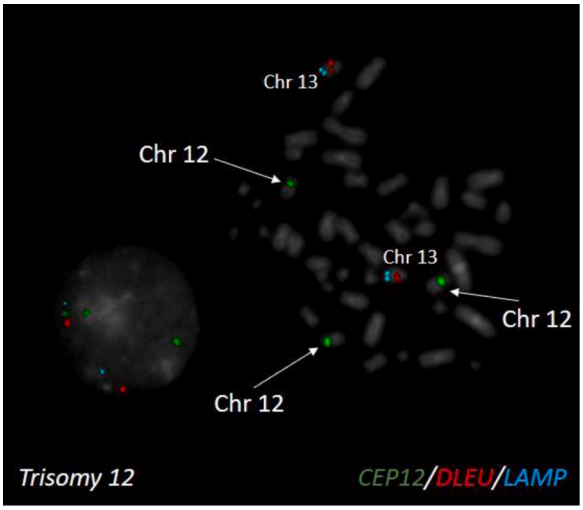

Figure 2. Two cells (metaphase and interphase) both showing one extra green signal (CEP12) suggestive of a trisomy 12. A normal pattern was observed for chromosome 13 (2 *DLEU* signals and 2 *LAMP* signals)

undertaken showing clinical deterioration with a Hb level at 7.9 g/dl, lymphocytosis with 82% of lymphocytes (ALC of 56,000/μL) and a WBC count of 67,000 with no evidence of hemolysis. The patient was admitted to the hospital and a new CT Scan was performed, revealing the presence of multiple infra-centimetric lymph nodes in the cervical, axillary, mediastinal and retroperitoneal regions along with a splenomegaly of 14.5 cm. A bone marrow biopsy, followed by flow cytometry analysis showed the presence of a CLL with, however there was no evidence of transformation into high grade lymphoma, while bone marrow karyotype analyses showed addition of a chromosome 12 along with a t(14;18)(q32;q21) in 90% of analyzed metaphases. This was confirmed on a follow up sample few weeks later (figure 1).

IGHV testing showed an unmutated *IGHV* gene status. Results of the CLL FISH panel revealed addition of a chromosome 12 in 80% of cells observed (Figure 2), with no TP53 rearrangement. The patient was immediately started on ibrutinib 420 mg daily (three tablets of 140 mg), and achieved complete remission upon 3 months of treatment, resulting in total normalization of hemoglobin, WBC and platelet counts. The patient is currently still in complete remission with no drug-related side effects upon 20 months of ibrutinib initiation.

In order to confirm the involvement of the *IGH* and *BCL2* genes in this t(14;18), FISH testing was performed using two brake-apart probes for *BCL2* and *IGH* (Metasystem, Germany), clearly demonstrating rearrangement of both genes in 75 % of examined cells (Figure 3).

Discussion

Our patient, a 53 year old woman with CLL had co-occurrence of 2 chromosomal abnormalities, t(14;18)(q32;q21) and trisomy 12, rarely described in CLL. While t(14;18)(q32;q21) is a characteristic of follicular lymphoma, it is reported in around 20% of germinal center-derived B-cell lymphomas [8]. It has also been described in few case of CLL, with, however unclear prognostic significance [8, 9]. The majority of CLL patients reported with t(14;18)(q32;q21) are men with a sex ratio of 2.5:1 and a median age at diagnosis of 51 years, suggesting a relatively younger occurrence compared to the average age of CLL diagnosis of around 70 years.

Among fourteen CLL patients with t(14;18)(q32;q21) reported to date, 7 had an additional trisomy 12 associated with atypical cellular morphological features including irregular nuclear contours and/or plasmacytoid differentiation as well as an atypical immunophenotype including negative CD5 expression, absence or weak CD23 expression, positive FMC-7, moderate to bright immunoglobulin light chain expression and bright CD20 expression. Furthermore, of the 10 patients tested for *IGHV*, 9 exhibited mutations (Table 1) [8] [9].

Thirteen out of all 14 reported cases required systemic chemotherapy with or without rituximab. Of those, six patients eventually died following progression of their disease (46%), suggesting an aggressive behavior with resistance to chemoimmunotherapy. Four out of those 6 patients (66%) had trisomy 12 in addition to t(14;18)(q32;q21).

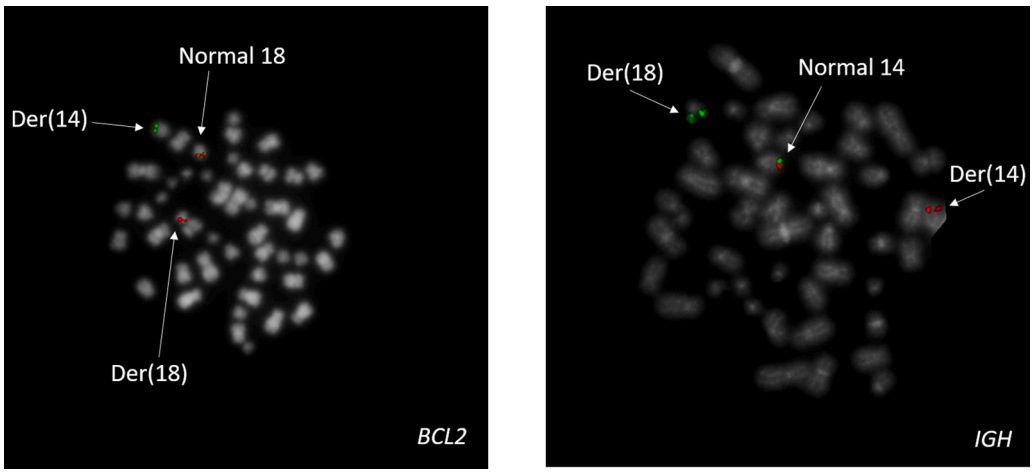

Figure 3. FISH images in two metaphase cells showing break-apart signals for *BCL2* and *IGH* probes, resulting in one abnormal chromosome 14 and one abnormal chromosome 18: der(14) and der(18)

Table 1
Summary of CLL cases with t(14;18)(q32;q21) along with treatment and outcome

Patient (gender)	Age	Karyotype	Trisomy 12	IGHV status	Treatment	Outcome
1 (F) [8]	45	46,XX,del(13)(q12q14)[3]/47,idem,+12,t(14;18)(q32;q21)[7]/46,XX[10]	+	MT	FCR	PAD
2 (F) [8]	55	46,XX,inv(6)(p21q21),t(14;18)(q32;q21)[7]/46,XX,t(14;18)(q32;q21)[7]/46,XX[6]	-	ND	CHOP, FCR, SCT	PAD
3 (F) [8]	69	47,XX,+12[5]/47,XX,t(6;7)(q15;p15),t(14;18)(q32;q21.3),+12[3]/46,XX[11]	+	MT	FC	PAD
4 (M) [8]	64	46,X,-Y,+12,t(14;18)(q32;q21)[6]/46,XY[8]	+	ND	FC	PAD
5 (M) [8]	44	47,XY,+12,t(14;18)(q32;q21)[7]/46,XY[13]	+	MT	FCR	AWD
6 (M) [8]	52	46,XY,t(14;18)(q32;q21.3)[6]/46,XY[8]	-	MT	FCR	AWD
7 (M) [8]	49	46,XY,t(14;18)(q32;q21)[16]	-	MT	FCR	CR
8 (M) [8]	50	46,XY,der(8;17)(q10;q10),+12,t(14;18)(q32;q21.3)[4]/47,XY,add(8)(p21),+12,t(14;18)(q32,q21.3)[3]/47,XY,+12,t(14;18)(q32;q21.3)[1]/46,XY[8]	+	MT	FCR	AWD
9 (M) [8]	78	46,XY,t(14;18)(q32;q21)	-	MT	-	AWD
10 (M) [8]	50	47,XY,+12,t(14;18)(q32;q21)[5]/47,idem,t(4;13)(q35;q21)[1]/46,XY[24]	+	ND	FCR	AWD
11 (M) [8]	41	46,XY,t(3;11)(q27;q22),add(4)(p16),add(6)(p23),t(14;18)(q32;q21.3)[8]/46,XY,t(3;11)(q27;q22),add(6)(p23),t(14;18)(q32;q21.3)[cp2]/46,XY[3]	-	U	FCR	AWD
12 (M) [8]	70	46,XY,t(14;18)(q32;q21)[12]/45,X,-Y,t(14;18)(q32;q21)[3]/45,X,-Y[8]/46,XY[4]	-	ND	FCR	PAD
13 (M) [9]	46	46,XY,t(14 ;18)(q32 ;q21)[6]/46,XY[12]	-	MT	Chlorambucil	AWD
14 (F) [9]	65	47,XX,+12,t(14 ;18)(q32 ;q21)[14]/46,XX[6]	+	MT	R	PAD
15 (F)	53	47,XX,+12,t(14;18)(q32;q21)[6]/46,XX[14]	+	U	Ibrutinib	CR

AWD, alive with disease; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone; CR, complete remission; F, female; FC, fludarabine and cylophosphamide; FCR, fludarabine, cyclophosphamide and rituximab; M, male; MT, mutated; ND; not determined; R, rituximab; PAD, progression and death; SCT, allogeneic stem cell transplant; U, unmutated

Trisomy 12 as a sole genetic aberration in CLL confers an intermediate prognostic risk, but when associated with additional chromosomal abnormalities, including t(14;18)(q32;q21), it portends a poor prognosis [10]. Therefore, all reported CLL patients with t(14;18)(q32;q21) have a younger age at diagnosis and are more likely to have *IGHV* mutations as well as a poor clinical course.

Our patient had a relatively young age (53 years) at diagnosis with a rapidly progressive disease. Cytogenetic analyses revealed the presence of a t(14;18)(q32;q21) with a trisomy 12, in parallel with an unmutated *IGHV* status. The patient was started on ibrutinib 420 mg daily, which was previously proven to be superior to chemotherapy as a frontline treatment of CLL patients with high-risk features (TP53 mutation, 11q deletion, and/or unmutated IGHV) such as our patient. In a phase 3 study evaluating ibrutinib versus chlorambucil in first-line CLL/SLL, ibrutinib reportedly results in an overall response rate of 92% (30% complete response), an increase in 5-year progression-free survival (PFS) rate from 12% to 70% (hazard ratio [HR], 0.15; 95% confidence interval [CI], 0.01–0.22) and in overall survival from 68% to 83% (HR, 0.37; 95% CI, 0.18–0.74) [11]. Our patient achieved complete remission, which is still maintained 20 months upon the initiation of the treatment.

When comparing the outcome of our patient to those treated before the era of targeted therapy, we notice that CLL patients with high-risk features have a better outcome when treated with targeted agents such as Bruton tyrosine kinase inhibitors (BTKi) or B-cell lymphoma-2 (BCL-2) inhibitors. Indeed, these agents were proven to be more potent in high risk CLL patients, impeding the poor prognostic impact of genomic rearrangements processes.

When initiating therapy, it is important to take into account the age of the patient. Indeed, while BTKi is an appealing treatment with high clinical efficacy, it however bears substantial risk of long term toxicity, resistance to treatment and other adverse events [12], particularly in younger patients, requiring maintenance therapy for a longer time span. In those younger patients, combinations strategies over a defined period of time can offer greater remissions durability with less toxicity. For instance, BCL-2 inhibitor venetoclax combined with the anti-CD20 monoclonal antibody obinutuzumab administered over a period of 6 months, followed by another 6 months of venetoclax, showed a higher PFS compared to chlorambucil and obinutuzumab treatment in previously-untreated CLL patients, with no difference in toxicity profile [13]. In a phase 2 study, the combination of venetoclax with ibrutinib over a period of 24 months in untreated and high-risk CLL patients was

associated with a rate of complete remission or complete remission with incomplete count recovery of 88% upon 1 year of therapy, with undetectable minimal residual disease in 61% of the cases [14]. The treatment strategies for CLL is drastically evolving, with several recently approved targeted agents. Combination of novel, chemotherapy-free regimens, would obviate the need for indefinite maintenance treatment while prompting deeper rates of molecular remission and improved survival.

Declaration of Competing Interest

The authors declare no potential conflicts of interest.

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