

ORIGINAL ARTICLE: CLINICAL

## Spontaneous regression of chronic lymphocytic leukemia to a monoclonal B-lymphocytosis or to a normal phenotype

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### Abstract

Spontaneous remission of chronic lymphocytic leukemia (CLL) is an unusual and poorly characterized event. We performed a search for spontaneous remission in patients with CLL. Cases must have had a pathological diagnosis of CLL with disease duration > 6 months. Spontaneous remission was defined as absence of lymphadenopathy or splenomegaly with lymphocyte counts  $< 5 \times 10^9/L$  for > 9 months without therapy. We identified 20 cases and included one additional case from our institution. Fourteen cases (67%) showed remission into monoclonal B lymphocytosis (MBL) and seven (33%) into a normal phenotype. There was no difference in age distribution, lymphocyte count or stage between groups. There was a significant difference in the median duration of CLL prior to remission, 13 years in the MBL versus 3 years in the normal phenotype group ( $p = 0.03$ ). This difference in the duration of CLL prior to remission could be due to a possible distinct pathophysiology for these events.

**Keywords:** Chronic lymphocytic leukemia, CLL, regression, monoclonal B lymphocytosis, MBL

### Introduction

Spontaneous remission of chronic lymphocytic leukemia (CLL) is an unusual phenomenon estimated to occur at a rate of 1% among cases of CLL [1]. Many authors have reported cases and series of patients who were diagnosed with CLL, but subsequently normalized their lymphocyte counts without cytotoxic therapy. For example, spontaneous remissions have occurred in the setting of smallpox vaccinations [2,3], viral infections [4,5], non-cytotoxic medications (e.g. angiotensin converting enzyme inhibitors and other antihypertensives) [6], after shock wave lithotripsy [7] and in the setting of secondary malignancies [8,9]. Although the prevalence of this occurrence is low, this phenomenon has intrigued many clinicians over the years, probably based on the hope of finding a common feature to direct novel treatment approaches for a common leukemia.

However, the definition of “spontaneous remission” of CLL is poorly characterized and ranges from simply a transient decrease in lymphocyte counts to durable complete resolution of one’s CLL through sensitive methods such as flow cytometry. There is little aggregate information about patients who have an established diagnosis of CLL by present-day standard diagnostic criteria and have developed a spontaneous remission. Furthermore, the majority of the current literature on spontaneous remissions of CLL does not distinguish between regression to a monoclonal B lymphocytosis (MBL) versus regression to a normal phenotype.

We present our findings from a detailed review of the literature on CLL regression, including a case found in our institution. Furthermore, we distinguish spontaneous remissions of CLL into those that regress into MBL versus those that demonstrate no evidence of CLL through immunophenotypical testing, as these could have a distinct pathophysiology.

### Methods

#### Literature search

We performed a PubMed search under the keywords “spontaneous remission” OR “spontaneous regression” OR “spontaneous recovery” AND “chronic lymphocytic leukemia” since 1950. References of these papers were also reviewed for additional reports. Cases were only included in this analysis if: (1) the diagnosis of CLL was firmly established with immunophenotypical analysis, (2) the patient’s elevated lymphocyte number at diagnosis was  $> 5 \times 10^9/L$  and persisted for > 6 months, confirming the initial diagnosis of CLL, (3) the lymphocyte number subsequently normalized to  $< 5 \times 10^9/L$ , (4) the lymphocyte count remained normal for greater than 9 months, (5) there was resolution of other features of CLL if previously present (no splenomegaly or lymphadenopathy) and (6) no intervening treatment was given to the patient, including radiation therapy or steroids.

#### Case selection

We reviewed the medical records from our institution between 1 January 1980 and 31 December 2011, looking for patients

with a diagnosis of CLL who had experienced remission into either an MBL or a normal phenotype, as long as all the criteria mentioned above were met. From a total of 167 medical records, we found one case meeting all inclusion criteria.

### Statistical analysis

We divided patients into two types of remission status, those who remitted to MBL and those who demonstrated a remission to normal phenotype by immunohistochemical or flow cytometry analysis, and we analyzed data separately for these two groups of patients. Only published reports that documented absence of a clonal B-cell population were considered to have regressed from CLL to normal. Characteristics are presented using descriptive statistics. Comparisons between groups were performed using Mann-Whitney and Fisher tests for continuous and categorical variables, respectively. Time from CLL diagnosis to remission was estimated using the Kaplan-Meier method, compared using the log-rank test. *p*-Values < 0.05 were considered statistically significant. Graphs and calculations were obtained using MedCalc (Mariakerke, Belgium).

## Results

### Patient

In November 2007, a 70-year-old man was noted on routine laboratory analysis to have a white blood cell count (WBC) of  $21 \times 10^9/L$  with 81% lymphocytes. His initial flow cytometry showed 69% of the lymphoid cells examined were kappa light chain restricted CD19+/CD20+ B-lymphoid cells (lymphocytic count  $7 \times 10^9/L$ ), which co-expressed CD5 and CD23. Markers for CD11b, CD11c, CD21, CD24, CD25, CD79b and CD52 were also positive. CD10, CD103 and FMC-7 were negative. CD38 was positive and ZAP-70 was negative.

The patient was asymptomatic at that time and his physical examination was normal with no lymphadenopathy or splenomegaly. The patient was classified as Rai stage 0 CLL and was managed by observation only. Over the next 2 years, the patient maintained a stable lymphocyte count. In April 2009, the patient suffered a myocardial infarction. During that hospitalization, the patient underwent cardiac catheterization, during which he developed an acute immune-related thrombocytopenia due to eptifibatid, which required platelet transfusions. One month later, after he recovered from his thrombocytopenia, his WBC count was  $13.4 \times 10^9/L$ , and his lymphocyte count was  $8.8 \times 10^9/L$ .

On his next hematologic follow-up, 5 months later, he was noted to have a normal WBC of  $5.6 \times 10^9/L$  and a normal lymphocyte number of  $2.6 \times 10^9/L$ . Over the next 28 months the patient maintained a normal WBC and lymphocyte count, and continues to maintain normal counts as of the time of this report. His last flow cytometry, in January 2012, showed 20% of the lymphocytes to be B-cells co-expressing CD5 and CD19 with kappa light chain restriction (absolute number  $0.36 \times 10^9/L$ ). CD38 and ZAP-70 were negative.

### Literature search results

In total, 92 abstracts were identified on our initial PubMed search. Eighteen published articles including 44 cases meeting

our initial criteria were reviewed in detail [1,6,7,10–17]. Of these 44 cases, 24 were excluded from the analysis due to lack of immunophenotypical data for confirmation of CLL upon diagnosis, lack of sufficient follow-up to document stability of remission, or because they received treatment in the form of chemotherapy, steroids or radiation. Twenty cases met our criteria for the diagnosis of spontaneous remission of CLL and are the basis for this analysis. We also report on and include one additional case from our institution in this analysis (case 1 in Table I).

### Spontaneous remission of CLL

Of the 21 cases that met our study criteria for this analysis, nine were female and 12 were male (Table I). Median age was 57 years (range 41–83 years). Lymphocyte counts upon diagnosis were reported in 20 cases, with a median of  $11.7 \times 10^9/L$  (range 5.7 and  $27.6 \times 10^9/L$ ). The median time from CLL diagnosis until remission was 4.5 years (range 1 and 29 years). The duration in remission at last reported follow-up ranged between 10 months and 10 years, with a median of 3 years.

### Spontaneous remission of CLL to MBL

Fourteen cases showed a persistent CLL clone while maintaining lymphocytic counts below  $4 \times 10^9/L$ . Of these, seven were males and seven were females. Median age was 57 years (range 41–74 years). Median lymphocyte count at diagnosis was  $11.7 \times 10^9/L$  (range 5.7– $27.6 \times 10^9/L$ ). CLL stage at diagnosis was reported in all 14 cases: eight cases were staged as Rai 0, three cases were Rai 1 and three cases were Rai 2. The median duration from diagnosis to remission was 13 years (range 1.6–29 years). CD38 was positive in eight cases, negative in two cases and was not reported in four cases. Case 1 showed a disappearance of CD38 upon remission. ZAP-70 was negative in nine cases and was not reported in five cases. The VH gene was mutated in eight cases, unmutated in one and not reported in five cases. Two cases (3 and 6) had preceding infections prior to the reported remission (i.e. flu-like syndrome and recurrent bronchitis). Case 1 had eptifibatid-induced transient thrombocytopenia prior to remission.

### Spontaneous remission of CLL to normal

Out of 21 cases, seven cases showed evidence of both clinical and immunophenotypical remission, confirmed by repeated flow cytometry. Of these, five were male and two were female. Median age was 57 years (range 49–83 years). Median lymphocyte count at diagnosis was  $12.8 \times 10^9/L$  (range 6– $20.9 \times 10^9/L$ ). CLL stage at diagnosis was reported in five out of the seven cases. Two cases were Rai stage 2 and three were Rai stage 1. Time from CLL diagnosis to remission was 3 years (range 1–14 years). None of these cases were reported to have a preceding infection or an immune related event.

### Comparison of spontaneous remission of CLL to MBL versus normal

When comparing the two groups, there was no difference in age distribution, lymphocyte count or stage prior to remission (Table II). However, there was a significant difference in the duration of CLL prior to remission. The MBL group had a median time of 13 years of persistent CLL prior to achieving

Table I. Published cases of CLL with spontaneous remission.

Reference	Age/sex	Stage at diagnosis (Binet/Rai)	Lymphocytes at diagnosis ( $\times 10^9/L$ )	Duration of disease	CD38	ZAP-70	IgVH mutation	Persistence of B-CLL clone	Type of remission	Remarks
Present report	70/M	A/0	7.0	2 years	+	-	NR	20%	CLL to MBL	Post-remission flow showed CD38 negativization; had eptifibatide-induced thrombocytopenia after MI
Thomas [16]	60/F	A/1	7.4	5 years	NR	NR	NR	4%	CLL to MBL	Trisomy 12 disappeared after remission
	54/M	A/0	9.1	4 years	NR	NR	NR	50%	CLL to MBL	Breast lump with CLL infiltrates; flu-like symptoms prior to CR
	57/M	A/2	25	13 years	NR	NR	NR	Persistent clone	CLL to MBL	
Del Giudice [1]	64/F	A/0	9.8	13 years	+	-	+	3%	CLL to MBL	
	51/F	A/0	11.6	21 years	+	-	+	27%	CLL to MBL	
	50/M	A/2	16.2	19 years	+	-	+	33%	CLL to MBL	
	63/M	A/0	10.6	13 years	+	-	+	63%	CLL to MBL	
	73/F	A/2	15.7	3 years	-	-	+	61%	CLL to MBL	
	53/F	A/0	27.6	29 years	+	-	+	52%	CLL to MBL	
	53/F	A/0	11.7	21 years	+	-	+	NR	CLL to MBL	
Gomez Garcia [6]	41/F	A/0	12.3	16 years	+	-	+	44%	CLL to MBL	
	64/M	A/1	21.6	20 months	-	NR	NR	0.5%	CLL to MBL	Lymphocytic count estimated from a graph
Bernard [10]	55/M	Binet A	15.4	3 years	NR	NR	+	2% in PB, 12% in BM	CLL to MBL	Had recurrent bronchitis
Denes [7]	52/M	Rai 1	NR	2.5 years	NR	NR	NR	Absent	CLL to normal	SWL for renal stones 10 months prior to remission
Buchi [11]	76/M	B/2	7.7	3 years	NR	NR	NR	Absent	CLL to normal	
Herishanu [12]	54/M	Rai 1	6	3 years	-	-	-	Absent	CLL to normal	
Holmes [13]	71/F	NR	20.9	14 years	NR	NR	NR	Absent	CLL to normal	
Mehta [14]	49/M	NR	17.8	1 year	NR	NR	NR	Absent	CLL to normal	
Ribera [15]	57/F	B/2	19.3	2.5 years	NR	NR	NR	Absent	CLL to normal	
Upshaw [17]	83/M	B/1	7.8	6 years	NR	NR	+	Absent	CLL to normal	T cell hyperplasia in BM

CLL, chronic lymphocytic leukemia; M, male; F, female; NR, not reported; PB, peripheral blood; BM, bone marrow; MBL, monoclonal B cell lymphocytosis; MI, myocardial infarction; SWL, shock wave lithotripsy, CR, complete remission.

spontaneous remission into MBL, while the patients who had a spontaneous remission into normal had a median time of 3 years of persisting CLL prior to remission ( $p = 0.03$ ; Figure 1).

## Discussion

Spontaneous remission of CLL is a poorly explained phenomenon. Many theories have been advanced to explain this entity, including *in vivo* overproduction of interferon due to

Table II. Comparison between spontaneous remission into MBL and remission into normal phenotype.

	CLL to MBL	CLL to normal	<i>p</i> -Value
Median lymphocyte count upon diagnosis (range)	12 (7-28) $\times 10^9/L$	13 (6-21) $\times 10^9/L$	NS
Median age (range)	56 (41-73) years	57 (49-83) years	NS
Rai Stage (0-1/2)	10/3 patients	3/2 patients	NS
Duration of CLL prior to remission (range)	13 (1.5-29) years	3 (1-14) years	$p = 0.03$

MBL, monoclonal B cell lymphocytosis; CLL, chronic lymphocytic leukemia; NS, not statistically significant.

viral induced host immune defense mechanisms [13], direct viral destruction of lymphocytes [15] and T-cell mediated reactivity [17]. However, there has been little effort to systematically characterize this entity. Furthermore, although spontaneous remissions of CLL have been reported since

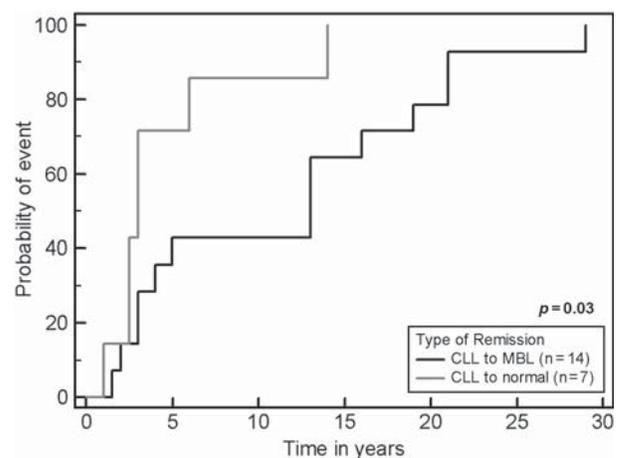


Figure 1. Estimated curves of time from CLL diagnosis to spontaneous remission according to type of remission.

the 1930s, most of the early reports were not well characterized due to the lack of availability of immunophenotypical analysis. More recently, however, many cases and series of spontaneous remission of CLL have demonstrated the persistence or absence of the CLL clone through flow cytometric analysis. This could allow for the division of patients with spontaneous remissions into two groups, those who remit to MBL and those who remit to a normal immunophenotype.

In this analysis of published patients, although small in number, we did not find a difference in the pre-remission characteristics of these two populations with regard to median age or lymphocyte count. However, a significant difference between these two groups was found in the median time from CLL diagnosis to remission: 3 years in the normal immunophenotype regression group and 13 years in the MBL regression group ( $p = 0.03$ ). Therefore, the spontaneous remission that results in a normal immunophenotype appears to occur earlier than in patients with a spontaneous remission into MBL. This is a novel observation, and it may offer some insight as to a differing pathophysiology amongst the two forms of spontaneous remissions. We should acknowledge, however, that this could be a finding associated with chance, given the retrospective nature of our study.

The progression of MBL to CLL has been postulated to be the result of acquiring new genetic mutations which promote cell growth and loss of apoptotic mechanisms [18–20]. The same theory has been proposed in patients who have monoclonal gammopathy of unknown significance (MGUS) and progress to multiple myeloma [21,22] and in patients who show progression of their CLL after a prolonged period of stability [23,24]. One could also postulate that the spontaneous remission resulting in complete absence of the CLL clone occurs early after diagnosis, prior to the CLL cell acquiring other mutations that may promote progression of the disease. The significance of this finding may have implications in the treatment of early stage CLL. Although treatment of CLL in early phases of the disease has not been shown to improve survival with standard therapies, many of the newer biological agents may induce apoptosis more effectively [25,26]. If the CLL cell is more susceptible to a complete phenotypical remission early on in its course, one therapeutic implication is that these agents may be more effective in inducing durable phenotypic remissions if used sooner in the disease process, prior to the development of additional genetic mutations that may make the CLL cell less responsive to treatment.

Additionally, this analysis also suggests that the CLL to MBL remission appears to occur later in the course of the disease. Furthermore, some cases reported of spontaneous remissions to MBL (three of 14 cases), and none of the spontaneous remissions to normal phenotype, appear to have had a preceding immunological event. This may suggest a possible differing pathophysiology for the spontaneous remission of CLL to MBL, possibly one that may be related to immune-related destruction of the CLL cell in these patients. Del Giudice and colleagues studied nine cases of spontaneous remissions of CLL to MBL with microarray analysis, and noted a distinctive pattern of overexpression of B-cell receptor (BCR)-related genes in the remaining CLL clone, hypothesizing that BCR signaling through immune stimulation

may play an important role in the spontaneous regression to MBL scenario [1]. Furthermore, a prolonged time of the diagnosis of CLL prior to the spontaneous remission to MBL, as described in this article, may support this theory, as one would need a prolonged time with their CLL in order to allow for such an event to occur. This is of particular importance with the advent of novel therapies directed at modulating BCR signaling, such as Bruton tyrosine kinase and phosphatidylinositol-3-kinase inhibitors [27,28]. Due to the rarity of the spontaneous remission event in CLL and the lack of large series with detailed immunophenotypical analysis, we feel these observations are noteworthy. However, given the small numbers of patients in our study, these results should be considered preliminary.

In the present series, in the 10 patients in whom ZAP-70 status was reported, all were ZAP-70 negative, and 10 of the 11 patients in whom immunoglobulin heavy chain variable (IgVH) mutational status was reported revealed a mutated IgVH gene. An unmutated IgVH and ZAP-70 positivity have been associated with a worse prognosis in patients with CLL [29,30]. Hence, it could be postulated that patients with CLL with good prognostic features might be more likely to regress to either MBL or a normal phenotype. This observation has been previously reported [1], but is nonetheless important to note.

## Conclusions

Spontaneous remissions of CLL are unusual; however, they can be divided into those that remit into MBL or into a normal phenotype. These two remission occurrences may differ in the time of diagnosis of CLL prior to their spontaneous remission. This may offer a clue as to the possible differing pathophysiology of these rare events and may have therapeutic implications for achieving phenotypically normal remissions. Larger studies are needed to confirm our findings.

**Potential conflict of interest:** Disclosure forms provided by the authors are available with the full text of this article at [www.informahealthcare.com/lal](http://www.informahealthcare.com/lal).

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