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– ORIGINAL PAPERS –

17p13.1 Deletion in Small B-cell Lymphocytic Lymphomas: A Prognostic Factor and Diagnostic Approach

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Abstract

B-cell small lymphocytic lymphoma (B-SLL) belongs to the category of indolent non-Hodgkin's lymphomas and is defined by the proliferation of mature, inert B lymphocytes and their accumulation in lymphoid structures. Although it is classified as the same entity as chronic lymphocytic leukemia (B-CLL), according to the World Health Organization and the International B-CLL Task Force [1, 2], there is little data on the management of lymphocytic lymphoma, accounting for only 10-15% of B-CLL/SLL cases [3, 4]. The aim of this study is to evaluate the presence of the 17p13.1 deletion in a series of "pure" lymphocytic lymphoma cases from 2017-2020, given that it is considered an identical entity to chronic lymphocytic leukemia. It is known that del17p13.1 provides resistance to chemotherapy and is a negative prognostic factor in B-CLL, but its routine evaluation is not routinely performed in practice as part of B-SLL diagnosis.

Our findings highlight the contribution of del17p13.1 identification in patients diagnosed with B-SLL, enhancing diagnostic accuracy and treatment management efficiency, suggesting its potential as a standard diagnostic tool in clinical settings. The review aims to provide a comprehensive overview for hematologists and pathologists, encouraging the adoption of del17p13.1 identification to improve patient outcomes in the management of B-SLL.

Keywords: small B-cell lymphocytic lymphoma, del17p13.1, treatment, prognosis.

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Introduction

B-cell small lymphocytic lymphoma (B-SLL) is a category of indolent non-Hodgkin's lymphomas and is defined by the proliferation of mature, inert B lymphocytes and their accumulation in lymphoid structures. Although it is classified as the same entity as chronic lymphocytic leukemia (B-CLL), according to the World Health Organization and the International B-CLL Working Group [1, 2], there is little data on the management of small B-cell lymphoma, accounting for only 10-15% of B-CLL/SLL cases [3, 4].

The diagnosis of chronic lymphoid leukemia requires the presence of at least $5 \times 10^9/L$ monoclonal B lymphocytes in the peripheral blood, clonality that requires confirmation by flow cytometry, in contrast to small B-cell lymphocytic lymphoma, where the number of clonal lymphocytes identified in the peripheral blood is less than $5 \times 10^9/L$, and the diagnosis is established by histopathological examination and confirmed by immunohistochemical tests [2].

The resistance to chemotherapy observed in del(17p13.1) patients is probably related to the malfunction of the tumor suppressor protein p53. In humans, the gene that regulates this protein (TP53) is located on the short arm of chromosome 17 (17p13.1)[5, 6]. Patients with this deletion have a homozygous TP53 gene, which becomes inactivated by mutation in the vast majority of these patients,[7, 8, 9] leading to a complete lack of function of the p53 pathway. To date, studies have indicated that ~80% of patients with del (17p13.1) also have TP53 gene mutations and only 4% to 18% of patients studied have TP53 mutations, but do not have del (17p13.1) [7, 9]. However, the deleted region is large and the loss of other associated genes in this area may also be causing instability of these genes. In response to cellular DNA damage, a normal cell responds by upregulating p53 protein levels [10].

With the advent of fluorescence in situ hybridization of interphase (FISH) and its increased diagnostic sensitivity, del(17p13.1) has been detected in ~7% of a large group of mostly untreated patients [11]. del(17p13.1) detection rates after fludarabine therapy have been reported to be up to 30%, [12] indicating clonal evolution of the disease to resist chemotherapy. Since abnormal p53 clones are resistant to chemotherapy, they initiate a negative

selection process that slowly increases the number of cells carrying these abnormalities, causing subsequent adverse clinical repercussions [13].

The aim of the study is to evaluate the presence of the 17p13.1 deletion in 'pure' lymphocytic lymphoma since it is considered an identical entity to chronic lymphocytic leukemia but in clinical practice the management of the two conditions is different. It is known that del17p13.1 provides resistance to chemotherapy and is a negative prognostic factor in B-CLL but its routine evaluation is not routinely performed in practice in B-SLL.

Material and method

Study design

In this retrospective study, 12 patients diagnosed with B-SLL in the period 2017-2020 in the Hematology Department of Constanța County Emergency Hospital were included. Of these, 4 were women and 8 were men, with a mean age at diagnosis of 66.5 years.

Diagnosis, staging, treatment

The diagnosis of B-SLL was established by histopathologic examination (lymph node biopsy) and immunohistochemical tests, performed in the Clinical Pathologic Anatomy Service of the County Emergency Hospital "Sf. Apostol Andrei", Constanța, and the number of clonal lymphocytes in the peripheral blood was less than $5 \times 10^9/L$. Assessment of del(17p13.1) was performed by fluorescence in situ hybridization (FISH) on paraffin-embedded lymphoid tissue sections using the CytoCell probe for P53 gene deletions (TP53 - LPS 037, Oxford Gene Technology IP Limited, UK). Sample preparation and analysis were performed according to the manufacturer's recommendations.

Anthropometric, clinical and paraclinical data were collected from the same hospital database. At initial presentation, each patient was evaluated and staged according to current protocols, samples were collected for laboratory investigations - complete blood count, biochemistry, viral screening, beta 2 microglobulin, lactate dehydrogenase. Prior to initiation of treatment all patients underwent imaging investigation by computed tomography and cardiological examination. The presence of B symptoms (involuntary weight loss in the last 6 months, night sweats, fever) was also evaluated.

Staging was performed according to the Ann Arbor classification and the International Prognostic Index (IPI). Assessment of comorbidities was performed using the Charlson index.

Initiation and choice of treatment were performed according to the current European guidelines ESMO (European Society of Medical Oncology) and the Romanian Association of Hematology, depending on the stage of disease at diagnosis and associated comorbidities. Subsequently, patients were clinically and paraclinically monitored, following the type of response to treatment and evolution.

The study was approved by the hospital's Local Ethics Committee.

Morphopathologic and immunophenotypic evaluation

All existing hematoxylin and eosin (H&E) stained sections and immunophenotypic studies performed on extramedullary tissue biopsies were reviewed. The following pathological features were examined in all lymph node specimens: lymph node size (largest diameter), extent and patterns of lymph node involvement by CLL phenotype cells, preservation of normal architectural features of the lymph nodes (sinuses, mantle area and germinal centers), presence or absence of proliferating centers, number of additional proliferating centers and percentages of germinating processes. The antibodies used for immunophenotypic diagnosis were CD20, CD19, CD79a, PAX5, CD5, CD23, BCL2, BCL6, CD15, CD30, p53, Cyclin D1, Ki67 (Biocare Medical, USA). The above-mentioned features were scored together by 2 observing anatomic pathologists; any discrepancies were resolved by discussion and a consensus score was determined for each parameter.

Classical fluorescence in situ hybridization studies

FISH studies were performed on whole 5 µm formalin-fixed, paraffin-embedded 5 µm tissue sections from 12 extramedullary tissue biopsies, without prior cytogenetic studies, using the following probe: CytoCell for P53 gene deletions (TP53 - LPS 037, Oxford Gene Technology IP Limited, UK). Signal patterns from at least 200 cells were labeled. Limits for determining positive samples were set

for the probe based on individual laboratory experience with clinical samples.

Results

Patients included in the study presented with a mean age at diagnosis of 66.5 years. The gender distribution was two females (16.6%) and ten males (83.3%). The main characteristics and laboratory values at the time of diagnosis are highlighted in Table 1. 16.6% of the subjects were diagnosed with limited disease stages (I-II) and 83.3% with advanced stages (III-IV). 41.6% had a prognostic index of 2 (low-intermediate risk category) and 58.3% a prognostic index of 3-4 (high risk category). Splenomegaly (assessed both clinically and imaging) was present in 58.3% of subjects. In terms of laboratory investigations, 33.3% of subjects had anemia at diagnosis and 50% thrombocytopenia, anemia and thrombocytopenia undetermined by medullary infiltration. 58.3% of subjects had a beta2myoglobulin value at diagnosis higher than 3.5mg/L, which correlated with advanced disease stages and increased prognostic index (>2).

In terms of treatment, only one patient fell into the watch and wait category, with initiation of treatment required in the remaining subjects. The indication for treatment was one of the following: progressive or symptomatic adenopathy and/or splenomegaly, autoimmune cytopenias, direct or extranodal organ infiltration, other (paraneoplastic syndromes, renal involvement, etc). Only one patient received concordant therapy with B-CLL, the remaining patients received therapies recommended for indolent lymphomas, as highlighted in Table 2. Of note, the dose used for Rituximab was the approved dose for lymphomas (375 mg/m² IV or 1400 mg subcutaneously) instead of the approved dose for B-CLL (500 mg/m² IV or 1600 mg subcutaneously).

In terms of response to treatment, 41.6% of patients had complete response, 16.6% partial response and 33.3% refractory disease, as shown in Table 3. Of note, lack of treatment response correlated with the presence of del17p13.1 (50% of cases).

Diagnostic characteristics

<i>Average age (years)</i>	66,5
<i>Ann Arbor Status</i>	
<i>I-II</i>	2 (16,6%)
<i>III-IV</i>	10 (83,3%)

IPI	
1	0
2	5 (41,6%)
3-4	7 (58,3%)
Splenomegaly	
Yes	7 (58,3%)
No	5 (41,6%)
Hemoglobin^a	
<12g/dl	4 (33,3%)
>12g/dl	8 (66,6%)
Thrombocytosis^b	
<150000/mm ³	6 (33,3%)
>150000/mm ³	6 (50%)
Beta2 microglobulin	
<3,5 mg/L	5 (41,6%)
>3,5 mg/L	7 (58,3%)

Table 1. Clinical features in patients diagnosed with B-SLL (a,b: anemia and thrombocytopenia are not determined by medullary infiltrate, according to the diagnostic criteria of B-cell lymphocytic lymphoma).

First line of treatment

FC	1 (8,3%)
CVP	4 (33,3%)
R-CHOP	6 (50%)

Table 2. First-line treatment in patients evaluated in the study (FC - fludarabine, cyclophosphamide. CVP - cyclophosphamide, vincristine, prednisone. R-CHOP - Rituximab, cyclophosphamide, doxorubicin, prdnison).

Type of treatment response

RC	5 (41,6%)
RP	2 (16,6%)
Refractory disease	4 (33,3%)

Table 3. Type of treatment response of the patients evaluated in the study (CR - complete response. PR - partial response).

Del 17p13.1

Present	6 (50%)
Absent	6 (50%)

Table 4. Presence of 17p13.1 deletion in patients evaluated in the study.

Debates

This study highlights the heterogeneity in the management of B-SLL in clinical practice given that most patients were treated with therapies used in indolent lymphomas. Although in international guidelines B-SLL and B-CLL are categorized as the same disease and receive the same treatment [2, 16, 17,18], the results of this study demonstrate that B-SLL has a similar management to indolent lymphomas. These observations are similar to another study from the clinical practice of 50 patients with B-SLL treated in Greece between 2007 and 2016 [19], highlighting that B-SLL is treated in practice as indolent lymphoma and not as B-CLL.

At the same time, patients with B-SLL were excluded from most clinical trials targeting B-CLL, but were enrolled in clinical trials evaluating chemo-immunotherapy in indolent lymphomas [20]. This was also the basis of our study on the evaluation of the presence of del17p13.1 in B-SLL. The results obtained (50% of the cases studied showed del17p13.1 coincides with the literature data that the presence of this abnormality, in patients diagnosed with B-CLL is associated with resistance to chemotherapy and is an independent negative prognostic factor [21, 22, 23, 24] thus supporting the idea that the approach and evaluation of the B-SLL patient should be similar to that of the B-CLL patient. The presence of del17p13.1 along with TP53 gene mutation have a negative prognostic impact in B-CLL patients suggesting the need for comprehensive evaluation of TP53 aberrations in these patients [25, 26]. In the study based on the analysis of two cohort studies including 103 patients, 53 from the German study group

clinical trials (GCLLSG) for B-CLL and 50 patients from outside the clinical trials, 'real-life', diagnosed with B-SLL in Greek centers, it was demonstrated that B-SLL patients are heterogeneously treated in clinical practice receiving therapies concordant with those of indolent lymphomas [19].

There are recent studies including patients with different histologic subtypes of lymphomas that have shown beta 2 microglobulin to be a potent prognostic indicator so this has led to its integration as a parameter in a new prognostic model in follicular lymphoma [14; 15]. There have been no studies evaluating the role of beta 2 microglobulin in B-SLL separately from B-CLL cases. In the present study 58.3% of subjects had a beta 2 microglobulin value at diagnosis higher than 3.5mg/L, which correlated with advanced disease stages and increased prognostic index (>2).

Conclusion

Our study emphasizes the contribution of 17p13.1 deletion identification in patients diagnosed with B-SLL, increasing diagnostic accuracy and efficiency of patient management, suggesting its potential as a standard diagnostic tool in the clinical setting. The review aims to provide a comprehensive overview for hematologists and pathologists, encouraging the adoption of del17p13.1 identification to improve patient response in the management of B-SLL and treat the patient in a similar way to that of the B-CLL patient.

Further extensive studies are needed to support the hypotheses discussed.

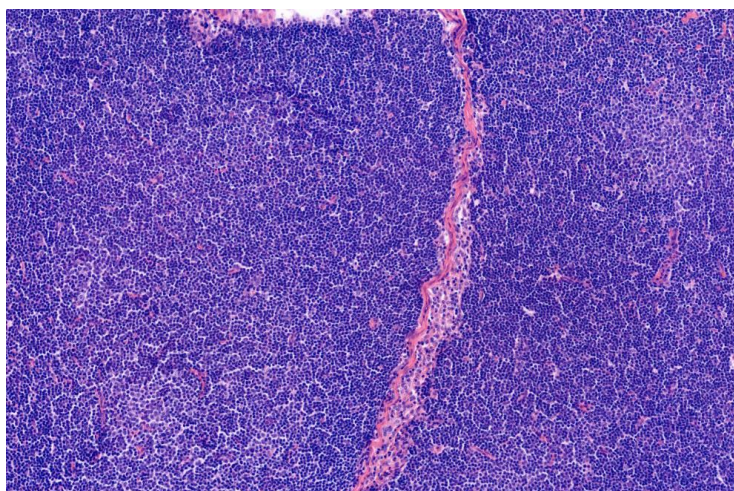


Figure 1. Microscopic appearance with focus on proliferation centers, of one of the cases of B-SLL with del17p.13.1 from the patients included in the study. (Ob. 40x, HE).

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Abbreviations

B-SLL - B-Small Cell Lymphocytic Lymphoma
B-CLL -Chronic lymphocytic leukemia
Del17p13.1 - Deletion of the 17p13.1 gene
ESMO - European Society of Medical Oncology
FISH - fluorescence in situ hybridization

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GCLLSG - German Chronic Lymphocytic Leukemia Study Group

IPI - International Prognostic Index

Conflicts of interest

"This research did not receive any grant from agencies in the public, commercial, or not-for-profit sectors. None of the authors has any conflict of interest. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Informed consent was obtained from all the patients included in the study."

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