

CASE REPORT

The composite lymphoma: chronic lymphocytic leukemia – classic Hodgkin's lymphoma

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Abstract

The composite lymphoma (CL) is defined by the presence in the same tissue or organ of two distinct histological aspects of non-Hodgkin's lymphoma (NHL), or NHL and Hodgkin's lymphoma (HL). The definition of the CL has evolved, requesting the identification of the immunophenotypic pattern and clonal distinct aspects for the two-lymphoproliferative lesions. We present a case of a 73-year-old farmer who presented with B-symptoms and multiple adenomegaly. The biopsy of a left cervical lymph node reveal a CL: a histological and immunophenotypic aspect of HL-mixed cellularity (CD15+, CD30+, CD20-) and a diffuse small cell infiltrate which meet the criteria for B-CLL (CD20+, CD23+, and CD5+). The lymphocytes in peripheral blood over 15 000/mm³ and marrow infiltrate with small lymphocytes also sustain the B-CLL diagnosis. The relationship between the two lymphoproliferations is discussed reported to the case above, but also considering the literature data. In most of the cases the two proliferative processes are clonal related which means they have a commune lymphoid progenitor, pre-GC or early-GC with individual detachment and transit through GC (also, the afferent related processes). It is also possible that the two proliferations, which form the composite lesion to have different cellular origins, possibility sustained by the analysis of the IgH rearrangements and of the somatic mutations identified in the two clones. The EBV-role in HL-pathogeny is related to the way of salvage or/and initiation of a clonal process in a GC-cell which has major deletions in the variable part of IgH.

Keywords: composite lymphoma, B-CCL, Hodgkin's lymphoma, Reed–Sternberg cell origin, Richter's syndrome.

Introduction

The composite lymphoma (CL), defined by the presence in the same tissue or organ of two distinct histological aspects of non-Hodgkin's lymphoma (NHL) or NHL and Hodgkin's lymphoma (HL), represents a rare pathological entity [1]. In most cases, the composite lesions are aggressive transformations of an indolent lymphoma, but clonal evolutions, over time, can be considered disease progression, rather than CL. It is true that all types of malignant process will eventually transform into more aggressive disease as part of their natural history [2], but it is also well demonstrated that about 30–40% of cases with Richter's syndrome had a second B-cell lymphoma of a different origin [3].

Many researchers now believe that the definition of the CL has evolved, requesting the identification of the immunophenotypic pattern and clonal distinct

aspects for the two-lymphoproliferative lesions [4]. The histological and immunophenotypic study sustains the existence of two or more distinct lymphoid proliferations, but it cannot guarantee the clonal relation between them. Only the genetic rearrangements of the heavy chain and/or cytogenetic abnormality could distinguish between common or distinct origin of the involved pathological processes [6].

The histological and immunophenotypic differences between the two (or three) lymphoproliferative lesions are relatively easy to identify. The clarification of the clonal relation proves to be challenging on two sides: the first is obtaining representative cellular samples, separate for the two proliferations (with care for contamination), and afterwards the cytogenetic study and/or the study of the IgH rearrangement [7].

Occasionally, simultaneous or successive aspects of indolent NHL and HL can be found in the same patient. B-Chronic Lymphocytic Leukemia (B-CLL) is one of

the indolent B-lymphoproliferative diseases with an increased rate of aggressive transformation. According to different authors, the chance for a patient with B-CLL to develop a second lymphoproliferative lesion varies between 5% and 10%, after a usual ten years of evolution [8].

The outcome is generally severe; the therapy can be effective, but usually on short term.

☐ Patient, Methods and Results

A 73-year-old patient, retired farmer (exposure to pesticides) presented in November 2008 at the Hematology Clinic of "Filantropia" Hospital, Craiova, with a histopathologic diagnosis of mixed cellularity HL.

First symptoms appeared four to five months ago when he observes an enlarged left lateral cervical lymph node and a slight asthenia.

Non-smoker for over 15 years, he smoked about 20 cigarettes a day for more than 30 years.

At the time of presentation, the patient had tiredness and significant nocturnal sweating as well as weight loss, which place him in B-stage; ECOG and Zubrod stage was 2.

Physical examination reveals cervical lymphadenopathy on left and right side with diameters up to 6 cm (left cervical lymph node). Axillary's and inguinal lymph nodes were also enlarged but in a lesser degree. He has moderate hepatomegaly, without splenomegaly.

Laboratory findings revealed leukocytosis (WBC = 23 440/mm³) with lymphocytosis (Ly = 83%), mild anemia (Hb = 8.2 g/dL), thrombocytosis (Plt = 477 000/mm³).

Peripheral blood smear presented relatively common "smear cells" (22%), moderate anisocytosis and discrete hypochromia. Bone marrow aspirate reveals lymphoid infiltrate (about 45%) with mature, small cells.

Inflammatory tests are deeply modified: ESR = 155 mm/hr, Fbg = 832 mg/dL, LDH = 292.63 U/L,

$\alpha_2 = 1.3$ g/dL. Total serum proteins = 8.2 g/dL, Alb = 54%, $\alpha_1 = 16\%$, $\alpha_2 = 12\%$, $\beta = 11\%$, $\gamma = 17\%$.

Cardiac assessment, including the left ventricular ejection fraction, liver and kidney function are normal.

CT-scans of neck, thorax, abdomen and pelvis reveal multiple lymphadenopathies with left cervical lymph node conglomerate, of 8.87/7.88/10 cm, significant hepatomegaly, predominantly the right lobe and normal spleen (10.6 cm).

A first therapeutic sequence ABVD, with 16 mg dexamethasone per day for three days, was applied and the histological and immunophenotypic reexamination is required.

The second ABVD-sequence had a minor therapeutic response. The patient's is lost because of the sudden death with no apparent hematological cause (neurological or cardiac).

The histopathological examination ("Victor Babeş" National Institute) revealed effaced lymph node architecture with two different patterns:

1. A diffuse small lymphocytic infiltrate, with rare proliferation centers (Figure 1); immunohistochemical, the malignant cells were positive for CD20 (B-cell markers) (Figure 2) and negative for CD45RO/UCHL1 (T-cell marker), and presented an aberrant expression for CD5 (T-cell markers, positive in some B-NHL) and CD23 (also follicular dendritic cell marker) (Figure 3); the features corresponded with a B-CLL;

2. Areas with more polymorphous cells infiltrate, with typically Hodgkin/Reed-Sternberg malignant cells into a reactive polymorphous background (small reactive lymphocyte, eosinophils, histiocytes) (Figure 4); immunohistochemical, the malignant cells were CD15 (Figure 5) and CD30 positive (Figure 6), and do not expressed B-cell (CD20) (Figure 7) and T-cell (CD45RO/UCHL1) markers, features corresponding to a classical HL, mixed cellularity subtype; the small reactive lymphocyte surrounding the malignant cells are predominantly CD45RO/UCHL1 positive T-cells (Figure 8).

The final diagnosis was CL: B-CLL and HL.

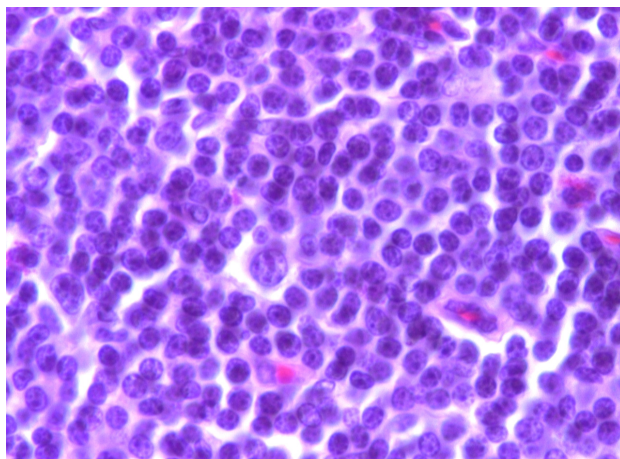


Figure 1 – Lymph node biopsy: diffuse small lymphocytic infiltrate, with rare proliferation centers (H&E stain, ob. 40x).

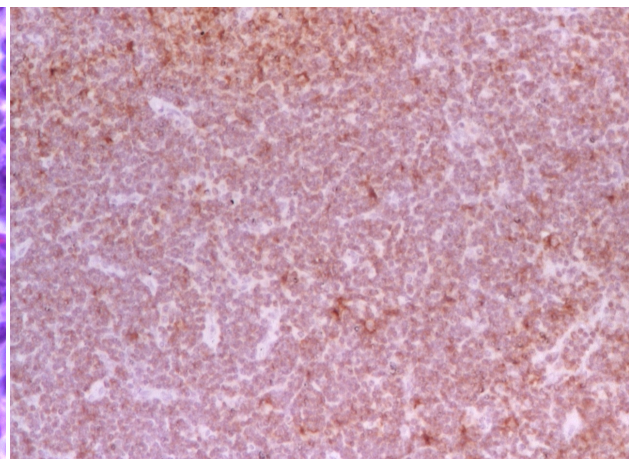


Figure 2 – Idem: the malignant cells were positive for the B-cell marker CD20 (IHC stain for CD20, ob. 10x).

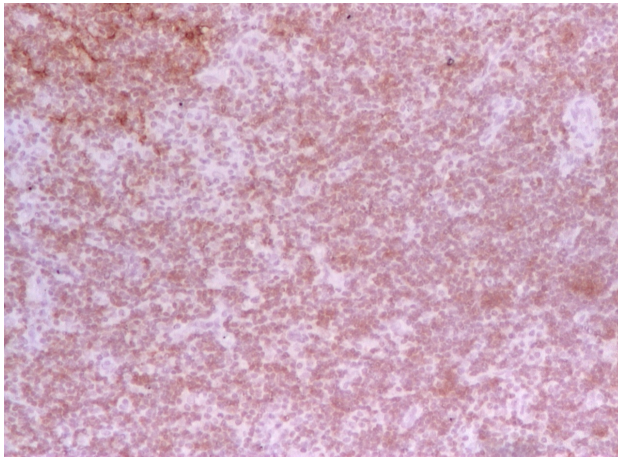


Figure 3 – Idem: the malignant cells also express CD23 (a follicular dendritic cell marker, frequently positive in B-CLL) (IHC stain for CD23, ob. 10×).

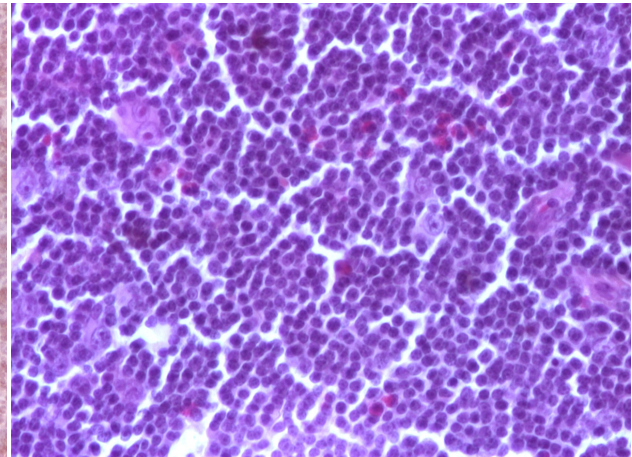


Figure 4 – The same lymph node: areas with typically Hodgkin's/Reed-Sternberg cells into a reactive polymorphous background (H&E stain, ob. 20×).

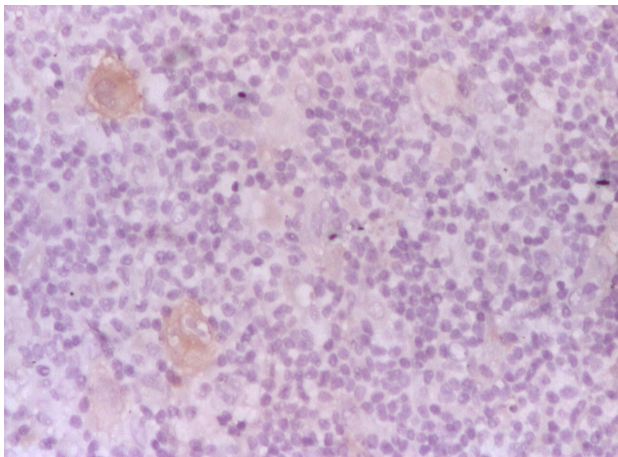


Figure 5 – Idem: the malignant large Reed-Sternberg cells were CD15-positive (IHC stain for CD15, ob. 20×).

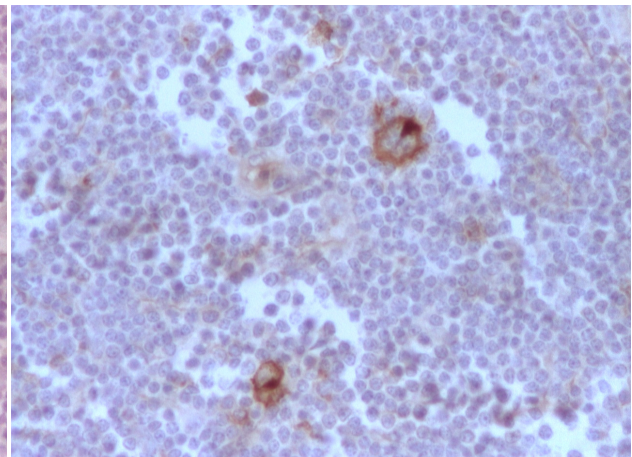


Figure 6 – Idem: the Reed-Sternberg cells also express CD30 (IHC stain for CD30, ob. 20×).

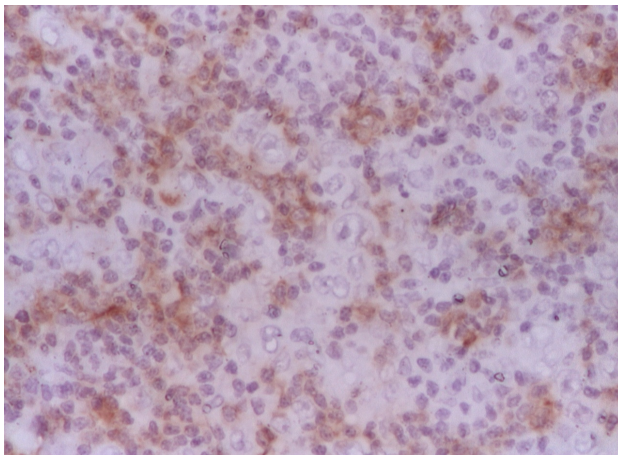


Figure 7 – Idem: B-cell marker CD20 was negative in Reed-Sternberg malignant cells (IHC stain for CD20, ob. 20×).

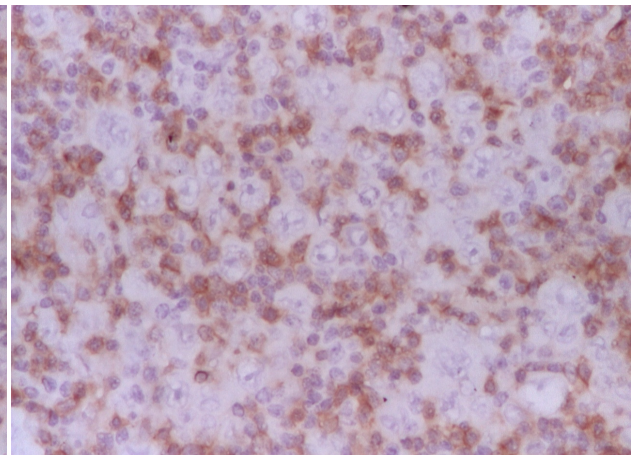


Figure 8 – Idem: the small reactive lymphocyte surrounding the malignant Reed-Sternberg cells are predominantly CD45RO/UCHL1-positive T-cells (IHC stain for CD45RO, ob. 20×).

Discussion

Histological and immunophenotypic aspects

They were two histological forms of the composite lymphoma B-CLL – HL: type I, in which Reed-Sternberg (RS) cells are present in a typical histological

B-CLL background, and type II, where RS-cells are placed in a polymorphous reactive cells background, characteristic for HL, while the indolent B-proliferation is adjacent. The first histological type associates more often a common clonal relation for both form of lymphoma [10]. The case presented can be included in

the second group whereas the Hodgkin's lesion has typical features.

The classic HL is relatively easy to diagnose and in most cases, the histological examination is enough. Composite lesions need immunophenotypic evaluation, even more necessary in the case of HL – B-CLL association, because morphologic aberrations (RS-like cells) can occur occasionally in classical B-CLL.

In our case, the histology and immunophenotype of malignant RS-cell (CD15+CD30+, negative for CD20) and CD45RO/UCHL1+ inside a polymorphous reactive background confirm without any doubt the HL.

Histopathological features (small lymphocytic proliferation with rare growth centers) and immunophenotype (the expression of CD20+, CD5+ and CD23+ by the malignant population) sustain the B-CLL diagnosis.

The origin of the RS-cell

The morphologic and the immunophenotypic aspects of HL offer little data regarding the origin of the RS-cell. The origin of this cell was disclosed along with the analysis of the genetic rearrangement of the Ig heavy chain (IgH) at unicellular level. The presence of the clonal VDJ regions rearrangement of the IgH sustains the B-cell lymphoid origin of the RS-cell [11]. Even further, on VDJ-area the sequential analysis had pointed out a high rate of somatic mutation events associated with extensive deletions, which end in an unfunctional gene. Together these data clarify the origin of the RS-cell in a B-cell of the germinal center (GC) or post-GC [11].

The peculiar absence of immunoglobulin gene expression in RS-cells appears to be due also to impaired activation of the immunoglobulin promoters and enhancers stemming from the lack of expression of the major B-cell transcription factors, accompanied by down regulated of proteins involved in downstream signaling of the IgH-receptor [12].

It is hypothesized that this switch in molecular identity is necessary for the RS-cell to survive in the absence of immunoglobulin receptor expression, which is required for the growth and survival of normal B-cells.

The RS-cells from non-immunosuppressed patients with HD display a phenotype consistent with germinal center B-cells in contrast with RS-cells in HIV-associated HD to which express transcription factors consistent with post-germinal center B-cells [13].

A question is still unsolved: if the new therapeutic protocols for active B-CLL, consisting in the fludarabine and Mo Ab 52, which drastically amplify the already existent immunosuppressed status, has any impact over the origin of the RS-cell like on the model presented above [14].

The clonal relation between B-CLL and HL

The idea that the RS-cell belongs to the GC finds its reason in several studies of the clonal relation between the B-cell population of B-CLL and RS in this type of CL. In most of the cases, it is the same clonal pattern of the IgH rearrangement for regarding these two cell populations [12].

The study of the clonal relation requires RS-cell microdissection technique, DNA-amplification, follo-

wed by the comparative study of the genetic rearrangements of IgH in both, B-CLL and RS-cell populations. In spite the fact that B-leukemic clone and RS-cell have the same origin, certified by the similar rearrangement of VDJ-region, there were different aspects at this level, generated by the further distinct evolution of the two clones [15].

The data, just mentioned, suggest the emergence of the two clones (B-CLL and RS-cell) by common early-B germinal center (GC) cell, with distinct further evolution for the two clones. We can consider that a GC-cell or germinal pre-center cell, which suffered early genetically lesions (the initiation of the malignant transformation), represent the common precursor for the two populations. Afterwards the two clones each pass separately the GC, with individual/private changes related to the somatic mutation. At the same time, the two proliferations acquire, individually, new genetic lesions perfecting the malign transformation.

A significant percent of cases with B-CLL – HL composite lesions present individual clonal features for the two-lymphoproliferative disease. Different genetic rearrangements of the variable zone of the IgH, as well as the somatic mutations with distinctive character, proclaim the origin in different cells of leukemic B-cell and RS-cell [16].

The impact of the biological features of B-CLL and HL on the composite lesion

B-CLL is an indolent B-lymphoproliferative disease with biological heterogeneity hard to guess in morphological monomorphism of the leukemic population. The relation between the biology of the two lymphoproliferative lesions, B-CLL and HL and the impact of the risk or/and prognostic factors of the B-cell leukemia on malignant evolution mechanisms of RS-clone, are far from being clarified. The main obstacles were the rarity of the cases, the complexity of the mechanisms involved in facilitation, maintenance and progression of the second neoplasia. The clear differences between the biology of these secondary malignances versus *de novo* neoplasia with similar morphology represent another challenge.

Composite lymphoma B-CLL – HL type and EBV

The clonal relationship between HL and B-CLL is reported from 50% to 80%, depending on the author and the number of cases included. For some authors the majority of the cases in which RS-cells have distinct origin from the leukemia clone have markers of the EBV-infection [17].

The role of the EBV in the pathogeny of *de novo* HL is sustained by the viral genome expression in 20–50% of the cases. The frequency of EVB is higher in the HL with mixed cellularity and lymphocyte-depleted subtype and, in most of the times, absent in nodular lymphocyte predominant HL. The EBV+ HL appears to be inversely related to the overall prevalence of HD in a given population; patients in non-industrialized countries and lower socioeconomic groups, as well as children who develop HD, are more likely to be EBV-positive, even with the NS-subtype, than those from high socioeconomic groups or young adults [19].

The survival of a B-cell in the GC is dependent of a major signal offered by BCR and by the positive selection process after the somatic mutation. In the absence of BCR or a reduce affinity of this receptor for the antigen, the B-cell population of GC goes to apoptosis.

The infection with EBV represents one of the ways of escape for this abnormal B-cells (RS-cell), which posses major molecular and biological abnormality (destructive mutations of IgH genes or/and down-regulated of the transcriptional factors and proteins involved in IgH-receptor expression or signaling) and even more, these cell can be the origin point for a new abnormal clone [20].

The advantage of survival and the blocking of the apoptosis of the RS-cell depend on the expression of three viral proteins: Epstein-Barr virus nuclear antigen 1 (EBNA1), latent membrane protein 1 (LMP1) and latent membrane protein 2 (LMP2). The first one is necessary to multiply the viral genome but seems also involved in other vital viral processes. LMP1 serves as the CD40 receptor and activates NFkB, a molecule with a major role in the differentiation and survival of the cells in the GC [21].

LMP1 can also activate the NFkB way by accelerating the turnover of inhibitor proteins of NFkB (IKB). LMP2a carries an immunoreceptor tyrosine-based activation motif (ITAM) which is present also on the BCR co-receptors, in this way accomplishing to activate the cytoplasmatic kinases associated to the transduction of the signal on BCR [19].

The expression of EBV in the RS-cell has a clonal character, indicating that the entire population comes from a single infected cell. Two possible explanations come forward: either the infection comes before clonal expansion, either in the later infection event; the infected clonagenic cells have the advantage of proliferation and survival [20].

Recently was described a new form of CL/Richter's syndrome (with an aggressive evolution) who associate B-CLL (sometime treated with fludarabine and/or Anti52 monoclonal antibody) and large B-cell NHL. This group of proliferations frequently associates also the infection with EBV, but the main pathogenic mechanism is probably immunodeficiency and cannot make the object of the current paper [22].

B-CLL features and HL evolving

The prognostic parameters, which define the risk levels in B-CLL, are different from those that facilitate the second hematological neoplasia, Richter's syndrome or HL [23].

The prognostic factors for an aggressive behavior of B-CLL are:

- the unmutated variable region IgH-type of B-CLL;
- the advanced stage of the disease;
- unfavorable cytogenetic abnormalities;
- the lymphocyte doubling time in untreated patients <12 months;
- the presence of ZAP70 or CD38 markers, etc.

These all factors seem to have any impact on the risk of progression to aggressive NHL or HL.

The mutated and unmutated variant of B-CLL has a significant prognostic impact for the chronic leukemia, but the developing of HL is possible in both cases. Although this feature balances the distribution of B-CLL cases, HL incidence is higher for those who have a mutation rate bellow 2%, without this being an independent risk factor [24].

The use of VH4-34 and VH-38 in the clonal rearrangement of the IgH variable region of leukemic B-cell grows the rate of association with HD [24], similar to a higher risk of the transformations in aggressive NHL, in case of some clonal rearrangement of IgH [25].

This hypothesis allows us to consider the impact of the antigenic pressure over the initiation of the clonal process in B-CLL. It is also possible that different pathogenic ways of the malignant transformations to influence the further biological features of B-leukemia and the process involved in the second neoplasia growth.

Although the data are far from being clarified, the idea mentioned above seems to be sustained by aggressive progression in MALT-lymphoma, which suggests that this may be dictated by the biologic profile of the indolent disease [26].

The definition of Richter's syndrome it is still under discussion: while some authors sustain that this entity includes any lymphoproliferation (aggressive NHL, HL, prolymphocytic transformation, etc.), which develop during B-CLL evolution, others believe that Richter's syndrome is represented only by aggressive NHL [27]. Even if we take into account the latest definition, we must consider Richter's syndrome as a heterogeneous entity, because the evolving of an aggressive lymphoma can be or not clonal related with chronic leukemia, while *de novo* large B-cell lymphomas have a variety and complex biology [25].

The prognostic score in the Richter's syndrome depend on [4]:

- Zubrod >1;
- LDH >1.5 above normal value;
- tumor volume >5 cm;
- Plt <100×10⁹;
- >1 previous therapy.

Average survival varies with the score: 1.12 years for score 0 or 1; 0.9 years for score 2; 0.3 years for score 3; 0.12 years for score 4 or 5.

Our patient has three of the negative prognostic elements as Richter's syndrome (Zubrod = 2, tumor volume >5 cm, LDH >1.5 above normal value) and concerning the prognostic staging of HL [28] he has all the negative prognostic factors (age, sex, advance stage, leukocytosis, low hemoglobin) except a low albumin.

Conclusions

The CL is defined by the presence in the same tissue or organ of two distinct histological aspects of non-Hodgkin's lymphoma (NHL) or NHL and Hodgkin's lymphoma (HL). They are rare entities if we exclude the process of progression/clonal transformation, specific for the indolent lymphoid proliferations. The immunophenotype, cytogenetic and molecular biology study are necessary for diagnosis and to disclose the relation between the two or three lymphoproliferative lesions.

A careful and depth assessment of these lesions give us data about the different natural history of the multiple disease entirely, prognosis and treatment modalities and for the possible pathogenic mechanisms of the inter-relationship of clonal evolution in lymphoma.

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