

# Transformation of Aggressive Non-Hodgkin Lymphoma in Acute Lymphoblastic Leukemia

István Benedek<sup>1</sup>, Erzsébet Lázár<sup>1</sup>, Annamária Pakucs<sup>2</sup>, Judit-Beáta Köpeczi<sup>2</sup>, István Benedek Jr<sup>1</sup>, Szende Jakab<sup>1</sup>, Johanna Sándor-Kéri<sup>1</sup>

<sup>1</sup> University of Medicine and Pharmacy, Tîrgu Mureş, Romania

<sup>2</sup> Clinic of Hematology and Bone Marrow Transplantation Unit, Tîrgu Mureş, Romania

## CORRESPONDENCE

### Annamária Pakucs

Str. Revoluției nr. 35  
540042 Tîrgu Mureş, Romania  
Tel: +40 265 218739  
E-mail: pakucs.annamaria@gmail.com

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István Benedek • Str. Gheorghe Marinescu nr. 38,  
540139 Tîrgu Mureş, Romania. Tel: +40 265 215 551.

Erzsébet Lázár • Str. Gheorghe Marinescu nr. 38,  
540139 Tîrgu Mureş, Romania. Tel: +40 265 215 551.

Judit-Beáta Köpeczi • Str. Revoluției nr. 35, 540042,  
Tîrgu Mureş, România, Tel: +40 265 218739

István Benedek Jr • Str. Gheorghe Marinescu nr. 38,  
540139 Tîrgu Mureş, Romania. Tel: +40 265 215 551.

Szende Jakab • Str. Gheorghe Marinescu nr. 38,  
540139 Tîrgu Mureş, Romania. Tel: +40 265 215 551.

Johanna Sándor-Kéri • Str. Gheorghe Marinescu nr.  
38, 540139 Tîrgu Mureş, Romania. Tel: +40 265 215 551

## ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing up to 30 percent of all lymphomas. DLBCL is a fast-growing, aggressive form of NHL, which can appear as a transformation from a less aggressive form of lymphoma or can be de novo pathology. The following article describes the case of a 55-year-old female patient who developed a DLBCL as a second malignancy after an R-CHOP-treated marginal zone splenic lymphoma. This was followed by the transformation of the DLBCL into an aggressive acute lymphoblastic leukemia, for which the patient needed aggressive treatment according to the international acute lymphoblastic leukemia protocol.

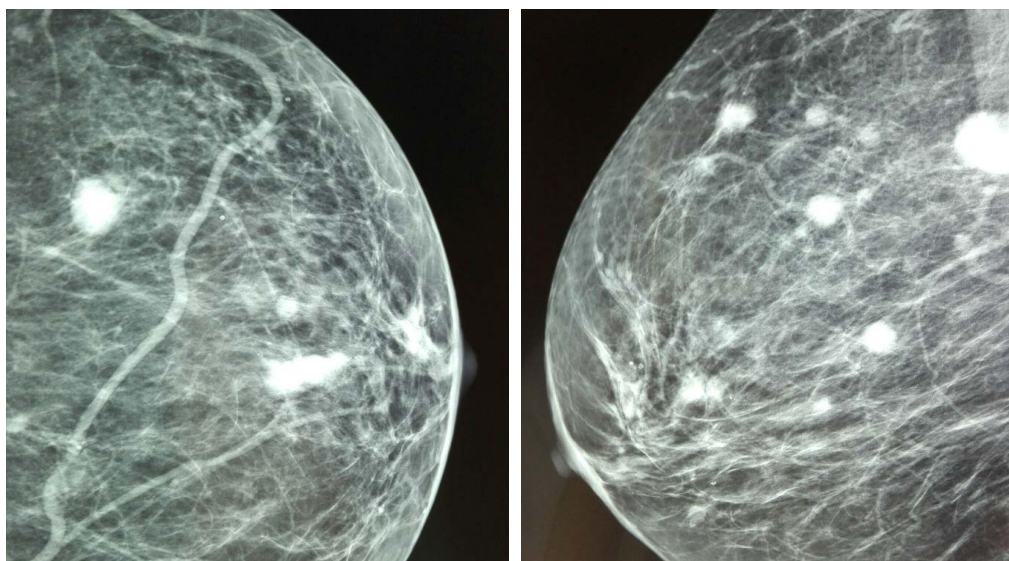
**Keywords:** DLBCL, acute lymphoblastic leukemia, immunophenotyping

## INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing up to 30 percent of all lymphomas. DLBCL is a fast-growing, aggressive form of NHL, which can appear either as a transformation from a less aggressive form of lymphoma or can be de novo pathology.<sup>1</sup>

DLBCL can arise in lymph nodes or outside of the lymphatic system, in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or central nervous system.

High-grade (aggressive) lymphomas generally require more intensive treatment than the low-grade types. A combination of chemotherapy and monoclonal antibody rituximab, with or without radiation therapy, can lead to complete remission in a large number of patients with this form of lymphoma.<sup>2,3</sup> The most widely used first-line treatment for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), which is usually given in



**FIGURE 1.** Mammography — multiple opaque lesions with irregular outline, dimensions between 6–26 mm, without calcification

28-day cycles. In 50% of the cases the initial treatment results in complete remission; however, in refractory or relapsed cases second-line high-dose therapies are needed and also stem cell transplantation can be performed.

DLBCL patients require complex management because of the wide heterogeneity of this disease.<sup>4</sup> In some cases we can see different clinical presentations, outcomes and processes among patients with similar histopathological diagnoses. The following case presents the appearance of a DLBCL as a second malignancy after a marginal zone splenic lymphoma and then the transformation of the DLBCL into an aggressive acute lymphoblastic leukemia.

### CASE PRESENTATION

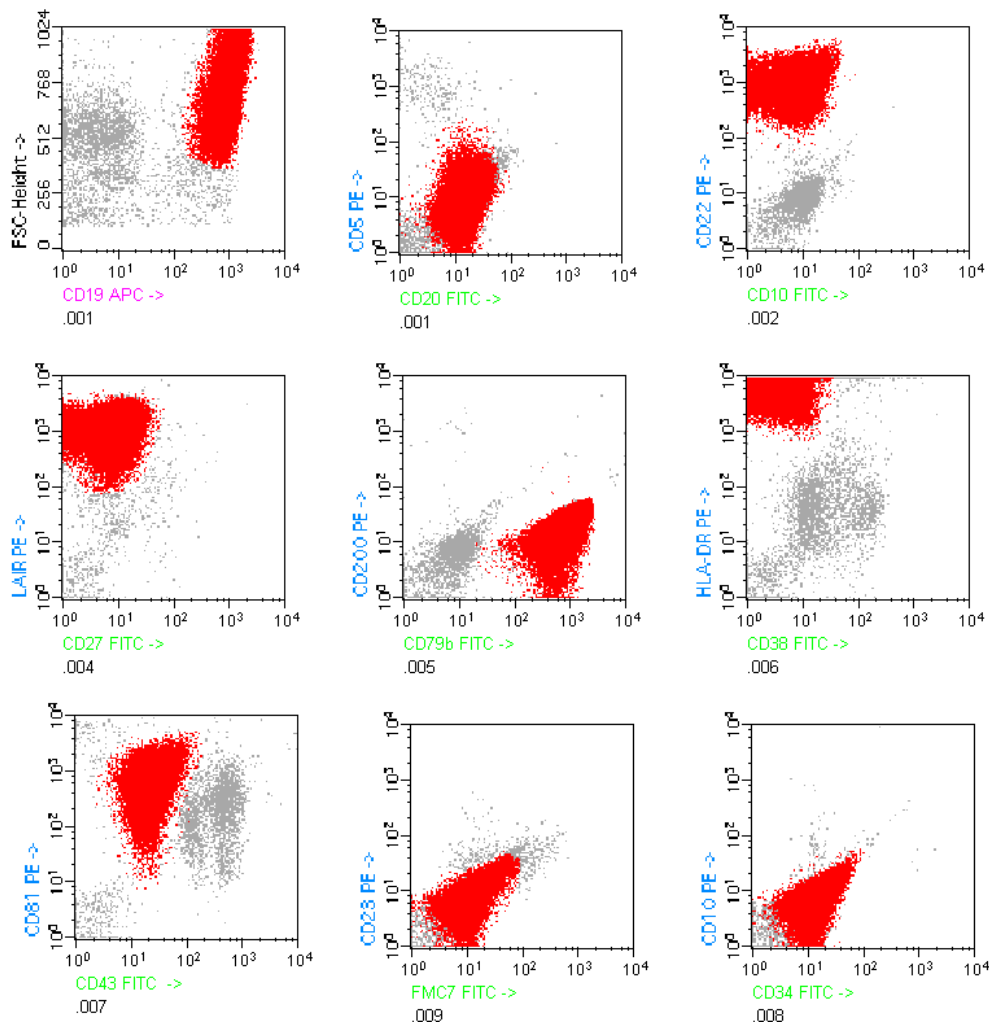
A 55-year-old female patient with rural provenience, with a history of chronic ischemic heart disease, depressive syndrome, and total hysterectomy, was admitted to our hematology clinic in August 2012 with the following symptoms: asthenia, fatigue, and abdominal discomfort. The clinical examination revealed a left submandibular lymphadenopathy of 2/3 cm, a massive splenomegaly, and normal paraclinical results. The dimensions of the spleen at splenectomy were 275 × 180 × 55 mm and its weight 1,750 g. Histopathological examination revealed that the white pulp had a reserved structure, while the red pulp presented predominantly CD20 positive lymphocyte infiltration (B lymphocytes). The MPO reaction showed myeloid elements in the red pulp, some of them with blastic

character. In some places a honeycomb aspect could be found (cells with uniform nucleus and clear, abundant cytoplasm). The histopathological result suggested the presence of a lymphoma. Osteomedullar biopsy was performed to clarify the diagnosis. The histopathological and immunohistochemical examination of the osteomedullar biopsy revealed osteomedullar tissue with a lymphoproliferative

**TABLE 1.** Laboratory data of the patient at the transformation (2016)

Hematological panel		
WBC, × 10 <sup>3</sup> /μL	248.18	3.6–10
Neutrophils [%]	0	42.2–75.2
Lymphocytes [%]	0	20.5–45
Monocytes [%]	0	2.2–8
RBC, × 10 <sup>6</sup> /μL	3.62	3.5–6
Hgb [g/dL]	11.3	12.17
MCV, fL	88.4	78–95
MCH, pg	31.2	27–36
Platelets, × 10 <sup>3</sup> /μL	29	150–450
Biochemistry		
AST [U/L]	119	0–46
ALT [U/L]	48	0–49
GGT [U/L]	121	7–52
Urea [mmol/L]	12.20	2.49–7.74
Creatinine [mg/dL]	1.44	0.50–1.20
LDH [U/L]	3,573	220–460

WBC – white blood cells, RBC – red blood cells; Hgb – hemoglobin; MCV – mean cell volume; MCH – mean corpuscular hemoglobin, AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT –  $\gamma$ -glutamyl transpeptidase; LDH – lactate dehydrogenase

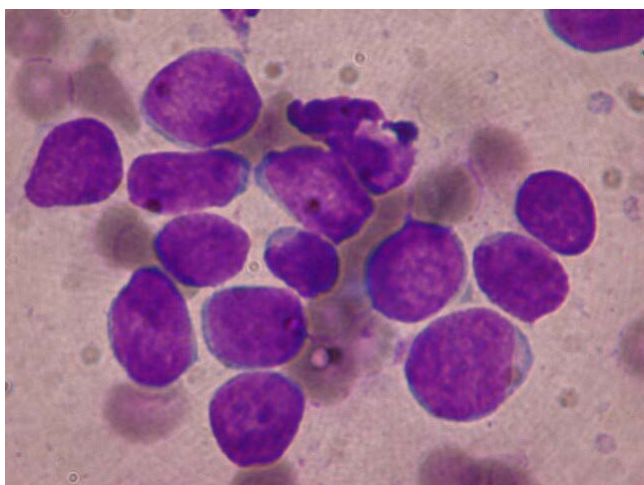


**FIGURE 2.** Immunophenotype of the aberrant B-cells (red) detected by flowcytometry in the peripheral blood sample (surface markers): 93%: positive for the following B-cell markers: CD19, CD22, CD79b, LAIR1, CD81, HLA-DR, negative for CD20, CD5, CD10, CD200, CD23, FMC7, CD27, CD43, CD38, CD34. Data were analyzed with Paint-a-gate software.

process with B cell origin, characterized by interstitial and intrasinusoidal nodular infiltration. The examined osteomedullar tissue presented cellularity in accordance with the patient's age, with hypercellular spaces due to the intense proliferation of lymphoid elements with plasmacytoid appearance, suggested by the imprecisely delimited, hyperchromatic nucleus organized in a nodular pattern, improving the inter-trabecular and peri-trabecular spaces, grouped and isolated cells that infiltrate the interstitium and the sinusoids' lumens. The tumor cells were: CD20+/CD5+, CD10, CD23-, CD3- and Cyclin D1-. The morphological appearance and the character of the infiltration (intra-trabecular and sinusoidal) as well as the tumor cells' immunophenotype claimed the diagnosis of a marginal zone splenic lymphoma.

R-CHOP scheme chemotherapy was initialized with 28-day cycles (6 cures) followed by a remission period.

In October 2015 the patient presents the appearance of a hardened, painless cutaneous lesion of 2/3 cm in the right inguinal region and multiple nodular lesions of 3–4 cm in the upper outer quadrant of the right breast, sensible to palpation, adherent to the underlying plans and mobile to the overlying plans. The mammography revealed multiple opaque lesions with irregular outline, sized between 6–26 mm, without calcification (Figure 1). No peripheral adenopathy or organomegaly was found on the physical examination. Computed tomography showed a lomboartocaval, interaorticocaval adenopathy of 17 mm. Histopathological and immunohistochemical examination was performed from the cutaneous lesion. Macroscopic description: ellip-

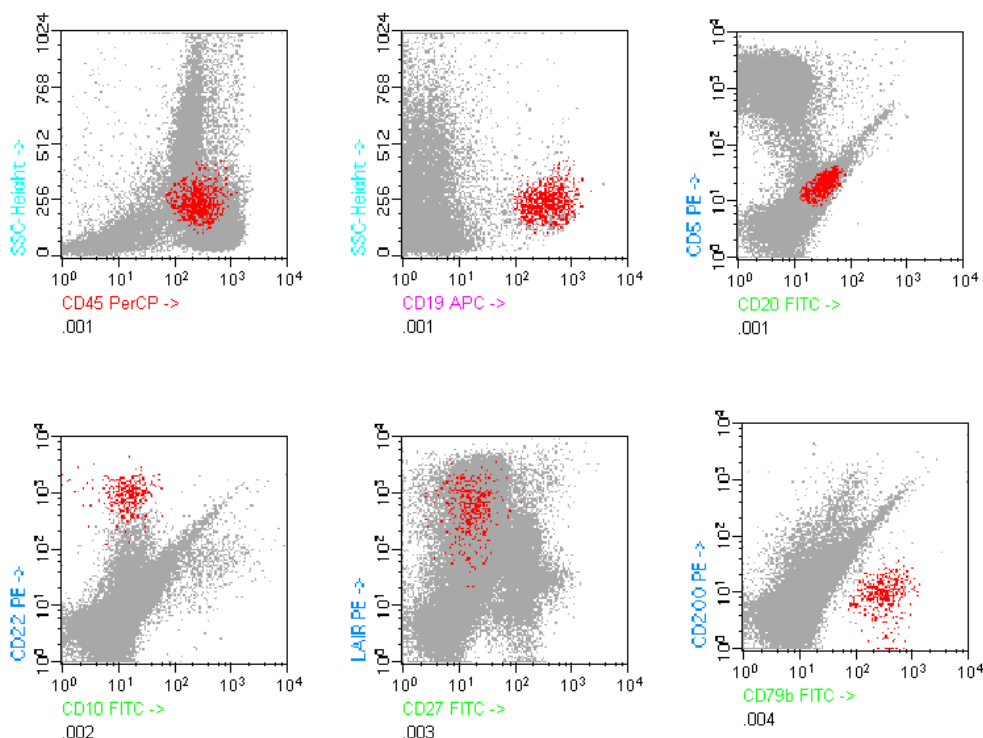


**FIGURE 3.** Morphology of the blasts stained with May-Grünwald-Giemsa (100×)

tical cutaneous flap with dimensions of 40 × 20 mm, subcutaneous tissue with a thickness of 12 mm. In section, on the dermal and hypodermal level a white-grayish 10 × 13 × 28 mm nodule was described. Microscopic description: the examined cutaneous pieces showed a lymphoprolifera-

tive process, which infiltrated the dermal and hypodermal region. The tumor tissue was composed of mid-sized cells with centrocyte and centroblast appearance and increased mitotic activity, expressing LCA, CD20, CD791, and PAX5, without CD10, Bcl2, TaT, and CD99 expression. The Ki67 proliferation index was 70–80%. The lesion involved all the examined tissues. Histopathological diagnosis: malignant cutaneous lymphoproliferative process — diffuse large B-cell lymphoma.

We consider that after the treatment of the first lymphoproliferative process, according to the histopathological and immunohistochemical examination, a second hematological malignancy appeared, and thus, second line DHAP (Dexamethasone, high-dose Ara-C, Platinol) chemotherapy was initialized. After the administration of 4 DHAP cures with relatively favorable evolution, the patient presented poor general status, physical asthenia, fatigue, predominantly inspiratory dyspnea during minimal efforts, low-grade fever (37.3 °C) without shivering, nocturnal sweating, loss of appetite, nausea, weight loss, and drowsiness. The clinical examination revealed: discreet mucosal and skin paleness, subpalpebral ecchymosis, post-splenectomy and post-hysterectomy abdominal cicatrices, with-



**FIGURE 4.** Immunophenotype of the aberrant B-cells (red) detected by flow cytometry in the bone marrow sample: 1%: positive for: CD19, CD22, CD79b, LAIR1, negative for CD20, CD5, CD10, CD200, CD27 are similar with the previous immunophenotype. Minimal residual disease: 1%. Data were analyzed with Paint-a-gate software.

out palpable peripheral lymphadenopathy, normal chest conformation, symmetric bilateral vesicular breath sound, rhythmical cardiac sounds; arterial blood pressure: 110/60 mmHg; ventricular rate: 100 beats/minute; liver with 6–7 cm under the right costal margin. The biological values showed leukocytosis (Table 1) and the immunophenotype determination from peripheral blood revealed the following results: 93% of lymphoid elements with the following antigenic profile: CD19+, CD20–, CD5–, CD22+, CD10–, CD200–, CD79b+, HLA-DR+, CD23–, FMC7–, CD27–, LAIR+, CD11c+, CD103–, CD81+, CD43–, CD38–, kappa+; Matutes score: 1 (Figure 2). The microscopic analysis of the peripheral blood revealed 90% young cellular elements with lymphoblastic morphological appearance of variable size with reduced cytoplasm, round nucleus with nucleolus (acute lymphoblastic leukemia appearance, Figure 3). The biological examination for BCR-ABL rearrangement was negative.

Analyzing the obtained results, we ascertained the leukemic transformation of the large B-cell malignant lymphoma and we initialized treatment according to the acute lymphoblastic leukemia protocol. After finishing the pre-induction, 1<sup>st</sup> and 2<sup>nd</sup> induction, and the 1<sup>st</sup> and 2<sup>nd</sup> consolidation, bone marrow immunophenotyping was repeated with the following results: 32.5% myeloid elements (SSC↓): the combination of 16/13/45/11b markers showed the myeloid series dysplasia, 7% mature monocytes, 3.5% immature monocytes, 0.1% eosinophils, 0.2% basophils, 30% lymphocytes, 1.5% myeloblasts, 0% pre-B lymphoblasts, 20% erythroblasts, 2% plasmocytes, 0.4% mastocytes, 1.8% dendritic cells, 1% lymphoid elements (SSC↑, FSC↑) with the following antigenic profile: CD19+, CD20–, CD5–, CD22+, CD10–, CD200–, CD79b+, HLA-DR+, CD27–, LAIR1+. Minimal residual disease: 1% (Figure 4), considering that disease had an adequate response to the treatment.

Currently the patient is under hematological follow-up and treatment in the 2<sup>nd</sup> re-induction phase, with long medullar aplasia likely due to multiple chemotherapy treatments.

## DISCUSSION

As in the case presented above, a patient with a previously treated indolent lymphoma that presents new symptoms,

such as night sweats, fever, or the appearance of rapidly growing lymph nodes, indicates that the patient needs to be urgently seen and evaluated by a clinical hematologist for the possibility of the appearance of a second lymphoproliferative malignancy. A full evaluation should include a biopsy and also the evaluation of the morphological and phenotypical characteristics for diagnosis and staging, in order to initiate a proper treatment.<sup>5,6</sup> In our case, the secondary cutaneous diffuse large B-cell lymphoma had a worse prognosis than a typical diffuse large B-cell lymphoma, because it evolved into an acute lymphoblastic leukemia.<sup>7</sup>

## PARTICULARITIES OF THE CASE

- The presence of two lymphoproliferative malignancies (marginal zone lymphoma and large B-cell lymphoma) in the same patient, in a relatively short period of time (3 years);
- A very aggressive evolution of the large B-cell lymphoma, with the appearance of leukemic transformation that required an aggressive treatment, in accordance with the acute lymphoblastic leukemia protocol.<sup>8</sup>

## CONFLICT OF INTEREST

Nothing to declare.

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