

Hodgkin's Lymphoma Variant of Richter's Syndrome

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ABSTRACT

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is low-grade malignant lymphoproliferation, that has tendency to convert to a higher-grade neoplasia over time. More common is the development of a diffuse large cell lymphoma or transformation into prolymphocytic cell population. In rare cases, 0.1–0.5% of patients develop multiple myeloma or Hodgkin's disease. We present 65-year old female with Hodgkin's variant of Richter's syndrome. On the basis of clinical symptoms, cytological, histological and immunohistological finding in April 2008 CLL/SLL were diagnosed. The patient was treated with 8 courses of R-CHOP. After 10 months, FNA of the one of the enlarged lymph node on the neck was performed. The diagnosis was Hodgkin's disease. Immuno-histological studies of the lymph node was consistent with type I Hodgkin's type of Richter's syndrome. Patient was treated with 3 courses of ABVD and radiotherapy.

Key words: Richter's syndrome, chronic lymphocytic leukemia, Hodgkin's disease, Reed-Sternberg cell

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) results from the neoplastic transformation and clonal proliferation of a population of B small lymphocytes expressing surface CD5^{1,2}. Clonal B-lymphocytes infiltrate bone marrow and/or lymph nodes with lymphocytosis in peripheral blood. Diagnosis is usually simple, but predicting the clinical course can be difficult³. Approximately one-third of CLL patients are affected by an indolent form of disease that does not require treatment or modify survival. Another third of patients present with leukemia that will require iterative therapies, profoundly affecting their quality and length of life¹. Although progression to acute lymphoid leukemia is very rare (like in the course of chronic myeloid leukaemia), a small fraction (2–8%) of CLL patients develop Richter syndrome (RS)^{1,4–6}. RS is represented in most cases by diffuse large B-cell lymphoma (DLBCL) arising from the transformation of the original CLL clone or, less frequently, representing a new or secondary lymphoid neoplasm¹. Moreover, population-based studies have de-

monstrated an increased risk of secondary cancers and autoimmune abnormalities (Coombs-positive autoimmune hemolytic anaemia and immune-mediated thrombocytopenia) following B-CLL⁷.

RS is a highly aggressive syndrome with a median survival of 5 to 8 months¹. RS, DLBCL transformation of CLL is associated with B symptoms, abdominal pain, progressive anaemia, thrombocytopenia and usually with rapid increase of peripheral blood lymphocyte counts^{1,8}. The syndrome was first described in 1928 by Maurice N. Richter, who reported a patient with rapidly fatal generalized lymphadenopathy and hepatosplenomegaly associated with CLL⁶. Subsequently, RS was expanded to include other lymphoid malignancies that develop in patients with CLL, such as prolymphocytic leukemia (PLL), Hodgkin lymphoma, the so-called Hodgkin variant of Richter's transformation, small noncleaved cell lymphoma, lymphoblastic lymphoma, and hairy cell leukemia. In rare cases, patients with B-cell CLL may develop mul-

multiple myeloma or high-grade, T-cell NHL⁶⁻¹⁰. Hodgkin variant of RS is also rare complication of CLL/SLL and it is characterized by the development of neoplasms that morphologically and immunophenotypically resemble Hodgkin lymphoma. Although the term »Hodgkin variant of Richter transformation« has been used, the term »Hodgkin transformation of CLL/SLL« describes this disease more accurately¹¹.

The large cells of Hodgkin transformation of CLL/SLL are characterized by morphologic and immunophenotypic features of Hodgkin and Reed-Sternberg (H-RS) cells of typical Hodgkin lymphoma and express CD15 and CD30¹²⁻¹⁴.

In this report we present a 65-year old female patient with CLL/SLL and Hodgkin variant (Hodgkin transformation) of Richter syndrome.

Case Report

A 65 year female patient was firstly seen in University Hospital »Sestre Milosrdnice« in April 2008, because of enlarged lymph nodes. At clinical examination beside enlarged axillary and on the neck lymph nodes, spleen was also palpable. Patient was admitted to our University Hospital and hematologic laboratory findings of peripheral blood (PB) revealed anemia (red blood count count-RBC: $3.6 \times 10^{12}/L$; hemoglobin-Hb: 88 g/L), thrombocytopenia (platelets-PLT: $99 \times 10^9/L$) and leukocytosis (white blood count-WBC: $48.9 \times 10^9/L$). Differential white blood count (DWBC) showed lymphocytosis (96% mature lymphocytes, 3% neutrophils; 1% monocytes) (Figure 1). Laboratory findings of renal and hepatic functions showed normal values pointing to normal renal and hepatic functions. Because of hematologic laboratory findings, fine needle biopsy (FNA) of bone marrow (BM) was indicated and BM cytomorphologic analysis revealed hypercellular hematopoiesis and numerous mature small lymphocytes with clumped chromatin comprising 91% of all nucleated BM cells (Figure 2). FNA cytomorphological analysis of axillary enlarged lymph node was consistent with small cell lymphocytic lymphoma (Figure 3). Ultrasound (US) of abdomen revealed periaortal and peri-

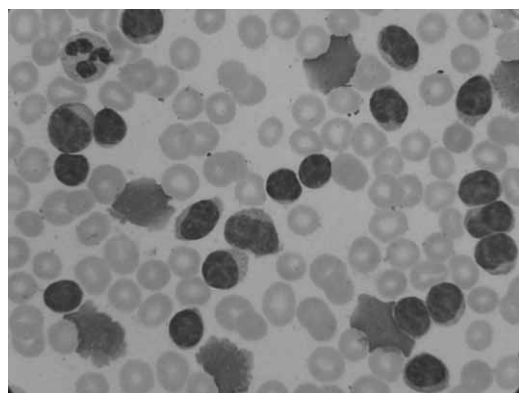


Fig. 1. Peripheral blood smear CLL/SLL (small lymphocytes and »smudge cells«), MGG $\times 100$.

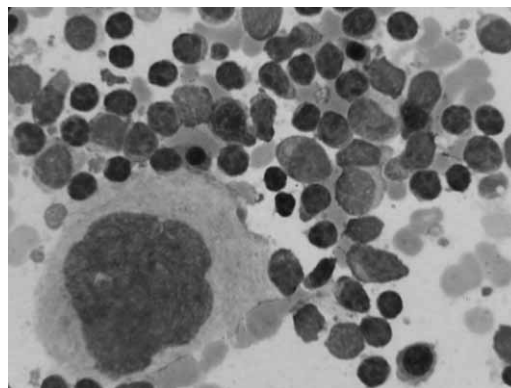


Fig. 2. Bone marrow aspirate CLL/SLL (infiltration of small lymphocytes and »smudge cells«), MGG $\times 100$.

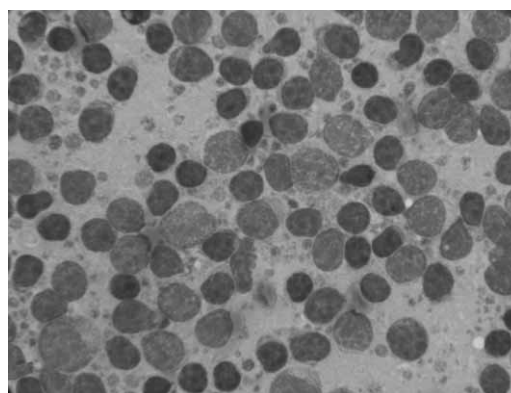


Fig. 3. FNA of lymph node CLL/SLL (small lymphocytes), MGG $\times 100$.

splenic lymphadenopathy. According all these findings biopsy of axillary lymph node was done and histological analysis revealed diffuse infiltrates of small lymphocytic cells in lymphatic node tissue. On immunohistochemistry small lymphocytic cells in lymph node were CD20 (clone B-Ly 1) and CD5 (clone 4C7) positive, thus confirming proliferation of B lymphocytes expressing also CD5 antigen. Small lymphocytic lymph node cells were also positive for CD23 (clone 1B12), CD43 (clone DF-T1) and JC12 (clone FOXP). Ki-67 (clone MIB-1) was also positive in 10% of lymphocytic cells and FOXP was positive in 3-5% lymphocytic cells.

On the basis of clinical presentation and hematological, cytological, histological and immunohistochemical findings CLL/SLL was diagnosed. The patient was treated with eight courses of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). Cycles were repeated every 28 days. Lymphocytosis gradually decreased and peripheral blood cytomorphology became normal shortly after the end of the treatment. The aspirated BM was normocellular with 24% erythroid precursors, 17% lymphocytes, 58% granulocytes and granulocytic precursors. Hematologic analysis of PB revealed recovery of anemia (RBC: $4.0 \times 10^{12}/L$, Hb: 147 g/L) and thrombocytopenia (PLT: $216 \times 10^9/L$) with normal

WBC count (WBC: $8.2 \times 10^9/L$) and normal DWBC (50% neutrophils, 40% lymphocytes and 7% monocytes).

Two months after the end of the therapy, on physical examination failed to identify palpable peripheal lymphadenopathy on the neck. Laboratory findings showed creatinine 66 g/L, lactate dehydrogenase (LDH) 165 U/L, and elevation of gamma-globulin levels. All other peripheral blood laboratory findings were within normal limits. A computed tomography (CT) of the chest and abdomen

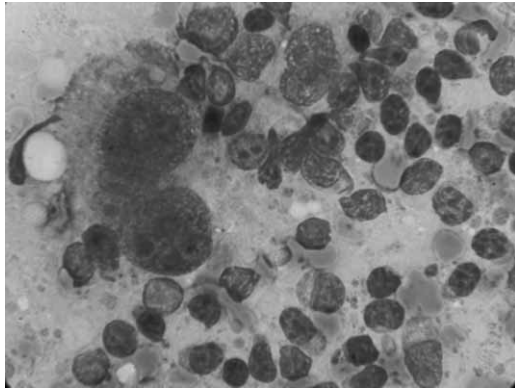


Fig. 4. FNA of lymph node Hodgkin's disease (Reed-Sternberg cell), MGG $\times 100$.

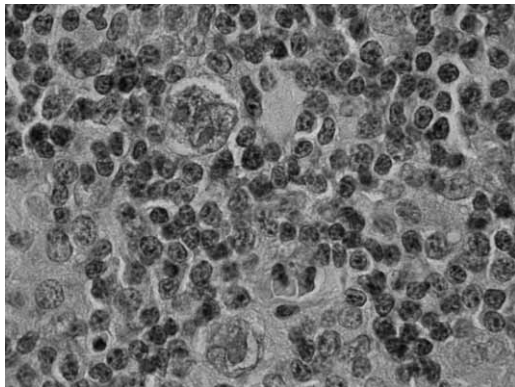


Fig. 5. Histopathology of lymph node Hodgkin's disease (Reed-Sternberg and Hodgkin's cells), H-E $\times 100$.

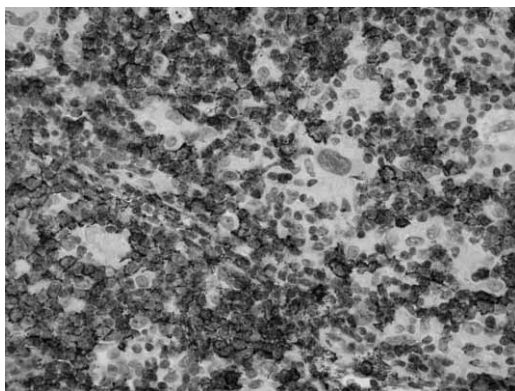


Fig. 6. Immunohistopathology of lymph node Hodgkin's disease (CD20 positive), IHC $\times 40$.

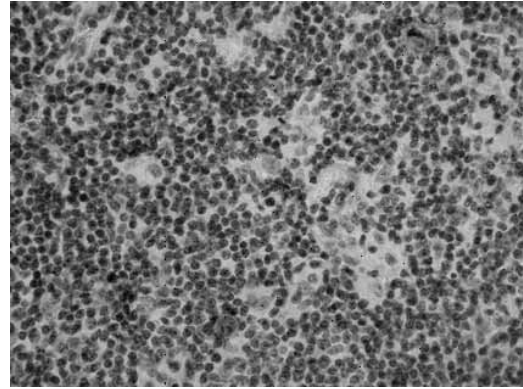


Fig. 7. Immunohistopathology of lymph node Hodgkin's disease (CD30 positive), IHC $\times 40$.

revealed mediastinal and abdominal lymphadenopathy. Ten months after initial diagnosis of CLL, FNA of the enlarged lymph node of the neck was performed. Abundant cytological specimen was obtained, with lymphocytes and multiple Reed-Sternberg (RS) and Hodgkin's (H) cells. (Figure 4). Histopathological assessment of the lymph node sections showed the presence of RS and H cells (Figure 5) with expression of CD30 (Figure 6), surrounded by small monomorphic lymphocytes with expression of CD20 (Figure 7). The patient is still on doxorubicin, bleomycin, vinblastine and dacarbazine (ABDV) therapy, the cycles are repeated every 21 days, up to three courses and radiotherapy is also planned.

Discussion

In the 1928, Richter^{6,13} first described the occurrence of »reticulum cell sarcoma« in patient with CLL and rapidly fatal generalized lymphadenopathy and hepatosplenomegaly. In this first reported patient histologic examination of the lymph nodes, liver, and spleen revealed two types of cells: leukemic and tumor cells⁶. Leukemic cells referred to lymphocytes of small size and tumor cells referred to numerous, polymorphous cells, several times as large as the lymphocytes, with abundant basophilic cytoplasm. Since that time, numerous reports have described the distinct clinicopathologic entity known as Richter's syndrome and in RS were also included other lymphoid malignancies that develop in patients with CLL, such as prolymphocytic leukemia (PLL), Hodgkin lymphoma (HL, so-called Hodgkin variant of Richter's transformation), small noncleaved cell lymphoma, lymphoblastic lymphoma, and hairy cell leukemia⁴. The reported incidence of transformation to RS in patients with CLL ranges from 2% to 8%, represented in most cases by diffuse large B-cell lymphoma¹. Hodgkin variant of Richter transformation seen in our patient, is rare ranging from 0.4 to 1.8 according some studies. The interval between CLL and the occurrence of Hodgkin's disease is variable. CLL and Hodgkin lymphoma can be diagnosed simultaneously with CLL, but Hodgkin lymphoma (Hodgkin variant of RS) is usually recognized several months

or years, as in our patient, after the initial diagnosis of CLL^{6,11}. According study of Tsimberidou et al. median time from CLL to HL diagnosis was 4.6 years (range 0–12.9 years), which is similar to median time of occurrence of other forms of Richter's transformation after CLL. Thus, in US Intergroup prospective group study was found that in patients with CLL and classic Richter's transformation median time was 21.9 months (range, 1–66 months) and for occurrence of PLL after CLL median time was 14.8 months (range, 1–36 months)⁶.

Clinical presentation of RS is characterized by a development of systemic symptoms (e.g. fever, weight loss and/or night sweats), sudden clinical deterioration, and usually, as in our patient, a rapid increase in the size of a lymphoid mass at one site¹². The most common feature in RS is an elevated LDH level, a marker of tumor growth, which was not seen in our patient⁶.

Two types of Hodgkin transformation of CLL/SLL have been described. Type 1 transformation is characterized by H-RS cells scattered in a background of CLL cells. In type 2 transformation, H-RS cells present in a typical polymorphous, inflammatory background separate from the CLL cells^{1,12}. According cytological, histopathological and immunohistochemical analysis our patient had type 1 of Hodgkin transformation of CLL/SLL while multiple H-RS cells were found together with numerous small mature lymphocytic cells. Immunohistochemistry of our patient node biopsy showed CD30 positivity of H-RS cells surrounded by CD20 positive small monomorphic lymphocytes.

Histologic and immunophenotypic findings suggest that H-RS cells in patients with type 1 transformation represent histologic progression of the underlying CLL cells, especially when the H-RS cells express B-cell markers¹⁴. Although, in type 2 transformation, 2 different disease types are considered to be present, the 2 lesions may be related according study of Ohno et al.¹⁵ demonstrating clonal relationship between CLL and H-RS cells by using polymerase chain reaction analysis and DNA sequencing in majority of CLL patients with HD^{15–18}.

Today, poor prognosis of CLL may be identified at diagnosis based on a combination of clinical, morphologic, immunophenotypic and molecular parameters. Thus, in

a univariate analysis of 620 patients with B-CLL in a French study, younger age, the presence of a peripheral tumoral syndrome, diffuse involvement as demonstrated in tissue specimens from BM, initial hemoglobin level <12 g/L (seen also in our patient), advanced Rai stage, LDH level greater than 1.25-fold the upper limit of normal and high β -2-microglobulin levels predicted the occurrence of RS⁶. Immunoexpression of CD38 and ZAP-70, as well as molecular indicators as absence of mutations in the IgV genes, presence of rare G allele and genomic aberrations such as deletions at chromosome 17p and 11q are recognized factors for poor prognosis of CLL and development of RS¹. Although, the precise role of Epstein-Barr virus (EBV) infections in Richter's transformation of CLL remains to be established, evidence supports that EBV infection is important in the Hodgkin variant of RS transformation. Although some of these cases may represent a coincidental occurrence, EBV via integration of its genome may play an important role in pathogenesis of some cases of Hodgkin lymphoma variant of Richter's transformation of CLL/SLL⁶.

The natural history of the Hodgkin variant of RS is difficult to determine because of limited reports. Also, it is unknown whether the type 1 and type 2 of Hodgkin lymphoma variant of Richter's transformation of CLL/SLL are associated with distinct clinical prognostic features⁶. But, patients with this variant generally present with a more advanced stage of disease than do patients with true Hodgkin lymphoma^{6,12}. According some studies patients with the Hodgkin variant of RS had similar response to therapy and survival as other patients with CLL and RS, but some studies implicate a better outcome in patients with Hodgkin variant of RS than those with classic RS⁶.

In conclusion, report of our patient, among other reports point that in patient with CLL and onset of lymph node enlargement cytological and histological analysis of more enlarged lymph nodes are required for establishing accurate diagnosis. Moreover, determination of some markers (ZAP-70, G allele) in CLL patients at diagnosis, beside standard immunophenotyping, should be also planned for recognizing patients with higher risk for RS and for further analyzing etiology and possible risks for disease progression of lymphoid cell tumors.

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HODGKINOVA VARIJANTA RICHTEROVOG SINDROMA

S A Ž E T A K

Kronična limfocitna leukemija/limfom malih stanica (CLL/SLL) je limfoproliferativna bolest niskog stupnja malignosti koja pokazuje tendenciju prelaska u neoplazme visokog stupnja. Češći je razvoj difuznog velikostaničnog limfoma ili prolimfocitne leukemije. U rijetkim slučajevima, 0,1–0,5% bolesnika razvija multipli mijelom ili Hodgkinovu bolest. Prikazujemo 65-godišnju ženu s Hodgkinovom varijantom Richterovog sindroma. Na bazi kliničkih simptoma, citologije, histiologije i imunohistologije, u travnju 2008. postavljena je dijagnoza CLL/SLL. Bolesnica je tretirana s 8 ciklusa R-CHOP. Nakon 10 mjeseci punktiran je limfni čvor na vratu i postavljena je dijagnoza Hodgkinove bolesti. Imunohistološki nalaz čvora je tip I Hodgkinove varijante Richterova sindroma. Bolesnica je na tretmanu s 3 ciklusa ABVD-a i radioterapijom.