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 neoplasm 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 month, 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 radiotherap.

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 CD51,2. 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 life4. Although progression to acute lymphoid leukemia is very rare (like in the course of chronic myeloid leukemia), 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 neoplasm5. Moreover, population-based studies have demonstrated 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 counts1,8. The syndrome was first described in 1928 by Maurice N. Richter, who reported a patient with rapidly fatal generalized lymphadenopathy and hepatosplenomegaly associated with CLL4. 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-
tiple myeloma or high-grade, T-cell NHL. 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 accurately.

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 CD30.

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: 3.6×10¹²/L; hemoglobin-Hb: 88 g/L), thrombocytopenia (platelets-PLT: 99×10⁹/L) and leukocytosis (white blood count-WBC: 48.9×10⁹/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 hematopoesis 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 peripheral 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 cytology 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: 4.0×10¹²/L, Hb: 147 g/L) and thrombocytopenia (PLT: 216×10⁹/L) with normal
WBC count (WBC: 8.2×10^9/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 peripheral 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 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, Richter⁶,¹³ 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 reportes 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 lymphoma⁵. 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. According study of Tsimeridou 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 oc-
currence 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 me-
dian time was 14.8 months (range, 1–36 months).8

Clinical presentation of RS is characterized by a de-
velopment 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 elavted LDH level, a marker of tumor growth, 
which was not seen in our patient8.

Two types of Hodgkin transformation of cLL/SLL 
have been described. Type 1 transformation is charac-
terized 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 cells12. According cytological, histopathological 
and immunohistochemical analysis our patient had type 
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 
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surrounded by CD20 positive small monomorphic lym-
phocytes.

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 mark-
ers14. 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 demon-
strating clonal relationship between cLL and H-RS cells 
by using polymerase chain reaction analysis and DNA se-
quencing in majority of cLL patients with HD15–18.

Today, poor prognosis of cLL may be identified at di-
agnosis 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, initail hemoglobin level 
<12 g/L (seen also in our patient), advanced Rai stage, 
LDH level greater than 1.25-fold the upper limit of nor-
mal and high β-2-microglobulin levels predicted the oc-
currence of RS9. 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 ab-
errations 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 Ep-
stein-Barr virus (EBV) infections in Richter’s transfor-
mation of cLL remains to be established, evidence sup-
ports 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 plays an important role in 
pathogenesis of some cases of Hodgkin lymphoma vari-
ant 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 fea-
tures8. But, patients with this variant generally present 
with a more advanced stage of disease than do patients 
with true Hodgkin lymphoma6.12 According some studies 
patients with the Hodgkin variant of RS had similar re-
sponse to therapy and survival as other patients with 
cLL and RS, but some studies imply a better outcome 
in patients with Hodgkin variant of RS than those with 
classic RS6.

In conclusion, report of our patient, among other re-
ports 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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