



Rare case of Richter's syndrome localization in liver and thyroid of a patient with a chronic lymphocytic leukemia (CLL) – Case report and literature

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Abstract

Richter's syndrome (RS) is a rare complication in which chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) transforms into a more aggressive type of lymphoma – diffuse large B cell lymphoma (DLBCL), or Hodgkin's lymphoma (HL). The review describes the clinical case of a patient with CLL and RS diagnosis. A computed tomography (CT) scan of the abdominal cavity detected numerous normodense areas in the liver. Simultaneously, ultrasound examination (USG) of the thyroid revealed the presence of a solid hypoechogenic lump. The material sampled from closed biopsies of liver and thyroid in both cases allowed the diagnosis of diffuse large B cell lymphoma (DLBCL). The liver and the thyroid are particularly rare locations of RS. However, those cases allowed the conclusion that RS may occur even in a very unexpected and less probable location.

Key words

liver, thyroid, chronic lymphocytic leukemia, Richter's syndrome

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is usually a lymphoproliferative disease with a chronic course [1, 2, 3]. It is the most commonly diagnosed type of leukemia in adults. The disease is characterized by the variety of clinical course, prognosis and response to cytostatic treatment; the start of treatment is individual for each patient and depends on the severity of the clinical or progressive nature of the disease. In some patients, mild course and long survival are observed, very often without cytostatic treatment. In the remaining patients, the disease is aggressive and despite intense therapy, it leads to death within 2–3 years.

Richter's syndrome is defined by the transformation of chronic proliferation of B-cells, which is chronic lymphocytic leukemia or lymphocytic lymphoma, into a more aggressive form of lymphoma. Most commonly, it is a diffuse large B-cell lymphoma (DLBCL-RS) [4], rarely Hodgkin lymphoma (Hodgkin variant of RS, HvRS) [5]. The frequency of

occurring of RS among patients with CLL is estimated to be 2%–10% [6]. The most frequent RS (80%–90%) stems from the same clone as CLL (clonally related RS). In a very small part, the tumor clone develops independently (clonally unrelated RS) [7]. The increased risk of RS occurring is related with the presence of genetic aberrations, such as del 11q and 17p [8, 9], unmutated IGHV, significant expression of ZAP-70, CD38 and CD49d [10, 11]. RS is characterized by very rapid clinical process. Among more than half of patients (about 59%) there is fever, weight loss or intensified, night hyperhidrosis [12, 13]. RS most commonly occurs in lymph nodes and bone marrow. Localization in the lymphatic system occurs in about 41% of cases. Particularly rare cases are those, where transformations occur in the liver and thyroid [14, 3].

CASE REPORT

In June 2007, 60-year-old woman, on the basis of histopathological examination of lymph node and immunophenotype of peripheral blood lymphocytes (CD19+/CD5+/CD23+; Ig lambda+), was diagnosed with chronic lymphocytic leukemia (stage 4 according to Rai classification). Complete peripheral blood count revealed:

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WBC 24.8 K/uL; Lymph. 21.0 K/uL; Hgb 9.9 g/dL; PLT 70.0 K/uL, concentration LDH 132.0 U/l (10–480). The patient had not reported any general symptoms. Leukemia cells indicated immunological phenotype ZAP70-/CD38+, without the presence of negative genetic aberrations, such as del 11q and del 17p. Physical examination revealed peripheral lymphadenopathy, and USG examination revealed increased size of lymph nodes in the abdominal cavity, without signs of organomegaly. Treatment was started (totally, 6 cycles with chlorambucil and prednisone), resulting in complete remission (CR) of the underlying disease. Afterwards, the patient was observed on an outpatient basis.

In February 2015, the patient was admitted to a hospital due to gradually increasing upper abdominal pain, anorexia and weight loss which had lasted for several weeks. Complete peripheral blood count revealed: WBC 9.79 K/uL, Lymph. 6.75 K/uL, Hgb 11.2 g/dL, PLT 133.0 K/uL and LDH 753.0 U/l. CT examination revealed also an increased liver size (200 mm in midclavicular line), with irregular outline, displacing neighbouring organs. Reduced vascular pattern, organ parenchyma with density about 40 u.H., almost the whole covered by numerous, segmentally confluent, round normodense areas, showing minor contrast enhancement. Areas of a similar character had been also observed on an increased in size (177mm) spleen (Fig. 1). Furthermore, there were observed numerous, increased in size, lymph nodes located in retroperitoneum. Leukemia lymphocytes indicated phenotype ZAP70-/CD38+ with increased, compared to the time of CLL diagnosis, share of CD38+ cells (36% vs 49%), again without presence of genetic aberrations. Biochemical examinations also revealed increased activity of transaminases: Alat 104.0 U/l (5–45) and Aspat 161.0 U/l (5–50). Patient also had closed core biopsy of the liver and a sample of the material was taken for histopathological examination. The biopsy revealed a large lymphoid cells infiltration with morphology of centroblasts and immunoblasts (CD20+; bcl6+; CD10-; bcl2-; CD3-; CD5-; cyclin D1-; Ig lambda+; Ki67 about 90%). Results of immunohistochemical examinations led to diagnose the transformation of CLL into diffuse large B-cell lymphoma – Richter's syndrome (Fig. 2).

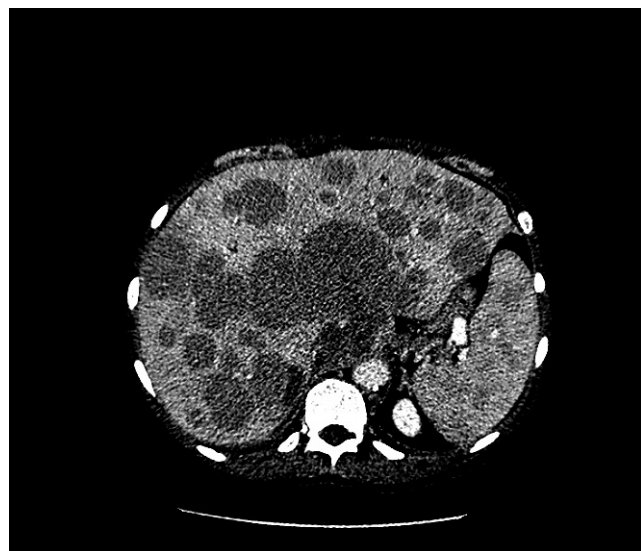


Figure 1. CT scan of the abdomen. Significantly enlarged liver with irregular contours, displacing neighbouring organs. Normodense circular areas in the liver and spleen

At the same time, CT of the chest suggested increased size of thyroid with presence of subcarinal set of lymph nodes (sized 40 x 30mm). USG examinations of the thyroid revealed the presence of a hypoechoic lump in the left thyroid lobe and isthmus of the thyroid gland. Concentration of hormones was equal to: TSH 1.67 uIU/ml (0.27–4.2); FT4 0.95 ng/dl (9.0–20.0); FT3 2.57 pg/ml (4.0–8.3). In the course of the performed fine-needle biopsy, a sample of thyroid and nearby lymph nodes were taken for histopathological examination. Immunohistochemical reactions of the large lymphoid cells infiltration presented the following expression: CD20+, bcl6+, CD10-, bcl2-, CD5-, CD3-, Ki67 about 90%. The final diagnosis indicated diffuse large B-cell lymphoma in both samples (Fig. 3).

From March – November 2015, the patient received 8 cycles of R-CHOP immunochemotherapy. In December, after performing evaluation of clinical condition of the patient (CT scan, punch biopsy), complete remission was observed of the underlying disease. The patient is still under clinical observation.

DISCUSSION

Richter's syndrome is defined by transformation of chronic proliferation of B-cells, which is chronic lymphocytic leukemia or lymphocytic lymphoma, into a more aggressive form of lymphoma. Most commonly, it is a diffuse large B-cell lymphoma (DLBCL-RS) [4], rarely Hodgkin lymphoma (Hodgkin variant of RS, HvRS) [5]. The frequency of occurrence of RS among patients with CLL is estimated to be 2%-10% [6]. The most frequent RS (80%-90%) stems from the same clone as CLL (clonally related RS). In a very small part, a tumour clone develops independently (clonally unrelated RS) [7]. The increased risk of RS occurring is related with presence of genetic aberrations, such as del 11q and 17p [8,9], unmutated IGHV, significant expression of ZAP-70, CD38 and CD49d [10, 11]. RS is characterized by very rapid clinical process. Among more than a half of patients (about 59%) there is fever, weight loss or intensified, night hyperhidrosis [12, 13]. RS most commonly occurs in lymph nodes and bone marrow. Localization in lymphatic system occurs in about 41% of cases [14].

The disease described is a case of rare localization of transformation into RS in the course of CLL disease. Usually among CLL patients, the thyroid is secondarily infiltrated by leukemia cells [15]. Lymphomas constitute only about 2% of all thyroid tumors, while those with the primary localization in this organ constitute only about 2.5% [16, 17]. Normal thyroid gland does not have lymphoid tissue. Its presence signifies ongoing pathological process, usually autoimmune inflammation. The literature presents very narrow number of patients with SLL/CLL and Hashimoto's inflammation or other tumors. We have not found a case of patient with Richter's transformation, either. Hashimoto's inflammation is often associated with occurrence of MALT type lymphoma (mucosa-associated lymphoid tissue; about 23% of lymphomas appearing on the thyroid) and DLBCL (most commonly occurring primary lymphoma of the thyroid, about 50% of cases) [18]. Bocian et al. and Reid-Nicholson et al. have stated simultaneous occurrence of CLL/SLL with such thyroid tumors as: medullary and papillary carcinoma and mixed papillary carcinoma [19, 20]. Shin et al. and Trumper et al.

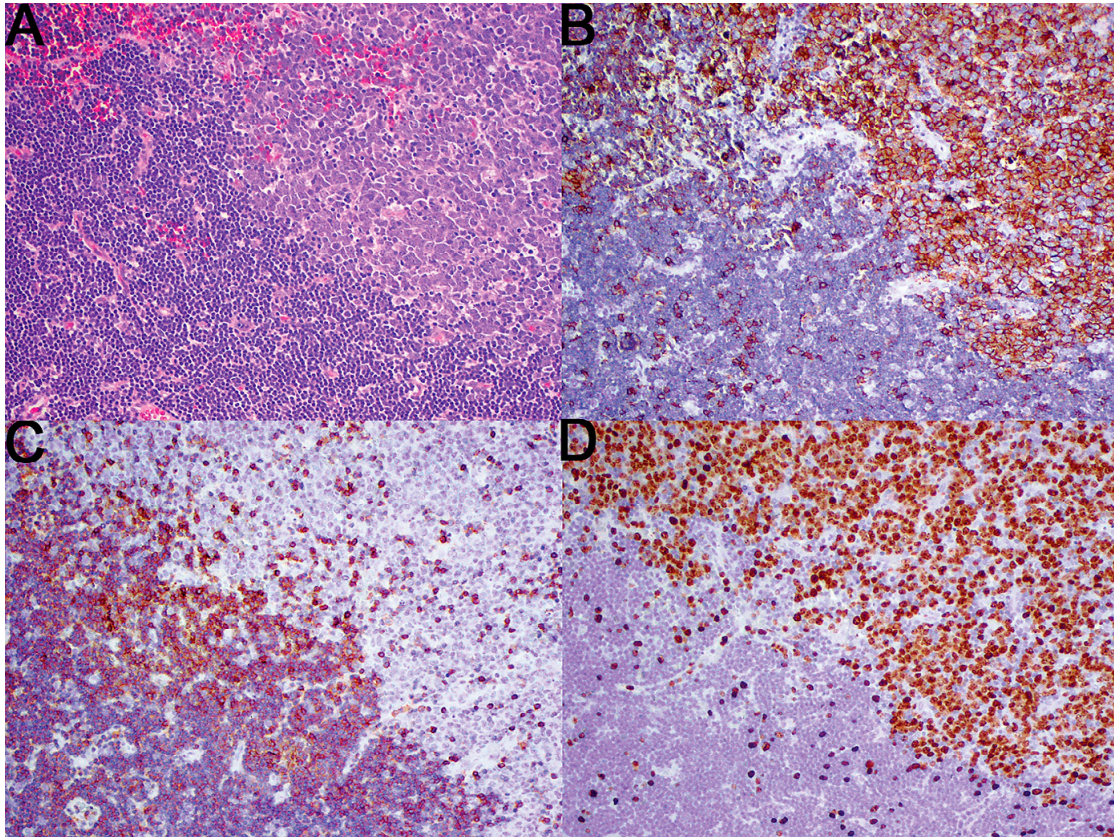


Figure 2. Transformation of chronic lymphocytic leukemia in diffuse large B-cell lymphoma (Richter syndrome) in the liver (A) and immunohistochemical reactions for CD20 (B), CD5 (C) and Ki67 (D) (A – HE; B, C, D – Dako EnVisionTM+/HRP; objective magn. 10x)

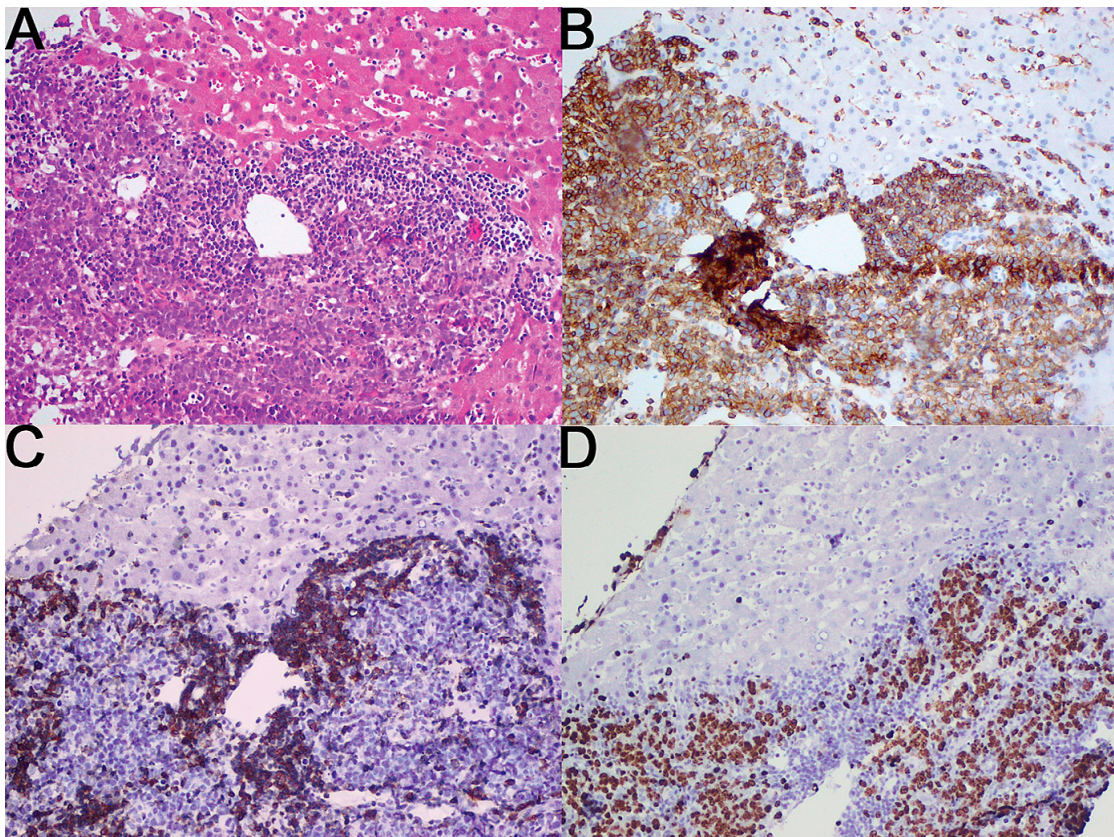


Figure 3. Transformation of chronic lymphocytic leukemia in diffuse large B-cell lymphoma (Richter syndrome) in the lymph node (A) and immunohistochemical reactions for CD20 (B), CD5 (C) and Ki67 (D) (A – HE; B, C, D – Dako EnVisionTM+/HRP; objective magn. 10x)

presented patients among whom diagnosis of lymphoma had been preceded by autoimmune inflammation with the presence of high concentration of antibodies against peroxidase and thyroglobulin [21, 22].

In the patient described in this case report, no preceding or accompanying inflammatory process was confirmed. Decrease in the concentration of FT3 and FT4 could be a result of so-called euthyroid sick syndrome. This phenomenon observed during numerous illnesses, including those related to tumours, however, is not accompanied by dysfunction of the organ itself [23].

In the available literature, only one case was found of RS localization (in the form of diffuse large B cell lymphoma) in liver, described by Tadmor et al. The case concerned a 72-year-old woman, initially treated with chlorambucil and prednisone. Analogously, as in the current case report, the authors observed a higher concentration of transaminases and a significant increase in LDH activity. There was also a very good reaction to immunochemistry therapy, which included vincristine, cyclophosphamide, doxorubicin, prednisolone and rituximab (R-CHOP) [24]. Maryniak et al. presented a case where transformation into Hodgkin lymphoma in the course of CLL was confirmed only after the results of autopsy examination of liver, spleen, adrenal glands and bone marrow [25]. Reddy et al., on the other hand, described HvRS in the liver of 59-year-old woman with a 10-year history of CLL, after many lines of cytostatic treatment (bendamustine, rituximab in monotherapy and with fludarabine). The first, quite unusual, clinical symptom of transformation was a significant increase of bilirubin and alkaline phosphatase concentration [26].

Of specific interest is a case presented by Salihoglu et al. which concerned a 52-year-old woman, where after observation and several more days of chemotherapy (chlorambucil, FC, R-COP), further progression of the disease was confirmed. Because of the detected deletion 17p, the patient was classified for allo-SCT, preceded by 6 CFAR chemotherapy courses (cyclophosphamide, fludarabine, alemtuzumab and rituximab). Clinical and immunophenotypic evaluation of peripheral blood and bone marrow before transplantation indicated complete remission. Repeated FISH test on the day 30 after allo-SCT did not indicate 17p deletion in bone marrow cells. However, 3 months after transplantation, sudden deterioration occurred in the patient's general health condition: diarrhea, skin lesions, ascites and significant increase of the liver size with the presence of numerous interstitial, focal lesions were all observed.

On the basis of histopathological examination of sample taken during biopsy, large B cell lymphoma was diagnosed, which suggested transformation into RS. The patient died several weeks after confirming RS. According to the authors, the significant factor in transformation into RS, despite accompanying GVHD, was an unfavorable genetic profile of the patient [27].

Attention is being focused on a number of chemotherapy lines. Much controversy has arisen from an opinion about the possible influence of previous treatment for RS development, in particular, specific cytostatic drugs. CLL/SLL ill patients, during their illness usually receive many different types of chemotherapies, therefore the precise definition of a drug with specific significance in this matter is difficult. Modern drugs, including monoclonal antibodies (rituximab,

alemtuzumab), may also probably be a significant factor in this process [28, 29].

However, in the presented case report, as well as in the case described by Salihoglu et al., the patients are the proof that RS may occur at any moment in the course of the disease, even only after one type of chemotherapy. At the same time, this and other cases indicating the possibility of occurrence of a diffuse large B cell lymphoma among patients with CLL after allo-SCT, always require differentiation with possible post-transplantation lymphoproliferative disorder (PTLPD) [30, 31].

CONCLUSIONS

Richter's syndrome is a rare complication of chronic lymphocytic leukemia, usually with an unfavourable prognosis. The liver and the thyroid are particularly rare locations of RS. On the basis of this case report and studies presented by other authors, it is not possible to clearly determine the influence of the site of transformation on the further course of disease, nor the factors influencing its development. However, such cases allow the conclusion that RS may occur even in the most unexpected and less probable place.

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