

Case Report

Transformation from chronic lymphocytic leukemia to classical Hodgkin lymphoma: an unusual Richter syndrome variant

Kaimin Li^{1*}, Jing Liu^{2*}, Weilong Li^{3*}, Qin Zhou¹, Lei Jiang², Xiaoxia Chu¹, Xubo Pan², Guimei Qu², Junqing Xu¹, Guohua Yu²

Departments of ¹Hematology, ²Pathology, ³Nuclear Medicine, Yantai Yuhuangding Hospital, Yantai, China. *Equal contributors.

Received December 7, 2017; Accepted July 2, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: We received a 58-year-old man who was diagnosed as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) by lymph node biopsy. Although active treatment was carried out, enlargement of lymph nodes reoccurred and the pathological findings were still confirmed as the primary disease. What's more unfortunate is that adrenal mass appeared which was pathologically confirmed as Hodgkin lymphoma and the disease was diagnosed as Richter Syndrome, meanwhile EB virus infection was detected positively. The patient was treated with multiple courses of FCD and ABVD chemotherapy, and finally died of severe infection.

Keywords: Richter syndrome, chronic lymphocytic leukemia, classical hodgkin lymphoma

Background

In 1928, Richter firstly reported one case of transformation from CLL to highly malignant tissue cell lymphoma. The patient, who died in a short time, was featured by extensive lymphadenopathy, large liver and spleen in a short time. As a kind of very unusual disease of lymphoid hematopoietic system, Richter syndrome strictly refers that the patients who have previously been diagnosed with chronic lymphocytic leukemia/small cell lymphoma, suffer highly malignant non-Hodgkin lymphoma transformation during clinical follow-up or treatment. The most common form was transformation from chronic lymphocytic leukemia/small cell lymphoma transformed to diffuse large B-cell lymphoma. With more concerns and deeper study of such kind of disease, it has been found that there are more cases for the transformation from other types of leukemia and/or lymphoma to lymphoma and/or leukemia with a higher degree of malignancy or the simultaneous existence. The incidence of the disease is low, while the prognosis is poor. In this study, a retrospectively summary has been made on the patient

with transformation from chronic lymphocytic leukemia to classical Hodgkin lymphoma and relevant literatures have been reviewed to improve the clinical diagnosis and treatment experience of this unusual kind of disease.

Case presentation

A male patient, 58 years old, firstly admitted due to the discovery of neck mass on Nov 19, 2012. In May 2012, the neck mass was inadvertently found on the patient. There was no pain, heat, night sweats and weight loss. At first, no enough attention was paid and he was admitted to our hospital when the tumor gradually increased on Nov 19, 2012. Physical examination after admission showed that a number of enlarged lymph nodes could be touched in the bilateral submandibular area, bilateral neck and supraclavicular fossa. The largest lymph nodes are located on the right side of the neck and the volume of the mass was about 4 cm×3 cm×3 cm. No abnormality was found in cardiovascular auscultation. Blood routine examination showed hemoglobin 156 g/L, platelets total 252×10⁹/L, the total number of white

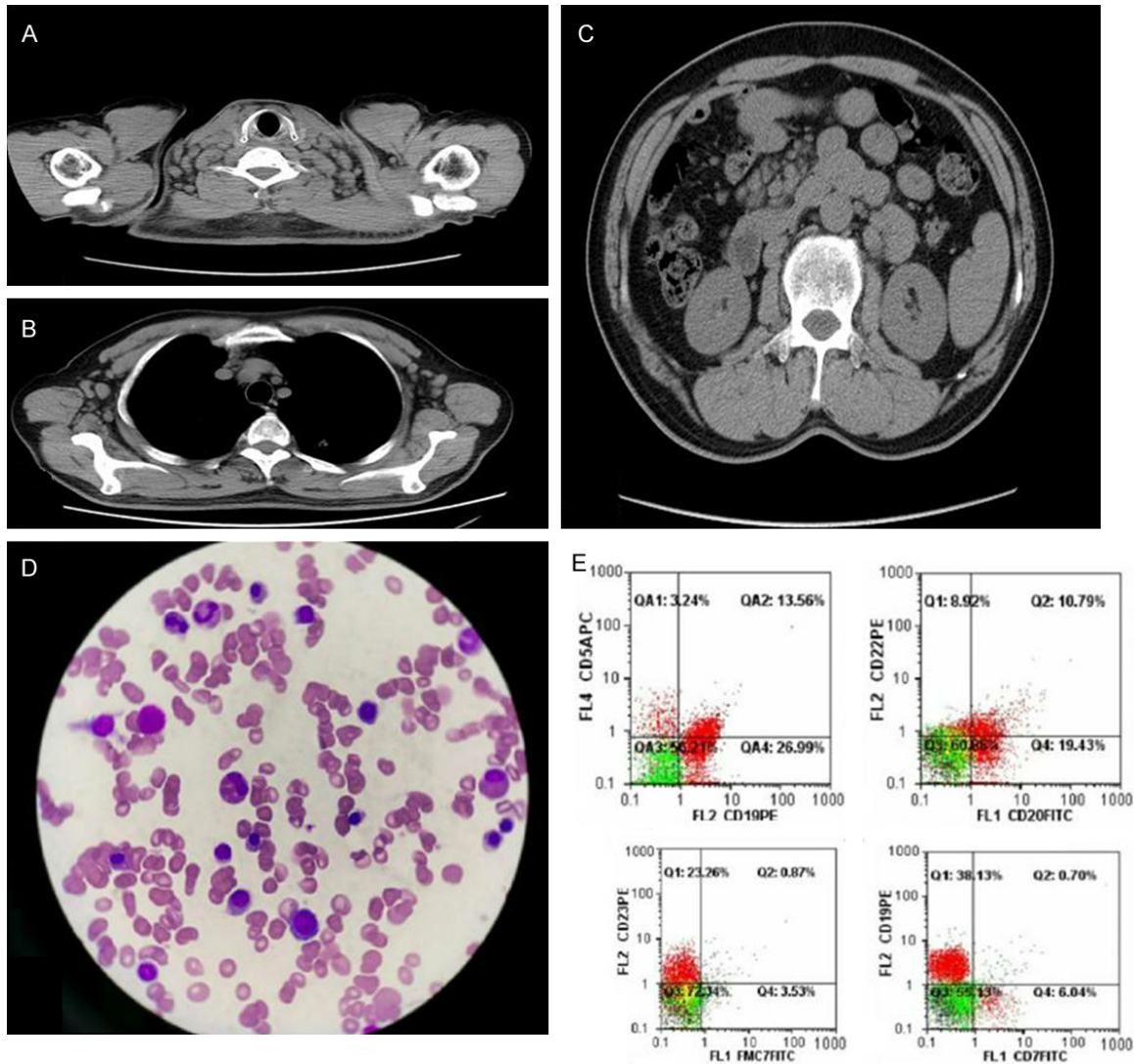


Figure 1. The results of imaging, bone marrow cytology and bone marrow flow cytometry at the first admission. Enlarged lymph nodes were found in bilateral neck (A), supraclavicular region, axillary (B), mediastinal, hilar area and retroperitoneal (C). Bone marrow cytology showed bone marrow hyperplasia was active (D). Flow cytometry of bone marrow revealed that lymphocytes expressed CD5, CD22, CD23, CD19 (E).

blood cells $36.84 \times 10^9/L$ and lymphocytes $27.92 \times 10^9/L$. Chest and abdomen CT showed large liver and spleen. Enlargement of lymph nodes were found in bilateral neck (Figure 1A), supraclavicular region, axillary (Figure 1B), mediastinal, hilar area and retroperitoneal (Figure 1C) which were consistent with lymphoma changes. Bone marrow cytology showed bone marrow hyperplasia was active and lymphocyte ratio was increased accounting for 56.5% (Figure 1D). Flow cytometry of bone marrow revealed that R1 cells account for 41.54% and 84% of lymphocytes shows CD19, CD20, CD23, Kappa, HLA-DR, weakly expressed CD5, CD22 (Figure 1E), whereas CD7, CD10, CD11c,

CD38, CD103, FMC7 and Lambda were all negative. Right cervical lymph node biopsy was conducted on Nov 25, 2012. The structure of the lymph node was destroyed (Figure 2A), which was replaced by a diffuse small lymphocyte (Figure 2B). Immunohistochemical staining showed the small lymphocyte were positive for CD20 (Figure 2C), CD5 (Figure 2D), CD23 (Figure 2E), Pax-5, and negative for CD3, CyclinD1. Ki67 was positive about 10% (Figure 2F). Based on histology and immunological staining, the diagnosis of chronic lymphocytic leukemia/small lymphocyte lymphoma was made. After six times of chemotherapy of FCD (fludarabine, cyclophosphamide, dexametha-

Richter syndrome: transformation from CLL to CHL

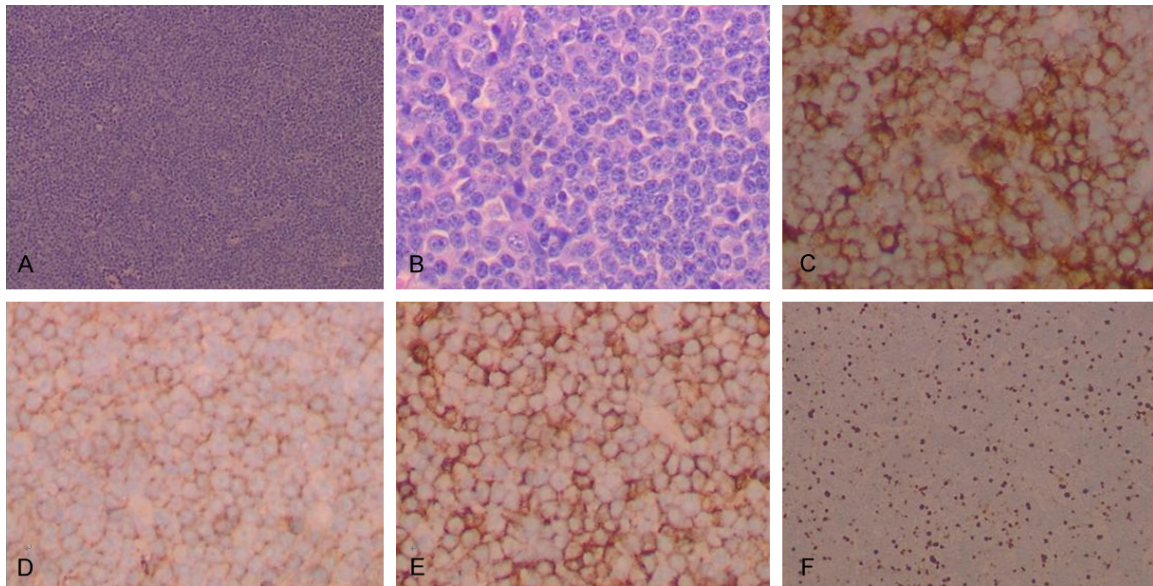


Figure 2. The results of biopsy from right cervical lymph node at the first admission. The structure of the lymph node was destroyed (A 10×). The cell size is small, the cytoplasm is little and the chromatin of the nucleus is delicate (B 40×). Immunohistochemical staining showed the small lymphocyte were positive for CD20 (C 40×), CD5 (D 40×) and CD23 (E 40×). Ki67 was positive about 10% (F 10×).

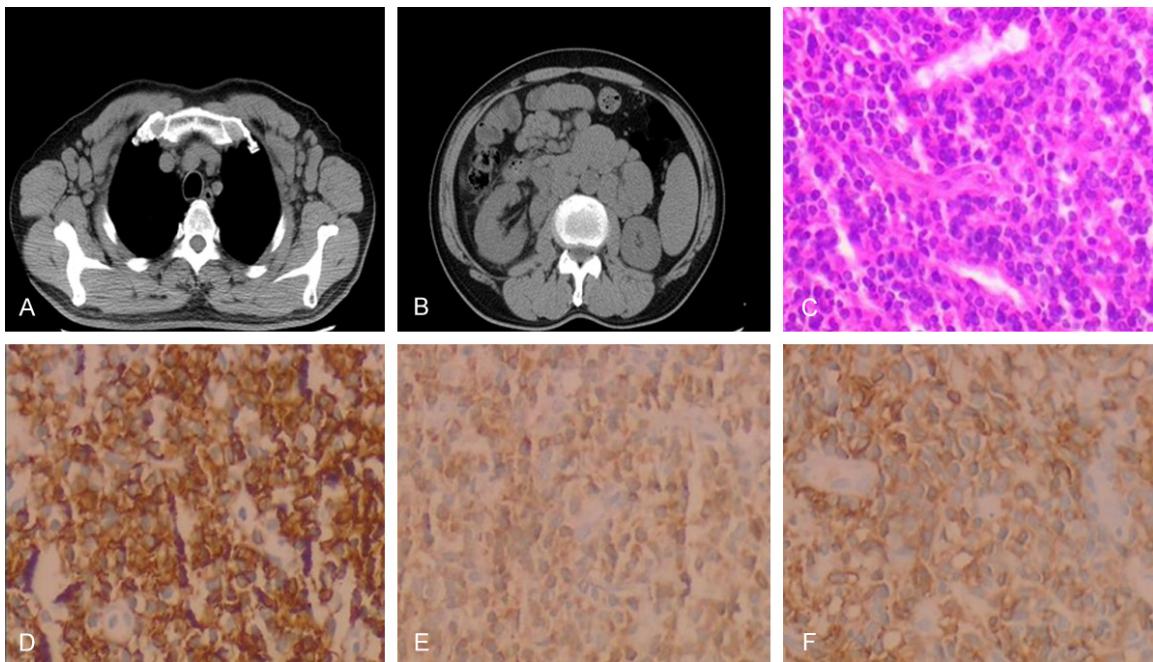


Figure 3. The results of imaging and pathology during the second hospitalization. CT showed enlarged lymph nodes in bilateral axillary (A), abdominal and retroperitoneal regions (B). Left anterior lymph node biopsy showed the tumor was consisted of small lymphocytes identically (C 40×) and the tumor cells were positive for CD20 (D 40×), CD5 (E 40×) and CD23 (F 40×).

sone), the lymph nodes get partially narrowed, and the ratio of lymphocytes in the bone marrow gradually returns to normal. On Dec 22, 2014 the patient was re-admitted due to left

ear lymph node enlargement for a half month. CT showed that compared with the first time the original film, enlarged lymph nodes increase in bilateral axillary (**Figure 3A**), abdominal and

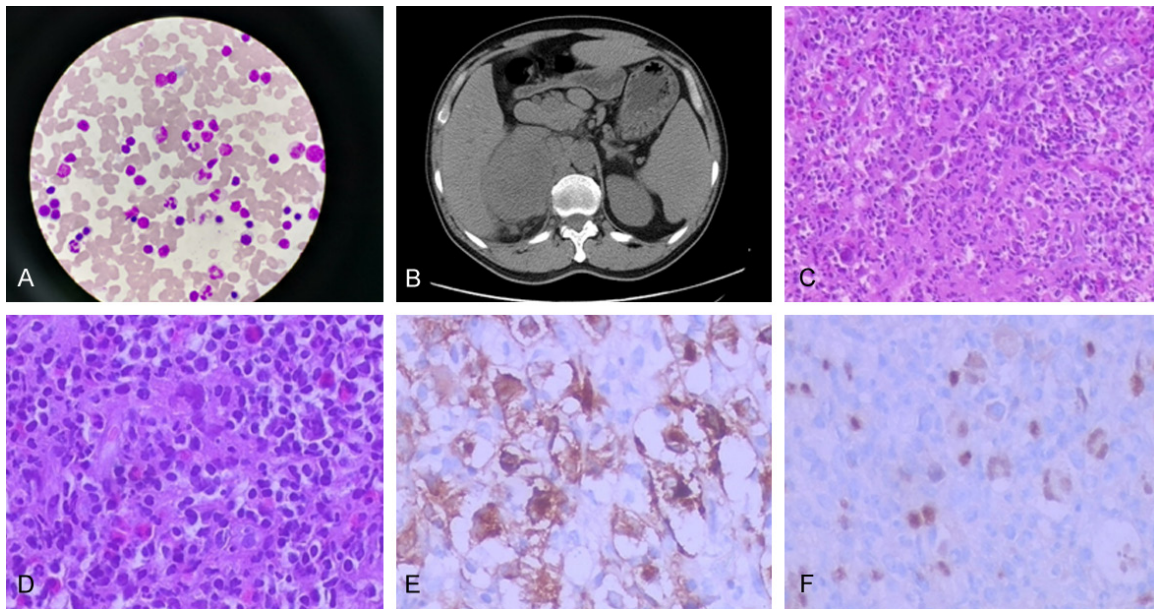


Figure 4. The results of bone marrow cytology, imaging and biopsy at the third admission. Bone marrow cytology showed naive lymphocytes could be detected (A). CT showed mass at right adrenal area (B). The pathology showed a small amount of large cells in a mixed cell background of right adrenal area mass under the microscope (C 20×). Large cells had mononuclear or multinuclear with obvious nucleolus (D 40×). Immunohistochemical staining showed large cells expressed CD30 (E 40×), Pax-5 (F 40×).

retroperitoneal regions (**Figure 3B**). After the ultrasound guided left anterior lymph node biopsy, pathological report showed the disease was diagnosed as small lymphocytic lymphoma (**Figure 3C**) and the tumor cells were positive for CD20 (**Figure 3D**), CD5 (**Figure 3E**) and CD23 (**Figure 3F**). After four times of FCD program to consolidate chemotherapy, the condition of the patient became stable and the chemotherapy was stopped. On June 15, 2016, the patient was admitted again due to cervical lymph node, so we check the blood routine: hemoglobin 86 g/L, the total number of platelets $79 \times 10^9/L$, the total number of white blood cells $7.64 \times 10^9/L$, lymphocytes $5.31 \times 10^9/L$, and EB virus gene detection was positive. Bone marrow cytology showed lymphocytes account for 70%, occasionally naive lymphocytes detected (**Figure 4A**). The cervical lymph node biopsy again, the pathology was consistent with the performance of chronic lymphocytic leukemia/small lymphocyte lymphoma. Chest and abdomen CT showed right adrenal area occupancy just like huge lymph nodes (**Figure 4B**). Right adrenal area mass puncture was done and the pathology showed that a small amount of heterozygous large cells in a mixed cell background interestingly (**Figure 4C**). Large cells had mononuclear or multinuclear with obvious nucleolus (**Figure 4D**). Immunohistochemistry

staining showed large cells expressed CD30 (**Figure 4E**), Pax-5 (**Figure 4F**), MUM-1 and negative for CD15, LCA, ALK, CD10, CD3, EMA, SMA. We considered as the classic Hodgkin lymphoma. The patient was then diagnosed as Richter syndrome and combined chemotherapy in ABVD regimen was performed on July 5, 2016. The patient had been treated with ABVD chemotherapy for 8 times. The patient's condition improved. But after two months of chemotherapy, the cervical lymph node was enlarged again and the primary disease recurred. It has been alive for 18 months up to now.

Discussion

Richter's syndrome (RS) is considered as CLL is transformed into diffuse large B cell lymphoma (DLBCL) or Hodgkin lymphoma (HL). About 2%-8% CLL patients can be converted to DLBCL and about < 1% CLL is converted to HL. The mechanism of occurrence of Richter syndrome is still unknown, may be caused by virus infection (such as the EB virus), No. 12 trisomy or 11 chromosome abnormalities.

Among the chromosomal abnormalities, +12 chromosomes are most common in RS patients, and patients with 11q-CLQ/SLL have higher risks of transformation to RS due to the loss of

ataxia telangiectasia pathogenicity gene (ATM) in the 11q22.3-23.1 region [1-3]. In the initial onset, the lymph node was confirmed as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). After active treatment the enlargement of lymph nodes reoccurred and the pathology was still confirmed as the primary disease. Interestingly, later adrenal mass appeared and pathologically confirmed as Hodgkin lymphoma. The disease was diagnosed as Richter syndrome hereafter, meanwhile EB virus infection was detected. There was no abnormality for the chromosomes and the pathogenesis of this patient might possibly relate to the infection with the EB virus which lead to progression of the disease.

After studying 1168 cases of CLL patients, Friedman [4] set the threshold value of peripheral blood mononuclear cells (AMC) at $1.545 \times 10^9/L$ in terms of risk stratification, which can be measured as a continuous variable, and was significantly associated with the first treatment time (TTT), there was no significant difference between the TTT results obtained from the AMC prognostic model and the AMC prognostic model, indicating that AMC was more predictive of TTT. However, the correlation between AMC and OS in the multivariate model was not significant. High AMC can make patients' diseases with rapid progression, and need to be treated. In the initial onset, this patient had relative high total number of peripheral blood mononuclear cells, which were greater than $1.5 \times 10^9/L$, and received early treatment, while the patient's disease had progressed rapidly with poor prognosis, which was consistent with the study by Friedman. Through the treatment of this patient, it has been found that, whether the future's monocyte-derived cells could it can be used as a target spot for CLL treatment, and meanwhile considered as a treatment indications of CLL initial treatment.

RS often occurs in the lymph nodes and bone marrow, and there are also extranodal symptoms as the performance of first outbreak, with the involved parts of the gastrointestinal tract, central nervous system, skin, eyes, testicles, lungs, kidneys, etc [5]. In the later stage, the disease was transformed in the kidney of the patient, fitting the common parts of the disease but still relatively rare, at this time it's neces-

sary to monitor the renal function and whether there's adrenal disease, after the inspection in many ways, there's no abnormalities for this patient, which may related to the early discovery.

Multivariate analysis [6-8] has demonstrated five independent prognostic factors for RS: physical condition ≥ 2 points, LDH > 1.5 times of the normal upper limit level, platelet count $< 100 \times 10^9/L$, mass diameter > 5 cm and previous treatment history > 2 . Based on these five factors (1 factor per factor), patients will be divided into four hazard groups: 0-1 point is of low risk, with the average survival time of 1.12 years; 2 points is relatively low risk, with the average survival time of 0.9 years; 3 points is relatively higher risk, with the average survival time of 0.33 years; 4 to 5 points is high risk, with the average survival time of 0.14 years. The point for this patient is of 2, with the average survival time of about 1 year, so the prognosis is very poor.

RS can occur in the early stage of chronic lymphocytic leukemia, and some even are diagnosed with chronic lymphocytic leukemia at the same time, some appear after the treatment of chronic lymphocytic leukemia, and the median time is 23 months after the diagnosis of chronic lymphocytic leukemia [9, 10]. Once the CLL patients are diagnosed, the annual probability of converting CLL to RS is 0.5% (2.1% and 4.8% of the probability of transformation into RS for 5 and 10 years respectively), wherein for the treated CLL patients, the probability of converting to RS per year is 1% (5% and 15.2% of the probability of transformation into RS for 5 and 10 years respectively), the reason may related to the late detection of some chronic lymphoblastic leukemia, and more likely is that certain types are easy to have early transformation. The patient had the transformation after 43 months of the diagnosis with chronic lymphocytic leukemia, which was later than the median, and it's considered to be relevant to the early active treatment of this patient.

Through the analysis on immunoglobulin heavy chain variable region (IgVH) gene sequencing, the relationship between RS and the original CLL clone can be determined [11]. RS can be divided into two subtypes of CLL clone relevant or in relevant, the former represents the real transformation, while the latter is non-second-

ary lymphoma. 80% of DLBCL is clone-relevant, while only 40% to 50% of HL is associated with CLL clones. Generally, survival for the clonal-related RS is only a few months, while clonal unrelated RS is similar to non-secondary lymphoma, there's also difference of the two groups in the biological characteristics, and the former usually gains new molecular abnormalities when CLL has the clinical - pathological transformation to RS [12]. Although this patient did not perform IgVH gene sequencing, the IgH gene rearrangement fragments in the adrenal and lymph node have the same size, which has indirectly confirmed that bone marrow or lymph nodes are the tumor of the same clonal source.

RS has extremely poor prognosis with the median survival of less than one year. As the pathogenesis of RS is unknown, there is no clear solution for the RS treatment. The treatment regimen shall be determined generally based on the type of CLL transformation [13]. The prognosis is often poor and the pathogenesis needs to be further clarified. The treatment regimen includes chemotherapy, monoclonal antibody and stem cell transplantation, with a low rate of mitigation, the median remission time is 5-8 months, and the median survival time is less than one year. After transformation into diffuse large B-cell lymphoma, R-CHOP, R-Hyper CVAD shall be used, with the reaction rate of up to 47%. OFAR regimen (oxaliplatin, fludarabine, cytarabine, rituximab) has the total reaction rate of 50%. ABVD program will be preferred after the transformation into Hodgkin lymphoma.

Clinical trial shall be preferred for RS patients with associated CLL clones, without suitable clinical trials. Patients with transformation into diffuse large B cell lymphoma could select R-CHOP as the initial treatment regimen, and sequential transplantation as the consolidation therapy [14, 15]. When the patient had previously received anthracycline treatment, the induction program based on platinum drugs should be considered and selected, e.g.: use R-PFA, R-DHAP to replace R-CHOP. Factors of age, general conditions of the body, comorbidities and sensitivity to chemotherapy shall determine whether the patient is suitable for transplantation. If there is a suitable donor and the age and physical condition allow, allogeneic hematopoietic stem cell transplantation will be preferred. Without the remission induction, it is

recommended to participate in clinical trials of new drugs and symptomatic and supportive treatment.

Therefore, it is possible to improve the therapeutic effect of RS by enhancing the awareness, carrying out timely biopsy, early detection of RS conversion and giving the appropriate treatment in the early. After transformation, young patients with a donor should receive allogeneic hematopoietic stem cell transplantation, which is expected to be cured. On the contrary, continuous treatment by chronic lymphocytic leukemia without detecting RS transformation, will surely make the disease continue to progress, leading to hematopoietic failure, or (and) combined infection, and difficult treatment in the end.

Acknowledgements

This article is supported by the Natural Science Foundation of Shandong Province, China (Grant No.ZR2017MH081, ZR2015HQ013) and the Research Fund of Yantai Yuhuangding Hospital (Grant No.201621). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure of conflict of interest

None.

Address correspondence to: Guohua Yu, Department of Pathology, Affiliated Yantai Yuhuangding Hospital, Qingdao University, 20, Yuhuangding East Road, Yantai 264000, China. Tel: +86-535-6691999 Ext. 83443; E-mail: ygh0535@hotmail.com; Junqing Xu, Department of Hematology, Affiliated Yantai Yuhuangding Hospital, Qingdao University, 20, Yuhuangding East Road, Yantai 264000, China. Tel: +86-535-6691999 Ext. 82309; E-mail: likai-min7229@126.com

References

- [1] Swords R, Bruzzi J and Giles F. Recent advances in the diagnosis and therapy of Richter's syndrome. *Med Oncol* 2007; 24: 17-32.
- [2] Jain P, Keating M and O'Brien S. Richter's syndrome-update on biology and management. *Expert Opinion on Orphan Drugs* 2014; 2: 453-463.

- [3] Bruzzi JF, Macapinlac H, Tsimberidou AM, Truong MT, Keating MJ, Marom EM and Munden RF. Detection of richter's transformation of chronic lymphocytic leukemia by PET/CT. *J Nucl Med* 2006; 47: 1267-1273.
- [4] Falchi L, Keating MJ, Marom EM, Truong MT, Schlette EJ, Sargent RL, Trinh L, Wang X, Smith SC, Jain N, Estrov Z, O'Brien S, Wierda WG, Lerner S and Ferrajoli A. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. *Blood* 2014; 123: 2783-2790.
- [5] Papajík T, Mysliveček M, Urbanová R, Buriánková E, Kapitáňová Z, Procházka V, Turcsányi P, Formánek R, Henzlová L, Flodr P, Jarošová M and Indrák K. 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography examination in patients with chronic lymphocytic leukemia may reveal Richter transformation. *Leuk Lymphoma* 2014; 55: 314-319.
- [6] Kauffman CA, Israel KS, Smith JW, White AC, Schwarz J and Brooks GF. Histoplasmosis in immunosuppressed patients. *Am J Med* 1978; 64: 923-932.
- [7] Badoux XC, Keating MJ, Wang X, O'Brien SM, Ferrajoli A, Faderl S, Burger J, Koller C, Lerner S, Kantarjian H and Wierda WG. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. *Blood* 2011; 117: 3016-3024.
- [8] Harting R, Venugopal P, Gregory SA, O'Brien T and Bogdanov E. Efficacy and safety of rituximab combined with ESHAP chemotherapy for the treatment of relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. *Clin Lymphoma Myeloma* 2007; 7: 406-412.
- [9] Lepretre S, Jäger U, Janssens A, Leblond V, Nikitin E, Robak T and Wendtner CM. The value of rituximab for the treatment of fludarabine-refractory chronic lymphocytic leukemia: a systematic review and qualitative analysis of the literature. *Leuk Lymphoma* 2012; 53: 820-829.
- [10] Dreger P, Döhner H, Ritgen M, Böttcher S, Busch R, Dietrich S, Bunjes D, Cohen S, Schubert J, Hegenbart U, Beelen D, Zeis M, Stadler M, Hasenkamp J, Uharek L, Scheid C, Humpe A, Zenz T, Winkler D, Hallek M, Kneba M, Schmitz N and Stilgenbauer S; German CLL Study Group. Allogeneic stem cell transplantation provides durable disease control in poor-risk for chronic lymphocytic leukemia: long term clinical and MRD results of the German CLL Study Group CLL3X trial. *Blood* 2010; 116: 2438-2447.
- [11] Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, Grant B, Sharman JP, Coleman M, Wierda WG, Jones JA, Zhao W, Heerema NA, Johnson AJ, Sukbuntherng J, Chang BY, Clow F, Hedrick E, Buggy JJ, James DF and O'Brien S. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl Med* 2013; 369: 32-42.
- [12] Wierda W, O'Brien S, Wen S, Faderl S, Garcia-Manero G, Thomas D, Do KA, Cortes J, Koller C, Beran M, Ferrajoli A, Giles F, Lerner S, Albitar M, Kantarjian H and Keating M. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. *J Clin Oncol* 2005; 23: 4070-4078.
- [13] Badoux XC, Keating MJ, Wang X, O'Brien SM, Ferrajoli A, Faderl S, Burger J, Koller C, Lerner S, Kantarjian H and Wierda WG. Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia. *Blood* 2011; 118: 2085-2093.
- [14] Castro JE, Sandoval-Sus JD, Bole J, Rassenti L and Kipps TJ. Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. *Leukemia* 2008; 22: 2048-2053.
- [15] Komrokji RS, Corrales-Yepez M, Kharfan-Dabaja MA, Al Ali NH, Padron E, Rollison DE, Pinilla-Ibarz J, Zhang L, Epling-Burnette PK, Lancet JE and List AF. Hypoalbuminemia is an independent prognostic factor for overall survival in myelodysplastic syndromes. *Am J Hematol* 2012; 87: 1006-1009.