Case Report
Chronic myelogenous leukemia following small lymphocytic lymphoma: a case report and review of literature

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Abstract: Chronic myelogenous leukemia (CML) following non-Hodgkin’s lymphoma (NHL) is extremely rare. Here we report a unique case of CML after small lymphocytic lymphoma (SLL). A 64-years-old Asian female was firstly diagnosed as SLL by biopsies of the retroperitoneal and the mesenteric root lymph nodes, with bone marrow (BM) involvement. BM chromosome showed no abnormalities, and the rearrangement of IgDH (DH1-6-JH) and IgK (Vk-Jk) gene were present. After treatment with three courses of fludarabine, cyclophosphamide, and rituximab (FCR) regimens, the patient achieved complete response. However, she progressed to CML 35 months later, with Philadelphia translocation and the major BCR/ABL fusion transcript (p210), and she has a good prognosis with imatinib. It is not clear whether BCR-ABL1 gene was present at the time of primary diagnosis for SLL, so we extracted genomic DNA from the patient’s paraffin-embedded BM biopsies at the first diagnosis of SLL for comparison, but real-time quantitative PCR assay for BCR-ABL1 gene was negative. Taken together, there is a strong possibility that FCR therapy caused the BCR-ABL1 gene rearrangement, and then became CML in 35 months.

Keywords: Small lymphocytic lymphoma, chronic myeloid leukemia, FCR

Introduction
Therapy-related acute myeloid leukemia or myelodysplastic syndrome (t-AML/MDS) secondary to non-Hodgkin lymphoma (NHL) are often reported [1-3], but chronic myelogenous leukemia (CML) after NHL has rarely been described. Here we report a unique case of CML following fludarabine, cyclophosphamide, and rituximab (FCR) treatment for small lymphocytic lymphoma (SLL), and we review the literature about the correlation between FCR chemotherapy and secondary CML.

Case report
A 64-year-old Asian female was admitted to hospital in September 2014 because of abdominal pain over more than 20 years. On physical examination, she had distending pain by abdominal palpation, and she showed splenomegaly 1 cm below the costal margin. The abdominal enhanced computed tomography (Figure 1) showed lymphoma and splenomegaly. Nuclear magnetic resonance imaging (abdominal) examination indicated lymphoma, splenomegaly, left renal cysts, and gallbladder polyps. B ultrasound examination implicated Hashimoto’s thyroiditis, without enlargement of bilateral neck lymph nodes. The chest X-ray findings showed no abnormalities. A complete blood count was normal, without lymphocytosis or left shift.

Tumor biopsy of the peritoneum was done by laparoscopic surgery. Multiple enlarged retroperitoneal lymph nodes were found, some stuck together with mesentery. Two mesenteric lymph nodes were removed from the mesenteric roots, and the intraoperative frozen-section examination indicated small cell lymphoma (Figure 2A). The post-operative biopsies of the retroperitoneal and the mesenteric root lymph nodes were performed. Histologic examination showed that the small lymphoid cells were increased, which were strongly positive for
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CD19, CD79a, Bcl-2, CD5, CD23, moderately positive for CD3, P53, CD99, MUM-1, Ki-67, p53, but negative for CD10, bcl-6, CyclinD1, CD38, TdT (Figure 2B). Based on these findings, the tumor was diagnosed as SLL.

Over half a month after operation, the patient had emaciation and abdominal distension, and the abdominal circumference increased. Complete blood count: WBC $3.7 \times 10^9/L$, RBC $3.87 \times 10^{12}/L$, hemoglobin 119 g/L, platelet 108 $\times 10^9/L$. Bone marrow (BM) aspirate (Figure 2C) revealed that the proportion of lymphocytes was within normal range, while small lymphocytes were be seen easily. BM biopsy sections (Figure 2D) showed 60% cellularity with scattered infiltration by mature small lymphocytes. BM chromosomes showed no abnormalities, and the rearrangement of IgDH (DH1-6-JH) and IgK (Vk-Jk) genes were detected. Flow cytometric examinations of BM (Figure 3) indicated SLL or chronic lymphocytic leukemia (CLL). It showed that lymphocytes accounted for 28% of all nucleated cells, B lymphocytes accounted for 62% of all lymphocytes, and (CD5+ CD19+ CD23+) cells accounted for 25.60% of all lymphocytes.

Consequently, the patient was diagnosed as SLL, stage IVA according to Ann Arbor classification. Then she received three cycles of FCR regimens (i.e. rituximab 600 mg on day 0, fludarabine 40 mg on day 1-3, cyclophosphamide 400 mg on day 1-3) in October, November, and December 2014, respectively.

The patient was followed in complete response (CR) until August 2017, at which point she presented with leukocytosis and thrombocytosis (WBC $21.3 \times 10^9/L$, Plt $603 \times 10^9/L$, hemoglobin 142 g/L). The peripheral blood smear showed increased immature granulocytes, with neutrophilic promyelocytes 0.01, neutrophilic myelocytes 0.08, and neutrophilic metamyelocytes 0.12.

BM smears (Figure 4) revealed extremely hypercellular BM and myeloid hyperplasia, in which eosinophils and basophils can be seen...
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Figure 3. Flow cytometric results of bone marrow indicated mature B lymphocyte proliferation disease (chronic lymphocytic leukemia or small lymphocytic lymphoma). Lymphocytes accounted for 28% of all nucleated cells, B lymphocytes accounted for 62% of all lymphocytes, and (CD5+ CD19+ CD23+) cells accounted for 25.60% of all lymphocytes.
frequently. The positive rate of neutrophil alkaline phosphatase was 1%, and the score was 1. Twenty cells were characterized by the presence of the Philadelphia translocation [t(9;22) (q34;q11)] in all analyzed mitoses. Reverse transcription - polymerase chain reaction (PCR) analysis performed on the BM aspirate found evidence for the major BCR/ABL fusion transcript (p210). The number of copies for BCR-ABL1 were 92862.00, and for ABL1 were 71180.00, BCR-ABL1/ABL1 was 1.305, IS BCR-ABL1/ABL1 was 0.966. The mutation of JAK2V617F gene, and the point mutations of BCR-ABL tyrosine kinase domain were not detected.

Based on these results, the patient was diagnosed as CML. Then she was treated with 400-mg/day imatinib. After one week, she stopped taking imatinib for two weeks because of rash with pruritus. Fortunately, the symptoms did not appear after oral imatinib again. Two weeks later, the complete blood count showed a complete hematologic response (WBC 5.7 × 10^9/L, hemoglobin 108 g/L, Plt 171 × 10^9/L). Three months later, BM aspirate showed no abnormalities, and the BCR-ABL1 gene rearrangement was not detected in peripheral blood and BM cells, and the Philadelphia chromosome was not detected in BM cells. Therefore, a complete CR was obtained after three months of therapy with imatinib. Our patient continued to be treated with 400-mg/day imatinib, and she was still being followed in our outpatient clinic with major molecular response.

Discussion

The primary tumor of our patient is SLL, with BM involvement. After surgery resection and treatment with three courses of FCR regimens, the patient progressed to CML 35 months later. CML has an annual incidence of 1-2 cases per 1,000,000 population, but the predisposing factors for CML are largely unknown [1]. It was reported that large doses of radiation was associated with the development of CML, evidenced by an increased incidence of CML in atomic bomb survivors [4]. It was also reported that CML was related to smoking and exposure to some toxic drugs [5]. Our patient did not receive irradiation treatment or other toxic drugs, but only received three courses of FCR chemotherapy.

The combination regimen, composed of the purine analog fludarabine (F), the alkylating agent cyclophosphamide (C), and the humanized anti-CD20 monoclonal antibody rituximab (R), has emerged as a highly effective frontline therapy for indolent lymphoma or CLL patients, but it often causes myelosuppression, infection, and digestive tract reaction [6]; and the incidence of therapy-related myeloid neoplasms (t-MNs) is significantly higher. Our patient had a transient decrease of blood cells during the treatment with FCR regimens, but this recovered soon after chemotherapy.

Zhou et al. [7] retrospectively analyzed 426 CLL/SLL patients receiving FCR treatment. The median follow-up time was 44 months, 28 patients developed secondary MDS/AML; 96% of patients had abnormal karyotypes, with frequent chromosomes 5 and 7 abnormalities. Benjamini et al. [8] retrospectively analyzed 234 patients of CLL receiving FCR treatment. Development of MDS/AML or Richter conversion was the most frequent in hematological diseases. Both studies show that t-MDS/AMLS are relatively common after CLL/SLL with FCR regimens, but therapy-related CML was not found. In addition, our patient had no chromosomes 5 and 7 abnormalities when she developed CML.

To define the characteristics of secondary CML, Aguiar et al. [9] reviewed 32 cases of secondary CML. Features of secondary CML were similar to those of de novo cases, and Hodgkin lym-
phoma was the most common primary tumor among hematologic diseases. In addition, some authors reported that secondary CML had a lower incidence of splenomegaly and hyperleukocytosis, and the prognosis was poor [10, 11]. However, our patient showed a good response to imatinib, and she achieved hematologic and molecular CR. One reasonable explanation is that our patient has no point mutations of \textit{BCR-ABL} tyrosine kinase domain, and has no other chromosomes abnormalities except Philadelphia chromosome.

Both SLL and CML are relatively common hematologic malignancies, but CML following SLL in one patient has not been reported yet. It is hard to discriminate our patient with CML is therapy-related or not. Maybe the patient had cells with \textit{BCR-ABL1} gene in her BM at the time of primary diagnosis for SLL, and myelosuppression associated with FCR therapy allowed them to expand. Thus we extracted genomic DNA from the patient’s paraffin-embedded BM biopsies at the first diagnosis of SLL for comparison. However, real-time quantitative PCR assay for \textit{BCR-ABL1} gene was negative. There is a strong possibility that FCR therapy causes the \textit{BCR-ABL1} gene rearrangement, and then became CML in 35 months.

In summary, we report a unique case of CML after FCR chemotherapy for SLL; she had no point mutations of \textit{BCR-ABL} tyrosine kinase domain or additional chromosomes abnormalities except Ph chromosome, and she had a good prognosis with imatinib.

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Disclosure of conflict of interest

None.

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