Sudden Isolated Diffuse Large B-cell Lymphoma Transformation in Splenic Marginal Zone Lymphoma after Complete Remission

Mingfeng Chen  
The Second Affiliated Hospital of Nanchang University

Jing Xu  
The Second Affiliated Hospital of Nanchang University

Wencan Ye  
The Second Affiliated Hospital of Nanchang University

Zhenjiang Li (lzjdgh@163.com)  
The Second Affiliated Hospital of Nanchang University

Yuan Song  
The Second Affiliated Hospital of Nanchang University

Aiping Tang  
The Second Affiliated Hospital of Nanchang University

Case Report

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Abstract

Background: Splenic marginal zone lymphoma (SMZL) is an indolent small B cell lymphoma, the clinical course is generally slow and mild; however, a small proportion of patients can transform to diffuse large B-cell lymphoma (DLBCL).

Case presentation: We report the case of a 61-year-old male patient with the diagnosis of SMZL stage IV A (Ann Arbor classification), who experienced recurrence twice during the disease course and resulted in complete remission (CR) after therapy. But nevertheless, it transformed to DLBCL with isolated abdominal mass, while the bone marrow sample revealed no neoplastic involvement in the third month after the second CR. At the first diagnosis, the patient was treated with the CHOP regimen (cyclophosphamide, vinorelbine, pirarubicin, and dexamethasone). After recurrence, he was given four cycles of rituximab in combination with CHOP regimen (R-CHOP) and achieved CR; however, isolated extranodal abdominal DLBCL transformation occurred within three months of CR. The patient underwent an additional cycle of R-CHOP chemoimmunotherapy and the second-line R-DHAP (rituximab, cisplatin, cytarabine, and dexamethasone) chemoimmunotherapy. Finally, he died of upper gastrointestinal bleeding and shock. The next-generation sequencing results from bone marrow at first diagnosis and abdominal mass tissue showed common gene mutations in both tumors, suggesting that they were clonally related.

Conclusions: We, therefore, hypothesized that SMZL had progressed to DLBCL rather than developed a second neoplasm during the disease course. To the best of our knowledge, this is the first report of SMZL transformed to DLBCL with the abdominal mass after CR. Although its a chronic course, histologic transformation of SMZL can occur at any stage.

Background

Splenic marginal zone lymphoma (SMZL) is a small B-cell lymphoma that accounts for approximately 2% of all non-Hodgkin's lymphoma cases.\(^1\) The median age of SMZL onset is 68 years (range, 22-79 years), and is equally prevalent in men and women (male to female sex incidence ratio 1:1).\(^2\) Most SMZL patients follow an indolent clinical course with favorable prognosis. However, during its chronic course, some cases may undergo transformation to diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma, classic Hodgkin's lymphoma, or Burkitt lymphoma.\(^3-7\) The reported transformation of SMZL to DLBCL can occur in the bone marrow, lymph nodes, spleen, liver, central nervous system, nasal septum, and thyroid gland.\(^8-14\) Available scientific literature suggests no recommendations for treating SMZL transformed into DLBCL with isolated abdominal mass. Here, we report a 61-year-old male patient diagnosed with SMZL stage IV A (Ann Arbor classification), who experienced recurrence twice during the disease course before it transformed to DLBCL with the abdominal mass, in the third month after second complete remission (CR).

Case Presentation
A 61-year-old man was hospitalized in May 2016 with dizziness, fatigue, and palpitation for the previous two weeks. Physical examination revealed bilateral cervical and right inguinal lymphadenopathy, and splenomegaly. A complete blood count analysis revealed the hemoglobin 63 g/L (normal range: 130-175 g/L), platelet count 60×10^9/L (normal range: 125-350×10^9/L), leukocyte count 13.58×10^9/L (normal range: 3.50-9.50×10^9/L), and lactate dehydrogenase (LDH) level 334.71 U/L (normal range: 120-250 U/L). Computed tomography (CT) of the neck and abdominal region showed cervical lymphadenopathy, enlarged upper mediastinal and retroperitoneal lymph nodes, and hepatosplenomegaly. Bone marrow smear revealed B-lymphocyte proliferation, accounting for 83.5% of total cells. Bone marrow flow cytometry analysis revealed that lymphocytes accounted for 79.34% of total cells, which were strongly positive for CD19, CD20, HLA-DR, CD22, and Lambda; weakly positive for CD200, CD25, and CD81 expression, and negative for CD5, CD117, CD23, CD10, cLambda, FMC7, CD34, CD33, cKappa, CD103, TDT, CD11c, MPO, cCD3, CD79b, and CD38 expression. Immunohistochemical staining of bone marrow samples demonstrated the cells were positive for CD20, CD79a, and BCL-2 expression, but negative for CD43, CD23, cyclinD1, CD10, Bcl-6, and CD5 expression (Figure 1A). Next-generation sequencing of bone marrow sample revealed the following: DNMT3A 9.38%, MYD88 71.53%, ETV6 33.20%, CXCR4 39.20%, SF3B1 3.25%, and TP53 76.46%. No abnormalities were observed in the fluorescence in situ hybridization results related to IGH/CCND1, CEP12, IgH, TP53, ATM, and RB-1, IGVH, IgDH, IGK, and IGL gene rearrangement detected by multiplex polymerase chain reaction. Hence, the patient was diagnosed with SMZL stage IV A. The patient refused rituximab for financial reasons. Due to the advanced stage of the disease, the combination chemotherapy regimen comprising cyclophosphamide, vinorelbine, pirarubicin, and dexamethasone (CHOP) was administered in June 2016. However, due to occurrence of serious pneumonia, the patient refused follow-up chemotherapy and chose Chinese medicine treatment instead. Although he received only one cycle of chemotherapy, his hemoglobin gradually increased to 149 g/L, platelet count reached 131×10^9/L, and the spleen size reduced progressively until it became normal (from December 2017 to April 2018); the hemogram remained stable during this period.

In August 2018, the patient complained of chest tightness and dyspnea with a decreased hemoglobin count. Physical examination showed splenomegaly, but not lymphadenopathy. A complete blood count revealed peripheral blood leukocytes at 9.43×10^9/L with 72.6% lymphocytes, hemoglobin 50 g/L, platelet count 57×10^9/L, and LDH level 264.05 U/L. The bone marrow biopsy and immunophenotyping results were consistent with initial diagnosis. In bone marrow specimen, the MYD88 mutation rate was 69.40%. As the patient had undergone recurrence, chemoimmunotherapy was initiated with rituximab in combination with CHOP regimen (R-CHOP) every four weeks. After the first cycle, the patient's spleen gradually shrank and the MYD88 mutation rate decreased to 1.91%. The spleen was found normal following color Doppler ultrasound after three cycles of chemoimmunotherapy. The complete blood count became normal after four cycles of R-CHOP chemoimmunotherapy in December 2018. However, the patient discontinued chemoimmunotherapy due to financial reasons.

In March 2019, the patient complained of right abdominal pain. Physical examination suggested a palpable mass in the right abdominal region. Contrast-enhanced CT of the abdomen revealed an irregular, large, soft tissue mass in the right hepatorenal recess area, measuring approximately 10.9×11.9 cm
Complete blood count was normal but the LDH level reached 481.07 U/L. Bone marrow sample revealed no neoplastic involvement. Abdominal mass tissue immunohistochemical staining showed that the cells were positive for CD20, PAX5, MUM-1, c-Myc (50%), BCL-2, CD38, and Ki-67 (70%) expression, and cyclinD1, CD21, CD10, Bcl-6, CD4, CD3, CD5, CD138, and MPO expression; EBER in situ hybridization result was negative (Figure 1B), confirming the diagnosis of activated B-cell DLBCL. Analyzing abdominal mass tissue using next-generation sequencing revealed the following results: MYD88 84.7%, TP53 78.4%, CXCR4 43.3%, ETV6 (Exon5) 36.6%, ETV6 (Exon6) 34.1%, B2M 64.7%, BCL6 46.8%, FBXW7 32.8%, SRP72 10.6%, KMT2D 12.9%, IRF4 81.5%, STAT5B 49.9%, TCF3 47.8%, and PRDM1 54.4%. The next-generation sequencing results from before and after recurrence showed common gene mutations in both tumors, suggesting that they were clonally related. Hence, we inferred that SMZL had progressed to DLBCL during the disease course. The patient underwent an additional cycle of R-CHOP chemoimmunotherapy in April 2019; however, the abdominal mass remained swollen and painful after one month. The patient again underwent an additional course of the second-line R-DHAP (rituximab, cisplatin, cytararbine, and dexamethasone) chemoimmunotherapy. Due to financial reasons, the patient refused ibrutinib and other therapeutic agents. The abdominal mass gradually increased in size, the patient condition deteriorated, and eventually, he died of upper gastrointestinal bleeding and shock in June 2019.

Discussion

SMZL is a rare subtype of malignant lymphoma and classified as a low-grade small B cell lymphoma with primary involvement of the spleen. Typical SMZL phenotype is considered CD5- and CD10-.

Histologic transformation of SMZL can occur at any stage and the frequency varies from 5% to 19%. Although the median time to histologic transformation is approximately four years, it can occur anytime from the time of SMZL diagnosis to 16 years after diagnosis. In our patient, the SMZL was well-defined. After the first cycle of CHOP was administered following the initial diagnosis, the peripheral blood cell count was normalized and the spleen shrunk to its normal size over a period of approximately two years. After recurrence, the patient underwent four cycles of R-CHOP chemoimmunotherapy and achieved CR; however, isolated extranodal abdominal DLBCL transformation occurred within three months of CR, which is extremely rare in SMZL.

At present, there is no conclusive way to predict the histologic transformation of SMZL. The presence of B symptoms, poor performance status, nodal and extranodal dissemination of the disease, high LDH levels, and failure to achieve CR after initial treatment are significantly associated with the risk of histologic transformation. Mutations in NOTCH2, KLF2, TP53, TNFAIP3, CACNB2, HTRA1 and, KLF4 among other genes, deletion of chromosome 7q, and the absence of somatic mutations in the IGHV have been associated with histological progression. The initial diagnosis for our patient revealed enlarged cervical, mediastinal, retroperitoneal lymph nodes, and elevated serum LDH levels as the main risk factors for the histological transformation, combined with the failure to achieve CR after initial treatment. During the SMZL diagnosis, mutations in MYD88, TP53, ETV6, CXCR4, SF3B1, and DNMT3A
were detected, which may be involved in molecular mechanism underlying DLBCL transformation. However, the transformation of extranodal DLBCL was suddenly observed three months after CR, and mutations in multiple genes, such as B2M, BCL6, FBXW7, SRP72, KMT2D, IRF4, STAT5B, TCF3, and PRDM1 were identified in the tumor tissue, which suggested clonal evolution during disease progression.

Transformed SMZL cases are usually excluded from clinical trials, and hence, currently, there is no consensus on the treatment of refractory SMZL. As a result, rituximab-based immunochemotherapy remains the first-line treatment for SMZL, which may also be combined with novel molecular targeted therapeutics, such as the Bruton tyrosine kinase (BTK) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, BCL-2 inhibitor, chimeric antigen receptor T-cell immunotherapy (CAR-T), and autologous stem cell transplantation. Most patients with isolated extranodal involvement are treated with radiotherapy alone at the transformed site, and some of them achieve CR. While transformation in the bone marrow is frequently refractory to therapy and associated with poor outcomes in SMZL, lymph nodes transformation responds well to chemotherapy with longer progression-free and overall survival. In our patient, SMZL transformed into DLBCL with isolated abdominal mass, and presented P53 mutation, indicating unfavorable outcomes. The R-CHOP and R-DHAP was successively administered, but no significant, long-term therapeutic effects were observed; moreover, the patient refused to use BTK inhibitor or CAR-T for financial reasons and ultimately succumbed due to gastrointestinal bleeding.

**Conclusion**

Although the clinical course of SMZL is generally slow and mild, the prognosis is very poor, with the survival time further shortening after histological transformation. Gene mutations and clonal evolution may play a significant role in histological transformation of SMZL and patient outcomes.

**Abbreviations**

SMZL: Splenic marginal zone lymphoma; DLBCL: Diffuse large B-cell lymphoma; CR: Complete remission; CHOP: Cyclophosphamide, vinorelbine, pirarubicin, and dexamethasone; R-CHOP: Rituximab in combination with CHOP; R-DHAP: rituximab, cisplatin, cytarabine, and dexamethasone; LDH: Lactate dehydrogenase; CT: Computed tomography; H&E: Hematoxylin and eosin; BTK: Bruton tyrosine kinase; PI3K: Phosphoinositide 3-kinase; CAR-T: chimeric antigen receptor T-cell immunotherapy

**Declarations**

**Ethics approval and consent to participate**

Ethical approval was obtained from the Ethics Committee of the Second Affiliated Hospital of Nanchang University, Nanchang, China, in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.
Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have stated that they have no conflicts of interest.

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Authors' contributions

Mingfeng Chen (First Author): Conceptualization, Methodology, Writing - Original Draft;
Jing Xu: Investigation;
Wencan Ye: Investigation;
Zhenjiang Li: (Corresponding Author): Conceptualization, Funding Acquisition, Supervision, Writing - Review & Editing;
Yuan Song: Supervision;
Aiping Tang: Supervision.

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References


**Figures**
Figure 1

A: Hematoxylin and eosin (H&E) staining of the bone marrow biopsy (original magnification ×200) revealed lymphocyte proliferation, the cells were positive for CD20, CD79a, BCL-2, but negative for CD10 and CD5. B: Abdominal mass tissue immunohistochemical staining demonstrated the cells were positive for CD20, C-Myc, Ki-67, PAX5, MUM-1, BCL-2, CD38, and negative for CD5, CyclinD1, CD3.

Figure 2

Arterial phase contrast-enhanced CT of the abdomen, revealed an irregular large soft tissue mass in the right hepatorenal recess area, measures about 10.9*11.9cm.