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CASE IMAGE

Anisolymphocytosis: A clue for Richter transformation

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Key Clinical Message

When chronic lymphocytic leukemia progressed to Richter syndrome, the coexistence of small and large lymphocytes was observed as a bone marrow finding. We consider this finding to be a clue for the progression of chronic lymphocytic leukemia to Richter syndrome.

KEYWORDS

anisolymphocytosis, chronic lymphocytic leukemia, Richter transformation, small lymphocytic lymphoma

A 70-year-old female with lymphadenopathy was referred to our hospital. Laboratory data included a white blood cell count of 13.1×10^9/L with 64% lymphocytes, a hemoglobin concentration of 12.4 g/dL, a platelet count of 114×10^9/L, a lactate dehydrogenase level of 413 U/L (reference range: 124–222), and a soluble interleukin-2 receptor level of 4509 U/mL (reference range: 204–587). A surface marker analysis revealed that lymphocytes expressed CD5 (55.1%), CD19 (93.0%), CD20 (43.5%), CD23 (45.9%), CD79a (95.1%), and restricted surface immunoglobulin λ (κ, 2.7%; λ, 87.1%), but not CD10 (0.1%). Since positivity for CD25 was less than 50%, a bone marrow examination and lymph node biopsy were performed to definitively differentiate mantle cell lymphoma. The bone marrow examination revealed hypercellular bone marrow with 83.2% lymphocytes, which were small and round with clumped chromatin and a scant cytoplasm (Figure 1). A chromosomal analysis identified 46,XX,+1,der(1;13)(q10;q10),t(10;14)(q24;q32)[20]. Lymph node biopsy showed the massive proliferation of small to medium-sized lymphocytes with clumped chromatin. Immunohistochemical staining revealed that lymphocytes were positive for CD5 and aberrantly positive for Ki-67 (Figure 2). Based on these findings, the patient was diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Since the test for the IGHV mutational status was not covered by the national health insurance system in Japan, it was not performed for the present case. Although first-line chemotherapy (rituximab and bendamustine) resulted in partial remission, the disease recurred 2 months after the last cycle. Ibrutinib therapy was initiated but did not slow disease progression. A follow-up bone marrow examination revealed the proliferation of large lymphocytes in addition to lymphocytosis, which was observed in the initial diagnosis (Figure 1). The result of a chromosomal analysis of bone marrow cells at this time was the same as that in the initial diagnosis. Six cycles of third-line chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) resulted in progressive disease. Lymph node biopsy was performed again and revealed the diffuse proliferation of medium-sized to large lymphoid cells. Immunohistochemical staining demonstrated that these

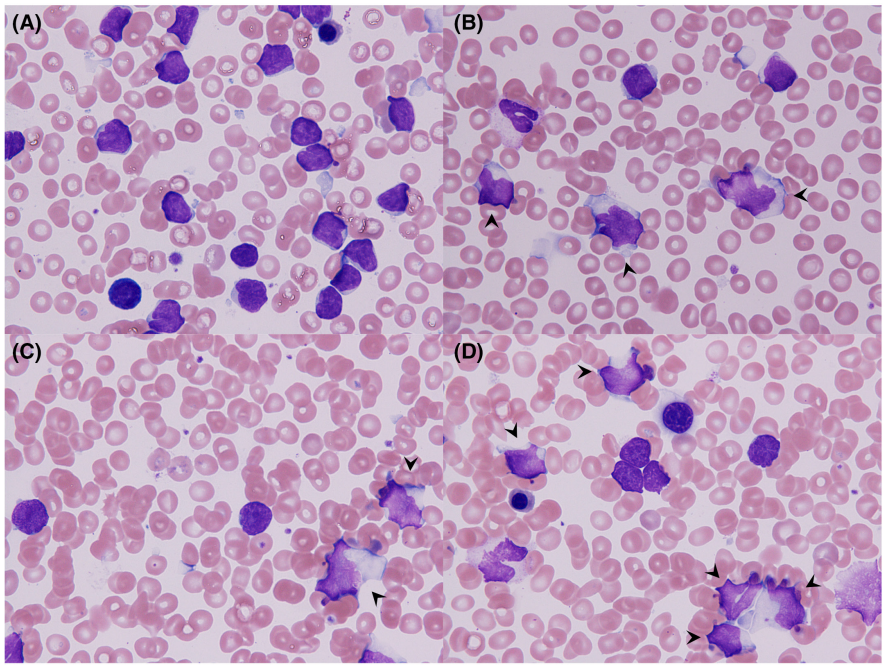

FIGURE 1 Bone marrow cells stained with May–Giemsa stain at the diagnosis of CLL (A) and in the follow-up (B–D). Although the uniform proliferation of small lymphocytes was observed at the time of the initial diagnosis (A), large lymphoid cells were detected at progression (B–D, *arrowheads*).

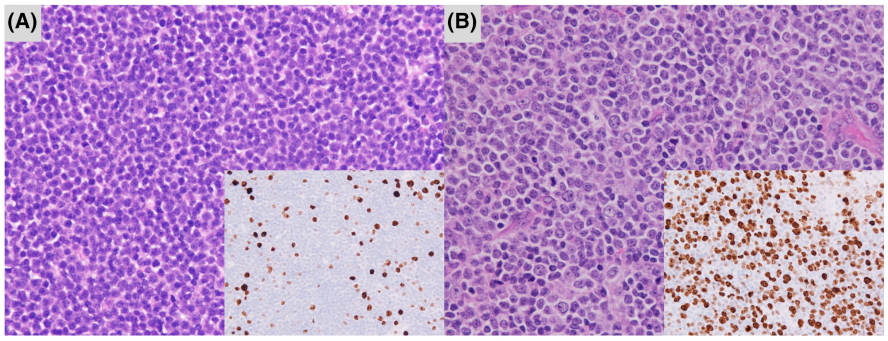

FIGURE 2 Pathological images of lymph nodes at the initial diagnosis (A) and at the diagnosis of Richter transformation (B). The lymph node was filled with small to medium-sized lymphocytes harboring clumped chromatin (A, Hematoxylin and eosin staining), which were replaced by large lymphocytes at Richter transformation (B, Hematoxylin and eosin staining). Ki-67 staining showed aberrant positivity at the initial diagnosis (A, inset), but strong positivity at disease progression (B, inset).

cells did not express CD5 but were strongly positive for Ki-67, in contrast to only aberrant positivity at the diagnosis of CLL/SLL (Figure 2). Therefore, a new diagnosis of Richter transformation to diffuse large B-cell lymphoma from CLL/SLL was made. Although three cycles of fourth-line chemotherapy (rituximab, etoposide, cyclophosphamide, cytarabine, and dexamethasone) and one cycle of fifth-line chemotherapy (rituximab, etoposide, cisplatin, cytarabine, and methylprednisolone) were administered, the patient died from disease progression 1 year and 7 months after the initial diagnosis.

In a recent large cohort study on 74,116 patients with CLL, 530 cases of Richter transformation were identified, with an incidence of 0.7%.[1] Biphasic lymphocytosis in the present case was considered to be a finding that confirmed the intermediate course of Richter transformation. Although de novo Richter transformation showed two cell populations of small and large lymphocytes at the initial diagnosis in previous cases,[2] it was possible to capture the process of change from monotonous small lymphocytes to the coexistence of small and large lymphocytes in the present case. Although Richter transformation during the course of CLL is not common, it needs to be considered when the coexistence of small and large lymphocytes, namely, "anisolymphocytosis," is detected in CLL patients.

AUTHOR CONTRIBUTIONS

Masahiro Manabe: Conceptualization; data curation; writing – original draft. **Naoyuki Inano:** Data curation; writing – original draft. **Yuuji Hagiwara:** Data curation; writing – original draft. **Satoru Nanno:** Conceptualization; writing – review and editing.

Ki-Ryang Koh: Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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REFERENCES
1. Elnair R, Ellithi M, Kallam A, Shostrom V, Bociek RG. Outcomes of Richter's transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): an analysis of the SEER database. *Ann Hematol*. 2021;100:2513-2519.
2. Chiecchio L, Cullis JO. De novo Richter transformation. *Blood*. 2017;129:2455.

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