Letter to the Editor
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A Patient With CD20-positive T-cell Lymphoma Concurrently Exhibiting B-cell Neoplasm-related Genetic Abnormalities Shows Clonal Escape Post CD20-targeting Treatment

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Dear Editor,

Aberrant B-cell antigen expression in mature T-cell neoplasm is very rare and may lead to misdiagnosis. The effectiveness of B-cell antigen-targeting agents is still controversial in such cases. Herein, we report the first Korean patient with CD20-positive peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), exhibiting genetic abnormalities in both T-cell and B-cell lymphomas. Notably, her refractory disease was likely caused by clonal escape following CD20-targeted therapy. Ours is a single case report that does not meet the definition of human subject research, and thus, was exempted from approval by an Institutional Review Board.

A 70-year-old Korean woman with multiple enlarged lymph nodes visited Asan Medical Center, Seoul, Korea, in January 2021. A complete blood cell count showed hemoglobin: 110 g/L, white blood cells: 21.6×10^9/L, and platelets: 256×10^9/L. Small-to-medium-sized, mature-appearing neoplastic lymphocytes comprised 66% of total leukocytes in the peripheral blood and 13% of total nucleated cells in bone marrow (BM) aspirate. BM infiltration patterns were paratrabecular and nodular. In immunohistochemistry, a BM biopsy section was positive for CD3, CD4, CD5, and CD20, but negative for CD8 and CD79a. In flow-cytometric immunophenotyping, her peripheral blood was positive for the T-lineage antigens CD2, CD3, cCD3, CD4, and CD5, but not CD7, and for the B-lineage antigen CD20, but was negative for all other B-lineage antigens (CD10, CD19, CD22, CD23, and FMC7), CD56, and TdT (Figs. 1A–F). The karyotype was 44, XX,der(1)del(1)(p13p21)add(1)(q12),?add(8)(q24.3),der(8)t(8;15)(p23;q15),-10,der(11)t(1;11)(q12;q22),del(13)(q14q21),-15,del(16)(q22),add(17)(p13)[15]/46,XX[15] (Fig. 1G). The patient was diagnosed as having PTCL, NOS with aberrant CD20 expression.

In immunohistochemistry, biopsied right neck and left inguinal nodes were positive for CD3, CD4, CD5, and CD20 and negative for CD8 and CD79a. Fluorescence *in-situ* hybridization revealed *ATM*, 13q14, and *TP53* deletions. Next-generation sequencing revealed a *PLCG1* S345F mutation plus *CDKN2A* and *CDKN2B* deletions. Clonal rearrangements in *IGK, TCRB*, and *TCRG*, but not *IGH*, were observed. Hence, the pathologic diagnosis was PTCL, NOS with aberrant CD20 expression.

The anti-CD20 monoclonal antibody obinutuzumab was administered combined with chlorambucil. Imaging analysis re-

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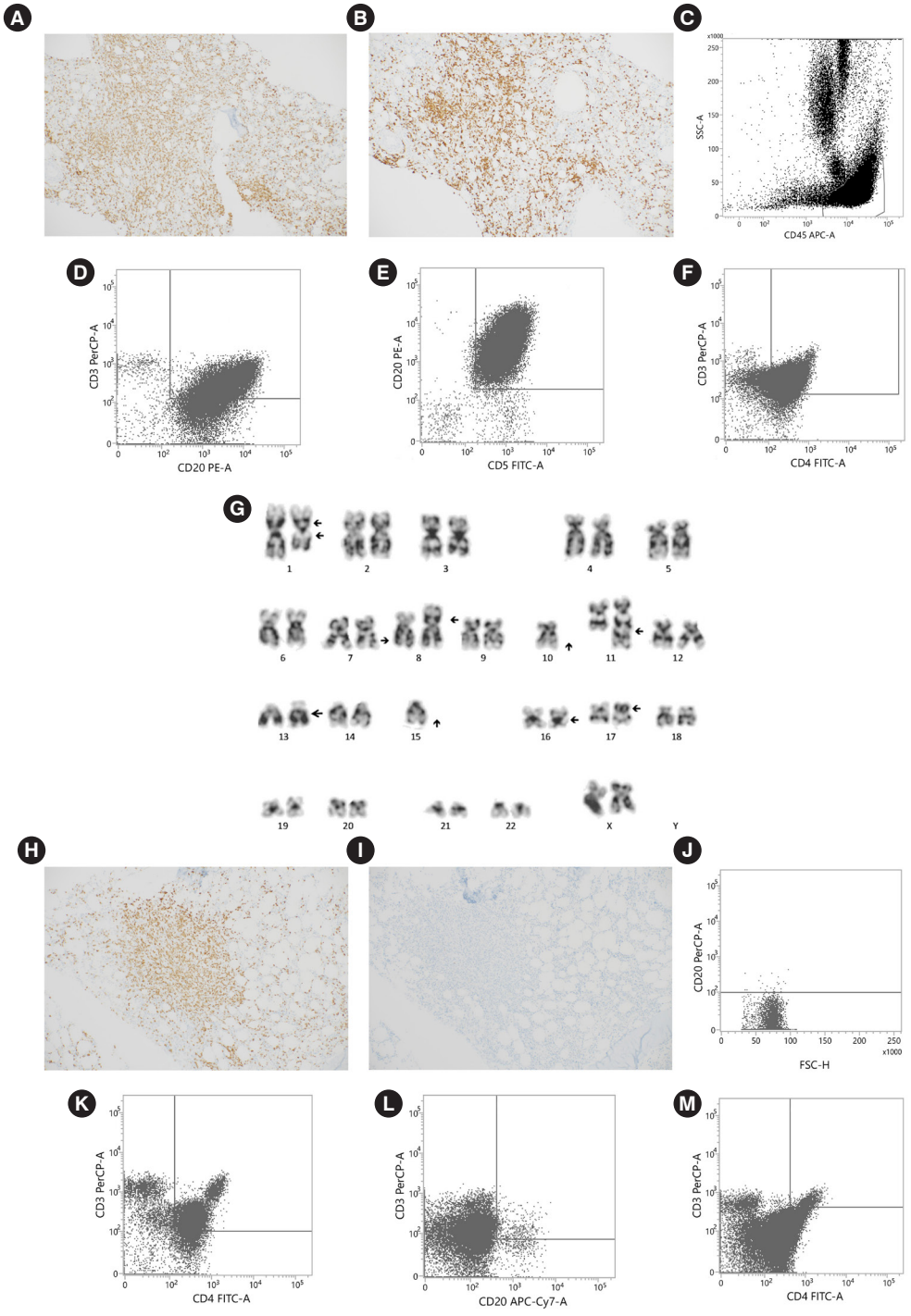

Fig. 1. Analysis and karyotyping of the patient. At the time of initial diagnosis, immunohistochemical staining of a BM biopsy sample was performed for (A) CD3 (100×) and (B) CD20 (100×), and flow-cytometric immunophenotyping of a peripheral blood sample was performed for (C) CD45 (with side scatter plot), (D) CD3 and CD20, (E) CD5 and CD20, and (F) CD3 and CD4. The karyotype at the time of diagnosis (G) was 44,XX,der(1)del(1)(p13p21)add(1)(q12),?add(8)(q24.3),der(8)t(8;15)(p23;q15),-10,der(11)t(1;11)(q12;q22), del(13)(q14q21),-15,del(16)(q22),add(17)(p13)[15]/46,XX[15]. The black arrows indicate the breakpoint in structural abnormalities. After CD20-targeted therapy, immunohistochemical analysis of a BM biopsy was performed for (H) CD3 (100×) and (I) CD20 (100×); flow-cytometric immunophenotyping of the BM was performed for (J) CD20 and (K) CD3 and CD4, whereas flow cytometric immunophenotyping of pleural fluid was performed for (L) CD3 and CD20 and (M) CD3 and CD4.
Abbreviation: BM, bone marrow.

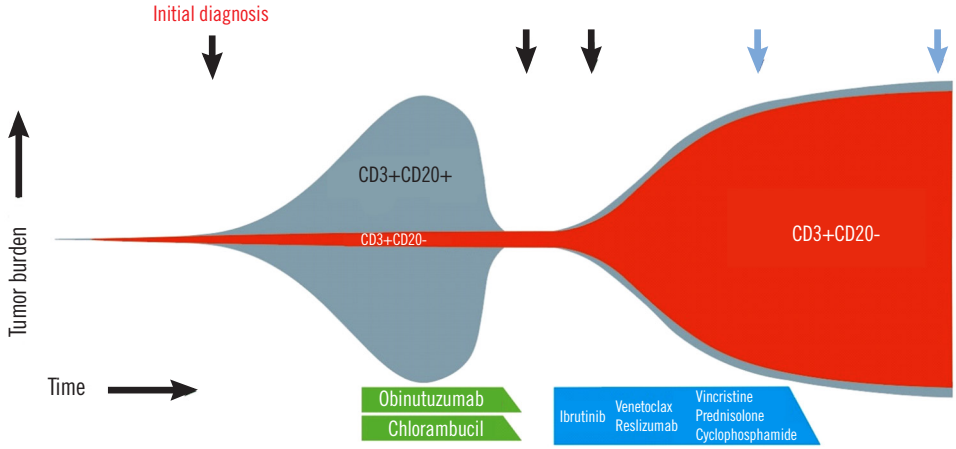

Fig. 2. Suggested model describing the clonal evolution of our patient's immunophenotype. The horizontal axis represents time and vertical axis represents the relative tumor burden. The black and blue arrows at the top indicate the times at which BM examinations and pleural fluid analysis were performed, respectively. The therapy regimens that the patient received in the respective time periods are highlighted in green and blue.
Abbreviation: BM, bone marrow.

vealed disease regression after eight weeks of treatment. In immunohistochemistry, a BM biopsy section showed a small aggregation of neoplastic lymphocytes that were positive for CD3 and CD4, but negative for CD20 and CD79a after anti-CD20 monoclonal antibody treatment (Fig. 1H and I). Flow-cytometric immunophenotyping of a BM aspirate at the same time point revealed neoplastic lymphocytes that were positive for CD3 and CD4, but negative for CD20 (Fig. 1J and K). However, the disease progressed four weeks later despite the addition of ibrutinib to the treatment regimen. Flow-cytometric immunophenotyping of pleural fluid revealed that most neoplastic lymphocytes were positive for CD3 and CD4, but negative for CD20, with a small fraction positive for both CD3 and CD20 (Fig. 1L and M). Venetoclax, reslizumab, vincristine, cyclophosphamide, and prednisolone were administered; however, the patient did not respond to therapy and died of septic shock 12 months later.

Most reported B-cell antigen-expressing T-cell lymphomas are CD20-expressing PTCL, NOS [1-9]; only three patients with this disease showed BM involvement. However, CD19 or CD79a can also be expressed [1-3], which can complicate the diagnosis given that CD20, CD19, and CD79a are considered to have near-absolute lineage specificity in mature lymphoid neoplasms. It is also important to distinguish T-cell lymphoma with CD20 expression from that admixed with non-malignant B-cells, which can be accomplished by confirming the co-expression of CD20 and other T-cell antigens, including CD2, CD5, CD7, and particularly, CD3 via flow cytometry or dual-stain immunohistochemistry.

Our patient is first reported to have CD20-positive T-cell lymphoma exhibiting the *PLCG1* S345F mutation, which dysregulates T-cell signaling and differentiation and is common in other T-cell lymphomas, but rare in PTCL, NOS [4], along with del(13)(q14q21) (possibly caused by *RB1* loss), del(16)(q22), and *TP53* and *CDKN2A/2B* deletions, which have been reported in both B- and T-cell lymphomas [10]. Add(8)(q24.3), which can alter the *MYC* gene expression, is observed predominantly in B-cell lymphoma and may explain the CD20 expression in our patient [10]. Our patient is also the first reported with concurrent clonal rearrangements in *IGK, TCRB*, and *TCRG* [1-9], which confirms the T-cell origin of this disease and substantiates the expression of CD20. Analysis of *IGK* rearrangement in a CD20-negative follow-up sample would help confirm our hypothesis.

Some previously reported patients with CD20-positive T-cell lymphomas responded to anti-CD20 therapy alone or in combination with chemotherapy [1, 2, 6, 8], whereas others did not [3, 4, 7]. The proliferation of CD20-negative T-lymphocytes after targeted therapy suggests the clonal escape of a very minor, undetectable population of these cells that evaded treatment in our patient (Fig. 2). This has not been reported previously. Our case serves to raise awareness that CD20-targeting therapy in such patients may cause clonal escape and refractory disease.

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AUTHOR CONTRIBUTIONS

Kim J collected the information and wrote the manuscript; Kim M supervised the manuscript; Cho YU, Hwang SH, Jang S, and Park CJ contributed to the diagnosis and monitoring of the disease; Seo EJ performed the cytogenetic study; Yoon DH treated the patient; and Go H contributed to the diagnosis and performed molecular genetic studies.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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