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B-cell Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, without the Development of Richter's Syndrome, with Neoplastic Cells Lacking CD20 Antigen Expression after Rituximab Treatment

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Abstract

A 40-year-old man was admitted to our hospital with systemic swelling of the lymphnodes (LNs). The histopathological findings of the neck LNs revealed a diffuse proliferation of neoplastic small lymphocytes. LN and bone marrow (BM) cells were subjected to immunostaining and flow cytometric analysis of the cell surface, showing CD5, CD19, CD20, and CD23 positivity and CD3, CD10, and cyclin D1 negativity. The patient was diagnosed with B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL). He received a cycle of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and 6 cycles of RFC (rituximab, fludarabine, and cyclophosphamide), after which complete remission was obtained. Fifteen months after the diagnosis, the lymphoma relapsed and massive systemic LN swelling and BM infiltration were observed, characterized by a lack of CD20 antigen expression in the neoplastic cells. Two salvage chemotherapy regimens proved ineffective and the lymphoma progressed. The patient died two months after the relapse. The pathological findings at autopsy revealed the multiple organ infiltration of CLL/SLL cells which lacked CD20 expression. There were no evidence of Richter's syndrome. Patients with relapsed B-CLL/SLL who are undergoing rituximab-containing therapy should be monitored for the loss of CD20 antigen expression in the neoplastic cells.

Keywords: B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma; CD20 antigen loss; rituximab

Introduction

B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL) is a mature B-cell lymphoid neoplasm characterized by the proliferation of monoclonal mature B-cell in the peripheral blood, bone marrow, and lymph nodes (LNs) [1-3]. SLL is typically characterized by the proliferation of neoplastic cells, mainly in the LNs, which is not accompanied by cytopenia due to bone marrow infiltration. In many ways, SLL is similar to CLL. The similarities include the characteristics of the neolpastic cells [1]. The B-CLL/SLL neoplastic cells strongly express CD5 and CD23 and weakly express cell-surface IgM/IgD, CD11c, CD19, CD20, CD22, and CD79a [4]. Approximately 3-15% of all B-CLL/SLL cases experience the transformation into diffuse large B-cell lymphoma (DLBCL), which is also known as Richter's syndrome (RS) in the narrow sense of the term [5]. Mauro et al. [6] reported the development of 22 RS patients, including 18 cases of DLBCL and 4 of Hodgkin's Lymphoma (HL), in their analysis of 1,011 B-CLL/SLL patients. It has been previously demonstrated that B-CLL/SLL transforms into DLBCL, HL, and hairy cell leukemia [1,6,7] and into high-grade lymphoma, which is also known as RS in the wider sense of the term [1]. The prognosis of patients who develop RS is very poor, with survival rate of 7 to 8-month, even in the patient treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) or a purine analogue regimen [1]. Aggressive cases of B-CLL/SLL, which develop into RS with cells that lack CD20 antigen expression have also been reported [8-10]. However, the cases of B-CLL/SLL with cells that lack CD20 antigen expression without RS development, are not fully understood.

We herein report a relapsed case of B-CLL/SLL, in which RS did not develop, which presented an aggressive clinical course due to presence of neoplastic cells that lacked CD20 antigen expression after the treatment with a rituximab-containing regimen.

Case report

A 40-year-old man was referred to our hospital for lymphadenopathy. A physical examination revealed systemic lymphadenopathy including neck and axillary LN swelling. A computed tomography (CT) scan (Figure 1) showed multiple lymphadenopathy of the neck (A), axilla (B), mediastinum and the abdomen (C). The results of a blood test performed on admission (Table 1) were as follows: white blood cells (WBC) 3300/μl (neutrophils 38.1%, lymphocytes 58.6%); red blood cells (RBC) 347 × 10^4/μl; hemoglobin (Hb) 12.4 g/dl; platelet (Plt) 21.3 × 10^4/μl; total protein (TP) 5.7 g/dl; albumin (ALB) 3.9 g/dl; LDH 221 IU/l; creatinine (CRE) 0.48 mg/dl; CRP 0.78 mg/dl; and soluble interleukin-2 receptor (sIL-2R) 2880 IU/l. The pathological findings of a cervical LN biopsy specimen (Figure 2) revealed the destruction of the basic structure of the LN and the diffuse proliferation of atypical

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Figure 1

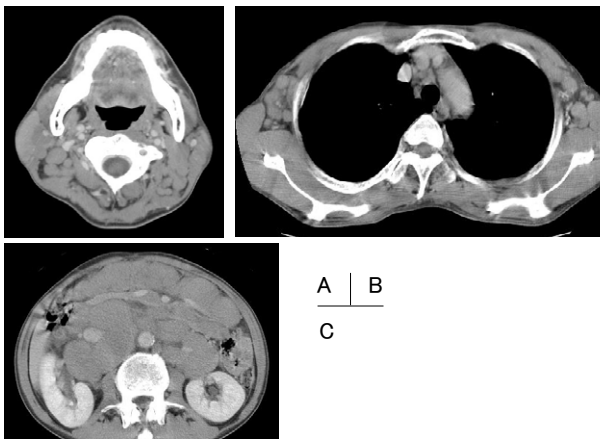

Figure 1: CT showed swelling of the cervical (A), axillary (B), and mesenteric lymph nodes.

WBC	3300/μl	TP	5.7g/dl	APTT	28sec
Neu	38.1%	Alb	3.9g/dl	PT	13.2 sec
Lym	58.6	T-bil	0.7mg/dl	PT-%	0.877
Mono	2	D-bil	0.1mg/dl	PT-INR	1.06
Baso	0.7	AST	21IU/l	FDP	2.5 mg/dl
Eos	0.6	ALT	11IU/l	D-dimer	0.6 mg/dl
RBC	347×10⁴/C	LDH	221IU/l		
H b	12.3g/dl	BUN	11.4mg/dl	FBS	108 mg/dl
H t	36%	Cre	0.48mg/dl	HbA1c(NGSP)	4.8
MCV	103.7fl	Na	142mEq/l		
MCH	35.5pg	K	4mEq/l	RPR	(-)
MCHC	34.2%	Cl	104mEq/l	HBsAg	(-)
Plt	21.3×10⁴/μl	CRP	0.78mg/dl	HCVAb	(-)
				HTLV-1Ab	(-)
				EBVVCA IgG	×80
				sIL-2R	2880 IU/I

Table 1: Laboratory data at diagnosis.

lymphocytes via hematoxylin and eosin (HE) staining (Figures 2A and 2B). The immunostaining of these atypical cells revealed that they were positive for CD5, CD20, CD23, and CD79a (Figures 2C-F), but negative for CD3, CD10, and cyclin D1. A flow cytometric analysis using Peripheral Blood (PB) was not performed at the time of the initial diagnosis because there were no atypical lymphocytes in the PB. Bone marrow mononuclear cells (BMCs) were found to be positive for CD5, CD19 (Figure 3A), CD20 (Figure 3B), CD23, CD25, and the λ-chain of the immunoglobulin light chain and negative for CD3 and CD10 by a cell surface marker analysis using flow cytometry. We were unable to make a definitive diagnosis at that point, however, DLBCL was initially doubted based on the histopathologic findings. Because the patient's LNs became further enlarged, CHOP therapy was administered as an initial treatment, and thereafter the LNs decreased in size. We obtained a second opinion consultation of his tissue samples from the Department of Pathology and Laboratory Medicine, Showa University School of Medicine. A definitive diagnosis of B-CLL/SLL was made according to the findings of diffuse proliferation of small and medium-sized atypical lymphocytes with a B-cell phenotype, of which 20% were found to be positive for Ki67 immunostaining. Furthermore, the long-arm deletion of chromosome 11 [del (11q)] was detected in 15 of 20 BMCs by the G-banding method. His clinical staging was determined to be intermediate risk II by the modified Rai classification [11], and B by the Binet classification [12]. We modified the treatment strategy to the RFC regimen (rituximab, fludarabine, and cyclophosphamide) after the definitive diagnosis. He achieved complete remission after

Figure 2

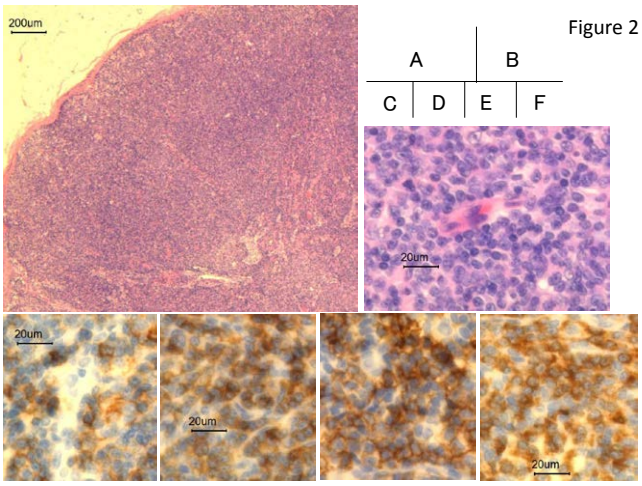

Figure 2: The pathological findings of the cervical lymph nodes at diagnosis. HE staining (2×) (A), (B) (20×) and immunostainings (20×) demonstrate positivity for CD20 (C), CD5 (D), CD23 (E) and CD79a (F).

Figure 3

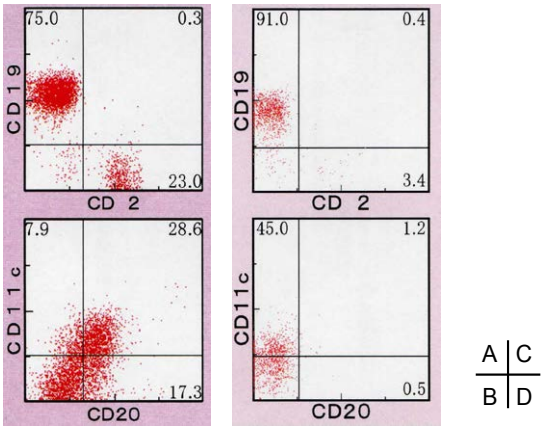

Figure 3: The immunophenotyping by flowcytometry of the bone marrow cells at diagnosis and at relapse after rituximab-including treatment. Before rituximab treatment, the neoplastic cells expressed CD19 (A) and CD20 (B). At relapse after treatment with the rituximab regimen, the tumor cells were positive for CD19 (C), but exhibited the loss of CD20 expression (D). These analyses were performed by SRL Inc., Tokyo, Japan.

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6 cycles of RFC. Fourteen months after the first admission, he felt an abdominal distension and CT revealed the presence of multiple enlarged abdominal LNs, and he was thus readmitted to our hospital. On this occasion, the blood test results were as follows: WBC 2100/μl (neutrophils 73.0%, lymphocytes 24.0%, monocytes 1.0%, eosinophiles 1.0%, and atypical lymphocytes 1.0%); RBC 289 × 10^4/μl; Hb 9.5 g/dl; Plt 4.2 × 10^4/μl; LDH 307 IU/l; CRP 3.2 mg/dl; and sIL-2R 1420 U/ml. The bone marrow examination showed that 90.6% of the total BMCs were atypical mature lymphocytes. Furthermore, the bone marrow neoplastic cells were positive for CD5, CD19 (Figure 3C), CD23, CD25, and λ-chain of immunoglobulin light chain and negative for not only CD3 and CD10, but also for CD20 (Figure 3D), which was found to be positive at the initial diagnosis (Figure 3B) by the cell surface marker analysis using flow cytometry. Complicated chromosomal abnormalities including abnormalities in chromosomes 3, 6, 7, 8, 9, 13, 15, 16, 17, and 19, were detected in 15 of 20 analyzed BMCs by the G-banding method. The abnormalities in chromosome 11, which were detected at the initial diagnosis, were not included. We ultimately determined that the patient had relapsed due to B-CLL without RS and with the loss of CD20 antigen expression.

Figure 4 shows the clinical course of the patient after the initial admission. He received one cycle of bendamustine monotherapy as the initial treatment of the salvage therapy, however, the number of bone marrow neoplastic cells increased. Afterwards, he received a cycle of hyper-CVAD; however, he presented life-threatening pneumonitis during the period of prolonged bone marrow suppression. Although the patient received several antibiotics and antifungal drugs with the support of mechanical ventilation, he died from a pulmonary hemorrhage associated with the pneumonitis 16 months after the initial admission. The pathological findings by HE staining at autopsy Figure 5 revealed the massive infiltration of neoplastic cells in the mesenteric LN (A), bone marrow (B), kidney (C), and Glisson's capsule of the liver (D). Both lungs showed diffuse hemorrhages and fluid retention. The weights of the right and left lungs were 1.7 kg and 1.3 kg, respectively. Lung parenchyma and intra vessels demonstrated the dissemination of Candida and focal pneumonitis. The stomach, colon and kidney

Figure 4

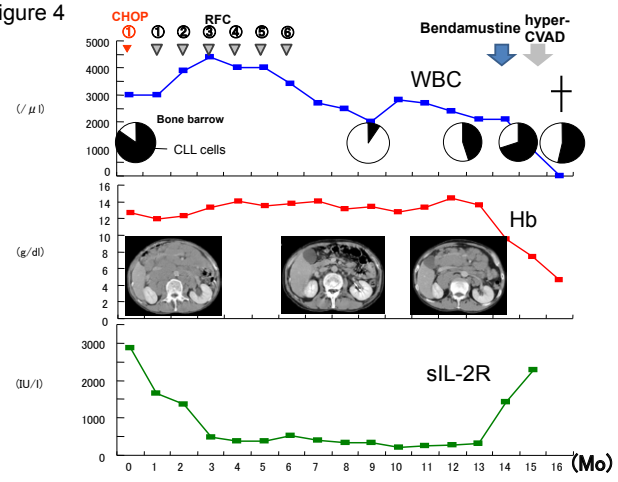

Figure 4: The clinical course. CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; RFC: rituximab, fludarabine, and cyclophosphamide; hyper-CVAD: cyclophosphamide, vincristine, doxorubicin, and dexamethasone; CLL: chronic lymphocytic leukemia; Mo: months.

Figure 5

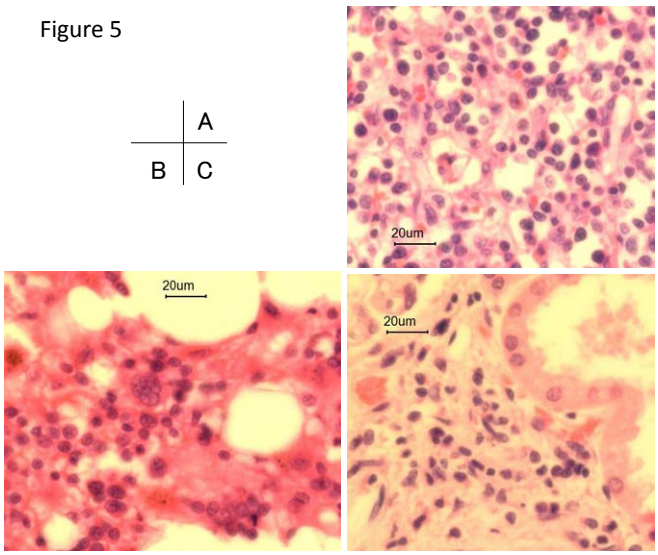

Figure 5: The pathological findings via HE staining (20X) at autopsy. Massive neoplastic cell infiltration was observed in the mesenteric lymph node (A), bone marrow (B), kidney (C).

Figure 5D

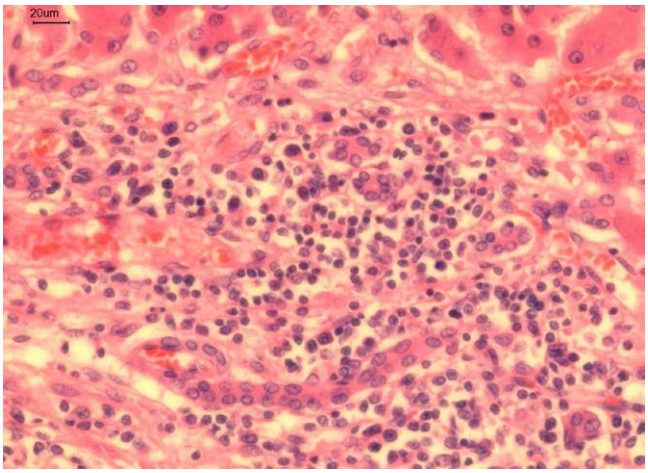

Figure 5D: Glisson's capsules of the liver

were also hemorrhagic. The cause of death was determined to be respiratory failure due to lung bleeding and pneumonia. Figure 6 shows the pathological findings of the mesenteric LN at autopsy. The atypical lymphocytes show negativity for CD20 (A) and positivity for CD5 (B), CD23 (C) and CD79a (D) by immunostaining, which was consistent with the characteristic B-CLL/SLL findings, without evidence of RS (including DLBCL). We ultimately concluded that the neoplastic B-CLL/SLL cells lost the expression of the CD20 antigen after the rituximab treatment.

Discussion

A recent search of the MEDLINE database revealed a limited number of cases of B-CLL/SLL demonstrating the loss of CD20 antigen expression after rituximab treatment. Including the present case, only

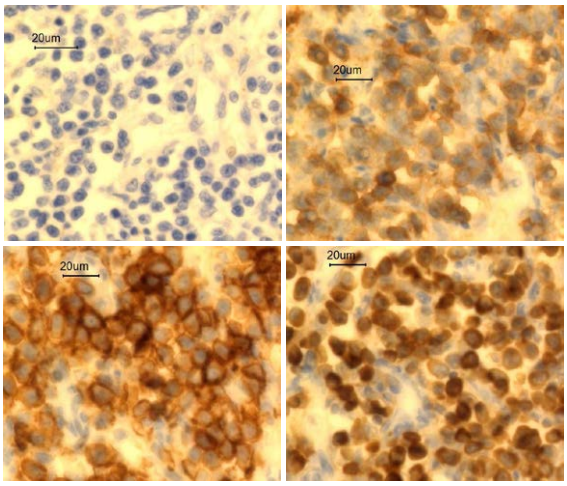

Figure 6: The pathological findings of the mesenteric lymph node at autopsy (20X). The immunostainings demonstrate negativity for CD20 expression (A) and positivity for the expression of CD5 (B), CD23 (C) and CD79a (D).

a small number of cases have been reported thus far [9,12-15]. The characteristics of 11 patients (including 6 males) whose details were described are listed in Table 2. Treatment regimens that included rituximab, such as R-CHOP or fludarabine-based regimens, were chosen for patients with B-CLL/SLL before the loss of CD20 expression was demonstrated. The expression of B-cell markers other than CD20, such as CD19, CD22 or CD23, were observed in the neoplastic cells after CD20 loss. Most cases received salvage chemotherapies according to the aggressive lymphomas after CD20 loss. Three of the eight confirmed cases developed into RS. In the five cases where survival was described, 3 cases (including 2 which developed into RS), died within 1-4 months after the loss of CD20 expression. Moreover, 1 of the 3 cases (the present case) which did not develop into RS showed chemoresistance and died within a short period of time. Although a further accumulation of cases is needed to clarify the prognosis of B-CLL/SLL that does not develop into RS, but demonstrates the loss of CD20 expression after rituximab treatment, the existence of such patients must be recognized.

It is not well understood how frequently CD20 antigen loss in tumor cells occurs in B-CLL/SLL patients after rituximab therapy. D'Auria et al. [9] reported that 4 of 8 (50%) tested CLL/SLL patients demonstrated CD20 antigen loss, half of whom later developed RS. Goteri et al. [13]

Case No. [references]	Age/ Sex	Status at Rituximab (R) therapy	R-regimen (cycles)	Response to R-regimen	Cell surface antigens after CD20 loss	Further clinical course after CD20 loss (final status)	Development of RS	Final outcome	Survival after CD20 loss (Mo)
1 [9]	67/M	Rel2 after CB and Flu	R-CHOP-like (6)	PR	CD5+,19+, 23+, 52+, Lambda+	Al, Ben → CD20+(PR)	no	A	26+
2 [9]	68/M	Rel1 after FC	R (6) + CB	PR	CD5+,19+, 23+, 52+, Lambda+	Al → CD20+→ R-Ben (PR)	no	A	25+
3 [9]	74/F	Rel1 after CB	R-FC (5)	NR	CD5+,19+, 23+, 52+, Lambda+	Evolution into CD20+ high grade lymphoma (RS) →R-CHOP (PD)	yes	D	1
4 [9]	61/M	Rel2 as CD20+ RS after FC and R-Ben	R-CHOP (4)	PR	CD5+,19+, 23+, 52+, Kappa+	CD20- high grade lymphoma (RS) → 4 regimens including ASCT	yes	D	4
5 [12]	64/F	Rel1 as RS after multiple CT	R-CHOP (6)	PR→PD	CD45+	Evolution into CD20- DLBCL (PD)	yes	N/A	NA
6 [14]	53/F	NA	NA	NA	CD5+, 19+, 22+	NA	NA	A	NA
7 [14]	42/M	NA	NA	NA	CD79a+	NA	NA	A	NA
8 [14]	77/F	NA	NA	NA	CD5+, 19+, 22+	NA	NA	A	NA
9 [15]	54/M	Initial treatment	R (2)	NA	NA	C-MOPP (PR)	no	N/A	NA
10 [15]	52/F	Treatment after CHOP and COP	R-CEPP (7)	NA	NA	R-ESHAP, CHASE, R-ESHAP + ASCT, R → (PR)	no	N/A	NA
11 [our case]	40/M	Initial treatment	CHOP (1) + R-FC (6)	CR	CD5+,19+, 23+, 11c+, 25+ Lambda+	Ben, Hyper-CVAD (PD)	no	D	2

Table 2: Cases with B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma showing the loss of CD20 antigen expression after rituximab treatment. No: Number; M: male; F: female; R: rituximab; RS: Richter's syndrome; CB: chlorambucil; Flu: fludarabine; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; Al: alemtuzumab; PR: partial response; FC: fludarabine, cyclophosphamide; Ben: bendamustine; NR: no response; Hyper-CVAD: cyclophosphamide (high dose), vincristine, doxorubicin, dexamethasone; ASCT: autologous stem cell transplantation; CVP: cyclophosphamide, vincristine, prednisone; CR: complete remission; SD: stable disease; PD: progressive disease; R-B: rituximab, bendamustine; NA: not available; C-MOPP: cyclophosphamide, vincristine, prednisone, procarbazine; COP: cyclophosphamide, vincristine, prednisone; CEPP: cyclophosphamide, etoposide, prednisone, procarbazine; ESHAP: etoposide, methylprednisolone, high-dose cytarabine, cisplatin; CHASE: cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide; CT: chemotherapy; Rel1: first relapse; A: alive; D: died.

indicated that 4 of 5 patients (80%) with CLL/SLL showed the loss of CD20 antigen expression after rituximab treatment in their investigation of 26 low-grade, non-Hodgkin's lymphoma (NHL) patients. Seliem et al. retrospectively analyzed the immunophenotypic changes in patients with B-cell NHL after rituximab therapy and showed a reduction or significant decrease in the CD20 expression of 5 patients, including 3 patients with B-CLL/SLL. Taken together, it appears that a certain percentage of B-CLL/SLL patients develop the loss (or reduction of the level) of CD20 antigen expression on the neoplastic cells after rituximab treatment.

Several mechanisms for the loss of CD20 antigen expression

on the neoplastic cells have been demonstrated in patients with B-CLL/SLL receiving rituximab therapy. Jilani et al. [16] tested the presence of rituximab on the surface of CLL lymphocytes using anti-mouse immunoglobulin antibodies to detect rituximab and found its presence in 3 of 65 B-CLL patients, despite the fact that most of them had no detectable CD20 expression. They speculated that the disappearance of CD20 expression may not only be due to a masking effect by rituximab, but also due to the down-modulation of CD20 expression or its internalization. Conversely, Hiraga et al. [17] proposed the epigenetic modulation of the CD20 antigen as an alternative explanation of the phenomenon. Moreover, Takei, et al. [18] demonstrated clonal selection and the expansion of CD20-negative cells in CLL/SLL patients after rituximab treatment. The fact that the neoplastic cells with chromosomal types that differed from the initial diagnosis developed after rituximab treatment in the present case may support this hypothesis. Although we cannot definitively determine which mechanism or mechanisms are associated with the loss of CD20 antigen on the neoplastic cells in the present case of B-CLL/SLL patients after rituximab treatment, the mechanism(s) should be further clarified in future investigations.

We chose bendamustine monotherapy as the salvage chemotherapy in the present case due to the loss of CD20 expression on the neoplastic cells. However, it was not effective for the present case. One of the other potential therapies may include the use of the humanized anti-CD52 monoclonal antibody alemtuzumab, which has been reported to be an active agent for CLL patients with high-risk genetic markers including del (17p) [3]. Moreover, D'Auria et al. [9] reported two cases of B-CLL in whom alemtuzumab was effective survived for more than 2 years after the loss of CD20 antigen expression following rituximab treatment (Case Nos. 1 and 2 in Table 2). However, it is not easy to administer alemtuzumab because it is not currently approved in Japan. Another potential therapy would be use of ofatumumab, a fully humanized antibody targeting a unique epitope on the CD20 molecule, which results in an increased binding affinity to CD20 and increased (in comparison to rituximab) cellular killing due to a greater CDC activity and similar ADCC activity [3]. It has been previously demonstrated that ofatumumab is effective for B-CLL/SLL cells expressing even low levels of CD20 [3]. The last choice may have been to perform an allogeneic stem cell transplantation (allo-SCT) before the present patient's relapse. In fact, we had considered performing allo-SCT at his first CR due to his age and risk factors, including del (11q), and we had searched for an HLA-identical sibling donor. There was no appropriate sibling donor, and we had to wait until the patient agreed to search for unrelated donors. Although the optimal therapeutic strategy for this case is unknown, further investigations are required to identify the risk factors for the loss of CD20 expression on the neoplastic cells in B-CLL/SLL patients after rituximab treatment.

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