

# Sustained Remission with Mogamulizumab in Peripheral T Cell Lymphoma with Aberrant CD20 Expression: Case Report and Literature Review

Kentaro Fukushima<sup>1</sup>, Hiroshi Sata<sup>1</sup>, Masami Imakita<sup>2</sup>, Takahiro Karasuno<sup>1</sup>

<sup>1</sup>Department of Hematology, Rinku General Medical Center, Izumisano, Osaka, Japan

<sup>2</sup>Department of Pathology, Rinku General Medical Center, Izumisano, Osaka, Japan

Email: kfukushi@bldon.med.osaka-u.ac.jp

**How to cite this paper:** Fukushima, K., Sata, H., Imakita, M. and Karasuno, T. (2018) Sustained Remission with Mogamulizumab in Peripheral T Cell Lymphoma with Aberrant CD20 Expression: Case Report and Literature Review. *Journal of Cancer Therapy*, 9, 179-187.

<https://doi.org/10.4236/jct.2018.93018>

**Received:** September 10, 2017

**Accepted:** March 3, 2018

**Published:** March 6, 2018

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## Abstract

A 82-year-old man presented with an enlarged multiple superficial lymph nodes. The histological diagnosis of lymph node was peripheral T cell lymphoma, not otherwise specified (PTCL-NOS), with an aberrant expression of CD20. Generally, PTCL lacks B cell antigen such as CD19 or CD20, however, rare cases have been reported in the literature that showed PTCL patients expressing the B cell antigens. It is considered that the prognosis of CD20 positive PTCL is poor, however, standard therapy has not been established. He was treated with eight cycles of CHOP regimen, but the enlargement of a part of lymph nodes still remained. Recently, it is reported that C-C Chemokine receptor type 4 (CCR4) is known to be expressed about 50% case of PTCL and CCR4 target therapy is effective. Our case was positive for CCR4 so mogamulizumab (anti-CCR4 antibody) was administered. Consequently, dramatic response was obtained and its combination of these therapy resulted in complete remission for 24 months. This is the first case of sustained remission by administration of mogamulizumab against CCR4/CD20 double positive PTCL. This strategy may be benefit to obtain the good prognosis.

## Keywords

Peripheral T Cell Lymphoma, CD20, PTCL-NOS, Aberrant Expression, Mogamulizumab

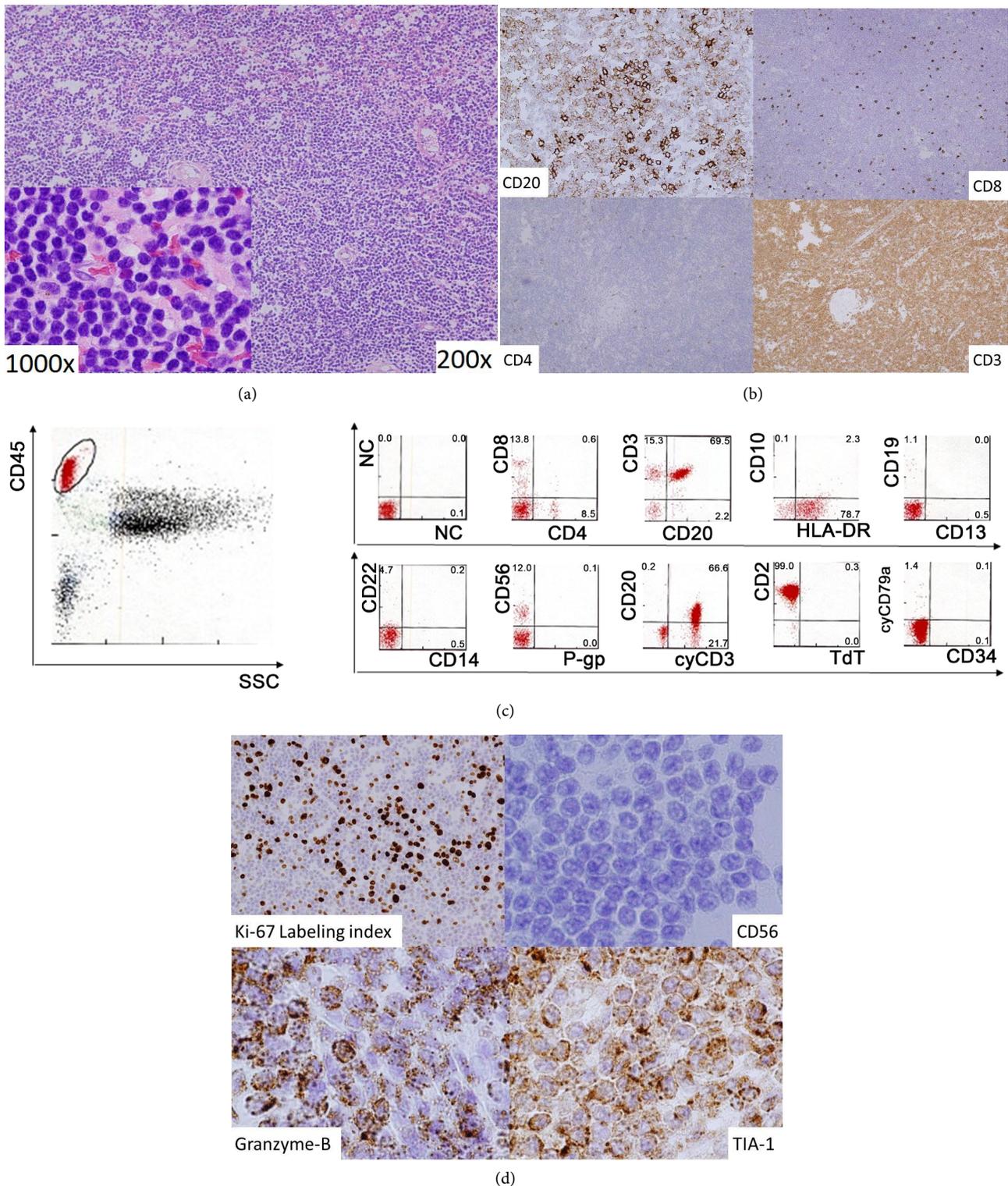
## 1. Introduction

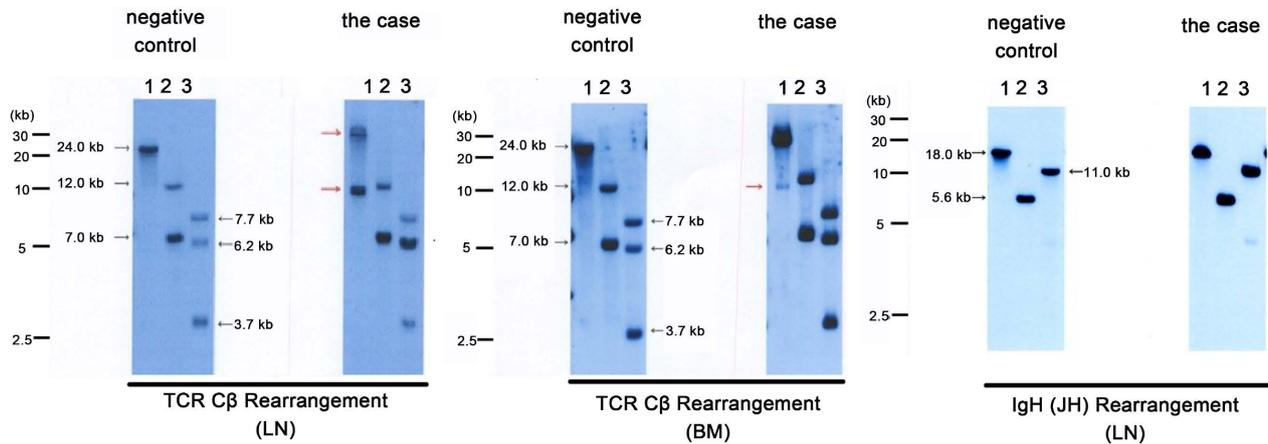
Generally, PTCL is known to be a kind of T cell malignancy and lacks B cell antigen, however, rare cases have been reported in the literature that showed PTCL

patients expressing the B cell antigens. It is considered that the prognosis of CD20 positive PTCL is poor, however, standard therapy has not been established. Recently, it is reported that CCR4 target therapy is effective for CCR4 positive PTCL. Here we present the first case of a successful combination chemotherapy followed by mogamulizumab treatment in peripheral T cell lymphoma with aberrant CD20 expression.

## 2. Patients

The 82-year-old man had appetite loss and general fatigue because of highly dehydration for two weeks and referred to our hospital. Physical examination revealed bilateral neck, axial and inguinal lymph nodes swelling and severe dry skin. The laboratory findings were as follows: white blood cell count of  $2620/\mu\text{L}$  with 22.4% neutrophils, a red blood cell count of  $395 \times 10^4/\mu\text{L}$ , and a platelet count of  $13.8 \times 10^4/\mu\text{L}$ . The level of lactate dehydrogenase (LDH) was elevated at 242 U/L despite normal levels of alanine aminotransferase and aspartate transaminase. Serum level of soluble interleukin 2 receptor was also elevated at 1060 U/L. Serum human immunodeficiency virus was negative. Chest X-ray showed blunting of the right costophrenic angle. Computed tomography (CT) scan of the whole body revealed enlarged lymph nodes in bilateral cervical, subclavicular, axial, mediastinal, abdominal-para-aortic and inguinal areas. Fluorodeoxyglucose-positron emission tomography (FDG/PET) scan revealed abnormal uptake in paratracheal lymph node with a maximum standardized uptake value (SUVmax) of 9.1, abdominal para-aortic lymph node with SUVmax of 8.9 and inguinal lymph node with SUVmax of 4.0. Inguinal lymph node biopsy was performed and it showed the highly monomorphous cytological spectrum and small-sized lymphocytes were infiltrated with diffuse feature (**Figure 1(a)**). Immunohistochemically, the tumor cells were positive for CD20 (L26), CD3, CD45RO (UCHL-1), TIA-1, CCR4, and Granzyme B, while were negative for CD4, CD8, CD5, CD56, CD79a, TdT, bcl-2, bcl-6, CD10, CD23, CD1a, and cyclin D1 (**Figure 1(b)**). Ki-67 labeling index was 19.4% (**Figure 1(d)**). Flow cytometric analysis showed 69.5% of CD3 positive cells were also positive for CD20 (**Figure 1(c)**). Southern blot analysis demonstrated T-cell receptor C beta-chain gene rearrangement but no rearrangement of immunoglobulin heavy chain (**Figure 2**). Karyotype of lymph node showed a complex chromosomal abnormality: 46, XY, t (1; 11) (p34; q23). Bone marrow biopsy showed the involvement of small-sized lymphocytes with co-expression of CD20 and CD3. These findings led to a diagnosis of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) with an aberrant expression of CD20. CHOP (Cyclophosphamide, doxorubicin, vincristine and prednisolone) was started. CT scan showed after 6 courses of CHOP, almost lymph nodes had been reduced but the enlargement of mediastinal lymph node and abdominal lymph nodes was still remained. Bone marrow examination revealed no infiltration of lymphoma cells. Our patient received an additional 2 courses of CHOP, but CT scan did not show the



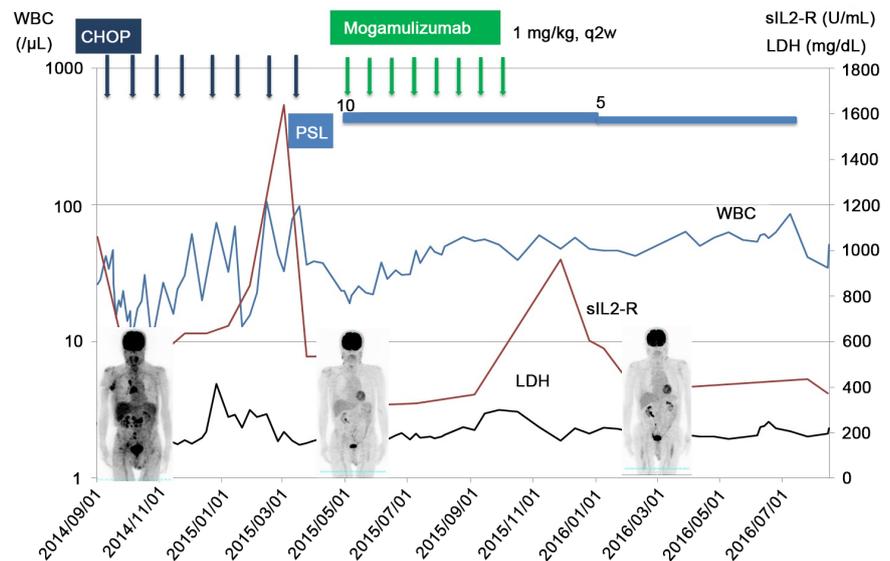


**Figure 2.** Southern blot analysis for T/B cell rearrangement on the biopsy specimen from the lymph node. Total genomic DNA was digested with BamHI: 1st lane; EcoRV: 2nd lane; HindIII: 3rd lane. The rearrangement bands of TCR C $\beta$ 1 were detected in lane 1 of the present case (b) compared with the negative control. The rearrangement bands of Ig(H) JH were not detected in any lane of the present case compared with the negative control.

disappearance of residual regions. Therefore, we decided the use of mogamulizumab for the second therapy. Mogamulizumab was administered at the dose of 1mg/kg every two weeks. After 8 courses of mogamulizumab monotherapy, FDG/PET scan revealed the resolution of FDG uptake (**Figure 3**). Two years has passed since the administration of mogamulizumab therapy and the patient remains in remission.

### 3. Discussion

PTCL is a kind of T cell malignancy which is generally originated from mature helper T cell/killer T cell and lack B cell lineage [1]. PTCLs are considered highly aggressive lymphoma and overall survival and progression free survival are lower (20% ~ 30%) than other lymphomas. With respect to prognostic factors for PTCL, PIT: prognostic index for PTCL-unspecified (PTCL-U) was proposed by Gallamini *et al.* and was frequently used [2]. The factors of this index include age, performance status, serum LDH level and bone marrow involvement. According to the PIT index, our case revealed group 4 that was estimated about 20% overall survival for 2 years. Phenotypically, PTCL-NOS is usually characterized by T-cell phenotype with frequent down regulation of CD5 and CD7 [1]. CD4/8 double negativity is occasionally seen [3]. Cytotoxic granule such as TIA-1 (T cell intracellular antigen-1) and granzyme B are exocytosed during specific interaction with target cells and CD8 positive cytotoxic T cells [4]. These granules are detected in anaplastic large cell lymphoma and extranodal NK/T-cell lymphoma, rarely detected in PTCL-NOS or adult T cell leukemia/lymphoma (ATLL). Asano *et al.* reported that complete remission rate was 30% for the cytotoxic molecule, TIA-1 and granzyme B positive PTCL, while it is 63% for the negative. As a result, cytotoxic molecule expression in PTCL-U is considered to be a significant prognostic factor, independent from other clinical factors or prognostic index scores. These criteria also suggested that our patient



**Figure 3.** Clinical course. 8-cycles CHOP were performed. During chemotherapy, soluble IL2-R value was gradually declined without febrile neutropenia at course 7. After chemotherapy, residual lesions were detected by FDG-PET-CT compared to initial evaluation. Then 8-courses of mogamulizumab were administered once bi-weekly. After mogamulizumab monotherapy, PET-CT revealed in complete remission. Each line shows that Blue line: White blood cell count (WBC); Red line: soluble interleukin 2-receptor (sIL2-R); Black line: lactate dehydrogenase (LDH).

had worse prognosis. Conventional chemotherapy such as CHOP or CHOP like regimen has remained as standard therapy for PTCL since 1970s, but it has not led to an adequate prolongation of prognosis [5] [6]. D'amore *et al.* reported the favorable outcome of the intensive chemotherapy followed by up-front autologous stem cell transplantation (ASCT) in PTCL as a large prospective phase II study [7]. On the other hand, Yam *et al.* indicated that ASCT did not appear to improve progression free survival [8]. Thus, no standard therapy for PTCLs has been established. It is reported that CD20 positive PTCL is a group of diseases with a very poor prognosis of about 7 months in total survival. Toya *et al.* showed that the overall survival rate of CHOP therapy for PTCL was 69.6% in CD20 negative PTCL, whereas it was only 33.3% in CD20 positive PTCL and the remission rate was also low in CD20 positive PTCL [9]. Although several cases using conventional chemotherapy or radiotherapy have been reported, favorable results have not been archived [10] [11] [12]. The significance of CD20 expression in PTCL were remained unclear, although it is speculated CD20 positive lymphoma arises from immature common lymphoid progenitors, which are able to differentiate not only B but also T cells [13]-[18]. During these past 20 years, administration of rituximab (anti-CD20 antibody) is recognized as a standard therapy in CD20 positive B cell malignancy. On the other hand, target therapy against CD20 seemed to be a novel therapy for CD20 positive PTCL compared with conventional chemotherapy. Then we summarized previous reports administrating rituximab for CD20 positive PTCL in **Table 1**. 6 cases were in relapse or dead within 12 months and

**Table 1.** Review of cases treated with MoAb for CD20-positive PTCL. Only 25% of previously reported 8 cases treated with Rituximab archived remission. Our case archived complete remission for 24 months. a) TCR: rearrangement of T cell receptor; b) IgH: rearrangement of B cell receptor (JH); c) CTx: Chemotherapy; d) MoAb: Monoclonal antibody.

Case	Reference	Age	Race	Disease	CD20	CD4	CD8	TCR <sup>a</sup>	IgH <sup>b</sup>	CTx <sup>c</sup>	MoAb <sup>d</sup>	Outcome
1	Rahemtullah <i>et al.</i>	77M	Caucasians	PTCL-U	dim	+	-	+	-	Y	Rituximab	Undergoing treatment (4M)
2	Rahemtullah <i>et al.</i>	36F	Caucasians	PTCL-U	dim	+	-	+	-	Y	Rituximab	CR → Relapse → Dead (16M)
3	Rahemtullah <i>et al.</i>	75M	Caucasians	PTCL-U	+	-	-	+	-	Y	Rituximab	Relapse(10M)
4	Magro <i>et al.</i>	65F	Caucasians	Cutaneous PTCL	+	NR	+	+	+	Y	Rituximab	Relapse(2Y)
5	Buckner <i>et al.</i>	84M	Caucasians	PTCL-U	dim	+	NR	+	NR	Y	Rituximab	Dead(6M)
6	Cumiskey <i>et al.</i>	84M	Caucasians	PTCL-U	+	+	NR	+	-	Y	Rituximab	CR
7	Makita <i>et al.</i>	59M	Oriental	PTCL-NOS	+	-	-	+	-	Y	Rituximab	PR → Relapse → Dead (16M)
8	Hirata <i>et al.</i>	74M	Oriental	PTCL-NOS	+	+	-	+	-	Y	Rituximab	CR → Relapse → Dead (1Y)
9	<b>This case</b>	<b>82M</b>	<b>Oriental</b>	<b>PTCL-NOS</b>	<b>+</b>	<b>-</b>	<b>-</b>	<b>+</b>	<b>-</b>	<b>Y</b>	<b>Mogamulizumab</b>	<b>CR(24M)</b>

the treatment efficacy of rituximab administration seemed to be limited [10] [19] [20] [21]. It is known that expression of CD20 in flow cytometry is weaker in PTCL than in B cell tumor. The expression intensity of CD20 may be associated with the effectiveness of rituximab [2] [10] [19].

Recently, CCR4 protein is reported as a chemokine receptor having two ligands: CCL17 which is also known as TARC (Thymus and activation regulated chemokine) and CCL22 known as macrophage-derived chemokine, and is found >90% of cases with adult T-cell lymphoma/leukemia (ATLL) and in 20% ~ 30% of cases with PTCL [22]. Moreover, mogamulizumab, which is a defucosylated humanized anti-CCR4 antibody, demonstrated potential efficacy and tolerability in patients with relapsed CCR4-positive PTCL and ATLL [23]. Common adverse events of mogamulizumab are neutropenia, thrombocytopenia and acute infusion reaction such as fever and rash. However, these adverse events were tolerable under the appropriate treatment such as corticosteroid. Thus, mogamulizumab would be also considerable for elderly patients and promising target therapy for CCR4-positive PTCL and ATLL.

Herein, we present the first case of a successful combination chemotherapy followed by mogamulizumab treatment. Thus, it is important that the expression of CCR4 chemokine is examined and then optimal treatment procedure for CD20 positive PTCL may be determined. Further investigation would be necessary for establishing strategy for CD20 and CCR4 double positive PTCL.

### Conflict of Interest

The authors state that they have no Conflict of Interest (COI).

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