A Case of Advanced Primary Thyroid Double-Hit B Cell Lymphoma in Which Complete Remission has been Maintained After High-Dose Chemotherapy and Autologous Peripheral Blood Stem Cell Transplantation Performed During the Second Remission, with a Review of the Literature

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Abstract A 50-year-old woman who presented with a mass in the thyroid gland was diagnosed as having diffuse large B-cell lymphoma (DLBCL) by biopsy in August 2011. The tumor had a complex chromosomal karyotype, including 8q24 (C-MYC) and 18q21(BCL-2), and fluorescence in situ hybridization confirmed split signals of C-MYC and BCL-2. BCL-2/IgH and C-MYC/IgH fusion signals were also observed. Three courses of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) therapy were given, followed by thyroid gland irradiation. She was achieved complete remission (CR). In January 2012, a mass appeared in the right breast, which was diagnosed as relapse by biopsy. CR was achieved again after the 4th course of R-CHOP therapy, and one course of rituximab, etoposide, methylprednisolone, cytarabine, cisplatin (R-ESHAP) therapy was given. Thereafter, CR has been maintained after high-dose chemotherapy and autologous peripheral blood stem cell

transplantation. There have been only 3 reported cases of primary thyroid C-MYC and BCL-2 double-hit lymphoma, including the present case; 2 of the cases were cases of DLBCL. R-CHOP therapy, irradiation and autologous peripheral blood stem cell transplantation are expected to be effective for such patients.

Keywords Double hit lymphoma · BCL-2 · C-MYC · Diffuse large B-cell lymphoma · Thyroid

Introduction

Malignant lymphomas of the thyroid gland are rare, accounting for 2–8 % of all malignant tumors of the thyroid gland [1–3], and 2.5–7 % of all extranodal non-Hodgkin lymphomas [4–6]. Diffuse large B-cell lymphoma (DLBCL) is the most common, accounting for 60–85 % of the cases [1]. In many cases, the tumors are diagnosed when they are still in the localized stage and the prognosis is good, however, the prognosis of advanced cases is still unknown. The patient reported here had a DLBCL that was classified as a BCL-2 and C-MYC double-hit lymphoma (DHL). In general, the prognosis of patients with DHL is extremely poor, with a reported median survival time of approximately 6 months and 1-year survival rate of 22 % [7], and no treatment has been established yet.

Double-hit lymphoma DLBCL of the thyroid gland is extremely rare and has been reported only in 3 patients, including the patient reported herein [8, 9] and its precise prognosis is unknown. Local irradiation and total body irradiation (TBI) have been reported to be effective for DHL [10, 11]; in our present case also, relapse did not

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Fig. 1 Imaging findings. **a, b** At the first onset, CT revealed an irregularly-shaped, low-absorption mass measuring 5 cm in diameter (red arrow) in the left lobe of the thyroid gland. **c** At the first onset, Ga scintigraphy showed strong accumulation in the thyroid gland (red

arrow) and slight accumulation in the right breast (yellow arrow); the latter was judged to represent costal cartilage inflammation at that time

Fig. 2 Pathological findings (×600) of the biopsy specimen from the mass in the thyroid gland at the first onset. **a** HE staining showed large tumor cells. **b** CD20 staining was positive. **c** CD5 staining was

negative and there were a small number of reactive T cells. **d** CD10 staining was positive. **e** BCL-2 staining was positive. **f** The Ki-67 index was high

Fig. 3 FDG-PET-CT images are shown. **a** At relapse, FDG accumulation was seen only in the right mammary gland (SUVmax, 7.9–13.0). **b** After autologous transplantation, FDG accumulation in the right mammary gland was no longer seen, indicative of achievement of complete remission

occur in the irradiated area of the thyroid gland, but in the breast outside the irradiation field. Therefore, irradiation is expected to be effective. In addition, the combination of autologous peripheral blood stem cell transplantation and high-dose chemotherapy is also expected to be effective, as complete remission (CR) has been maintained during 14 months by this treatment in our patient.

Case Presentation

A 50-year-old woman developed a swelling in the right front neck in August 2011, and visited a local hospital. She had no significant past medical or family history. CT revealed an irregularly-shaped, low-absorption mass measuring 5 cm in diameter in the left lobe of the thyroid gland (Fig. 1a, b), and gallium scintigraphy showed accumulation of radioactivity in the thyroid gland as well as slight accumulation in the right chest; the latter of which was judged to be uptake by the costal cartilage (Fig. 1c). The reason for this conclusion was that palpation and CT yielded no abnormal findings. Based on the above findings the thyroid gland was concluded to have been the primary

Fig. 4 Clinical course after visit to our hospital. The mass in the right breast disappeared after R-CHOP therapy. After R-ESHAP therapy, autologous peripheral blood stem cells were collected, and MCVAC therapy was given as pretreatment. After autologous peripheral blood stem cell transplantation, complete remission was confirmed by PET-CT. The patient remains in complete remission until date (February

2013). *R-CHOP* indicates rituximab, cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, prednisolone; *R-ESHAP* rituximab, etoposide, methylprednisolone sodium, cytarabine, cisplatin; *MCVAC* ranimustine, cytarabine, etoposide, cyclophosphamide; and *PBSCT* peripheral blood stem cell transplantation

Table 1 Laboratory findings on admission

CBC	
WBC	3,400/ μ L
Neut	64.6 %
Ly	23.6 %
Mono	7.1 %
Eo	1.4 %
Ba	0.6 %
RBC	453×10^4 / μ L
Hb	12.3 g/dL
Ht	40.2 %
Plt	32.9×10^4 / μ L
Biochemistry	
AST	21 IU/L
ALT	10 IU/L
LDH	267 IU/L $\uparrow$ (119–229)
T-Bil	0.7 mg/dL
BUN	12 mg/dL
Cr	0.52 mg/dL
Ca	9.2 mg/dL
P	5.2 mg/dL $\uparrow$ (2.5–4.7)
CRP	≤ 0.3 mg/dL
Immuno-serological findings	
IgG	1,034 mg/dL
IgA	185 mg/dL
IgM	109 mg/dL
Antinuclear antibodies	$< \times 40$
SIL-2R	232 U/mL
CEA	0.8 ng/mL
Calcitonin	23 pg/mL
TSH	1.54 μ IU/mL
F-T4	1.2 ng/dL
F-T3	2.8 pg/mL
Thyroglobulin antibodies	24.0 IU/mL
TPOAb	34.1 IU/mL $\uparrow$ (< 16)
TSH receptor antibodies	< 0.4 %
HTLV-1 antibodies	Negative
HIV antibodies	Negative
Coagulation	No abnormalities
Urinalysis	No abnormalities

site. Examination of biopsy specimens from the thyroid mass by HE staining showed large tumor cells with a starry appearance (Fig. 2a); immunohistochemical staining revealed that the cells were positive for CD20 (Fig. 2b), negative for CD5 with a small number of intervening T cells (Fig. 2c), positive for CD10 (Fig. 2d) and positive for BCL-2 (Fig. 2e), and showed a high Ki-67 index (Fig. 2f); the results of staining for LMP-1 and EBER were negative (data not shown). Chromosome analysis (G-banding)

revealed a karyotype of 48, XX, add (8) (q24.1), +12, del (13) (q12q14), t (14;18) (q32;q21.3), +mar in 4 out of the 20 cells analyzed. From the above, the mass was diagnosed as EB virus-negative, CD5-negative, CD10-positive and BCL-2-positive DLBCL. The lymphoma was classified as stage IE and the patient was judged to be a low-intermediate (L-I) risk case, with only an increase of the serum LDH, according to the age-adjusted international prognostic index (AA-IPI). Bone marrow or cerebrospinal fluid examination was normal. Three courses of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) therapy were given from September 2011, and the thyroid gland region including the lymph nodes was irradiated externally at 40 Gy, followed by additional irradiation to the tumor bed at 18 Gy, she was achieved CR in November 2011. But a mass developed in the right breast in January 2012, and the patient visited the Department of Breast and Endocrine Surgery of our hospital in February 2012. PET-CT showed FDG accumulation (SUVmax 7.9–13.0) only in the right mammary gland (Fig. 3a). The mass was diagnosed as a relapse of the DLBCL by biopsy, and the patient was admitted to our department (Fig. 4). The site of the mass in the right breast was consistent with the site of gallium accumulation on scintigraphy at the previous hospital (Fig. 1c). On admission, no abnormalities were observed, except for a 2.5×2 cm-sized, mobile, elastic soft mass in the right breast.

Laboratory findings are shown in Table 1. HIV antibodies were negative and serum soluble IL-2 receptor levels were within normal range. No abnormalities were found except for a slight increase of the serum LDH. Histopathological examination of biopsy specimens from the mass in the right breast by HE staining revealed large tumor cells (Fig. 5a) that were positive for CD20 (Fig. 5b), negative for CD5 with a small number of intervening T-cells (Fig. 5c), positive for CD10 (Fig. 5d) and positive for BCL-2 (Fig. 5e); the Ki-67 index was high (Fig. 5f). In addition, the staining results for LMP-1 and EBER were negative (data not shown). From the above, the mass was diagnosed as EB virus-negative, CD5-negative, CD10-positive, BCL-2-positive DLBCL. The diagnosis was similar to that of the mass in the thyroid gland, suggestive of disease relapse. Fluorescence in situ hybridization (FISH) on paraffin-embedded sections showed BCL-2 (Fig. 6a) and C-MYC (Fig. 6b) split signals, but not BCL-6 (Fig. 6c) or CCND1 (Fig. 6d) split signals. The FISH showed 90 % BCL-2/IgH (Fig. 6e) and 9 % MYC/IgH (Fig. 6f) fusion signals. Our case was suffered from double-hit B-cell lymphoma because of chromosomal breakpoint affecting the MYC/8q24 locus (Fig. 6b) in combination with BCL-2/IgH fusion (Fig. 6e).

Fig. 5 Pathological findings ($\times 600$) of the biopsy specimen from the mass in the right mammary gland at relapse. **a** HE staining showed large tumor cells. **b** CD20 staining was positive. **c** CD5 staining was negative, and there were a small number of reactive T cells. **d** CD10 staining was positive. **e** BCL-2 staining was positive. **f** The Ki-67

index was high. From the above, the mass was diagnosed as CD5-negative CD10-positive BCL-2 positive Burkitt's lymphoma-like diffuse large B cell lymphoma, the diagnosis being the same as that of the primary thyroid tumor

Bone marrow and cerebrospinal fluid examinations showed no evidence of infiltration. Based on these findings, the diagnosis of relapse of primary thyroid DLBCL only in the right breast was made. The fourth course of R-CHOP therapy was given, and the mass in the right breast disappeared. She was achieved CR again. The first course of rituximab, etoposide, methylprednisolone, cytarabine, cisplatin (R-ESHAP) therapy was administered and autologous peripheral blood stem cells were collected in March. Pretreatment (MCVAC therapy; ranimustine, cytarabine, etoposide, cyclophosphamide) was administered in May 2012 and autologous peripheral blood stem cell transplantation (number of CD34+ cells infused, $12.2 \times 10^6/\text{kg}$) was performed. Engraftment was confirmed 9 days after the transplantation, and the patient was discharged in June. CR was confirmed by PET-CT in July 2012 (Fig. 3b). Now, in August 2013, the patient is under follow-up on an outpatient basis and continues to be in CR. (The CR has been maintained for 14 months.)

Discussion

Malignant lymphomas of the thyroid gland are rare, being estimated to account for 2–8 % of all malignant tumors of the thyroid gland [2, 3], and 2.5–7 % of all extranodal

non-Hodgkin lymphomas [4–6]. It is said that DLBCL is the most common histological type, accounting for 60–85 % of the cases, followed by MALT (15–40 %), and then FL, which is extremely rare [1]. In the majority of the patients (54–100 %), the tumor is localized stage (I or II) and few are in advanced stage at diagnosis [1, 3, 12–16]. This is likely to be because swelling of the thyroid gland, which occurs as a visible neck swelling, and hoarseness facilitate early detection [17, 18]. In our present patient also, the swelling of the thyroid gland led to the detection of the disease. The reported prognostic factors of localized-stage DLBCL include the expression status of Forkhead box-P1 (FOXP1) expression [16], age and PS [19], infiltration status of the lymph nodes and presence/absence of B symptoms [20], age and erythrocyte sedimentation rate [21], tumor size ($</\geq 10$ cm), stage II/vs. other stages, presence/absence of thyroid dysfunction due to tumor, presence/absence of rapid enlargement and presence/absence of infiltration of the mediastinum [14], in addition to the IPI. Chemotherapy alone or chemotherapy with local irradiation yields a good prognosis, with a CR rate of 90 [19] to 94 % [17] and a 5-year survival rate of 81 [21] to 90 % [17]. However, the prognosis and prognostic factors of advanced disease are still unknown, and it is necessary to accumulate cases for analysis.

Fig. 6 The chromosomes (FISH) of the thyroid tumor cells are shown. **a** Presence of BCL-2 split signals was examined in 100 tumor cells. The *red arrows* indicate the telomeric sides and the *green arrows*, the centromeric sides. The split signals was positive in 38.0 % of the cells. **b** Presence of c-MYC split signals was examined in 100 tumor cells, and 36.0 % of the cells were positive. The MYC gene was split, so that the telomeric sides (*red arrows*) and centromeric sides (*green arrows*) were separated. **c** Presence of BCL6 split signals was examined in 100 tumor cells, and none of the cells was positive. **d** Presence of CCND1 split signals was examined in 100 tumor cells, and 2.0 % of the cells were positive. **e** Presence of BCL-2/IgH fusion signals was examined in 100 tumor cells. The *red arrows* indicate BCL-2 and the *green arrows*, IgH. The fusion signals was positive 90.0 % of the cells. **f** Presence of C-MYC/IgH fusion signals was examined in 100 tumor cells. The *red arrows* indicate MYC the *green arrows*, IgH. The fusion signals was positive in 9.0 % of the cells

The patient reported herein had BCL-2 and C-MYC double-hit DLBCL. BCL-2 and C-MYC DHL is included in “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (i-DLBCL/BL)” in the WHO classification [22]. Johnson et al. reported that it was found in 21 % of 167 DLBCL cases [23]. According to a report by Tomita et al., DHL has an extremely poor prognosis, with a median survival time of approximately 6 months and 1-year survival rate of 22 % [7]. In the majority of cases, it is at an advanced stage at diagnosis, with bone marrow and central nervous system infiltration, with some reports suggesting that these patients have elevated serum LDH levels and are resistant to chemotherapy [8], and others suggesting a poor prognosis [9, 24].

It has been reported that R-CHOP therapy yields a better PFS and OS in DLBCL patients positive for C-MYC alone

than in patients who are negative for C-MYC, and that both the PFS and OS were poor only when both the tumor was positive for both BCL-2 and C-MYC [23]. On the other hand, there is also a report that salvage therapy with R-ICE and R-DHAP and autologous transplantation did not improve the PFS or OS in C-MYC-positive DLBCL [25]. Thus, this issue still remains controversial.

As shown in Table 2, to the best of our knowledge, there have been only 3 reported cases of BCL-2 and C-MYC DHL of the thyroid gland, including the present case [8, 9]. All 3 patients were women in their fifties. DLBCL was the common histological type and L-I was the common International Prognostic Index (IPI). There were no particular underlying diseases or comorbidities in the thyroid gland. One patient received chemotherapy with cytarabine and methotrexate, but died of the primary disease 29 months after the diagnosis, suggesting a very poor prognosis. Another patient received R-CycloBEAP therapy and is still alive after 9 months. The present patient achieved CR and is still disease-free and alive, after approximately 1 year and 7 months. However, longer term follow-up is considered necessary for a precise assessment of the prognosis.

There are reports that local irradiation and TBI are effective for DHL [10] and that hematopoietic stem cell transplantation with a TBI regimen may improve the prognosis of DHL [11]. In the present case also, relapse did not occur in the irradiated area of the thyroid gland, but in the breast outside the irradiation field, and irradiation is expected to be effective for the disease in the localized stage. In addition, since the present patient remains in CR after autologous peripheral blood stem cell transplantation, transplantation is also expected to be effective.

Table 2 Reports of c-MYC and BCL2 double-hit lymphomas of the thyroid gland

Case	Age/sex	Histological type	Stage	International prognostic index	Treatment	Effect	Outcome	Reference
1	50/F	DLBCL	IV	LI	R-CHOP RX ↓ R-CHOP R-ESHAP MCVAC AUTO	CR → Relapse ↓ CR	Still alive after 19 Mo	This case
2	54/F	NHL	N.A	N.A	Ara-C MTX	N.A	DOD 29 Mo later	[8]
3	59/F	DLBCL	N.A	LI	R-CycloBEAP	N.A	Still alive after 9 Mo	[9]

NHL non Hodgkin lymphoma; F female; LI low intermediate; R-CHOP rituximab, cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, prednisolone; RX radiation; R-ESHAP rituximab, etoposide, methylprednisolone sodium, cytarabine, cisplatin; MCVAC ranimustine, cytarabine, etoposide, cyclophosphamide; AUTO auto peripheral blood stem cell transplantation; Ara-C cytarabine; MTX methotrexate; R-CycloBEAP rituximab, cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin, prednisone; CR complete remission; Mo month; NA not available; DOD died of primary disease

Conflict of interest The authors declare that they have no conflict of interest.

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