Gray zone lymphoma effectively treated with cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab chemotherapy: A case report

Nobumasa Hojo, Makoto Nagasaki, Yasuha Mihara

BACKGROUND
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (BCLu-DLBCL/cHL), also referred to as gray zone lymphoma (GZL), is known to share features with cHL and DLBCL. However, GZL is often difficult to diagnose. There is no consensus regarding the optimal therapeutic regimen. Most reported cases of GZL have been in Caucasian and Hispanic individuals, and its incidence is lower in African-American and Asian populations, including the Japanese population.

CASE SUMMARY
A 69-year-old female presented at our hospital with a growing mass on the right side of her neck. An elastic, soft mass measuring 9 cm × 6 cm was palpable in the right cervical region. Laboratory analyses showed pancytopenia, increased serum lactate dehydrogenase levels, and markedly increased levels of soluble interleukin-2 receptor. Enhanced computed tomography (CT) and fluorodeoxyglucose positron emission tomography (PET)/CT revealed multiple lesions throughout her body. She was diagnosed with GZL based on the characteristic pathological findings, the immunophenotype [CD20+, PAX5+, OCT2+/BOB1 (focal+), CD30+, CD15−], and the strong positive expression of neoplastic programmed cell death protein ligand 1 (PD-L1) in her lymphoma cells. The lymphoma was stage IV according to the Lugano classification and high-risk according to the International Prognostic Index for aggressive non-Hodgkin
lymphoma. The patient received cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab (R-CHOP) chemotherapy because the tumor cells were CD20+. She has remained in complete remission for 3 years.

CONCLUSION
GZL was diagnosed based on histopathology and immunophenotyping with ancillary PD-L1 positivity. R-CHOP chemotherapy was an effective treatment.

Key Words: Classical Hodgkin lymphoma; Diffuse large B-cell lymphoma; Gray zone lymphoma; Programmed cell death protein ligand 1; R-CHOP; Case report

INTRODUCTION
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (BCLU-DLBCL/cHL), also referred to as GZL, was first recognized in the World Health Organization (WHO) classification of lymphoid neoplasms in 2008[1,2]. The recognition of the disease as a distinct pathological and clinical entity has increased, although its diagnosis remains complex[3]. The diagnostic category was formally included in the WHO classification, which defined the histological and immunophenotypic criteria. In general, GZL tends to have a more aggressive clinical course and is associated with poorer outcomes than either cHL or primary mediastinal large B-cell lymphoma (PMBL). The application of rituximab chemotherapy appears to be beneficial for improving GZL patient outcomes[4,5].

Here, we report the case of a patient with GZL, which is rare in Asian populations[6-9], who was successfully treated with cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab (R-CHOP) chemotherapy.

CASE PRESENTATION
Chief complaints
A 69-year-old female presented at the surgical outpatient department of our hospital with a growing mass on the right side of her neck.

History of present illness
The patient was admitted to the hospital for further examination and treatment. The patient had no B symptoms, such as fever, night sweats, or weight loss.

History of past illness
The patient had a past medical history of subarachnoid hemorrhage resulting in the impairment of
higher cognitive functions at 61 years of age.

**Personal and family history**
There was no personal history of tobacco or alcohol consumption or any other family medical history.

**Physical examination**
Anemia was suspected based on the color of the palpebral conjunctiva. An elastic, soft mass measuring 9 cm × 6 cm was palpable in the right cervical region. Other superficial lymph nodes and the liver and spleen were not palpable. An increased bleeding tendency was not observed.

**Laboratory examinations**
Laboratory analyses showed pancytopenia (white blood cells, 1500/μL; red blood cells, 371 × 10^4/μL; hemoglobin, 10.7 g/dL; mean corpuscular volume, 87.3 fl; and platelets, 5.0 × 10^4/μL), increased serum lactate dehydrogenase levels (451 U/L; reference value 124–222 U/L), and markedly increased levels of soluble interleukin-2 receptor (6220 U/mL; reference value 145–519 U/mL).

**Imaging examinations**
Enhanced CT (Figure 1) and fluorodeoxyglucose PET /CT (Figure 2) revealed multiple lesions throughout the patient’s body, including the right neck.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

**Makoto Nagasaki, MD, PhD, Chief of Clinical Laboratory, Department of Pathology, National Hospital Organization Hamada Medical Center**

A bone marrow biopsy was obtained from the iliac crest. Fine-needle biopsies were obtained from the right cervical mass (supraclavicular lymph node). Pathological examinations were performed using immunohistochemical (IHC) studies and outsourced flow cytometry (FCM). IHC staining and Epstein–Barr virus (EBV)-encoded small RNA in situ hybridization (EBER-ISH) were performed using standard methods with an automated immunostainer (Ventana Benchmark Ultra, Tucson, AZ, United States). Antibodies against the following markers were used: CD20 (L26, Ventana), CD3 (GV6, Ventana), CD30 (BerH2, Ventana), CD15 (MMA, Ventana), PAX5 (DAKO-Pax5, Dako, Agilent Technologies, Inc., Santa Clara, CA, USA), CD45 (PD7/26,2B11, Nichirei Biosciences, Tokyo, Japan), OCT2 (Oct-207, Leica Biosystems, Wetzlar, Germany), BOB1 (TG14, Leica), CD79a (JCB117, Nichirei), MUM1 (MUM1p, Dako), and ALK (ALK1, Dako). Appropriate positive controls were used for IHC staining. The immunostaining of programmed cell death protein ligand 1 (PD-L1) (clone SP142, Ventana OptiView, Roche) was outsourced.

Histopathological analysis of the iliac crest biopsy revealed hemophagocytosis without bone marrow infiltration. Supraclavicular lymph nodes were infiltrated by large, atypical, and pleomorphic cells (Figure 3). These cells showed sheet-like proliferation and were scattered among the inflammatory cells [small lymphocytes (CD3+ T-cells) and histiocytes]. These large, atypical cells, including Hodgkin and Reed-Sternberg cells or lacunar-like cells, were immunohistochemically positive for CD20, CD79a, CD30, CD45, OCT2, BOB1 (focally), PAX5, and MUM1 but negative for CD15 and ALK. EBV was not detected by EBER-ISH (some of the results are shown in Figure 4). CD20 and PAX5 expression levels were strong, and CD30 expression levels were variable (weak to strong). Nearly 50% of the lymphoma cells were MUM1-positive. As shown in Figure 5, PD-L1 expression (clone SP142) was found in > 75% of the tumor cells (neoplastic PD-L1). Clonal expression of surface and cytoplasmic light chains (sIg and cyIg, respectively) was not detected by FCM (sIg, kappa 12.5%, lambda 12.9%; cyIg, kappa 13.2%, lambda 11.9%). On the other hand, immunoglobulin heavy chain gene rearrangement was detected (data not shown).

**FINAL DIAGNOSIS**
The patient was diagnosed with stage IV GZL according to the Lugano classification, the International Prognostic Index 4 (high-risk lymphoma) for aggressive non-Hodgkin lymphoma, and the International Prognostic Score 4 for Hodgkin lymphoma.

**TREATMENT**
The patient was initially treated with a reduced dose (60% of the scheduled dose) of CHOP chemotherapy to prevent tumor lysis syndrome, and it was initially unclear whether the tumor cells
Figure 1 Enhanced computed tomography showing a right cervical mass (A) and multiple low-density lesions in the liver and spleen (B).

Figure 2 Fluorodeoxyglucose positron emission tomography/computed tomography revealed multiple lesions throughout the patient's body. A: Abnormal lymph node enlargement in the right neck, right clavicular region, and anterior mediastinum; B: Abnormal lymph node enlargement around the hepatic portal region, pancreatic head, and paraaortic region. Multiple nodular lesions in the liver and spleen; C: Multiple bone lesions in the left skull, thoracic and lumbar vertebrae, bilateral ribs, right clavicle, bilateral scapulae, lower end of the sternum, sacrum, bilateral ilia, left pubis, and bilateral femora.

were CD20-positive. Subsequently, five cycles of R-CHOP chemotherapy were administered at standard doses.

OUTCOME AND FOLLOW-UP

The patient achieved complete remission and has remained in complete remission for 3 years since the last chemotherapy session.

DISCUSSION

GZL is known to share features with cHL and DLBCL; however, it is often difficult to diagnose[10]. The differential diagnosis of the present case included DLBCL [common DLBCL with CD30 expression and anaplastic variant DLBCL (avDLBCL)], T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), PMBL, and cHL.
Regarding the clinical manifestations, the patient had an elastic, soft mass in the right cervical region. Enhanced CT and fluorodeoxyglucose PET/CT revealed abnormal lymph node enlargement in the right neck, right clavicular region, and anterior mediastinum. Multiple lesions in the lymph nodes throughout the body, including the liver, spleen, and multiple bones, were also found. DLBCL involves nodal or extranodal lesions in any location, including the liver, spleen, and bone marrow[11]. THRLBCL mainly involves the lymph nodes, but bone marrow, liver, and spleen involvement is frequently found [12]. CHL also involves the liver, spleen, and bone marrow [13]. PMBL usually lacks bone marrow lesions [14]. Therefore, PMBL was excluded from the differential diagnosis. The most common presentation of GZL is a large anterior mediastinal mass, with or without the involvement of supraclavicular lymph nodes. The tumor may spread directly to the lung, and spread to the liver, spleen, and bone marrow can also be observed [5].

Pathologically, the distribution of large, atypical cells, including centroblastic cells and lacunar-like cells, varied from sheet-like to scattered (with predominantly sheet-like proliferation). Except for the moderate expression of MUM1, the immunophenotype of the tumor cells [positive for CD30 (variable expression) and CD20 (diffuse, strong expression), and negative for CD15] was compatible with the diagnosis of consensus-confirmed GZL but not with cHL [10]. The Lymphoma Study Association has proposed a classification system for GZL with four subcategories based on the morphological and phenotypical spectrum [15]. According to this classification system, the patient’s tumor was categorized into the transitional group of cHL-like GZL and large B-cell lymphoma-like GZL. The FCM analysis of the same pathologic specimen did not detect clonal sIg and cyIg expression, although CD20+ B-cells represented a minor population in the gated fraction. Kappa or lambda Ig expression in large tumor cells cannot be estimated by IHC due to background staining. Strong nuclear expression of OCT2 was present in > 50% of the cells; on the other hand, most of the cells were weak to faintly positive for BOB1 (Figure 4E and F), with strong expression observed in only 7.5% (Figure 4E and F, inserted). As previously reported, positive evaluation of OCT2 and BOB1 was based on at least 30% of large tumor cells [16-18], and in one study, strong staining intensity was also a condition [17]. Thus, we interpreted the focal positive BOB1 expression as abnormal in the present case. The focal expression of BOB1 and lack of detectable clonal expression of slg and cyIg in the FCM analysis were possibly related to abnormal regulation of immunoglobulin expression, similar to cHL but not ordinal DLBCL. The findings were not compatible with the diagnosis of THRLBCL due to the presence of a sheet-like growth area and the positive expression of CD30. Because the primary site of the tumor was not considered to be the mediastinum, PMBL was not considered. Because large tumor cells did not display a sinusaloid growth pattern, the diagnosis of avDLBCL was incompatible.

Recently, neoplastic PD-L1 has been found to be a useful marker of GZL [17-20], enabling researchers to differentiate GZL from nodal avDLBCL [18]. We detected abundant PD-L1-positive (clone SP142) large lymphoma cells (75%) without an EBV association (EBER-ISH negative). Tanaka et al [20] reported PD-L1 IHC expression (30% cut off) in 77% of GZL cases (10/13). Sakakibara et al [21] reviewed PD-L1 expression (clone SP142) and found it to be useful for the diagnosis of GZL (Nodal DLBCL, EBV-negative 0/275 (0%); Nodal GZL, EBV-negative 3/3 (100%); Nodal avDLBCL, EBV-negative 0/11 (0%)). Considering these findings, we diagnosed this patient with nodal GZL.

GZL can be divided into mediastinal GZL (MGZL) and nonmediastinal GZL (NMGZL) depending on the presence or absence of mediastinal lesions, and there are several clinical differences between these two subtypes. It has been reported that patients with MGZL more commonly have bulky disease than patients with NMGZL. Patients with NMGZL are typically significantly older, have a higher likelihood of bone marrow involvement, more often have extranodal disease sites, and present much more
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Figure 4 Immunohistochemical staining of lymphoma cells. A: The cells were strongly and uniformly positive for CD20 (× 400); B: Strongly positive for PAX5 (× 400); C: Variably positive for CD30 [weakly positive (C1) or moderately to strongly positive (C2)] (× 400); D: Moderately to strongly positive for MUM1 (× 400); E: OCT2 was strongly positive for large atypical cells (80%); F: BOB1 strongly positive large atypical cells (inserted) were found in small numbers (< 10%).

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commonly with advanced-stage disease[5]. The patient in this case was elderly, had bone marrow involvement, and was diagnosed with advanced-stage disease; therefore, the patient’s clinical manifestations were similar to those of NMGZL.

Most reported cases of GZL have been in Caucasian and Hispanic individuals, and its incidence is lower in African-American and Asian populations, including the Japanese population[6,7]. Therefore, reporting cases of rare diseases is important, especially when these diseases occur in regions where they are usually not prevalent. This practice aids in investigating the factors underlying the epidemiology of the disease.

According to the National Comprehensive Cancer Network guidelines, aggressive large B-cell lymphoma treatment regimens are preferred for GZL, though there is no consensus regarding the optimal regimen. If the tumor cells are CD20+, the addition of rituximab to the chemotherapy regimen should be considered[22]. R-CHOP or dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) regimens are recommended[23-25].

Recently, brentuximab vedotin, an anti-CD30 antibody, has been used to treat Hodgkin lymphoma and CD30-positive lymphoma[9,26,27]. Pembrolizumab, an anti-PD-L1 monoclonal antibody, is also used for patients with refractory GZL[28]. If the response to the abovementioned chemotherapy regimens is poor, tandem high-dose chemotherapy supported by autologous stem cell transplantsations and consolidative radiotherapy can be considered[29]. In this case, the tumor cells were CD20+, and the patient was initially treated with one cycle of CHOP followed by five cycles of R-CHOP chemotherapy.
She has remained in complete remission for 3 years. These regimens can also be considered for treating recurrent disease.

**CONCLUSION**

GZL was diagnosed based on histopathology and immunophenotyping with ancillary PD-L1 positivity. R-CHOP chemotherapy was an effective treatment.

**FOOTNOTES**

**Author contributions:** Hojo N and Mihara Y were the patient’s doctors in charge, reviewed the literature and contributed to manuscript drafting; Nagasaki M was the patient’s pathologist, made the pathological diagnosis, reviewed the literature and contributed to manuscript drafting; and All authors issued final approval for this version to be submitted.

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**Country/Territory of origin:** Japan

**ORCID number:** Nobumasa Hojo 0000-0003-0880-0101; Makoto Nagasaki 0000-0002-1344-2364; Yasuha Mihara 0000-0001-8379-3748.

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