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Original Article

Clinical Features and Outcomes of 9 Patients with Immunodeficiency-Associated Lymphoproliferative Disorders Treated at a Single Institution

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Immunodeficiency-associated lymphoproliferative disorders (LPD) represent a rare life-threatening clinical entity characterized by heterogeneous histological findings that range from polymorphic to monomorphic proliferated abnormal lymphocytes. Currently, there is no standard treatment for LPD. To elucidate the clinical features and treatment outcomes of immunodeficiency-associated LPD patients with rheumatoid arthritis (RA), we retrospectively evaluated 9 cases observed over a 5-year period. The diagnoses of these patients included 5 diffuse large B-cell lymphomas, 3 LPD, and 1 mucosa-associated lymphoid tissue lymphoma. At initial diagnosis, 6 patients had advanced-stage RA, and half of these underwent total knee arthroplasty. All patients with RA received methotrexate (MTX) and low-dose prednisolone. Biologics were administered to 4 of 9 patients. After the development of immunodeficiency-associated LPD, MTX discontinuation resulted in 5 complete remissions (CR), 1 partial remission, and 3 cases of stable disease. Relapse was observed in 3 of 5 CR patients in the MTX-withdrawal remission group. Subsequently, conventional chemotherapy, rituximab, and radiation were administered to 4, 3, and 1 patient, respectively. These treatments induced a second CR. In the chemotherapy group, 1 patient developed acute myocardial infarction and another experienced ileus and pulmonary abscess. In the rituximab group, no severe complications were observed. Consequently, all patients remained disease-free during the median 23-month follow-up period. Our results indicate that, depending on the RA disease stage, performance status, and extent of treatment response, less intensive treatments than those commonly indicated for non-Hodgkin lymphoma, involving MTX discontinuation and subsequent therapy containing rituximab, might be an efficient therapeutic strategy for immunodeficiency-associated LPD. 〔*J Clin Exp Hematop 54(3) : 187-196, 2014*〕

Keywords: immunodeficiency-associated lymphoproliferative disorder, rheumatoid arthritis, less intensive treatments, discontinuation of methotrexate, rituximab-combined treatment

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive, chronic autoimmune inflammatory disease that is currently treated with various immunosuppressive agents, such as prednisolone (PSL), methotrexate (MTX), rituximab, anti-tumor necrosis factor-α inhibitors, and anti-interleukin-6 receptor inhibitors.[1-4] Of these, MTX is considered the mainstream treatment of RA.[5,6]

The incidence of malignant lymphoma (ML) has been reported to be higher in patients with RA than in the general population.[7-9] Moreover, immunosuppressive agents such as MTX have been reported to increase the risk of ML development.[7-9] Immunodeficiency-associated lymphoproliferative disorder (LPD) is a rare and lethal clinical entity characterized by heterogeneous histological findings that range from polymorphic to monomorphic proliferated abnormal lymphocytes according to the World Health Organization (WHO) classification; the condition often develops following MTX administration for autoimmune diseases such as RA.[10-15] Because published reports regarding immunodeficiency-asso-

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ciated LPD are limited, its clinical features, standard treatment, and prognosis remain unclear. One currently established treatment for LPD is rituximab, which is a chimeric human/mouse anti-CD20 monoclonal antibody that effectively treats patients with $CD20^+$ B-cell lymphoma and RA.[16-21] In this study, we report the clinical characteristics and treatment outcomes for 9 patients with immunodeficiency-associated LPD observed at our institution over a 5-year period.

PATIENTS AND METHODS

Immunodeficiency-associated LPD was diagnosed in 9 of 245 patients (3.7%) with ML who were admitted to Miyazaki Prefectural Miyazaki Hospital between January 1, 2006, and December 20, 2010. These patients included 2 men and 7 women aged between 45 and 87 years (median age: 62 years). We retrospectively studied the incidence, etiology, clinical manifestations, diagnosis, treatment, and prognosis of immunodeficiency-associated LPD in these patients. The diagnosis of immunodeficiency-associated LPD was based on a combination of clinical characteristics, radiological findings, and histological features of the tumors. Case 5 has been reported on in detail as a case report.[22]

Pathological studies were performed via H&E staining and immunohistochemical analysis of formalin-fixed, paraffin-embedded tissue sections.

According to the WHO classification and a previous report,[15] histological findings were categorized into four types: (i) diffuse large B-cell lymphoma (DLBCL), (ii) mucosa-associated lymphoid tissue (MALT) lymphoma, (iii) polymorphic B-cell LPD, and (iv) Hodgkin lymphoma-like LPD. The histological features of each type were as follows: (i) DLBCL: Atypical large CD20-positive B cells were observed. Lymphoma cells were positive for Epstein-Barr virus-encoded small RNAs (EBER) in EBER-positive cases. (ii) MALT lymphoma: Atypical lymphoid cells had small to medium-sized irregular hyperchromatic nuclei with lymphoepithelial lesions and atypical cells were positive for CD20. (iii) Polymorphic B-cell LPD: Atypical Hodgkin-like cells (smaller than Hodgkin lymphoma [HL] cells), but not Reed-Stemberg cells, were observed. These atypical cells were positive for CD30, occasionally positive for CD20, but negative for CD15. (iv) HL-like LPD: Atypical Hodgkin-like cells (smaller than HL cells), but not Reed-Stemberg cells, were observed. These atypical cells were positive for CD30 and CD15, and occasionally positive for CD20.

Regarding the treatment strategy for immunodeficiency-associated LPD patients, immediate MTX withdrawal was indicated when a clinical diagnosis of the condition was made. After MTX withdrawal, each patient was followed up with periodic physical examinations, including peripheral blood tests, and by radiological methods (chest radiography or abdominal ultrasound). When exacerbation of immunodeficiency-associated LPD was observed during the follow-up period after MTX withdrawal, administration of systemic chemotherapy was considered according to each patient's histological findings.

Approximately 4 weeks after MTX withdrawal without progression of immunodeficiency-associated LPD, final evaluation of treatment response was conducted using treatment response criteria. In consideration of each patient's performance status (PS), RA stage, organ dysfunction, treatment response, residual tumor, histological findings, and personal preferences, subsequent treatment was chosen from the following: rituximab, R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), ABVD (doxorubicin [adriamycin], bleomycin, vinblastine, and dacarbazine) chemotherapy, or radiation therapy. Rituximab alone was indicated for polymorphic B-cell LPD; rituximab or R-CHOP, for DLBCL; and ABVD, for Hodgkin lymphoma-like LPD.

Specifics of the treatment regimens were as follows: In the rituximab alone group, 8 courses of rituximab at a dose of 375 mg/m^2 were administered every 6 months as 4 weekly infusions (days 1, 8, 15, and 22) for 1 year; the rituximab plus CHOP therapy was administered under a schedule consisting of rituximab (375 mg/m^2) plus doxorubicin (50 mg/m^2), vincristine (1.4 mg/m^2), and cyclophosphamide (750 mg/m^2) on day 3, with prednisolone (60 mg/m^2) administered for 5 days every 4 weeks for 6-8 courses; ABVD therapy was administered under a schedule consisting of doxorubicin at 25 mg/m^2 intravenously (IV), bleomycin at 10 IU/m^2 IV, vinblastine at 6 mg/m^2 IV, and dacarbazine at 250 mg/m^2 IV on days 1 and 15, every 4 weeks for 8 cycles.

The International Working Group 1999 response criteria recommended for non-Hodgkin lymphoma (NHL) were utilized to evaluate the treatment response of immunodeficiency-associated LPD.[23] Complete response (CR) was defined as the disappearance of all clinical, microscopic, and radiographic evidence of disease. Partial response (PR) was defined as a 50% reduction in the sum of the products of the greatest diameters of measurable disease without the appearance of new lesions.[23] Stable disease (SD) was defined as failure to attain CR/PR or progressive disease.[23] Progressive disease or relapsed disease in other lesions was defined as a 50% increase from the nadir in the sum of the products of measurable disease or the appearance of new lesions.[23] The definitions of CR, PR, and SD required each criterion to be observed for a period of at least 4 weeks.[23]

We did not perform a statistical analysis owing to the small number of cases involved. This retrospective study was conducted in compliance with good clinical practice and the ethical principles of the Declaration of Helsinki. Prior approval was obtained from the ethics review board at our institution.

RESULTS

The clinical characteristics of RA at immunodeficiency-associated LPD diagnosis

Patients' clinical observations, physiological findings, radiological findings, and treatment were studied. The baseline characteristics of all patients are summarized in Tables 1 & 2. The patients included 2 men and 7 women aged between 45 and 87 years (median age: 62 years). The median history of RA was 5 years (range: 1-30 years). At initial diagnosis, 6 patients were diagnosed with advanced-stage RA, 3 of whom underwent total knee arthroplasty. However, 3 of 9 patients had early-stage RA. Thus, patients with immunodeficiency-associated LPD had a tendency to possess poor prognostic factors of RA, such as the destruction of joints, positive findings of anti-cyclic citrullinated peptide antibody (anti-CCP antibody), high levels of rheumatoid factor, and high activity of RA. Surprisingly, immunodeficiency-associated LPD developed at both early and advanced stages of RA. Initial treatment for RA was patient-specific and included MTX, low-dose PSL, cyclosporine, mizoribine, and biologics in 9, 9, 1, 2, and 4 of the 9 patients, respectively. The median MTX dose was 8 ± 4 mg (range: 4-18 mg) per day, and the median duration of MTX treatment was 48 ± 29 months (range: 3-84 months). Four patients were treated with biologics consisting of infliximab, etanercept, or tocilizumab in 2, 1, and 1 patient, respectively. The complications observed at diagnosis included aortic regurgitation, paraplegia, non-tuberculous mycobacteria, and diabetes mellitus. One patient (case 4) exhibited paraplegia due to the depression of spine lesions.

The clinical characteristics and treatment outcomes of immunodeficiency-associated LPD

Similarly, patients' clinical observations, physiological findings, pathological findings, and treatment outcomes were studied for immunodeficiency-associated LPD. The baseline characteristics of all patients are summarized in Tables 1 & 2. Initial symptoms at the development of immunodeficiency-associated LPD are presented in Fig. 1. Half of the patients experienced general fatigue, arthralgia, lymphadenopathy, and fever (Fig. 1). Most of these symptoms were not unique to immunodeficiency-associated LPD. In 6 of 9 patients, laboratory findings of serum lactate dehydrogenase values were slightly elevated (Tables 2 & 3). Moreover, in 8 of 9 patients, laboratory values of serum soluble interlen-2 receptor were also slightly elevated (Tables 2 & 3).

The histological findings of immunodeficiency-associated LPD are summarized for each case in Fig. 2. There were 5 cases of DLBCL, 3 LPD cases, and 1 MALT lymphoma case. Of the 3 LPD cases, there was 1 HL-like LPD case, 1 case of LPD with histological findings, and 1 with clinical diagnosis. Extranodal ML was observed in the liver, spleen, stomach, oral area, salivary gland, spine, lungs, and skin in at least 1 of the 9 patients enrolled. Thus, more than half of the immunodeficiency-associated LPD patients (5/9) had DLBCL and extranodal lesions were observed in most. However, Epstein-Barr virus (EBV) positivity was detected in only 1 case of immunodeficiency-associated LPD. Most patients had advanced-stage disease (8/9, 88.8%) and were classified as being at high risk according to the international prognosis scoring system (7/9, 77.7%) at the time of immunodeficiency-associated LPD development.

Table 1. Patient characteristics of rheumatoid arthritis at diagnosis

Case	1	2	3	4	5	6	7	8	9
Age	56	59	87	74	60	65	64	76	62
Sex	Female	Female	Female	Female	Male	Female	Male	Male	Female
History of RA (year)	5	2	1	10	3	30	15	4	13
Steinbrocker Stage	IV	I	I	IV	IV	IV	III	I	IV
Anti-CCP antibody	9.3	≧ 100	1.2	283	45	n.e.	n.e.	n.e.	7.6
RF	< 5	284	< 5	10	5,850	563	n.e.	< 5	17
CRP	0.6	7.7	2.4	3.2	9.1	1.7	0.5	15.8	1.3
Treatment for RA (at diagnosis)	MTX: 8 mg PSL: 2 mg	MTX: 8 mg PSL: 4 mg	MTX: 4 mg PSL: 2 mg	MTX: 8 mg PSL: 2 mg	MTX: 12 mg PSL: 6 mg	CSP PSL: 4 mg MTX: 4 mg	MTX: 18 mg PSL: 5 mg	MTX: 12 mg MZR: 150 mg PSL: 4 mg	MTX: 8 mg MZR: 150 mg PSL: 4 mg
Biologics	TCZ	-	-	IFX	-	ETN	IFX	ETN	-
Duration of MTX administration (month)	30	3	5	49	36	120	60	48	84
Complication	-	-	AR	paralagia	NTM	DM	-	-	-

RA, rheumatoid arthritis; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; n.e., not examined; CRP, C-reactive protein; MTX, methotrexate; PSL, prednisolone; CSP, cyclosporin; MZR, mizoribine; TCZ, tocilizumab; ETN, etanercept; IFX, infliximab; AR, aortic regurgitation; NTM, non-tuberculous mycobacteria; DM, diabetes mellitus

Table 2. Summarization of patient characteristics of rheumatoid arthritis and immunodeficiency-associated lymphoproliferative disorders (LPD) at diagnosis and treatment outcome

Case	No. (%) or Median ± SD [Range]
Age (yr)	64 ± 10 (45-87)
Male/Female	2/7
History of RA (yr)	5 ± 9 (1-30)
RF	5/9
CCP	5/9
CRP (mg/dL)	2.4 ± 5.2 (0.48-15.87)
RA (Steinbrocker Stage by X-ray)	I: 3, III: 1, IV: 5
DMARDs	MTX (9), CSP (1), MZR (2)
Dose of PSL (mg)	4 (2-6)
Biologics	IFX (2), ETN (2), TCZ (1)
Diagnosis	DLBCL (5), LPD (3) (Hodgkin-like LPD, LPD, clinical diagnosis), MALTl (1)
LDH	310 ± 142 (197-628)
sIL-2R	1600 ± 922 (537-3450)
Clinical stage	IV (7), III (1), I (1)
Extra-nodal lesion	Liver (1), lung (1), skin (1), spine (1), stomach (2), salivary gland (1)
IPI	Low (1), HI (4), High (3)
The response following discontinuation of MTX	CR (5), PR (1), SD (3)
Subsequent treatment	Rituximab (2), Radiation (1), R-CHOP (2), No medication (4)
The outcome following treatment	1st CR (5), PR (1), Relapse (3)
The treament for relapse	ABVd therapy (1), Rituximab (1), R-CHOP therapy (1)
Complication	Lymphorrhea, APS, AMI, Ileus, Pulmonary abscess
RA control	Low-dose PSL (8), tacrolimus (3), salazopyrine (4), bucillamine (3)
Survival (months)	23 ± 19 (10-71)

No., number; RA, rheumatoid arthritis; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DMARDs, disease modifying antirheumatic drugs; MTX, methotrexate; PSL, prednisolone; CSP, cyclosporin; TCZ, tocilizumab; ETN, etanercept; IFX, infliximab; MZR, mizoribine; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma; LDH, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor; IPI, International prognosis score; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, and prednisolone; MTX, methotrexate; HI, high-intermediate CR, complete remission; PR, partial response; SD, stable disease; ABVd, doxorubicin, bleomycin, vinblastine, and dacarbazine; APS, antiphospholipid syndrome; AMI, acute myocardial infarction

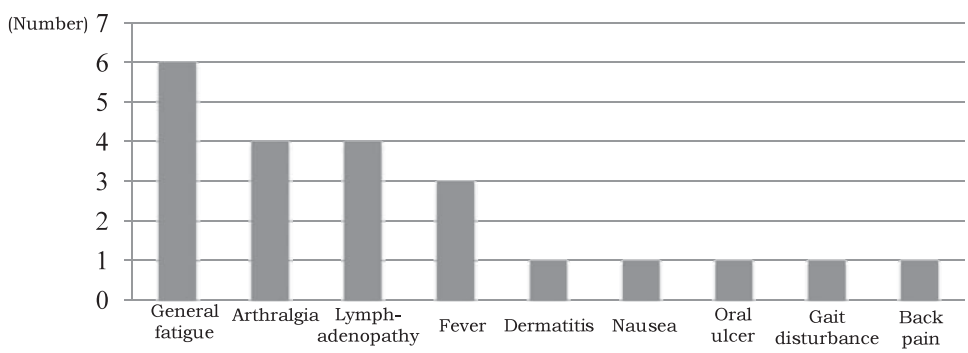

Fig. 1. Initial symptoms at the development of immunodeficiency-associated lymphoproliferative disorders. Half of the patients experienced general fatigue, arthralgia, lymphadenopathy, and fever. These symptoms were not unique to immunodeficiency-associated lymphoproliferative disorders.

Table 3. Patient characteristics of immunodeficiency-associated lymphoproliferative disorders (LPD) at diagnosis and treatment outcome

Case	1	2	3	4	5	6	7	8	9
Diagnosis	Hodgkin-like LPD (EBV−)	LPD	Clinical diagnosis	DLBCL (EBV+)	DLBCL (EBV−)	MALT	DLBCL (EBV−)	DLBCL (EBV−)	DLBCL (EBV−)
LDH	310	197	338	270	450	224	169	330	628
sIL-2R	960	755	3,450	1,600	2,120	1,270	537	2,420	1,930
Clinical stage	IV	I	IV	IV	IV	IV	III	IV	IV
Ectra-nodal lesion	Liver	−	Lung, Skin	Spine	Stomach	Salivary gland	Oral lesions	Sromach	−
IPI	n.d.	Low	High intermediate	High	High	High intermediate	High intermediate	High	High intermediate
The response following discontinuation of MTX	CR	CR	CR	SD	CR	SD	CR	SD	PR
Subsequent treatment	No	No	No	Radiation 30 Gy	Rituximab (8)	Rituximab (8)	No	R-CHOP (2) + Rituximab (4)	R-CHOP (6)
The outcome following treatment	Relapse	Relapse	CR	CR	CR	CR	Relapse	CR	CR
The treament for relapse	ABVd therapy (8) → 2nd CR	Rituximab (8) → 2nd CR	No	−	−	−	R-CHOP (6) → 2nd CR	−	−
Complication	Lymphorrhea	−	−	−	−	−	APS AMI	Ileus, Pulmonary abscess	−
RA control	BUC + PSL 5 mg	TAC 2 mg + SASP + PSL 4 mg	PSL 2 mg	SASP + PSL 5 mg	BUC + TAC 2 mg + PSL 5 mg	TAC 3 mg + PSL 4 mg	SASP + PSL 2 mg	SASP + PSL 5 mg	−
Survival (months)	21	23	12	13	35	71	31	10	23

DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr Virus; MALT, mucosa- associated lymphoid tissue lymphoma; LDH, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor; IPI, International prognosis score; n.d., not done; ABVd, doxorubicin, bleomycin, vinblastine, and dacarbazine; R-CHOP, rituximab, doxorubicin, vincristine, cyclophosphamide, and prednisolone; MTX, methotrexate; CR, complete remission; PR, partial response; SD, stable disease; APS, antiphospholipid syndrome; AMI, acute myocardial infarction; RA, rheumatoid arthritis; BUC, bucillamine; TAC, tacrolimus; SASP, salazopyrine; PSL, prednisolone

The treatment outcomes for all 9 patients with immunodeficiency-associated LPD are shown in Fig. 3. Following the development of immunodeficiency-associated LPD, MTX treatment was immediately discontinued in all patients. Approximately 4 weeks later, discontinuation of MTX led to CR, PR, and SD in 5, 1, and 3 patients, respectively. Thus, the response rate was 67% (6 of 9 patients). Relapse was observed in 3 of 5 CR patients in the MTX withdrawal remission group. Cases 1, 2, and 7 relapsed at 1, 10, and 12 months after CR, respectively. Since discontinuation of MTX was not sufficient for maintaining CR, subsequent treatment was provided on the basis of each patient's age, PS, RA stage, degree of treatment response, histological findings, residual tumor, and personal preferences. Conventional chemotherapy, rituximab alone, and radiation were administered to 4, 3, and 1 patient, respectively. For chemotherapy, polymorphic B-cell LPD patients received rituximab, whereas those with DLBCL received rituximab or R-CHOP, and HL-like LPD patients had ABVD.

Specifically, in CR (case 5) and SD patients with smaller tumor and fewer local lesions (cases 4 and 6), less intensive treatments than those commonly indicated for NHL were administered, including rituximab or radiation therapy. Eight courses of rituximab were administered in cases 5 and 6. Radiation therapy at 30 Gy was administered for the spine lesions in case 4 because of local lesions of immunodeficiency-associated LPD and poor PS. One patient (case 3) maintained CR without additional treatments.

Furthermore, in patients with large tumors (1 PR patient [case 9] and 1 SD patient [case 8]), the standard treatment for NHL with rituximab plus CHOP therapy was used. The regimen was administered for 2 courses in case 8 and 6 in case 9. In case 2, 4 additional courses of rituximab treatment were administered in lieu of 4 courses of rituximab plus CHOP therapy due to the onset of complications involving ileus and pulmonary abscess observed during treatments.

After relapse occurred in 3 of 4 patients in the MTX-withdrawal remission group, subsequent ABVD therapy (8 courses), rituximab (8 courses), or rituximab plus CHOP therapy (6 courses) was administered, leading to a second CR in cases 1, 2, and 7, respectively.

Thus, these treatments resulted in the attainment of CR in all 9 patients. The mean duration from diagnosis to CR was 91 days (range: 26-210 days). All patients maintained their disease-free status during the 23-month median follow-up period.

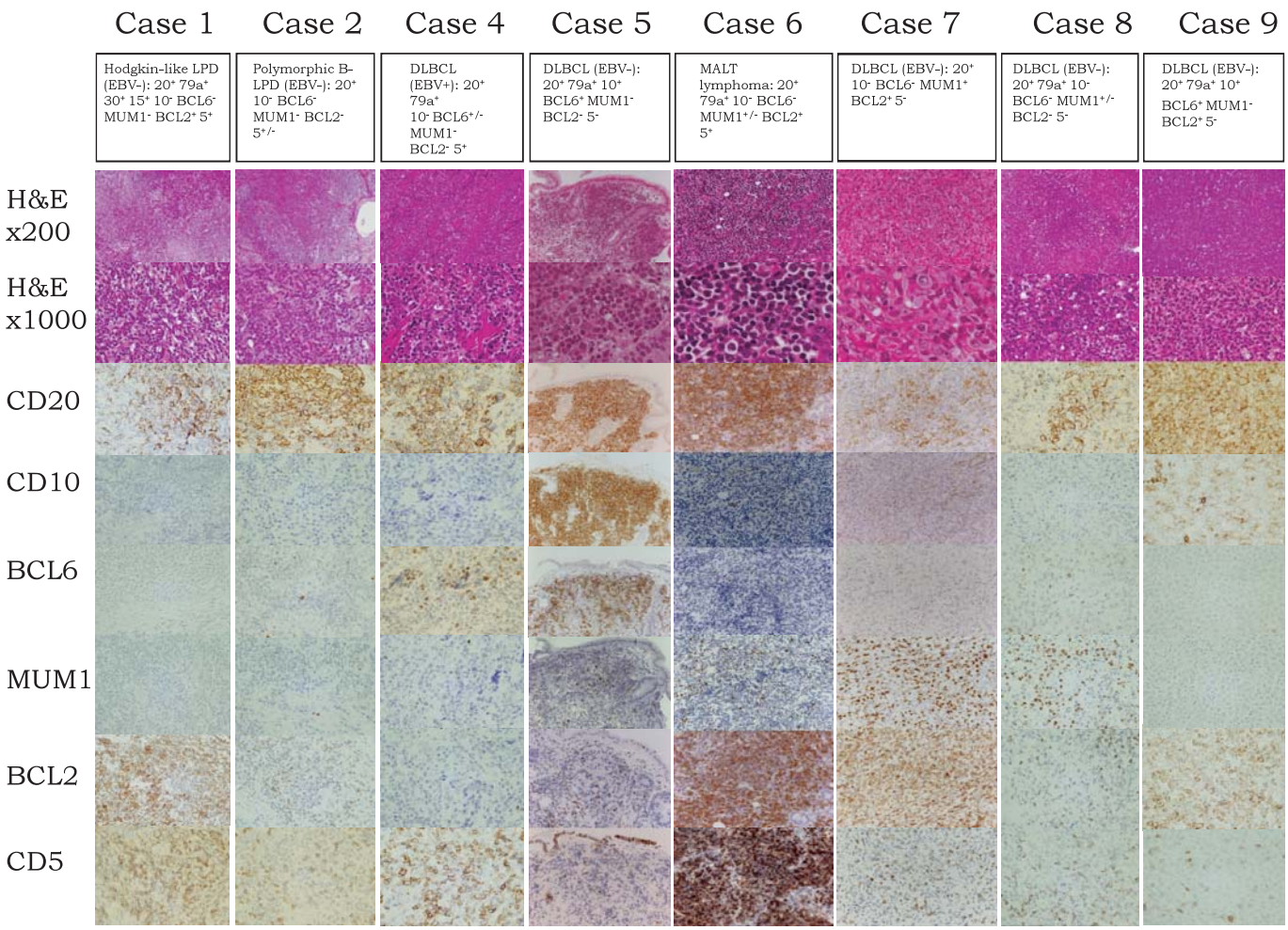

Fig. 2. Summary of histological findings in 9 immunodeficiency-associated lymphoproliferative disorder (LPD) patients. According to the World Health Organization classification and a previous report (Ohshima *et al*.), histological findings were categorized into 4 types: (i) diffuse large B-cell lymphoma (DLBCL), (ii) mucosa-associated lymphoid tissue (MALT) lymphoma, (iii) polymorphic B-cell LPD, and (iv) Hodgkin lymphoma-like LPD. There were 5 DLBCL cases, 3 LPD cases, and 1 MALT lymphoma case. Of the 3 LPD cases, there was 1 Hodgkin lymphoma-like LPD case, 1 case of LPD with histological findings, and 1 with clinical diagnosis.

Complications observed during treatments included lymphorrhea (case 1), antiphospholipid syndrome (APS; case 7), acute myocardial infarction (case 7), ileus (case 8), and pulmonary abscess (case 8). In case 7, acute myocardial infarction (AMI) developed during the treatment. Subsequent analysis showed that case 9 also manifested APS. In the LPD patient group receiving conventional chemotherapy such as rituximab plus CHOP, severe complications including antiphospholipid syndrome, AMI, ileus, and pulmonary abscess tended to occur during chemotherapy. In contrast, patients treated with less intensive treatment such as rituximab did not develop these severe complications.

RA control diminished during MTX discontinuation. However, in patients receiving regimens containing rituximab, the clinical symptoms and activity of RA were transiently well controlled. Therefore, subsequent RA treatments were provided, including low-dose PSL, tacrolimus, salazopyrin, and bucillamine in 8, 3, 4, and 2 cases, respectively. Surprisingly, 1 patient who received rituximab plus CHOP therapy showed long-lasting control of RA without further therapy.

DISCUSSION

Immunodeficiency-associated LPD with RA is reportedly most prevalent in elderly female patients with a longstanding history of RA, advanced-stage LPD, and B-cell phenotypes such as diffuse large B-cell lymphoma.[11-14] However, the clinical features, standard treatment, and prognosis of patients with immunodeficiency-associated LPD remain unclear ow-

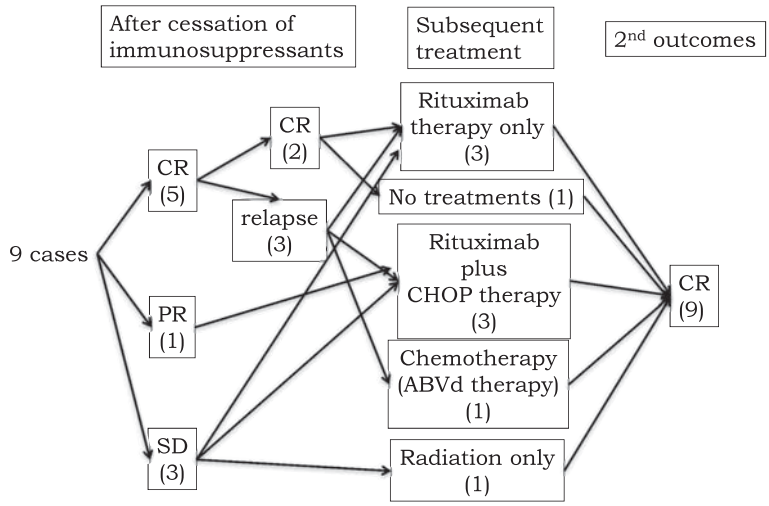

Fig. 3. Treatment outcomes of 9 patients with immunodeficiency-associated lymphoproliferative disorders (LPD). After the development of immunodeficiency-associated LPD, discontinuation of methotrexate (MTX) resulted in complete remission (CR), partial remission (PR), and stable disease (SD) in 4, 2, and 3 patients, respectively. Relapse was observed in 3 of 4 CR patients in the MTX-withdrawal remission group. Subsequently, conventional chemotherapy, rituximab alone, and radiation were administered to 4, 3, and 1 patient, respectively. These treatments induced a second CR. Consequently, all patients remained disease-free during the median 23-month follow-up period. CHOP, doxorubicin, vincristine, cyclophosphamide, and prednisolone; ABVd, doxorubicin, bleomycin, vinblastine, dacarbazine

ing to limited available reports (Table 4).[11-14] A recent report suggested that the risk factors predicting clinical outcomes in patients with immunodeficiency-associated LPD might be associated with older age (> 70 years), histology, EBV positivity, and monoclonality of immunoglobulin heavy chain gene.[15]

Thus, immunodeficiency-associated LPD patients may exhibit a different clinical course and treatment outcome than that commonly observed in NHL patients with respect to regression following MTX discontinuation, extranodal lesions, advanced stage, RA-related complications before treatment, manifestation of complications during treatment, and especially the relatively good prognosis. Consequently, the clinical management of immunodeficiency-associated LPD patients may require a therapeutic strategy that differs from that often applied for NHL patients.

In the present retrospective study, we described the current clinical characteristics and treatment outcomes of immunodeficiency-associated LPD, including: (1) the development of immunodeficiency-associated LPD in both early and advanced stages of RA with various complications; (2) advanced-stage disease (8/9, 88.8%) with high risk in the international prognosis scoring system at diagnosis in immunodeficiency-associated LPD; (3) a higher self-remission rate (66%) at diagnosis yet better response rate at relapse (100%) despite histological findings of EBV negativity and advanced stage in patients with immunodeficiency-associated LPD; (4) good prognosis from less intensive treatments, including MTX discontinuation and subsequent rituximab or rituximab-containing treatment based on RA disease stage, performance status, and the extent of treatment response despite the limited number of patients enrolled; and (5) the need for careful treatment management owing to the tendency to develop severe complications during rituximab plus CHOP therapy.

Thus, we herein described four clinically important points in the treatment and treatment management for immunodeficiency-associated LPD patients that may result in good outcomes.

First, immediate MTX withdrawal might be essential in the management of immunodeficiency-associated LPD. However, without other treatments, such withdrawal might only be transiently effective and the disease would eventually relapse. In previous reports,[7-13] the regression rate of immunodeficiency-associated LPD was approximately 30-40%, with a higher tendency observed in EBV-positive than in EBV-negative patients. In our study, the regression rate of all patients was 66%, whereas that of EBV-negative patients was 75% and the overall relapse rate was 75%. Surprisingly,

Table 4. Previous reports of immunodeficiency-associated lymphoproliferative disorders (LPD) and present cases at our institution

Reference (year)	No. of pts	Median age	Histology	EBV	Clinical stage > III	Extra-nodal lesions	Mean duration of RA	Treatment	Outcome
Mariette X, *et al.* (2002)	25	n.d.	NHL: 18 cases B: 16 cases T: 2 cases Hodgkin's lymphoma: 7 cases	8 cases (25)	n.d.	13 cases (25)	16 years (2.5-49)	(1) MTX withdrawal: 9 cases (2) MTX withdrawal + chemotherapy: 15 cases	Median survival time 34 months (25-54 months)
Hoshida Y, *et al.* (2002)	22 (53 collagen disease pts)	60	NHL: 21 cases B: 18 cases T: 3 cases Hodgkin's lymphoma: 1 case	30%	11 cases (22)	11 cases (22)	162 months (24-312)	(1) 37 cases treatment (53) Chemotherapy: 28, Radiation therapy: 7, Chemotherapy and radiation therapy: 2	5 year survival: 57%
Niitsu N, *et al.* (2010)	29	62	NHL: 27 cases DLBCL: 27 cases	7 cases (29)	17 cases (29)	12 cases (29)	8 years (1-20)	(1) MTX withdrawal: 4 (2) MTX withdrawal + chemotherapy: 25 (Rituximab 12/29)	5 year survival: 74%
Ichikawa A, *et al.* (2013)	102	69	DLBCL: (53) Hodgkin lymphoma: (9) Polymorphic B-LPD: 20 Reactive lymphadinitis: (11) Peripheral T-cell lymphoma: (4) Composite lymphoma: (3) Follicular lymphoma: (3)	56 cases (= 56/93)	n.d.	36 cases (89)	4 years (0.05-18)	(1) MTX withdrawal + chemotherapy: (49) (2) Chemotherapy (25) *Rituximab monotherapy: 3 cases for 2 LPD and Hodgkin lymphoma. (3) Not done/unknown (28)	5 year survival: 80%
Present cases (2012)	9	62	DLBCL: 5 cases MALT: 1 case LPD: 3 cases	1 case (9)	8 cases (9)	7 cases (9)	5 years (1-30)	(1) MTX withdrawal: 1 (2) MTX withdrawal + chemotherapy: 7 cases (Rituximab combined therapy 6) (3) MTX withdrawal + radiation therapy: 1 case	Median survival time: 23 months All alive

No., number; pts, patients: n.d., not done/unknown NHL, non-Hodgkin's lymphoma; EBV, Epstein-Barr virus; DLBCL, diffuse large B-cell lymphoma; RA, rheumatoid arthritis; MTX, methotrexate, MALT, mucosa-associated lymphoid tissue lymphoma

during the 4-week period of MTX withdrawal, we did not observe exacerbation of immunodeficiency-associated LPD. Thus, our major concern was the subsequent therapeutic strategy for immunodeficiency-associated LPD following MTX discontinuation.

Second, less intensive treatments than those commonly indicated for NHL successfully provided good outcomes for patients in our study. Most of them had advanced-stage diseases (8/9, 88.8%) and were classified as at high risk or high/intermediate risk according to the international prognosis scoring system (7/9, 77.7%) at the time of immunodeficiency-associated LPD development. In a previous report describing NHL patients without RA,[25] the 5-year survival rates of those at high risk and high/intermediate risk were reported to be 46% and 32%, respectively. In our retrospective study, although the observation period was relatively short (median: 23 months), all 9 immunodeficiency-associated LPD patients showed good response and good survival. These RA patients already had several complications and decreased PS prior to immunodeficiency-associated LPD treatment; thus, the less intensive treatments provided might be efficient therapeutic modalities in this patient population when properly adjusted on a case-by-case basis.

Third, LPD (polymorphic B-cell LPD and clinical diagnosis) was the second most prevalent histological finding (3/9 cases), although DLBCL was the most common (5/9 cases). These LPD patients were speculated to belong to the oligoclonal-polyclonal group in the multi-step oncogenesis mechanism of LPD. According to a previous report,[15] rituximab is effective in some polymorphic B-cell LPD patients, which was also the case in our study. Such effectiveness might be due to the atypical cells in polymorphic B-cell LPD occasionally being positive for CD20. On the basis of the response to MTX discontinuation and patient background, it may be appropriate to treat those with lower residual tumors that respond to MTX discontinuation with rituximab. According to previous reports on the safety, effectiveness, and feasibility of rituximab for the treatment of newly diagnosed low-grade lymphoma with low tumor burden, relapsed or refractory low-grade lymphoma, and DLBCL,[26-29] the agent was recently approved for immunodeficiency-associated LPD via the procedure of public knowledge-based application by the Japanese Ministry of Health, Labour and Welfare. In the future, rituximab therapy may become a mainstay therapeutic strategy for immunodeficiency-associated LPD.

Finally, severe and potentially lethal complications such as AMI, pulmonary abscess, and ileus were promptly diagnosed and well managed by our team of excellent cardiologists and surgeons. Two of the 3 immunodeficiency-associated LPD patients receiving rituximab plus CHOP therapy developed severe complications such as ileus and pulmonary abscess (case 8), AMI, and APS (case 7). In the group with large residual tumor that does not respond to MTX discontinuation, it may be appropriate to treat with rituximab combined

with chemotherapy, while keeping in mind that rituximab plus CHOP therapy may be associated with more severe complications during treatments. Since there were only a few cases in this study, further investigation might be necessary to confirm the efficiency of rituximab plus CHOP therapy in immunodeficiency-associated-LPD patients with RA.

In the future, the incidence of immunodeficiency-associated LPD may increase due to the use of immunosuppressive agents such as MTX in the early stages of RA. In our study, immunodeficiency-associated LPD developed in both early and advanced stages of RA. According to the recent guidelines for RA management, the treatment aim is defined as remission even at early stages of RA, with low disease activity being an alternative goal in patients with longstanding disease.[24] Moreover, RA patients have a higher risk for developing ML than the general population owing to the onset of RA itself, the use of immunosuppressive agents, and RA activity.[7-9] Therefore, physicians should be cautious about immunodeficiency-associated LPD during the course of immunosuppressive treatment for RA patients. Furthermore, future studies with larger patient cohorts and longer follow-up periods are needed to clarify the exact nature and clinical features of immunodeficiency-associated LPD.

In conclusion, the results of our retrospective study indicate that, depending on the patient background, less intensive treatments consisting of MTX discontinuation and subsequent rituximab-containing treatments might be an efficient therapeutic strategy for the treatment of immunodeficiency-associated LPD. In the examination and follow-up of RA patients, the combination of careful physical examination, serological examination (lactate dehydrogenase and soluble interleukin-2 receptor), radiological examination, and histological examination were essential to clarify and identify the exact diagnosis of immunodeficiency-associated LPD. These case-oriented studies should be helpful to the physicians who directly care for immunodeficiency-associated LPD patients and may provide a future direction for improving the treatment modality.

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CONFLICT OF INTEREST

None declared.

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