Review Article

Iatrogenic immunodeficiency-associated lymphoproliferative disorders of B-cell type that develop in patients receiving immunosuppressive drugs other than in the post-transplant setting

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In the current revised 4th edition of the World Health Organization (WHO) classification, 'other iatrogenic immunodeficiency-associated lymphoproliferative disorders (Oii-LPDs)' is listed in the last section in the chapter on immunodeficiency-associated lymphoproliferative disorders. Oii-LPDs cover a broad spectrum from benign lesions to lymphoma, and correspond to one of the subtypes in the WHO classification for immunocompetent patients.

The WHO classification does not clearly indicate the histological subtype of this disease category; however, the framework of subtype classification is similar to the classification of post-transplant lymphoproliferative disorders, and recent studies have attempted to subcategorize Oii-LPDs that fit this unique disease type. In this review, we provide an overview of B-cell-type Oii-LPDs regarding their histopathology and immunophenotype, genetics and clinical behaviors.

Keywords: immunodeficiency, lymphoproliferative disorder, methotrexate, Epstein-Barr virus

INTRODUCTION

Although advances in medicine have benefitted humans with disease, some patients who are treated using immunosuppressive agents for autoimmune disease develop lymphoproliferative disorders (LPDs). More than a quarter of a century has passed since the recognition of the association between methotrexate (MTX) usage and the occurrence of LPD.[1] In the current WHO classification, these cases are summarized in the chapter entitled "Immunodeficiency-associated lymphoproliferative disorders"[2] and the definition of other iatrogenic immunodeficiency-associated lymphoproliferative disorders (Oii-LPDs) is "lymphoid proliferations or lymphomas that arise in patients treated with immunosuppressive drugs for autoimmune disease or conditions other than in the post-transplant setting".

Most Oii-LPDs are B-cell lineage LPDs, and Oii-LPDs cover a broad spectrum from benign to malignant lesions. Mucocutaneous ulcers are a newly-described disease entity in the current WHO classification that belongs to B-cell LPDs. A subset of mucocutaneous ulcers belong to Oii-LPDs[3] and will be described in detail by Ikeda *et al*. in the latter part of this issue. Here, we describe the histological spectrum from benign to malignant Oii-LPDs, mainly focusing on B-cell lineage Oii-LPDs regarding their pathology, genetics and clinical course.

ETIOLOGY OF OII-LPDS

A subset of patients who are administered immunosuppressive drugs for an underlying primary disease subsequently develop Oii-LPD. Among patients with Oii-LPDs, the most common underlying disorder is rheumatoid arthritis and other underlying disorders include dermatomyositis, Sjogren disease, systemic lupus erythematosus, inflammatory bowel disease. Although several large studies have analyzed Oii-LPDs, all of them were restricted to patients who were administered a particular drug, such as MTX, or patients with a specific underlying disease such as rheumatoid arthritis. Thus, the perspective of Oii-LPDs is unclear. Although patients who are administered immunosuppressive drugs are under an immunocompromised condition, the primary autoimmune disease itself is predisposed to cause LPD. For example, a nationwide cohort study revealed that autoimmune

disease increases the risk of non-Hodgkin lymphoma and the overall incidence of lymphoma was approximately two-times higher in patients with an autoimmune disease than in the immunocompetent population.[4,5] Therefore, the etiology of Oii-LPDs is not simple and may be multifactorial. However, as Oii-LPDs spontaneously regress after discontinuation of the administered immunosuppressive drug, these therapeutic agents indeed provoke LPDs in subsets of patients.

In the current WHO classification, cancer therapy-related LPDs are not included in Oii-LPDs, although there are many case reports and several small case series of patients who developed LPDs after treatment with chemotherapeutic agents for hematological malignancies, including myeloid neoplasms.[6,7] Pina-Oviedo *et al.* summarized these cases and reported a high frequency of Epstein-Barr virus (EBV) infection among patients with LPDs, implying that these patients were in an immunocompromised state after receiving chemotherapy.[7] The number of patients with cancer therapy-related LPDs is insufficient to be recognized as a distinct disease entity, and a systematic analysis is needed to evaluate the immune condition of the host and ascertain a relationship with the particular Oii-LPD.

HISTOPATHOLOGICAL CLASSIFICATION OF OII-LPDS

The current WHO classification of Oii-LPDs does not take into consideration histopathological classification; however,

the histological subtype of post-transplant lymphoproliferative disorder (PTLD) was developed based on studies that analyzed Oii-LPDs/MTX-related LPDs.[8] Currently, MTX is the most common reagent associated with the development of Oii-LPDs; therefore, the frequencies of histological subtypes in MTX-LPD generally reflect those in Oii-LPDs. The relative frequencies of histological subtypes, including benign and borderline lesions, and lymphoma among MTX-LPD cases in large cohorts to date are shown in Figure 1A.[9,10] The most frequent histological subtype of MTX-LPD is the large B-cell (LBCL) type, including diffuse large B-cell lymphoma (DLBCL) with or without EBV infection. Other frequent subtypes are as follows: reactive lymphoid hyperplasia (RH), classic Hodgkin lymphoma (CHL), polymorphic B-cell LPD (poly-LPD), indolent lymphoma including follicular lymphoma, etc. Thus, most MTX-LPD cases are B-cell lineage LPDs.

Benign and borderline lesions of Oii-LPDs

In the category of PTLD in the WHO classification,[8] benign and borderline lesions are described as reactive hyperplasia (RH) and polymorphic B-cell LPD (poly-LPD), respectively. RH and poly-LPD are differentiated according to whether the architecture of the involved tissue is preserved; the architecture of lymphoid tissue is preserved in RH (Figure 2), whereas the original tissue architecture is effaced by B-cells and plasma cells of varying sizes and maturation stages in poly-LPD (Figure 3). A subset of these
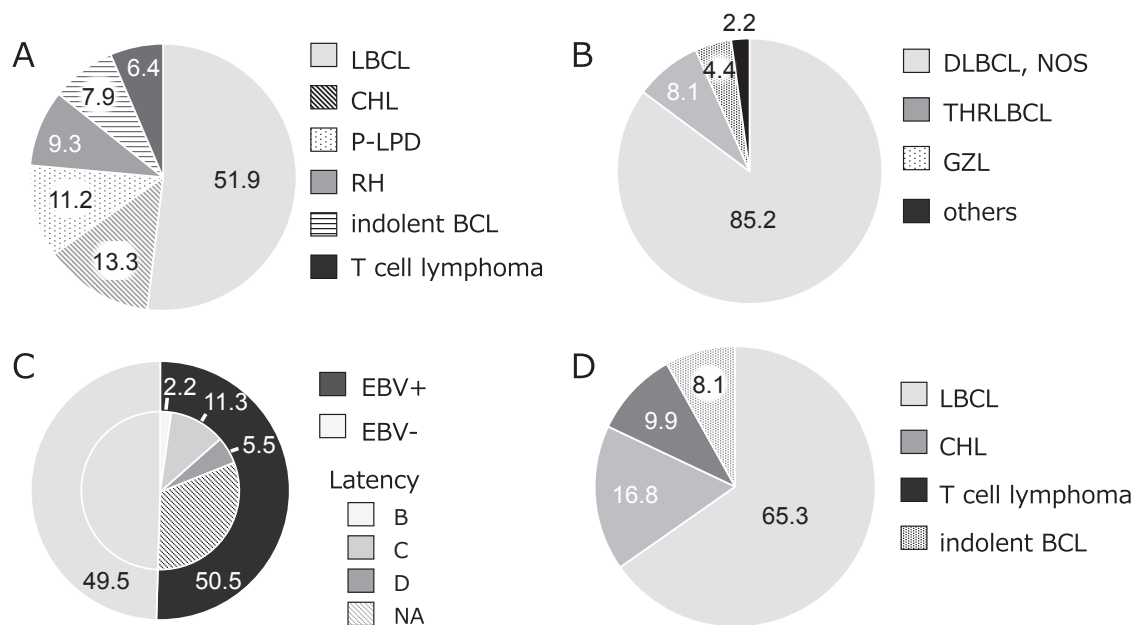
Fig. 1. (*A*) Frequency of subtypes in 281 MTX-LPD cases from studies that included non-lymphomatous lesions[9,10]. (*B*) Histological subtypes of large B-cell lymphoma-type MTX-LPDs indicated in Figure 1A. (*C*) Frequency of EBV positivity in LBCL-type LPD cases and latency of EBV infection[9,10,13-16,19-22]. Outer circle indicates positivity or negativity for EBV. Inner circle indicates latency of EBV infection. LBCL, Large B-cell lymphoma; RH, reactive hyperplasia; P-LPD, polymorphic-lymphoproliferative disorder; CHL, Classical Hodgkin lymphoma; BCL, B-cell lymphoma; DLBCL, NOS, diffuse large B-cell lymphoma, not otherwise specified; THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; GZL, gray zone lymphoma (B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma); EBV, Epstein-Barr virus; NA, not applicable/available. (*D*) Frequency of lymphoma subtypes in 334 MTX-LPD cases with details described in series reports[9,10,13,19-21].

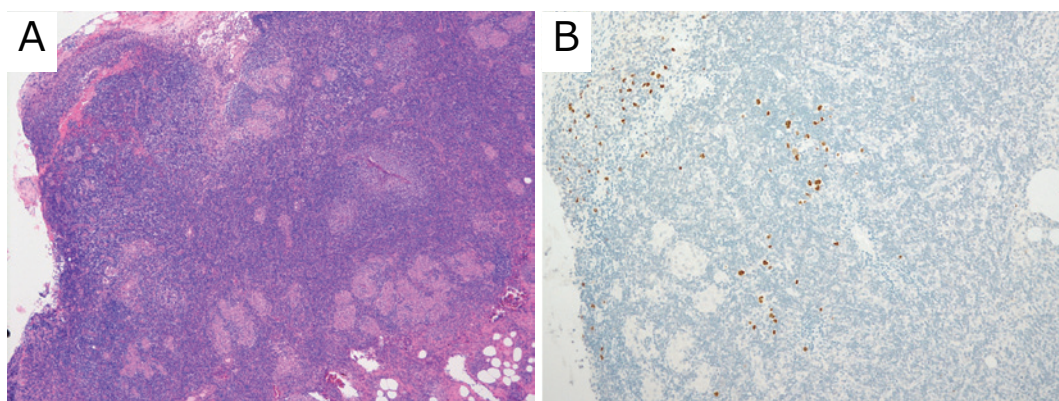**Fig. 2.** Reactive hyperplasia in a patient with Oii-LPD. (**A**) Preserved architecture of lymph node tissue and scattered epithelioid cell granulomas were seen in interfollicular regions. (**B**) EBV-infected cells detected by EBER *in situ* hybridization were observed in the interfollicular area.
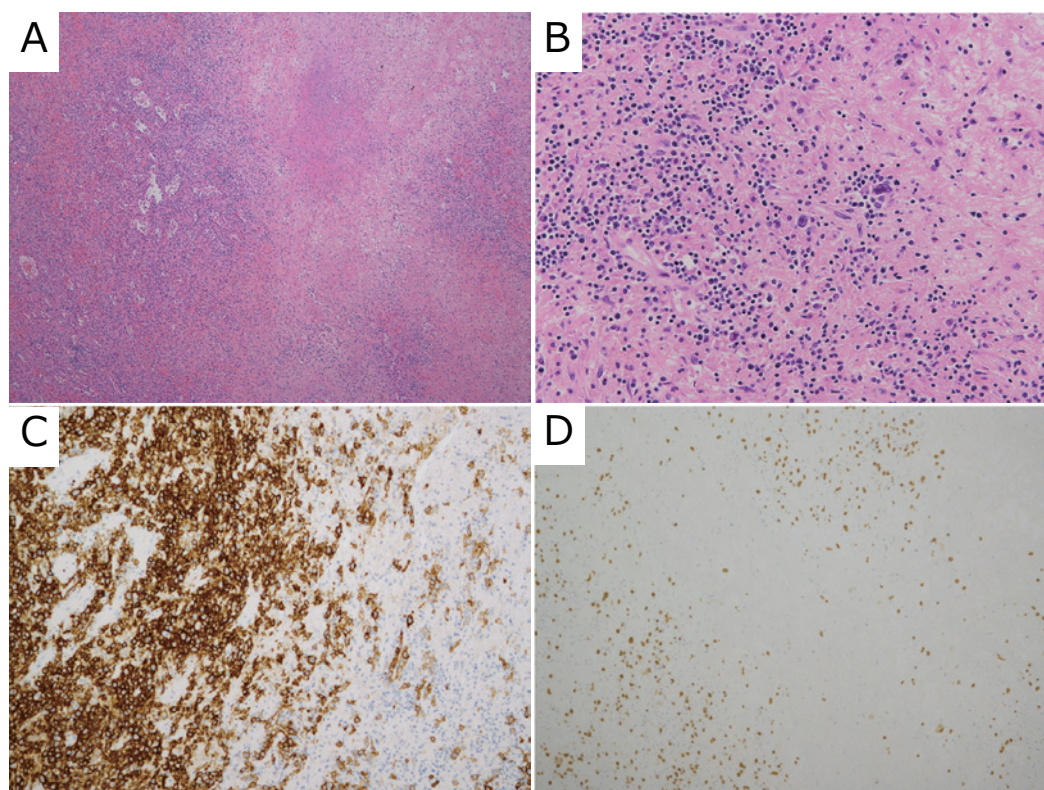

Fig. 3. B-cell lymphoproliferative disorder in a patient with Oii-LPD. Surgically resected specimens of the spleen were evaluated. (**A**) The architecture of the spleen was destroyed by infiltration of a variety of lymphoid cells from small mature lymphocytes and plasma cells to large atypical B-cells. (**B**) Scattered atypical "Hodgkin-like" cells were seen. (**C**) Immunostaining for CD20 demonstrated marked B-cell infiltration. (**D**) EBV-infected cells were detected by EBER *in situ* hybridization.

lesions spontaneously regresses even if the lesions have a population of monoclonal B cells after withdrawal of the immunomodulator agent such as MTX.[9,11] The frequencies of monoclonality of IGH and karyotypic abnormalities are higher in poly-LPD than in RHs,[9-11] suggesting multistep lymphomagenesis in the immunocompromised setting from RH to poly-LPD and sequential development to monomorphic LPD, e.g., DLBCL.

In RH, the architecture of the involved tissue is preserved and EBV-infected lymphoplasmacytic cells are present,

resulting in the involved tissue being in a local immunocompromised state. EBV-infected cells are usually observed in interfollicular areas but are also found in lymphoid follicles. Proliferation of immunoblasts has also been observed in approximately 40% of these cases,[10] and marked plasmacytic infiltration is a common feature that can be observed in PTLDs.

In poly-LPD, there is a variety of lymphoid cells from small mature lymphocytes and plasma cells to large atypical B-cells, and in some cases, Hodgkin/Reed-Sternberg (H/

RS)-like cells are found in the lesion, which are referred to as "Hodgkin-like lesions". Differential diagnostic points between poly-LPD (Hodgkin-like lesion) and the CHL type are as follows: First, the presence of typical H/RS cells is important to diagnose CHL-type LPD. Second, EBV infection is restricted to H/RS cells in CHL-type LPD, whereas EBV infects a variety of cells from small lymphocytes to large B-cells in B-LPDs. Third, on immunophenotyping, poly-LPD is positive for CD20 and negative for CD15. On the other hand, CHL-type LPD is similar to *de novo* CHL and is negative or weakly positive for CD20, and up to 60% of cases express CD15 (Table 1). Necrosis and fibrosis are often observed in poly-LPDs. However, poly-LPD, including Hodgkin-like lesions, is not a definite disease entity but rather in the spectrum leading to monomorphic malignancy. Therefore, there are patients in whom a differential diagnosis between poly-LPD and CHL-type LPD cannot be made in daily practice.

Mucocutaneous ulcer (MCU), a newly-described disease entity in the current WHO classification, is also included in poly-LPDs. MCU will be described in detail by Ikeda *et al*.

Large B-cell lymphoma-type LPD

Among patients with large B-cell lymphoma (LBCL)-type LPD, proliferation of atypical large B cells has been noted and patients should be subclassified according to the WHO classification of lymphoma in immunocompetent patients. The frequency of each B-cell type in patients with MTX-LPDs is shown in Figure 1B, summarized from two large cohorts.[9,10] The most frequent histological type corresponding to immunocompetent patients was DLBCL, NOS (Figure 4) (85.1%, 115/135 cases), followed by T-cell/

Table 1. Immnunohistochemical features of MTX-related CHL

	Total	Kurita *et al.*	Gion *et al.*	Loo *et al.*
CD20	4/49 (8.2%)	0/26	1/17	3/6
CD30	49/49 (100%)	26/26	17/17	6/6
CD15	29/48 (60.4%)	13/26	10/16	6/6
PAX5	24/26 (92.3%)	20/20	ND	4/6
CD79a	7/29 (24.1%)	5/19	0/6	2/4
BCL6	0/2 (0%)	0/2	ND	ND
IRF4/MUM1	2/2 (100%)	2/2	ND	ND

These data were obtained from the following reports of case series of MTX-related CHL: Kurita *et al.*,[10] Gion *et al.*,[15] Loo *et al.*[35]
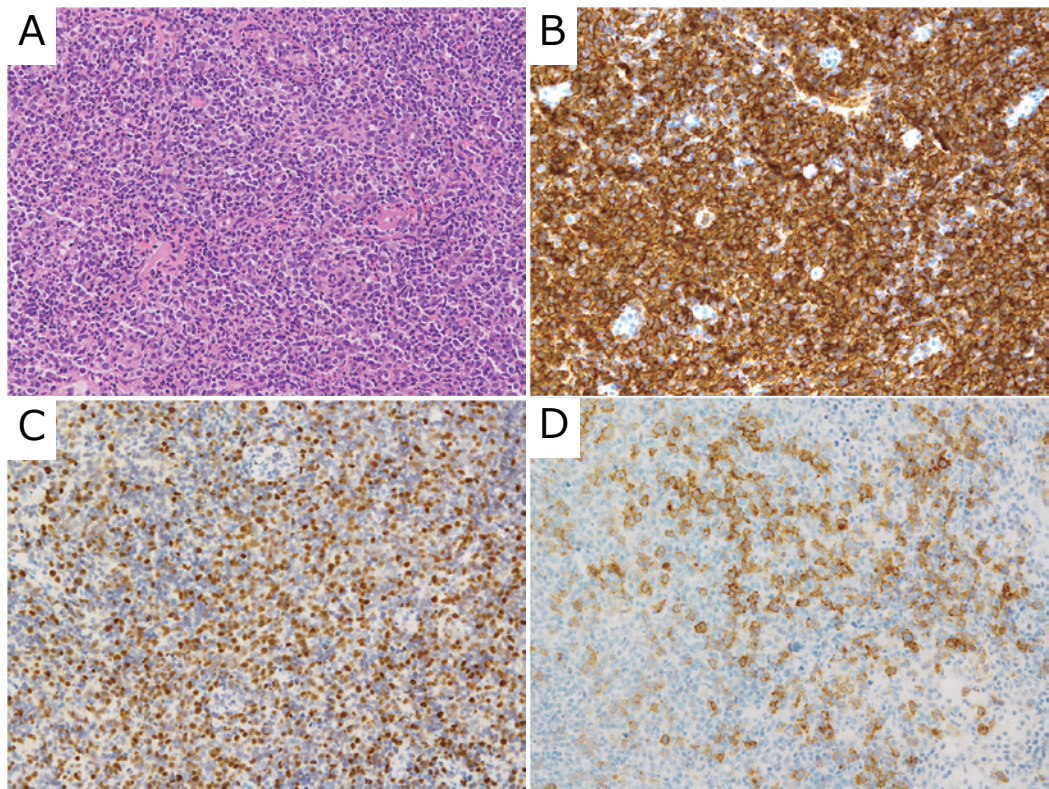ND, not done

Fig. 4. EBV-positive DLBCL-type Oii-LPD. (*A*) Marked infiltration of large atypical cells was seen in a lymph node. The atypical cells were positive for CD20 (*B*), positive for EBV on EBER *in situ* hybridization (*C*) and partially positive for CD30 (*D*).

histiocyte-rich large B-cell lymphoma (8.1%, 11/135 cases), B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL (Gray zone lymphoma) (2.2%, 3/135 cases), and lymphomatoid granuloma, plasmablastic lymphoma and primary mediastinal large B-cell lymphoma (0.7%, 1/135 cases for each). Most cases exhibited destruction of the involved tissue by infiltration of large atypical B-cells accompanied by inflammatory cells. The degree of atypical B-cell population varied among cases. On one hand, marked and sheet-like atypical B-cell proliferation can be seen in DLBCL, NOS in immunocompetent cases, whereas cases having sparse infiltration of atypical cells with a variety of background inflammatory cells, such as T cell/histiocyte-rich large B-cell lymphoma, are present at the opposite extreme of the spectrum of large B-cell lymphoma. Among the cases in this category, atypical cells may exhibit Hodgkin/Reed-Sternberg cell-like morphology. In relation to the varying inflammatory backgrounds in this subtype, granuloma/granulomatous change and necrosis are common in LBCL-type MTX-LPD.[10-13] Immunohistochemical findings of LBCL-type MTX-LPD are summarized in Table 2.[9,10,14-16] Nearly all cases expressed CD20 (214/222, 96.4%) and most cases retained other B-cell markers such as CD79a (58/60, 96.7%) and PAX5 (14/15, 93.3%). Nearly half of the cases expressed CD30 (62/137, 45.3%), 8.3% (8/96) of the cases expressed CD15, 18.1% (32/177) expressed CD10, 62.4% (93/149) expressed BCL6 and 69.0% (98/142) expressed IRF4/MUM1. The rates of CD10 and BCL6 expression in patients with LBCL-type MTX-LPD were lower than those in immunocompetent patients with conventional DLBCL, NOS,[17] but the rates were similar to those in patients with EBV-positive DLBCL.[18] Approximately two-thirds of LBCL-type MTX-LPD cases belong to the non-GCB type according to the Hans classification of cell of origin (Table 2).

EBV in tumor cells was detected in 157 (50.5%) of 311 LBCL-type MTX-LPD cases by Epstein-Barr encoding region (EBER) *in situ* hybridization, and type I, II or III latent EBV infection was observed in 11.9% (7/59), 59.3% (35/59) and 28.8% (17/59) of cases, respectively (Figure 1D).[9,10,13-16,19-22] Even if patients have an immunodeficiency background, only half carry EBV in large B-cell-type lymphoma cells.

In recent years, there has been growing evidence of activation of the PD-1/PD-L1 axis to escape from immune surveillance.[23] A subset of tumor cells in DLBCL was reported to express PD-L1 and these patients have a poor prognosis,[24] and higher expression of PD-L1 was observed in EBV-positive DLBCL cases than in EBV-negative DLBCL cases.[25] However, there has been no retrospective cohort study of PD-L1 and PD-1 expression in Oii-LPDs, including MTX-LPDs.

Although little is known about genetic alterations in patients with Oii-LPDs, Carreras *et al*. investigated the genomic profile of 20 cases of DLBCL-type MTX-LPD (MTX-DLBCL) and identified genomic features that are characteristic to MTX-DLBCL, i.e., 3q, 12q and 20p gains, and 13p loss.[14] The gain of 3q to *BTLA*, *PLOD2* and *KLHL6*, and 12q to *SELPG* was positively correlated with protein expression, proliferation, and differentiation and maintenance of the microenvironment of MTX-DLBCL. Some of these genomic alterations may be associated with the infiltration of M2-like macrophages and CD8+ T cells in the tumor microenvironment of MTX-DLBCL. However, genetic alterations in patients with MTX-DLBCL are largely unknown. Therefore, further investigation is necessary.

Classic Hodgkin lymphoma-type Oii-LPD

Classic Hodgkin lymphoma (CHL)-type Oii-LPD is a common histological subtype that accounts for approximately 13.3% of Oii-LPDs (Fig. 1A and 1C). We searched for CHL-type Oii-LPD cases and found 84 previously reported cases. Features of these cases are summarized in Supplementary Table 1.[1,9,13,15,19,21,22,26-44] The median age of the patients was 58 years (range, 8 to 84 years). The male-to-female ratio was 1:1.7, and this unusual ratio compared with that in immunocompetent cases may have been caused by the present or past history of RA. Fifty-seven (70.4%) of the 81 patients had rheumatoid arthritis and 3 also had another autoimmune disease. Seventy-three (86.9%) of 84 cases of CHL-type Oii-LPDs were treated by MTX, and other immunosuppressive and/or immunomodulating agents, such as TNFα inhibi-

Table 2. Immnunohistochemical features of MTX-related DLBCL

	Total	Tokuhira *et al.*	Kurita *et al.*	Carreras *et al.*	Gion *et al.*	Niitsu *et al.*
CD20	214/222 (96.4%)	33/34	104/105	20/20	30/34	27/29
CD30	62/137 (45.3%)	13/25	40/92	7/20	ND	ND
CD15	8/96 (8.3%)	4/14	4/62	0/20	ND	ND
PAX5	14/15 (93.3%)	3/3	11/12	ND	ND	ND
CD79a	58/60 (96.7%)	7/8	51/52	ND	ND	ND
CD10	32/177 (18.1%)	4/15	15/91	3/20	1/22	9/29
BCL6	93/149 (62.4%)	11/17	46/83	16/20	ND	20/29
IRF4/MUM1	98/142 (69.0%)	13/16	50/77	20/20	ND	15/29
GCB vs. non-GCB/ABC type	51/99 (total 150 cases, 34.0%)	4/9(13)	32/56 (88)	3/17 (20)	ND	12/17 (29)

These data were obtained from the following reports of case series of MTX-related DLBCL: Tokuhira *et al.*,[9] Kurita *et al.*,[10] Carreras *et al.*,[14] Gion *et al.*,[15] Niitsu *et al.*[16]

ND, not done

tors, etanercept, azathioprine, or prednisolone, were co-administered with MTX in 30 (41.1%) of the 73 cases.

CHL-type Oii-LPD is characterized by scattered mononuclear and multinucleated giant cells surrounded by a marked variety of infiltrated non-neoplastic inflammatory cells (Figure 5). Although typical cases of CHL-type Oii-LPD are simple to diagnose based on their morphological and immunohistochemical findings, some cases border between poly-LPD and DLBCL-type Oii-LPD. Currently, there is no consensus on the boundary between poly-LPD and DLBCL-type Oii-LPD; this is a similar situation to that for immunocompetent cases of CHL in relation to DLBCL, which is a known category of gray zone lymphoma between CHL and DLBCL. Furthermore, in immunocompromised cases of Oii-LPDs, "Hodgkin-like lesions", as described above, can be found in poly-LPDs and these lesions lead to complications. Immunohistochemical findings revealed a similar pattern of diagnostic markers (CD20, CD30, PAX5 and CD15) between CHL-type Oii-LPDs and *de novo* CHL. However, CD15 expression in CHL-type Oii-LPDs is lower than that in *de novo* CHL (Table 2, 60% vs. 80-85%).[45] Moreover, on comparison between CHL-type Oii-LPD and poly-LPD, the rate of CD15 expression was higher in CHL-type Oii-LPDs (75-85%) than in B-LPDs (0%).[10] Therefore, CD15 expression may be a differential diagnostic marker. However, it is difficult to distinguish between B-LPD and CHL-type Oii-LPDs in daily practice because both categories are in the same disease spectrum. Therefore, integrative understanding, including analyses of pathology, genetics, and clinical outcome, is needed to clarify this heterogeneous disease in order to provide satisfactory treatment.

Other B cell lymphoma-type Oii-LPDs

Mature B-cell lymphoma-type LPDs other than LBCL-type LPDs account for less than 10% of Oii-LPDs (8.1%, 27/334 cases, Figure 1D). However, the precise incidence of mature B-cell lymphoma-type LPDs other than LBCL-type LPDs, especially indolent lymphoma, among Oii-LPDs is unknown. A meta-analysis of lymphoma risk by Simon *et al.* revealed an increased risk in patients with RA.[46] The standardized incidence ratio for all lymphomas was 2.46, and the ratios for Hodgkin lymphoma and non-Hodgkin lymphoma were 2.26 and 3.21, respectively. However, the risk for non-Hodgkin lymphoma in RA patients who were treated using MTX was not significantly higher than that in the general population in France.[22] Although the underlying autoimmune disease results in chronic antigen stimulation and provokes polyclonal lymphocytic proliferation, whether the incidence of lymphoma in patients with autoimmune disease is higher remains controversial.

Regarding mature B-cell lymphoma-type LPDs other than LBCL-type LPDs, only a small number of cases has been reported and the precise frequency is unknown. Furthermore, follicular lymphoma was the most frequent subtype among indolent B-cell lymphoma-type LPDs and only one of 11 cases of follicular lymphoma was positive for EBV on EBER *in situ* hybridization according to previous reports (Table 3).[9,13,21,32] Therefore, whether follicular lymphoma developing in autoimmune disease-treated patients develops as Oii-LPD or as a coincidental lesion is unclear. On the other hand, low-grade B-cell lymphoma with plasma cell differentiation, especially marginal zone lymphoma

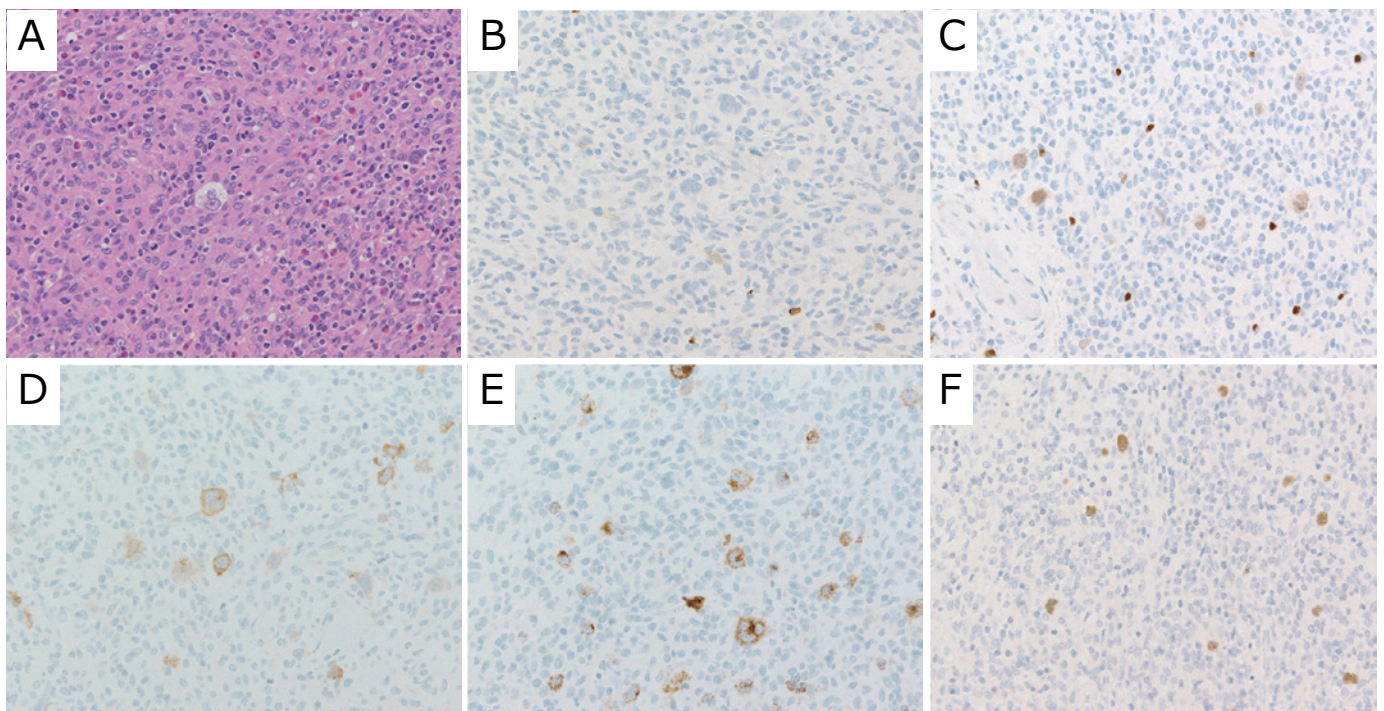

Fig. 5. Classic Hodgkin lymphoma-type Oii-LPD. (*A*) Typical Hodgkin/Reed-Sternberg (H/RS) cells were surrounded by prominent inflammatory cells (eosinophils, small lymphocytes, histiocytes, endothelial cells, etc.) in a lymph node. HRS cells were negative for CD20 (*B*), weakly positive for PAX5 (*C*), and positive for CD30 (*D*), CD15 (*E*) and EBV on EBER *in situ* hybridization (*F*).

Table 3. Positivity for EBV in indolent B-cell lymphoma-type Oii-LPDs

	FL	MALT	LPL
Tokuhira *et al*.	0/4	0/2	-
Kojima *et al*.	-	0/1	-
Hoshida *et al*.	0/5	-	0/2
Hasserjian *et al*.	1/2	0/1	
Total	1/11	0/4	0/2

FL, follicular lymphoma; MALT, MALT lymphoma; LPL, lympho-plasmacytic lymphoma
These data were obtained from the following reports of case series of indolent BCL: Tokuhira *et al*.,[9] Kojima *et al*.,[13] Hoshida *et al*.,[21] Hasserjian *et al*.[32]

and plasmacytoma, may be related to the immunodeficient background induced by the primary disease or it may be a secondary therapeutic outcome. As the incidence of Oii-LPD is low, further investigation and accumulation of cases are needed.

CONCLUSION

Oii-LPDs cover a broad spectrum regarding their cytological composition, histological variation, immunophenotype, molecular and genetic/genomic findings, and clinical outcome. Furthermore, Natkunam *et al*. proposed a common framework for immunodeficiency-associated-LPDs irrespective of causative background. This study will improve the use of common terminology in diverse clinical settings and aid in developing novel treatment strategies.[47]

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Supplementary Material

Supplementary Table S1. Clinicopathologic Features of 84 Cases of Oii-LPDs of CHL

References		Age	Sex	Primary Immune Disease	Immunomodulator	EBV	LMP-1	EBNA2	subtype	Biopsy Site	Stage	Therapy	Outcome
Aksu et al.[26]		44	M	Ankylosing spondylitis	MTX, etanercept	NA	+	NA	MC	LN neck	I	ABVD, radiation	NA
Bai et al.[27]		35	M	Crohn's disease	MTX, IFX	+	+			Rectum	I	Chemotherapy	DF, 8 mo
Brown et al.[28]	1	29	M	NA	IFX	NA				NA	NA	NA	NA
	2	43	F	NA	IFX	NA				NA	NA	NA	NA
	3	68	M	NA	MTX, etanercept	NA				NA	NA	NA	Dead
Cassaday et al.[29]		54	F	Crohn's disease	AZA, adalimumab	+	ND			LN neck	III	Stanford V	DOD
Colburn et al.[30]		62	M	Wegener granulomatosis	AZA	NA				LN mediastinal	NA	BCNU	DOD, 4 mo
Ferraccioli et al.[31]		61	M	RA	MTX, AZA	+	+	-	MC	LN axilla	I	Discontinue immunomodulator, MOPP radiation	
Gion et al.[15]	1	45	F	RA, SS	MTX, PSL	+	+			LN	IV	Rituximab, ADR, CY	PD, 3 mo
	2	63	M	RA	MTX, etanercept	+	NA			LN	III	ABVD	CR, 4.6 y
	3	69	F	RA	MTX	+	+			Cerebellum	I	ABVD	CR, 6.5 y
	4	79	F	RA	MTX	+	+			LN	III	ABVD	CR, 1.7 y
	5	65	F	RA	MTX, PSL	+	+			LN	III	ABVD	CR, 3.1 y
	6	63	M	RA	MTX, bucillamine, PSL	+	+			LN	I	ABVD	CR, 5.8 y
	7	63	F	RA	MTX, PSL	+	NA			LN	IV	ABVD	CR, 4.7 y
	8	84	M	RA	MTX, PSL	-	-			LN	III	ABVD	CR, 1.9 mo
	9	53	F	RA	MTX	+	-			LN	III	ABVD	CR, 1.7 y
	10	64	F	RA	MTX, adalimumab, PSL	+	-			LN	IV	-	DF, 1.7 y
	11	63	F	RA	MTX, IFX	+	+			LN	III	ABVD	CR, 3.4 y
	12	73	F	RA	MTX	+	+			Oral cavity	I	ABVD	CR, 3 y
	13	81	M	RA	MTX	-	-			LN	III		DF, 6 mo
	14	48	F	RA	MTX, PSL	+	-			LN	III	ABVD	CR, 9 y
	15	64	F	RA	MTX	+	+			LN	IV		DF, 3.4 y
	16	73	F	RA	MTX	+	NA			Tonsils	I		DF, 1 mo
	17	56	F	RA	MTX	-	NA			Liver	IV	ABVD	-
Hasserjian et al.[32]	1	63	F	Crohn's disease	MTX, IFX	+	NA		NA	LN neck	NA	NA	NA
	2	60	M	Psoriasis	Efalizumab	+	NA		NA	Ileum	NA	NA	NA
	3	51	F	RA	MTX, etanercept	+	NA		NA	LN inguinal	NA	Chemotherapy	DF, 3 y
Hecker et al.[43]		21	M	Crohn's disease	AZA					Colon	IV	MOPP	DF, 6 mo
Hoshida et al.[21]	1	53	F	RA	MTX	+	NA		MC	LN	IV	Discontinue immunomodulator, chemotherapy	DF, 3.5 y
	2	59	F	RA	MTX	+			MC	LN	III	Discontinue immunomodulator	DF, 9 mo
	3	68	M	RA	MTX	-			MC	LN	IV	Discontinue immunomodulator, chemotherapy	DF, 20 mo
	4	NA	NA	RA	MTX					NA	NA	NA	NA
	5	NA	NA	RA	MTX					NA	NA	NA	NA

References		Age	Sex	Primary Immune Disease	Immunomodulator	EBV	LMP-1	EBNA2	subtype	Biopsy Site	Stage	Therapy	Outcome
Imundo et al.[31]	6	NA	NA	RA	MTX	NA			NA	NA	NA	NA	NA
		17	F	Juvenile RA	MTX, etanercept			NA	NA	LN supraclavicular	II	Chemotherapy	DF, 4 mo
Kamel et al.[1]		65	F	Dermatomyositis	MTX	+	+	NA	NS	LN inguinal	IV	Discontinue immunomodulator	DF, 15 mo
Kamel et al.[34]	1	8	F	Juvenile RA	MTX	-			MC	LN	IV	Chemotherapy	DF
	2	47	M	Psoriasis	MTX	+			MC	LN neck	NA	Discontinue immunomodulator, Radiation	DF, 1 y
	3	58	F	Psoriasis	MTX	-			MC	LN	NA	Radiation	NA
	4	78	F	RA	MTX	-			MC	LN axilla	III	Discontinue immunomodulator, Radiation	CR
Kamel et al.[42]		58	F	Psoriasis	MTX	NA				LN inguinal	NA	NA	NA
Kojima et al.[13]	1	52	M	RA	MTX	+	+		MC	LN neck	I	Chemotherapy, radiation	DF, 5 y
	2	63	F	RA	MTX	-	-		NS	NA	III	Chemotherapy, radiation	AWD, 2 y
	3	57	F	Thyroiditis	MTX	+	-		NS	NA	III	Chemotherapy, radiation	AWD, 6 y
Loo et al.[35]	1	25	F	Dermatomyositis	MTX, thalidomide, PSL	+	+		NS	Scalp	I	ABVD radiation	DF, 6 y
	2	56	F	RA	MTX, adalimumab	-	NA		NS	LN mediastinal	IV	NA	NA
	3	56	F	Autoimmune hepatitis	AZA, PSL	+	+		MC	LN inguinal	II	ABVD	DF, 14 mo
	4	49	F	Crohn's disease	AZA, prednisone	+	+		NOS	Small intestine	I	ABVD; surgical resection	DF, 12 mo
	5	76	F	RA	MTX, adalimumab	+	-		NOS	LN axilla	II	CHOP	DF, 12 mo
	6	40	F	RA	MTX, etanercept	-	-		NOS	LN axilla	III	ABVD	DF, 27 mo
	7	45	M	RA	MTX	+	+		NOS	LN axilla	IV	ABVD	DF, 7 y
	8	77	F	RA	MTX	+	-		NOS	LN pelvic	IV	COPP	DF, 7 y
	9	48	F	SLE	AZA, PSL	+	-		NOS	Anal canal	NA	NA	NA
	10	51	F	SLE	AZA, PSL	+	+		NOS	NA	NA	NA	NA
Mariette et al.[22]	1	55	M	RA	MTX	-	NA		MC	LN	III	NA	NA
	2	39	M	RA	MTX	+	NA		MC	LN	III	NA	NA
	3	43	M	RA	MTX	+	NA		ND (liver)	Liver	IV	NA	NA
	4	46	M	RA	MTX	+	NA		MC	LN	III	NA	NA
	5	55	F	RA	MTX	+	NA		MC	LN	III	NA	NA
	6	65	M	RA	MTX	-	NA		NS	LN	II	NA	NA
	7	82	F	RA	MTX	+	NA		MC	LN	III	NA	NA
Patel et al.[36]		55	M	RA, SLE	MTX, AZA	NA				LN neck	III	Discontinue immunomodulator	NA
Saburi et al.[37]		59	M	RA	MTX, PSL, IFX	+	+	-		Liver	IV	ABVD, predonine	CR.
Salloum et al.[38]		70	F	RA	MTX	+			NS	NA	II	Discontinue immunomodulator	AWD
Sliesoraitis et al.[39]		48	M	SLE	MTX	NA			NS	LN mediastinum	I	EVA	DF, 1 y
Svensson et al.[40]		48	F	RA	MTX	-	NA		NA	Bone marrow	II	Discontinue immunomodulator	DF, 1 y
Tokuhira et al.[9]	1	54	F	RA	MTX	+			MC	BM	IV	ABVD	Dead, PD, 4.8 y
	2	79	M	RA	MTX	+				LN neck	IV	ABVD	alive, 2.0 y
	3	64	M	RA	MTX	+				LN inguinal	III	ABVD	alive, 5.6 y
	4	79	F	RA	MTX	-				BM	IV	PSL	Dead, 0.8 y

No.	References	Age	Sex	Primary Immune Disease	Immunomodulator	EBV	LMP-1	EBNA2	subtype	Biopsy Site	Stage	Therapy	Outcome
5		56	F	RA	MTX, PSL, Tocilizumab	-				LN	II	ABVD	CR, 5.1 y
6		71	F	RA	MTX, PSL	+				LN axilla	IV	ABVD	Dead, 0.9 y
7		60	F	RA	MTX, PSL	+				LN inguinal	IV	ABVD	Dead, PD, 3.3 y
8		67	F	RA	MTX, PSL	+				LN axilla	IV	ABVD	Dead, PR, 2.0 y
9		63	M	RA	MTX, PSL, FK	+				LN axilla	IV	ABVD	alive, 2.4 y
10		54	F	RA	MTX	+				BM	IV	ABVD	alive, 14.8 y
	Vieites et al.[41]	74	M	Ulcerative colitis	IFX	+	NA		MC	Scalp	I	Lomustine, etoposide, prednisone	DF, 1 y
1	Yamakawa et al.[42]	65	F	RA	MTX	+	+	-		LN left axilla	II	ABVD, C-MOPP, radiation	DF, 6.5 y
2		65	F	RA, SS	MTX	+	+	-		LN right axilla	IV	ABVD	Dead (due to bleomycin-induced interstitial pneumonia)
3	Yildirim-Toruner et al.[43]	76	M	RA	MTX	-				LN right axilla	III	Discontinue immunomodulator	Alive
1		11	F	Juvenile RA	MTX, etanercept, IFX, cyclosporine	NA			NA	LN neck	II	ABVD	NA
2		15	F	Juvenile RA	MTX, etanercept	NA			NA	LN neck	II	Chemotherapy	DF, 8 mo
3		9	M	Juvenile RA	MTX, IFX, etanercept	NA			NS	LN axilla	IV	Chemotherapy, radiation	DF, 8 mo

AWD indicates alive with disease; DF, disease-free; DOD, dead of disease; LN, lymph node; NA, not available; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. MTX: methotrexate, AZA: azathioprine, infliximab, PSL: prednisolone