Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders

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Abstract: Other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OII-LPD) is defined by the World Health Organization classification 2016 as lymphoid proliferations or lymphomas that arise in patients treated with immunosuppressive drugs for autoimmune disease or conditions other than in the post-transplant setting. OII-LPD patients have a relatively high incidence of extranodal disease (40–50%). The distinct feature of OII-LPD is spontaneous regression after discontinuation of immunosuppressive drugs. The clinical course of OII-LPD after discontinuation of immunosuppressive drugs can be roughly divided into three categories: regression, transient regression followed by relapse or recurrence, and progression. Regression after discontinuation of immunosuppressive drugs was seen in 70% of OII-LPD patients. About 33% of these patients...
who experienced transient regression had experienced relapse or recurrence. The remaining 30% of patients were without regression even after discontinuation of immunosuppressive drugs. Higher absolute lymphocyte count in peripheral blood at the time of development of OII-LPD and Epstein-Barr virus-encoded RNA (EBER)-positivity are predictive factors of regression.

**Keywords:** malignant lymphoma; methotrexate; MTX-related lymphoma; other iatrogenic immunodeficiency-associated lymphoproliferative disorders; spontaneous regression

**INTRODUCTION**

Patients with congenital or acquired immunodeficiencies have a significantly higher incidence of malignant lymphomas (ML). ML in patients with immunodeficiencies has a distinct feature, including the frequent presence of extranodal disease and an association with Epstein-Barr virus (EBV) (1, 2). The World Health Organization (WHO) classification 2016 classifies immunodeficiency-associated lymphoproliferative disorders into four subtypes: lymphoproliferative disease associated with primary immune disorders, lymphomas associated with human immunodeficiency virus infection, post-transplant lymphoproliferative disorders, and other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OII-LPD). The WHO classification 2016 further defines OII-LPD as lymphoid proliferations or lymphomas that arise in patients treated with immunosuppressive drugs for autoimmune disease or conditions other than in the post-transplant setting (3). This subtype was formerly categorized as the methotrexate-associated lymphoproliferative disorders (MTX-LPD) in the WHO classification 2001, and it was replaced by OII-LPD in the WHO classifications 2008 and 2016 (4).

The precise prevalence of OII-LPD is unknown. However, OII-LPD includes ML developed in rheumatoid arthritis (RA) patients treated with methotrexate (MTX) (3). Although the incidence is low, development of hepatosplenic T-cell lymphoma among patients treated with anti-tumor necrosis factor therapy has also been reported (5). Two studies, in France and Japan, reported the incidence of ML in patients with RA using MTX (6, 7). In the French study, 25 ML cases comprised 18 non-Hodgkin lymphoma (NHL), and 7 Hodgkin lymphoma (HL). The estimated annual incidence rate of NHL was 33.3×10^{-5} (95% confidence interval (CI) 0–80.5) among men and 16.7×10^{-5} (95% CI 0–33.3) among women. Also, the estimated annual incidence rate of HL among men and women was 27.8×10^{-5} (95% CI 0–70.1) and 2.8×10^{-5} (95% CI 0–9.6), respectively (6). The Japanese study, comprised of 66,953 patient-years over a period of 10 years, reported that the ML risk in RA patients was significantly higher (standardized incidence rates 3.43, 95% CI 2.59–4.28) compared to the general population. Furthermore, significant risk factors for onset of ML were higher age (odds ratio 1.04 per additional year of age), use of MTX (odds ratio 3.5, 95% CI 2.0–6.3), and use of tacrolimus (odds ratio 3.9, 95% CI 1.9–7.4) (7).

The etiology of OII-LPD is still controversial, but there are several theories. The first one is the use of immunosuppressive agents. MTX is the first reported
MTX-related lymphoma

immunosuppressive drug associated with lymphoproliferative disorders (8). Secondly, the development of OII-LPD can be associated with Epstein Barr virus (EBV). EBV was detected in HL (~80%) and in DLBCL (~25–60%) in OII-LPD (3). Other hypotheses for the development of OII-LPD include genetic predisposition and immune stimulation by severe chronic inflammation (9).

The pathological subtype of OII-LPD mainly consists of diffuse large B-cell lymphoma (DLBCL), HL, and lymphoproliferative disorder (10). However, it is not frequent; OII-LPD includes EBV-positive mucocutaneous ulcer (11), and hepatosplenic T-cell lymphoma (5). The distinct clinical course of the OII-LPD is spontaneous regression after discontinuation of immunosuppressive drugs. A previous study reported that regression after MTX withdrawal was seen in 70% of patients. Among the patients who experienced a regression, 33% of patients relapsed. On the other hand, the remaining 30% of patients were without regression even after MTX withdrawal (10). This chapter mainly focuses on ML that occurs in RA patients using MTX.

ETIOLOGY

The potential of lymphomagenesis is increased in patients receiving MTX (7, 12). MTX suppresses the activation and adhesion molecule of T cells in a dose-dependent manner. Several mechanisms of action, such as cytokine modulation, adjusting folate antagonism, generating reactive oxygen species, and interfering adenosine signaling (13), have been proposed. The spontaneous regression of MTX-LPD by discontinuing MTX implies the putative pathogenic role of MTX (14). In Japan, MTX has been used for RA since 1999 and the frequency of MTX-LPD has been increasing from 2007 (15). Among 9426 cases of ML diagnosed during 2007–2014 in Japan, the frequency of MTX-LPD cases increased from 0.11% to 1.6%. The increased frequency is probably due to the more prevalent use of MTX in Japan, as MTX has become the mainstay of the treatment since 2011.

EBV is a plausible predisposing factor for MTX-LPD (16). EBV is a gamma herpesvirus and primarily targets B lymphocytes (17). EBV is the most common and persistent virus in humans, approximately 95% of the world’s population are infected asymptomatically. EBV infects “latently” in healthy persons without having any pathogenicity in steady state. However, EBV develops several different lymphoid and epithelial malignancies. EBV-encoded latent genes induce B-cell transformation in vitro and constitutively activate key cell-signaling pathways (17). Patients with RA have impaired control of EBV infection (18). Their peripheral blood T lymphocytes are less efficient in preventing the outgrowth of EBV-infected B cells. Therefore, RA patients have a higher risk for developing EBV-associated LPDs. The positivity rate of EBV among MTX-LPDs is variable. EBV is detected more frequently in HL (~80%) than in DLBCL or other B-cell lymphomas (~25–60%) (3, 19). RA is a possible risk factor for developing lymphoma. The association of RA and lymphoma has been investigated, and three theories have been proposed: genetic predisposition, persistence of long-standing disease activity with continued immune stimulation, and the role of anti-RA therapy (9).
HISTOLOGICAL SUBTYPES

Kurita et al. conducted a nationwide study of MTX-LPDs in Japan (20). A total of 219 patients with newly diagnosed MTX-LPD were analyzed at Kurume University between 2004 and 2015. The results are summarized in Table 1. The median duration from MTX withdrawal to LPD onset was 22 months, and the median duration of MTX administration was 4.3 years. They classified MTX-LPDs into four diagnostic categories: (i) reactive lymphoid hyperplasias (RHs)—lesions of lymphoid proliferation that characteristically have retained architecture of the involved tissue; (ii) polymorphic LPDs (Poly-LPDs)—lesions comprising infiltration of plasma cells, immunoblasts, and variably sized lymphocytes that efface the architecture of lymph nodes or form destructive extranodal masses and that do not fulfill any of the criteria for lymphoid neoplasms; (iii) B/T-cell NHL—lesions that fulfill the criteria for one of the B/T-cell neoplasms that are recognized in immunocompetent hosts and described in the WHO classification 2016; and (iv) classic Hodgkin lymphomas (CHLs)—lesions that fulfill both the morphologic and immunophenotypic criteria of CHL. With caveat, the RHs are not included in the text of WHO classification 2016 (3).

The distribution of histological subtypes of MTX-LPD differs from that of non-MTX-LPD. This is because of the slightly increased frequency of CHL or CHL-like diseases (3). Although the dominant subtype of MTX-LPD is DLBCL-not otherwise specified (NOS) (35–60%), CHL or CHL-like variants are more common, estimated to consist of 12–25% of all MTX-LPDs. Among CHLs, the mixed-cellularity subtype is more frequent than nodular sclerosis (21). With lesser frequency, cases of follicular lymphoma, Burkitt lymphoma, extranodal marginal

| TABLE 1 | Clinicopathologic features of MTX-LPDs according to subtypes (20) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | RH              | Poly-LPD        | DLBCLs          | CHL             |
| Extranodal involvement | 13.8% (4/29)   | 36.4% (12/33)   | 69.5% (73/105)  | 15.4% (4/26)    |
| EBER positivity    | 55.2% (16/29)  | 71.9% (23/32)   | 45.3% (48/106)  | 76.9% (20/26)   |
| Necrosis           | 0% (0/29)      | 51.5% (17/33)   | 34.3% (36/105)  | 12.0% (3/25)    |
| HRS-like cells     | 17.2% (5/29)   | 50.0% (14/28)   | 19.8% (21/106)  | NA              |
| Median duration from MTX withdrawal to the disease regression | 10.4 months | 3.0 months | 4.2 months | 2.7 months |
| Regression without chemotherapy (%) | 14/17 (82.4%) | 22/30 (73.3%) | 31/70 (44.3%) | 2/19 (10.5%) |

CHL, Classic Hodgkin lymphoma; DLBCLs, Diffuse large B-cell lymphomas; EBER, EBV-encoded small RNAs; HRS-like, Hodgkin or Reed-Sternberg-like; MTX-LPDs, Methotrexate related lymphoproliferative disease; NA, Not available; Poly-LPD, Polymorphic-LPD; RH, Reactive lymphoid hyperplasia.
zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), and peripheral T-cell lymphoma have been reported (3). Polymorphic subtype comprises 19.6% of MTX-LPD, which resembles polymorphic post-transplant lymphoproliferative disorders (PTLDs) (22). Rare peripheral T-cell lymphomas have a common extranodal presentation, characterized by cytotoxic profile (23, 24). The immunophenotype of lymphoproliferative disorder in immunosuppressed hosts does not differ from that of the lymphomas in non-immunosuppressed (3). However, in terms of MTX-LPD, the profile of molecular classification of DLBCL is different from that of non-immunosuppressed. DLBCL can be divided into subgroups with germinal center B-cell-like (GCB), activated B-cell-like (ABC), and other gene expressions, namely type 3 using a complementary DNA (cDNA) microarray (25). Among non-immunosuppressed cases of DLBCL, the majority (52.8%) is GCB. ABC and type 3 are 28.9% and 18.3% respectively. Hans et al established a convenient immunohistochemistry technique as a substitute for cDNA microarray to determine the GCB and non-GCB subtypes of DLBCL. Among MTX-associated DLBCL, the majority is ABC immunophenotype (~85%), especially EBV-positive cases (26). The dominant classification of DLBCL (GCB or ABC) is different between MTX-LPD and non-MTX-LPD. Furthermore, EBV-positive MTX-associated DLBCLs commonly express CD30 (19, 26).

Representative pathological figures of MTX-LPD are shown in Figure 1. Most cases of DLBCL exhibit remarkable effacement of architecture with proliferation of

Figure 1. Representative pathological figures of MTX-LPD. A, Sheet-like proliferation of centroblastic variant of DLBCL not otherwise specified (DLBCL-NOS; HE ×400). B, Diffusely proliferated CD20-positive cells of DLBCL-NOS (×400). C, Proliferation of transformed cells is positive for Epstein-Barr virus-encoded RNA (EBER) in DLBCL-NOS (×400). D, Scattered or loose clustered transformed B-cells with abundant small lymphocytes in T-cell/histiocyte-rich large B-cell lymphoma subtype (×100). E, Typical Hodgkin or Reed-Sternberg cells (HRS cells), which exhibit large mononucleated or multinucleated cells, are shown in mixed-cellularity classic Hodgkin lymphoma (×400). F, HRS cells are positive for CD15 (×400). G, HRS cells are also positive for EBV latent membrane protein-1 (LMP-1; ×400). H, Circumscribed ulceration is seen in polymorphic-LPD (×100).
monoclonal transformed B-cell similar to conventional DLBCL (Figure 1A) (20). The sheet-like proliferated cells are positive for CD20 and Epstein-Barr virus-encoded RNA (EBER) (Figure 1B and 1C). In T-cell/histiocyte-rich large B-cell lymphoma, a subtype of DLBCL, exhibit more significantly extensive necrosis ($P = 0.038$), eosinophil infiltrate ($p = 0.035$), Hodgkin or Reed-Sternberg-like cells ($p = 0.009$), and EBER positivity ($P = 0.002$) (Figure 1D) (20). The subtype of CHL fulfills the criteria for CHL described in the WHO classification both morphologically and immunohistologically (3). Typical Hodgkin or Reed-Sternberg cells (HRS cells), which exhibit large mononucleated or multinucleated cells are found (Figure 1E). HRS cells are positive for CD15 and EBV latent membrane protein-1 (LMP-1) (Figure 1F and 1G). Around 10% of MTX-LPD are polymorphic lymphoproliferative cases exhibit an effaced architecture lymph nodes or destructive lesions of extranodal sites with extensive necrosis, including geographic areas. Compared to DLBCL, polymorphic lymphoproliferative cases exhibit more ulceration ($P = 0.029$) (Figure 1H), capsule fibrosis ($P = 0.021$), granulomatous response ($P = 0.043$), and HRS-like cells ($P = 0.002$) (20).

To diagnose CHL-like MTX-LPD while excluding typical CHL, immunophenotyping is crucial. In CHL-like MTX-LPDs, the large cells are typically CD20+/CD30+/CD15-, whereas in CHL the large cells are CD20-/CD30+/CD15+. Immunophenotyping of EBV is also useful as a diagnostic tool. EBV “latency” exhibits the status of viral infection determined by the expression of EBV-encoded nuclear antigens or latent membrane protein (17). Type II latency is associated with expression of EBNA1, LMP1, LMP2A, and EBER and commonly seen in CHL and a subset of posttransplant lymphoproliferative disorders (PTLDs) (27). Type III is characterized by the expression of all 6 EBV nuclear antigens (EBNA1, 2, 3A, 3B, 3C, and LP), three latent membrane proteins (LMP1, 2A, and 2B), and EBER. Type III latency is observed in patients with a subset of PTLDs. With regard to MTX-LPD, type II latency is more common than type III (3). The positivity rate of EBV among MTX-LPD is variable. EBV is detected more frequently in HL (~80%) than in DLBCL (~45%) or other B-cell lymphomas (20). According to the compiled data, the EBV positivity is higher in polymorphic/lymphoplasmacytic infiltrates and Hodgkin lymphoma (70.6% and 82.6%, respectively). On the contrary, EBV positivity is only 41.7% in DLBCL subtype (3).

Of note, MTX-LPD is not limited to B-cell malignancies. MTX-LPD of T-cell phenotype is also reported, although relatively rare (4–8% of MTX-LPDs). MTX-LPD of T-cell phenotype had more frequent spontaneous regression ($p = 0.061$) (28).

**CLINICAL FEATURES**

A previous study reported patients’ characteristics of OII-LPD. Tokuhira et al. reported 28 MTX-LPD patients, consisting of MTX-LPD cases diagnosed with biopsy (7 patients) and clinically diagnosed MTX-LPD cases without biopsy (21 patients). There were 9 men and 19 women, and the median age was 65.0 (range, 29–86) years at the onset of MTX-LPD. The median MTX duration and dose at the
onset of MTX-LPD were 5.9 years (range, 0.2–19.7 years) and 8.0 mg/week (range, 4–12 mg/week), respectively. The autoimmune diseases as comorbidities were RA only (22 patients), RA and Sjogren’s syndrome (3 patients), RA, Sjogren’s syndrome and systemic sclerosis (1 patient), psoriasis vulgaris (1 patient), and RA vasculitis (1 patient) (29).

The initial manifestations of these 28 MTX-LPD patients were lymphadenopathy (14 patients), fever (9 patients), respiratory manifestation (4 patients), extranodal mass (1 patient), gingival swelling with ulcer (1 patient), and back pain (1 patient) (29). Moreover, 40–50% of MTX-LPD patients have extranodal disease (3, 22). A previous study reported extranodal disease among 89 OII-LPD patients. The location of extranodal disease was liver (10 patients), spleen (10 patients), lung (7 patients), skin (7 patients), adrenal gland (3 patients), pleura (3 patients), bone (3 patients), gingiva (2 patients), kidney (1 patient), small bowel (1 patient), and breast (1 patient) (22). Furthermore, according to the WHO Classification 2016, a total of 274 MTX-LPDs were extracted from several references and the results were compiled. Especially, DLBCL and polymorphic/lymphoplasmacytic infiltrates are likely to arise as extranodal manifestations (73.3% and 100%, respectively). HL tends to be nodal localization (extranodal presentation is only 10.5%) (3).

The clinical stage at onset, determined based on physical examination and imaging results, was as follows: stage I in three patients, stage II in nine patients, stage III in four patients, and stage IV in 12 patients. The median values of serum lactate dehydrogenase level, C-reactive protein level (CRP), and soluble interleukin-2 receptor (sIL-2R) level were 228.5 (range, 148–593) U/L, 1.7 (range, 0–15.3) mg/dL, and 1756 (range, 256–8150) mg/dL, respectively (29).

The distinct feature of OII-LPD is spontaneous regression after discontinuation of immunosuppressive drugs. The clinical course of OII-LPD after discontinuation of immunosuppressive drugs can be roughly divided into three categories; regression, transient regression followed by relapse or recurrence, and progression (4). The three clinical courses are illustrated in Figure 2. A previous study reported that regression after MTX withdrawal was seen in 70% of MTX-LPD patients; 33% of these patients who experienced transient regression had experienced relapse or recurrence. Moreover, the median duration from the time

![Figure 2. The three clinical courses of OII-LPD after discontinuation of immunosuppressive drugs. The arrows indicate discontinuation of immunosuppressive drugs. OII-LPD, Other iatrogenic immunodeficiency-associated lymphoproliferative disorders.](image-url)
of MTX withdrawal to the time of relapse or recurrence was 10.6 months (range, 0.7–35.6 months). On the other hand, the remaining 30% of patients were without regression even after MTX withdrawal (10). Suggested clinical management of OII-LPD is shown in Figure 3. When ML does not regress or has a relapse or recurrence, chemotherapy should be performed without delay (4).

The rate of regression varies by histological type, and the rate varies greatly among each report. Furthermore, according to the WHO classification 2016, a total of 274 MTX-LPD was extracted from several references, and the results were compiled. As to spontaneous regression by the discontinuation of MTX, polymorphic/lymphoplasmacytic infiltrates were likely to regress more frequently (71.4%) than DLBCL and HL (30.4% and 44%, respectively). Although these results were not analyzed in a coherent pathological laboratory, rather integrated data from multiple studies and datasets, it is useful to grasp the overview of the clinicopathological features of MTX-LPD (3). As described above, spontaneous regression by discontinuing MTX was seen in 30–44% among MTX-related DLBCL. Another small study of MTX-LPDs, including 34 cases of DLBCL-type and 17 cases of CHL-type, reported the regression rate according to the disease subtypes (30). In this study, DLBCL achieved regression without chemotherapy, and CHL-like MTX-LPD achieved spontaneous regression temporarily. The discontinuation of MTX was not sufficient to resolve the CHL-type MTX-LPD, and additional chemotherapy was required in 76% of the patients eventually.

Several factors associated with regression have been reported (31). Firstly, an absolute lymphocyte count (ALC) in peripheral blood is associated with regression. For details, ALC was investigated among 33 MTX-LPD patients; the percentage of MTX-LPD who regressed (R group), once regressed but relapsed (R/R group), and progression (P group) were 41%, 35%, and 24%, respectively. The median ALC at the time of MTX withdrawal due to MTX-LPD development in R group, R/R group, and P group were 1146/µL (range, 517–1647/µL), 570/µL (range, 248–902/µL), and 780/µL (range, 324–1491/µL), respectively. There was a significant difference in the ALC values between R group and R/R group.

Figure 3. Suggested clinical management of OII-LPD. ALC, Absolute lymphocyte count in peripheral blood at the time of development of OII-LPD; EBER, Epstein-Barr virus-encoded RNA; OII-LPD, Other iatrogenic immunodeficiency-associated lymphoproliferative disorders.
MTX-related lymphoma

(p = 0.0002), R group had a higher ALC than R/ R group. But there was not a
significant difference between R group and P group (p = 0.298). As for the transi-
tional changes in ALC, in R group, the ALC gradually increased until 24 months
after MTX withdrawal. The ALC in R/R group was significantly recovered after
1 month after MTX withdrawal but it started to decrease after one month. The
decrease of ALC continued until the relapse of MTX-LPD. In P group, there is no
statistically significant difference in ALC between the time of MTX withdrawal
due to MTX-LPD development and 1 month later. In other words, there seems to
be no change in the ALC values (31).

Another study reported the association between EBER positivity and regression (32). Among lymphoproliferative disorders in patients with autoimmune dis-
ease treated with immunosuppressive drugs, EBV was detected by EBER probe in
43% (29 out of 67 examined cases). Of the 29 patients, immunosuppressive drugs
were discontinued in 23 patients. The remaining 6 patients were treated with
chemotherapy. Among 23 patients with discontinued immunosuppressive drugs,
regression was observed in 82.6% (19/23 patients), while stable and progressed
diseases were observed in 17.3% (4/23 patients). In this study, multivariate analy-
sis of predictive factors associated with regression after withdrawal of immuno-
suppressive drugs showed that EBER positivity was an independent factor
(p = 0.022) (32).

PROGNOSIS

According to a nationwide study of MTX-LPDs in Japan, a total of 219 patients
with newly diagnosed MTX-LPD were analyzed at Kurume University between
2004 and 2015. The median progression-free survival (PFS) in the overall cohort
was 46 months (range, 1 to 91 months), while the median OS could not be esti-
mated. However, the estimated survival rate after 5 years was 83.8%. PFS differed
significantly between the RH, Poly-LPD, DLBCL, and CHL groups. Although none
of the RH patients died of the disease, median PFS time was shorter among DLBCL
and CHL (20 months and 5 months, respectively). By contrast, overall survival
(OS) was not significantly different among the 4 groups (20). Moreover, a previ-
ous study reported that OS was not significantly different between the DLBCL and
CHL subtype (91% vs. 94%, respectively; P>0.05) (20). If EBER is positive, sponta-
neous regression is more likely than that of EBER-negative cases (6, 33).
Nevertheless, the EBER positivity does not affect OS (22). Taken together, the
subtype of MTX-LPD and EBER positivity correlates to the spontaneous regres-
sion. It is uncertain whether these factors correlate to OS.

There are several factors associated with prognosis. A significant difference in
OS was detected in patients with CRP > 5 mg/dl (p = 0.0244) and sIL-2R>4000
U/L (p = 0.0135). The patients with sIL-2R>4000 and CRP > 5 mg/dl had a shorter
OS (29). Moreover, according to another study, poor PFS was associated with
advanced stage (p = 0.024), worse performance status (p = 0.031), and CHL his-
tology (p = 0.013). Moreover, as for antibodies specific to EBV, a viral capsid
antigen (VCA) immunoglobulin (IgG) titer over 1:640, or any level of detectable
early antigen (EA) IgG is defined reactivation pattern. The patients who had reac-
tivation pattern of EBV-related antibodies also had poor PFS (p = 0.029) (32).
CONCLUSION

OII-LPD arises in patients treated with immunosuppressive drugs. The majority of cases are patients using MTX. However, a few cases of patients with anti-tumor necrosis factor therapy have been reported. The distinct feature of this disease is spontaneous regression after discontinuation of immunosuppressive drugs. However, there are some cases that do not regress even after discontinuation of immunosuppressive drugs. Furthermore, there are cases that relapse even after experiencing transient spontaneous regression. This phenomenon deserves to be kept in mind in clinical practice. Patients who discontinued immunosuppressive drugs require close observation. When ML does not regress or has a relapse, chemotherapy should be performed without delay.

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REFERENCES

2. Oertel S H, Riess H. Immunosurveillance, immunodeficiency and lymphoproliferations. Recent Results Cancer Res. 2002;159:1–8. https://doi.org/10.1007/978-3-642-56352-2_1


