

## Risk of Lymphoproliferative Disorders in Spondyloarthritis during Treatment with Methotrexate: A Case Report and Literature Review

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### Abstract

Unlike rheumatoid arthritis, risks of lymphoproliferative disorders (LPDs) in spondyloarthritis (SpA) are not well established. Recent studies suggest that the overall risk of lymphoma does not seem to be increased compared to the general population, however, SpA patients taking disease-modifying anti-rheumatic drugs including methotrexate (MTX) may link to higher occurrence of LPDs. We herein report a 40-year-old man diagnosed with non-radiographic axial SpA according to the Assessment of Spondyloarthritis International Society (ASAS) classification criteria. While initiation of oral MTX and celecoxib treatments appeared to gradually improve symptoms, cervical lymphadenopathy appeared accompanied by fever and deteriorated arthritis following 13 months. Laboratory results showed increased serum levels of inflammatory markers, liver transaminases, soluble interleukin-2 receptor and ferritin as well as thrombocytopenia in combination with hepatosplenomegaly detected by Computed Tomography. Furthermore, hemophagocytosis also existed in bone marrow. Diagnostic lymph node biopsy pathologically revealed diffuse large B-cell lymphoma (DLBCL), resulting in a diagnosis of DLBCL concomitant with lymphoma-associated hemophagocytic lymphohistiocytosis (LA-HLH). Since the DLBCL persisted following four weeks of MTX discontinuation, chemotherapy was initiated and finally resulted in remission. To our knowledge, there is no report on LPDs concomitant with LA-HLH in a patient with SpA during MTX treatment. This suggestive case supports the recent estimation in which the risk of LPDs in SpA patients is increased and also demonstrates the importance of chemotherapeutic treatment for LPDs concomitant with LA-HLH.

**Keywords:** Spondyloarthritis; Lymphoproliferative disorder; Diffuse Large B Cell Lymphoma; Methotrexate; Hemophagocytic Lymphohistiocytosis

### Introduction

Higher risks of lymphoproliferative disorders (LPDs) compared with the general population have been reported in rheumatic diseases characterized by chronic inflammation. In rheumatoid arthritis (RA), it has widely been recognized that the risk of LPDs induced by RA itself is more than double depending on disease activity and severity.

Spondyloarthritis (SpA) is one of the most common forms of chronic inflammatory arthritis affecting 0.1%-1.5% of western populations [1]. There are limited studies evaluating malignancy risk in SpA patients. Recent studies have reported that risks of LPDs for SpA do not seem increased compared to the general population [2]. In general, serum inflammatory marker levels are not significantly increased in SpA compared to patients with RA; however, persistent chronic inflammation and the use of immunosuppressive drugs might be related to the occurrence of malignancies.

Besides chronic inflammation, treatments of rheumatic diseases have also been linked to risks for LPDs. Although methotrexate (MTX) is one of the pivotal drugs for autoimmune diseases such as RA, there are numbers of reports on MTX-associated LPDs (MTX-LPDs) in patients with RA [4,5]. MTX is also used for SpA treatment to alleviate clinical symptoms, especially when targeting peripheral arthritis [3].

However, there is no established consensus on the risk of MTX-LPDs in patients with SpA.

Hemophagocytic lymphohistiocytosis (HLH), also referred to as hemophagocytic syndrome, is a life-threatening clinical syndrome characterized by fever, splenomegaly, pancytopenia, liver dysfunction and coagulopathy. HLH is classified into two groups based on the underlying pathogenesis: genetic (primary) and acquired (secondary). While primary HLH is characterized by genetic defects, secondary HLH is a condition resulting from hyper-reactive immunologic activation, mostly secondary to systemic infection, autoimmune disorders, or malignancies including LPDs. In particular, HLH induced by LPDs are termed lymphoma-associated hemophagocytic lymphohistiocytosis (LA-HLH). Although HLH associated with rheumatic diseases such as RA and adult onset Still's disease have been reported to date [6,7], to our knowledge, there is no report on LA-HLH in a patient with SpA during MTX treatment.

Here we report a very rare case in which a patient with non-radiographic axial SpA later developed diffuse large B-cell lymphoma (DLBCL) concomitant with LA-HLH possibly induced by MTX and chronic inflammation originated from SpA.

### Case Report

A 40-year-old man was presented to a rheumatology clinic complaining of fatigue, chronic low back pain lasting more than 6 months, bilateral swollen fingers, and arthralgia in bilateral metacarpophalangeal, proximal interphalangeal and proximal

interphalangeal joints. The features of low back pain included early morning stiffness, relief with exercise, lack of improvement with rest, and nocturnal pain, strongly implying the existence of inflammatory back pain. He had no history of skin diseases including psoriasis, abdominal pain, diarrhea or hematochezia. He was only sexually active with his girlfriend and had no history of sexual transmitted disease. Physical examination demonstrated peripheral arthritis and dactylitis in his bilateral fingers and enthesitis in his bilateral ankles [Figure 1A(i,ii)].



**Figure 1A:** Clinical manifestations and findings of imaging studies; (i) Dactylitis observed in right thumb, (ii) Swollen bilateral achilles tendons.

No skin rash, abnormalities in his eyes, and neurological deficits were detected. The result of Lasègue test (straight leg test) was negative and Schorber's test was 4.5 cm (normal  $\geq 4$  cm). Lateral spinal flexion was 15 cm on both sides (normal  $>10$  cm), chest expansion was 5 cm (normal  $>2.5$  cm), cervical rotation was  $80^\circ\text{C}$  to both sides (normal  $>70^\circ\text{C}$ ), and tragus-to-wall distance was 13 cm (normal  $<15$  cm) [8,9].

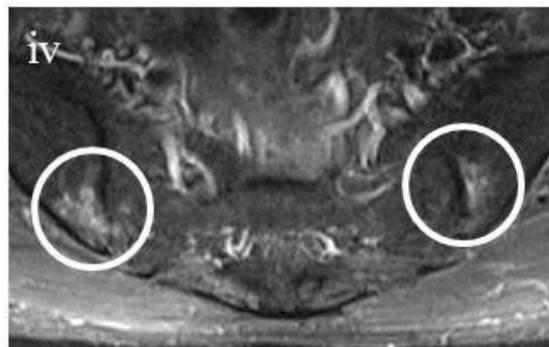
Laboratory studies showed increased levels of serum inflammatory markers such as C-reactive protein (CRP) (3.24 mg/dL) and erythrocyte sedimentation rate (ESR) (42 mm/hr). Rheumatoid factor (RF) was normal (4 IU/mL, normal range: less than 10) and anti-cyclic citrullinated peptide (anti-CCP) antibodies were also negative. Polymerase Chain Reaction (PCR) test in urine for antigens of *Chlamydia trachomatis* and gonorrhea were negative. The serology test for HLA-B27, the most well-known and strongest genetic risk factor for SpA [10], was positive. Right ankle X-ray showed Achilles tendon calcification, suggesting the existence of chronic tendinitis in this area [Figure 1A (iii)].



**Figure 1A (iii):** Achilles tendon calcification implied chronic enthesitis.

X-rays of the lumbar spine did not show any relevant abnormality and the sacroiliac joints appeared normal (grade 0; New York Criteria),

but MRI clearly showed bone edema in bilateral sacroiliac joints with no erosions, bone sclerosis, bony bridges or major fat deposits, suggesting very early stage of sacroiliitis [Figure 1A (iv)].



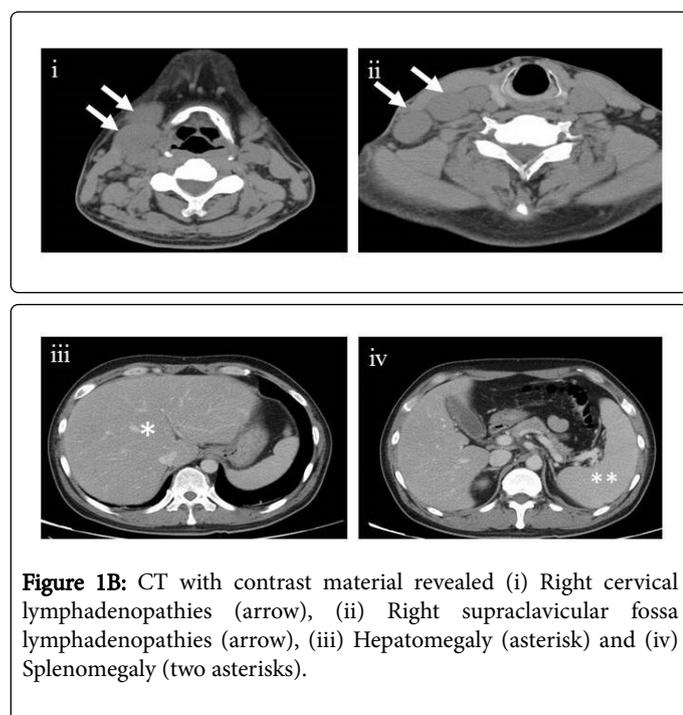
**Figure 1A (iv):** Bilateral bone edema in both sacroiliac joints detected by T2-weighted MRI with the administration of contrast material.

Based on these results, the patient was diagnosed with axial SpA at the preradiographic stage (non-radiographic axial SpA) according to Assessment of Spondyloarthritis International Society (ASAS) classification criteria [11]. Besides physiotherapy, treatment was initiated with celecoxib (200 mg/day) and salazosulfapyridine (SASP). However, two weeks later, skin rash caused by SASP was revealed on his upper and lower extremities and trunk. Instead of SASP, oral MTX (8 mg/week) was initiated to alleviate peripheral arthritis. The dose of MTX was gradually increased to 16 mg/week. Although clinical symptoms seemed to gradually improve after increasing the dose of MTX, the disease activity still persisted. We recommended the patient for the initiation of anti-tumor necrosis alpha inhibitors (TNFi) such as infliximab or adalimumab for controlling clinical symptoms as well as serum inflammatory markers, but the patient refused them due to medical costs and concerns about side effects.

Thirteen months after treatment initiation, the patient was admitted to our hospital for evaluation after reporting the presence of palpable lumps in the right side of his neck that had developed over the preceding few weeks. The patient also complained of malaise, pyrexia ( $38^\circ\text{C}$ - $39^\circ\text{C}$ ), night sweats and weight loss (3 kg in last 3 weeks). His vital signs at the time of admission were: temperature  $37.9^\circ\text{C}$ ; heart rate 101/min and regular; respiratory rate 16/min and unlabored; blood pressure 122/75 mmHg. Physical examination confirmed that the cervical lymphadenopathies were non-tender, firm and relatively immobile. No other lymphadenopathy including the axillary and superficial inguinal chains could be detected. There was slight swelling and tenderness in his bilateral shoulder, wrist and knee joints. Apart from non-tender hepatosplenomegaly, the rest of the physical examination including skin (no psoriasis) and neurological manifestations were normal.

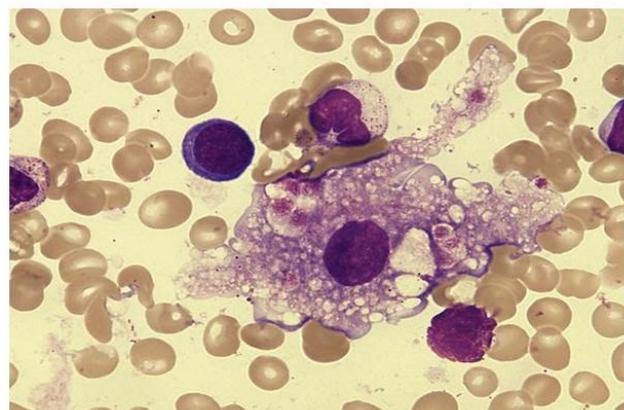
Laboratory data on admission revealed a white blood cell count of  $9800/\mu\text{L}$  with 89.1% neutrophils, 4.5% lymphocytes and 3.3% monocytes. Atypical lymphocytes were not present. Hemoglobin levels were within normal range; however, thrombocytopenia was evident ( $37,000/\mu\text{L}$ ), and decreased fibrinogen (136 mg/dL) as well as increased fibrin/fibrinogen degradation products (FDP) ( $20 \mu\text{g/mL}$ ) and D-dimer ( $15.7 \mu\text{g/mL}$ ) were elevated, demonstrating the diagnosis

of disseminated intravascular coagulation (DIC) based on the diagnosis criteria of International Society on Thrombosis and Haemostasis (ISTH) [12]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated at 192 IU/L and 127 IU/L, respectively. Renal function tests were normal. Levels of CRP and ESR were elevated at 208 mg/L and 46 mm/hr, respectively. The level of serum soluble interleukin-2 receptor (sIL-2R) was elevated at 3850 U/mL (normal range: 121–383). Serum ferritin level was also elevated at 2579 ng/dL (normal range: 30–300). Tests for Epstein-Barr virus (EBV) and cytomegalovirus were post-infection patterns. Human immunodeficiency viruses, which can cause secondary lymphoma, were negative. Three sets of blood culture test showed no growth of bacteria. Chest radiography demonstrated clear lung fields. Computed tomography (CT) with contrast medium showed enlarged lymph nodes in the right cervical chain and supraclavicular fossa [Figure 1B (i, ii)], of diameter 30 mm–40 mm, and confirmed the presence of hepatosplenomegaly [Figure 1B (iii, iv)].



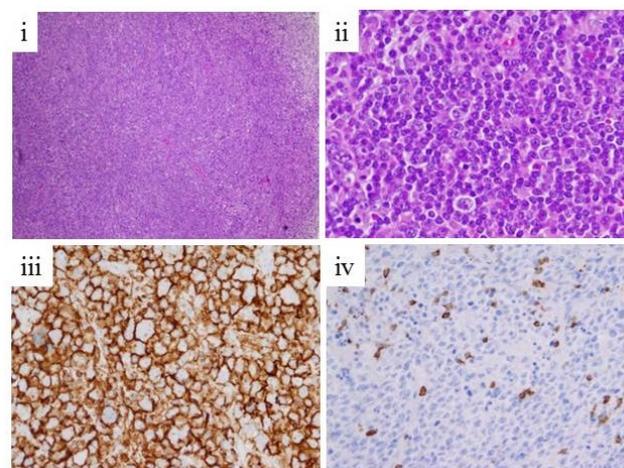
**Figure 1B:** CT with contrast material revealed (i) Right cervical lymphadenopathies (arrow), (ii) Right supraclavicular fossa lymphadenopathies (arrow), (iii) Hepatomegaly (asterisk) and (iv) Splenomegaly (two asterisks).

Bone marrow aspiration showed normoplastic marrow with 40–50% cellularity (Nuclear cell count was  $14.6 \times 10^4/\mu\text{L}$ ), mild to moderate myeloid hyperplasia and hemophagocytosis (Figure 2A).



**Figure 2:** (A) Bone marrow smear showed phagocytosed platelets by Macrophage.

No definite malignant foci were seen. Histopathological examination of the lymph node biopsy specimen revealed the proliferation of large atypical lymphocytes diffusely, which was consistent with DLBCL. The cell surface markers of lymphoma cells showed the positive for CD20, MUM1, Bcl-6, and negative for CD3, CD10, and CD25. The expression of EBV Latent Membrane Protein 1 (EBV-LPM1) was not detected. On the basis of pathological findings, the patient was histologically diagnosed with DLBCL, non-germinal center B (GCB) cell type [Figure 2B (i–iv)].



**Figure 2:** (B) Pathological results of supraclavicular fossa lymph nodes; (i) (ii) Hematoxylin and Eosin (H-E) staining revealed diffuse large atypical lymphocytes (i: 40 $\times$ , ii: 400 $\times$  magnification), (iii) positive for anti-CD20 stain (200 $\times$  magnification), and (iv) negative for anti-CD3 stain (200 $\times$  magnification).

As well as DLBCL, the patient satisfied the diagnostic criteria for HLH proposed in HLH 2004 [13], as he had persistent pyrexia in excess of 38 $^{\circ}\text{C}$ , splenomegaly, hypofibrinogenemia (fibrinogen level  $\leq 150$  mg/dL), bone marrow hemophagocytosis, and substantially elevated serum ferritin (ferritin level  $\leq 500$   $\mu\text{g/dL}$ ) and sIL-2R levels.

After excluding the possibility of infections and other autoimmune diseases, the patient was diagnosis with DLBCL concomitant with LA-HLH induced by MTX and/or chronic inflammation caused by SpA. Furthermore, DIC was also complicated with this severe condition. MTX was immediately discontinued and the lymphadenopathy began to regress within next 4 weeks but still persisted. On the basis of persistent LPD, the emergence of rapidly progressing LA-HLH and DIC, chemotherapy with a 3-week interval of R-CHOP therapy was initiated, consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (Figure 3).

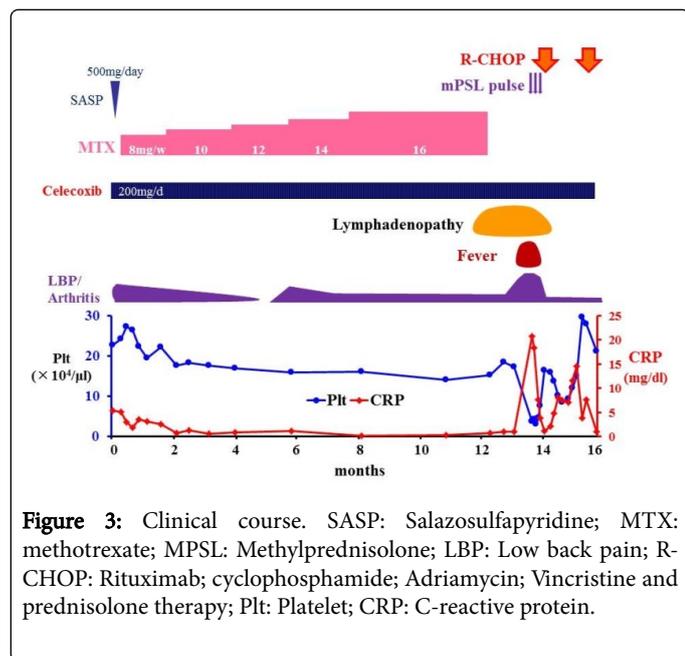
Six cycles of R-CHOP chemotherapy had been completed without relapse of DLBCL or SpA.

## Discussion

### The risk of LPDs in SpA

In RA, it has been well-established that the risk for development of LPDs is significantly increased, correlating with the degree of inflammation and disease severity [14-16]. Reports have been shown that the relative risk of developing LPDs in patients with RA is approximately 2.0 to 5.5 times higher than that observed in the general population [17,18]. Baecklund et al., also reported that in RA, high inflammatory activity was the most prominent risk factor for LPDs, with an odds ratio of 25.8 when compared with low inflammatory activity [14].

The exact pathophysiological mechanism underlying this observation is unclear, but chronic continuous stimulation causes B-cell transformation leading to development of LPDs [19]. However, there is no established consensus as to whether patients with SpA have an increased risk for LPDs as a consequence of persistent chronic inflammation and the use of long-term immunosuppressive agents. A recent large cohort study (more than 8,700 patient with AS and almost 20,000 patients with PsA) published by Hellgren et al. reported the hazard ratio (HR) in the occurrence of lymphoma in patients with AS and PsA compared to general population were 0.9 (95% confidence interval [95% CI] 0.5-1.6) and 1.2 (95% CI 0.9-1.7) respectively [2]. This data demonstrates that the risk of LPDs in SpA does not seem to be increased as previously reported [20,21] (Table 1).



Author, (ref.)	Year	Source country	of Study design	Subtype of SpA	No. of involved patients with SpA	Risks of incident of LPD (95% CI)	Outcome of LPD risks
Asking [20]	2006	Sweden	Population-based case-control	AS	NA	RR: 1.0 (0.6-1.7)	No increase
Mellemkjaer [21]	2008	Sweden	Population-based case control	AS	25,941	RR: 1.1 (0.6-1.8)	No increase
Rohekar [27]	2008	Canada	Cohort	PsA	665	RR: 0.7 (0.3-1.8)	No increase
Anderson [28]	2009	US	Population-based case control	AS	NA	RR: 1.1 (0.7-1.5)	No increase
Hellgren [2]	2014	Sweden	Population-based case control	AS	8,707	HR: 0.9 (0.5-1.6)	Increase only in PsA patients taking SASP and/or MTX
				PsA	19,283	HR: 1.2 (0.9-1.7)	
						HR: 1.7 (1.0-3.1)*	
Gross [29]	2014	US	Cohort study	PsA	2,970	0.04/100 patient-year	N/A

**Table 1:** Reports in the last 10 years showing risks of LPDs in patients with SpA \*Hazard ratio of PsA patients taking SASP and/or MTX. SpA: Spondyloarthritis; Lpds: Lymphoproliferative Disorders; 95% CI: 95% Confidential Interval; AS: Ankylosing Spondylitis; Psa: Psoriatic Arthritis; NA: Not Available; RR: Relative Risk; HR: Hazard Ratio; RA: Rheumatoid Arthritis; SASP; Salazaosulfapyridine; MTX: Methotrexate.

However, it was also shown that HR in specific patients taking MTX and/or SASP was 1.7 (95% CI 1.0-3.1), suggesting the possibility of higher increased ratio of LPDs in SpA patients taking conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

There are several explanations for the discrepancy between LPD risk in RA and that in SpA. In RA, activated autoimmune B-cells characterized by production of RF and anti-CCP and systemic inflammation continuously stimulate chronic immune response, leading to development of lymphoma [22,23]. This is made apparent by observing increased B-cell type lymphomas such as DLBCL in RA patients [15]. On the other hand, T-cell lymphomas are higher in other autoimmune diseases including psoriasis [24,25]. Our patient was diagnosis with DLBCL which may be uncommon to SpA, but such incidents have been previously reported [2]. Considering the disease activity of SpA in this case gradually subsided through the induction of MTX treatment, the possibility of SpA being a significant contribution towards the development of DLBCL seems to be low. However, given the aspect of increased risk of LPDs after diagnosis of RA in the last 5-10 years [26], persistent chronic inflammation could partially lead to the occurrence of DLBCL.

### MTX-induced LPDs in SpA

This case strongly suggests the contribution of MTX for the occurrence and development of DLBCL. MTX is now the most frequently prescribed DMARD for RA and well established for its long-term safety [30]. As discussed earlier, increases in the risk of LPDs associated with RA mainly relate to higher levels of disease activity of RA, but LPDs are also widely known to be associated with MTX use in patients with RA which was first reported by Ellman et al. appeared in 1991 [31]. Estimation for the independent risk of MTX for MTX-LPDs in RA is still unclear because RA patients taking a higher dose of MTX tend to have higher disease activity. However, given that there are some cases in which MTX-LPDs spontaneously regress exclusively after the discontinuation of MTX, it appears the usage of MTX itself is strongly correlated with the appearance and development of LPDs.

Hoshida et al. reported the median duration between initiation of MTX and the occurrence of LPDs was 132 months (range 3-360 months) [4]. Another study reported the median duration to be 56 months, with a median cumulative dose of 864 mg among 29 RA patients with MTX-LPDs [32]. Given a 13-month duration of treatment and 360 mg cumulative dose of MTX, LPD in our case developed after a relatively short period and with a small cumulative dosage of MTX, suggesting that other factors including SpA related chronic inflammation may contribute to the development of DLBCL. Hoshida et al. also reported the frequency of DLBCL among all lymphomas to be 60.4% in patients with MTX-LPDs, which was higher than in sporadic LPDs patients (42.7%). Although the detailed pathophysiological mechanisms in MTX-LPDs are not fully understood, several hypotheses have been advanced: activation of latent EBV infection; direct oncogenic action; decreased apoptosis of infected B-cells; and decreased natural killer (NK) cell activity. EBV in particular is a well-known risk factor for inducing LPDs in patients treated with MTX. Malignant transformation of B-cells or epithelial cells infected with EBV can result in the development of various EBV-associated cancers in both children and adults. Mariette et al. reviewed 12 cases of DLBCL induced by MTX in patients with RA and found that two patients had positive EBV serology [33]. In our case, we excluded the possibility of association with EBV, as the expression of

EBV-LPM1 was not pathologically detected and serum tests for EBV were post-infectious patterns.

MTX is also used to treat arthritis, enteritis and psoriasis in patients with SpA. Although MTX is of questionable benefit in AS [34], MTX is preferably used for peripheral arthritis in SpA and it is recommended as standard therapy in recent guidelines, especially in PsA [35,36]. However, it has been very rarely reported the occurrence of LPDs in patients with SpA treated with MTX. A report published by Homsy et al. presented a case of a 70-year-old woman with PsA who had bilateral lung infiltrates, pleural effusion, splenomegaly, and inguinal lymphadenopathy during treatment with MTX. Similarly to our case, this patient was diagnosed with DLBCL induced by MTX and the authors recommended that clinicians consider the possibility of LPDs in patients with PsA treated with MTX [37]. Another report published by Jin et al. showed the case of thyroid marginal zone B-cell lymphoma in a patient with PsA treated with MTX and etanercept (ETN), one of the TNFi drugs [38]. They concluded that the synergetic effect of TNFi and conventional immune modulators including MTX may increase the risk for development of malignancies including LPDs. Based on these report, it appears to be significantly important to consider the possibility of LPDs in SpA patients with lymphadenopathy, especially for patients taking immunosuppressive agents including MTX.

### LPDs and HLH

The patient fulfilled the diagnostic criteria for HLH based on 6 out of 8 diagnostic criteria (HLH-2004); fever, splenomegaly, hypofibrinogenemia (fibrinogen level  $\leq 150$  mg/dL), hemophagocytosis in the bone marrow, and increased serum levels of ferritin ( $>500$   $\mu$ g/L) and sIL-2R ( $>2400$  U/mL) [13]. HLH is a severe condition which may be fatal. Although the pathogenesis of HLH remains unclear, excessive amount of proinflammatory cytokines such as TNF- $\alpha$ , interleukin (IL)-1 $\beta$  and IL-6, released from prolonged and intense activation of macrophage, histiocytes and CD8+ T-cells, lead to uncontrolled hyperinflammatory conditions. Dysregulated ability of cytotoxic T-cells (CTLs) to remove antigen-presenting cells (APCs) including macrophage and histiocytes leads to chronic stimulation of CD8+ cytotoxic lymphocytes and the release of huge amounts of cytokines resulting in various clinical manifestations and laboratory abnormalities observed in HLH [39].

There is an extremely rare case report published by Lou et al. showing that macrophage activating syndrome (MAS), a form of HLH, is caused by the activity of AS itself [40], but this seems unlikely for our patient, as the disease activity of SpA gradually improved when DLBCL emerged. Considering the appearance of HLH and DLBCL at the same time, HLH in our patient seemed to be induced by DLBCL.

The majority of HLH-associated malignancies has been reported in T-cell (T-LAHLH) and NK-cell lymphomas, but can also occur during the development of other hematological malignancies including B-cell lymphoma and Hodgkin's lymphoma [41,42]. Interestingly, B-cell lymphoma-associated with HLH (B-LAHLH) have primarily originated from Asian populations [43]. Takasaki et al. reported nearly half of Japanese patients with LA-HLH have B-LAHLH (68 cases in 142 patients) [44]. Although the mechanism of B-LAHLH still remains unclear, Ohno et al. reported much higher levels of IL-6, IL-10 and TNF- $\alpha$  in patients with B-LAHLH compared to patients with T-LAHLH, whereas the latter presented with higher levels of IFN- $\gamma$ . These results imply a difference in the pathogenesis of LAHLH in B- and T- lymphomas [39].

### Treatments of MTX-LPDs associated with HLH

The prognosis of secondary HLH is strongly influenced by the underlying etiology and appropriate treatment. While the 5-year survival rate of HLH induced by infection or autoimmune diseases is reported 83%-90%, that of HLH induced by T-cell lymphoma and B-cell lymphoma is 12% and 48%, respectively [45]. This result strongly indicates that early diagnosis and treatment especially for B-cell lymphoma is crucial.

The treatment of MTX-LPDs remains controversial. Some reports have suggested that the optimal initial treatment of MTX-LPDs is observation (watch and wait) after MTX discontinuation; however, the outcomes from this approach are not uniformly excellent. Mariette et al. showed that among 18 patients with RA and MTX-LPDs, only one achieved long-term clinical remission after withdrawing MTX alone [33]. Another report showed that tumor size reduction was seen only in 20%-30% of cases of MTX-LPDs [46]. Tokuhira et al. reported that the tendencies for spontaneous regression of MTX-LPDs were less disease activity and lymphadenopathy subsided within 4 weeks [47]. Additionally, Ichikawa et al. demonstrated that the spontaneous regression rate of MTX-LPDs was significantly higher in patients with EBV-induced lymphoma and non-DLBCL. According to these reports, only discontinuation of MTX does not seem to be sufficient treatment for MTX-LPDs. However, Kawakami et al. recommended stopping MTX before starting chemotherapy whenever possible, as they observed chemotherapy as the first-line treatment without discontinuation of MTX did not always result in a preferable outcome due to complicated infections [48].

In the current case, given that persistence of DLBCL even after 4 weeks despite discontinuing MTX, no relationship with active EBV infection and the existence of LA-HLH, it was strongly recommended to initiate the chemotherapy. After six cycles of R-CHOP chemotherapy, DLBCL achieved remission and there has been no recurrence of SpA.

### Conclusion

We presented a very rare case of DLBCL concomitant with LA-HLH in a patient with non-radiographic axial SpA. Similar to RA, chronic inflammation and disease activity of SpA seemed to increase the risk of LPDs in SpA, but recent studies have demonstrated that the risk of LPDs in SpA is not increased relative to general population. However, our case indicated that it is important to consider the possibility of LPDs in SpA patients with lymphadenopathy, especially for patients taking immunosuppressive agents including MTX. Although the first choice treatment for MTX-LPDs may be withdraw of MTX, the patient should carefully be assessed the prognostic factors and immediately initiate treatment with chemotherapy when the LPD does not seem to spontaneously regret. To establish more confirmed evidence on risks of LPDs in SpA, further investigations are necessary.

### Conflict of Interest (COI)

Authors state no Conflict of interest.

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