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〔Case Report〕

Spontaneous regression of methotrexate-related lymphoproliferative disorders in rheumatoid arthritis: reports of three cases followed for up to 5 years

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Abstract

Methotrexate-related lymphoproliferative disorder（MTX-LPD）is a serious complication of methotrexate（MTX）treatment in patients with rheumatoid arthritis. We treated 3 patients with MTX-LPD associated with rheumatoid arthritis. Patient 1 was a 55-year-old woman whose chest X-ray showed abnormal shadows 16 years after she started MTX treatment. Patient 2 was a 63-year-old woman who had signs/symptoms of viral rhinitis and whose chest X-ray showed multiple shadows and lung infiltrates. A definitive diagnosis of MTX-LPD was obtained from a bronchoscopic biopsy specimen. Patient 3 was a 44-year-old woman whose chest computed tomography scans showed incidental bilateral axillary lymphadenopathy after anaphylactic shock associated with an injection of a biosimilar of infliximab. After MTX discontinuation, the LPD resolved in all 3 patients and has not recurred through up to 5 years of follow-up.

***Key words*: Spontaneous regression, methotrexate-related lymphoproliferative disorders, rheumatoid arthritis, mid-term clinical course, case reports**

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Ⅰ. Introduction

Methotrexate（MTX）is an anchor drug used worldwide to treat patients with rheumatoid arthritis（RA）. MTX is said to be more effective in treating RA and has fewer side effects than other disease-modifying antirheumatic drugs（DMARDs）[1]. In Japan, doses of MTX of up to 16 mg/week were approved for coverage by insurance in 2011. MTX-related lymphoproliferative disorder（MTX-LPD）is a serious complication of MTX treatment in patients with RA[2,3]. MTX-LPD is a rare condition, and its treatment is unclear. We have treated 3 RA patients with MTX-LPDs and observed their clinical courses for up to 5 years. Background characteristics and clinical courses of these three cases, including medical history, initial symptoms, time of onset, site of

Table 1 Patient characteristics

	Patient 1	Patient 2	Patient 3
Gender	Woman	Woman	Woman
Age at onset of RA, years	16	37	20
Age at LPD, years	55	63	44
Disease duration of RA at LPD, years	39	26	24
RA stage I/II/III/IV	III	IV	IV
DAS28-CRP	4.6	4.7	4.1
CDAI	20	14	16
CRP, mg/dL	1.65	8.7	1.2
RF, IU/mL	213	24	412
Anti-CCP antibody, U/mL	18.6	500	71
sIL-2R at LPD, U/mL	425	1694	6076
MTX duration at LPD, years	16	3	6
MTX maximum dose, mg/week	12	16	12
MTX dose at LPD, mg/week	12	16	12
Biologics use before the diagnosis of LPD	No	Abatacept	Infliximab Golimumab

RA: rheumatoid arthritis; LPD: lymphoproliferative disorder; DAS: disease activity score; CRP: C-reactive protein; CDAI: Clinical Disease Activity Index; RF: rheumatoid factor（positive > 15 IU/mL）; CCP: cyclic citrullinated peptide（low positive > 4.5 U/mL, high positive > 13.5 U/mL）; sIL-2R: soluble interleukin-2 receptor; MTX: methotrexate

Table 2 Clinical manifestations of LPDs and RA treatment

	Patient 1	Patient 2	Patient 3
LPD site	Lung	Lung	Axillary lymph nodes
Superficial / deep lymphadenopathy	Deep	Deep	Deep
Extranodal involvement	Yes	Yes	No
Diagnostic classification of LPD	Clinical	Pathological	Clinical
RA treatment after LPD			
GC	PSL	PSL	PSL
csDMARDs	Salazosulfapyridine Iguratimod Bucillamine	Salazosulfapyridine	Salazosulfapyridine
bDMARDs	No	Tocilizumab	Tocilizumab
JAKi	No	No	Baricitinib
RA flare	No	Yes	Yes
LPD relapse	No	No	No
Clinical course of RA	Low disease activity	Clinical remission	Clinical remission
Follow-up period, years	4	4.5	5

GC: glucocorticoid; csDMARD: conventional synthetic DMARD; bDMARD: biological DMARD; JAKi: janus kinase inhibitor; PSL: prednisolone

lymphoma, method of diagnosis, and RA treatment after MTX discontinuation, are reported here (Table 1-2).

Ⅱ. Case

Patient 1

This patient was a 55-year-old woman seropositive for RA (rheumatoid factor[RF]213 IU/mL and anti-cyclic citrullinated peptide[CCP]antibody 18.6 U/mL) who was diagnosed with RA at 16 years of age and underwent left wrist surgery at 27 years of age. She had a medical history of seasonal allergic rhinitis and did not drink alcohol or smoke tobacco. Her family history was unremarkable. She was referred to our hospital at the age of 34 years and was started on MTX (4 mg/week) treatment at the age of 39 years. The MTX dose was increased to 6 mg/week when she was 41 years old and to 10 mg/week when she was 43 years old, because RA was poorly controlled. When she was 48 years of age, the MTX dose was increased from 10 mg/week to 14 mg/week every 6 months, but at the age of 52, the dose was reduced to 10 mg/week because of liver damage. However, joint destruction was observed in the metacarpophalangeal joints of both fingers and in the 3rd, 4th, and 5th metatarsophalangeal joints of both feet, accompanied by pain in both shoulders, elbows, and hands. Biologics were difficult to prescribe for economic reasons; therefore, the MTX dose was increased to 12 mg/week when she was 53 years old.

At the age of 55 years, 16 years after initiation of MTX, a chest X-ray showed abnormal shadows (Fig. 1a). Computed tomography (CT) revealed scattered nodular shadows immediately beneath the pleura of both lungs (Fig. 2a). Laboratory data included the following: sialylated carbohydrate antigen KL-6 of 352 U/mL (normal < 500 U/mL), soluble interleukin (IL)-2 receptor of 425 U/mL (normal 121–613 U/mL), β-D-glucan < 2.16 pg/mL (normal < 11.0 pg/mL), and C-reactive protein (CRP) 1.65 mg/dL. Lung abscess and pulmonary tuberculosis were ruled out by a negative sputum culture and a negative tuberculosis blood test. MTX-LPD was suspected, and administration of MTX was discontinued. A pulmonologist performed a bronchoscopy but was unable to collect a sample because of a peripheral lesion near the diaphragm. The patient refused a CT-guided biopsy or a thoracoscopic biopsy. Four months after the discontinuation of MTX, the tumor had spontaneously regressed (Figs. 1b and 2b). LPD was completely resolved 2 years later (Fig 2. c, d).

Four years after MTX discontinuation, the patient, aged 59 years, has been stable with low RA activity and without recurrence of LPD. She receives maintenance therapy with prednisolone (PSL) 6 mg/

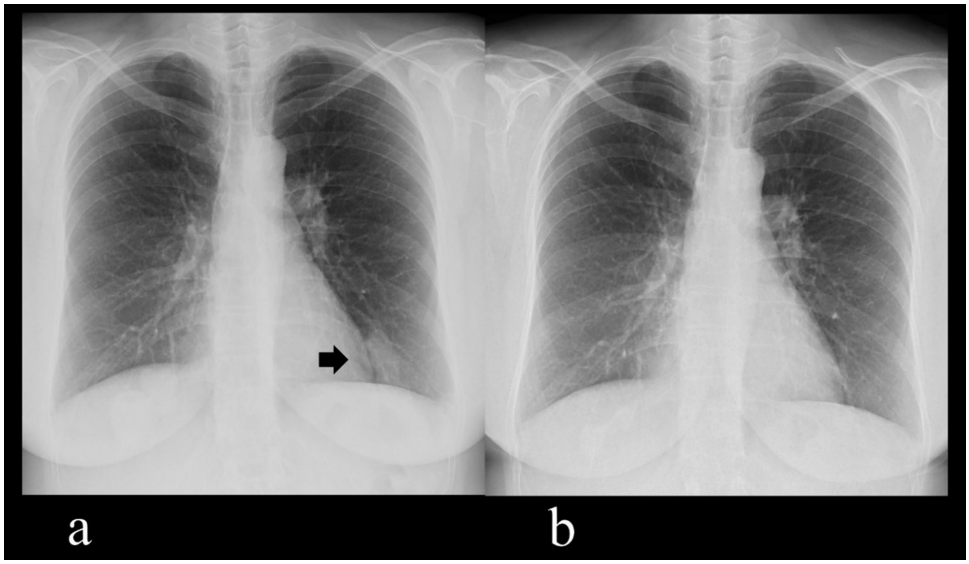

Fig. 1 Changes in chest X-rays of Patient 1. (**a**) Nodule at the time of the diagnosis of lymphoproliferative disorder (LPD) (arrow). (**b**) The nodule disappeared 4 months after discontinuation of methotrexate (MTX).

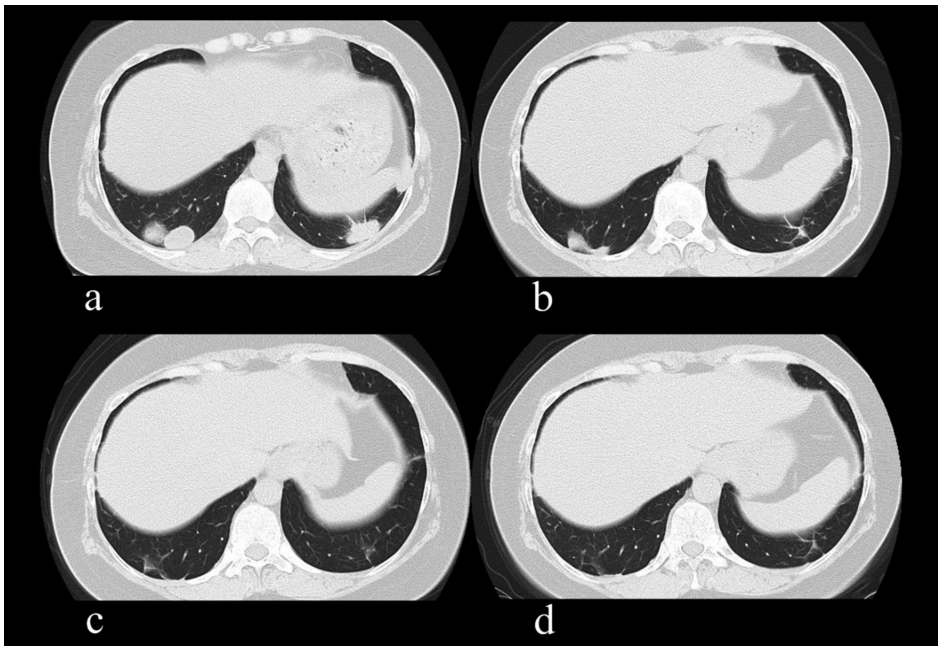

Fig. 2 Changes in chest computed tomography (CT) images of Patient 1. (**a**) Nodular shadows are scattered immediately beneath the pleura of both lungs at the time of the diagnosis of lymphoproliferative disorder (LPD). (**b**) The nodular shadows in lungs were reduced markedly 4 months after discontinuation of MTX. (**c**) The nodular shadows had almost disappeared 17 months after discontinuation of MTX. (**d**) No recurrence of LPD 24 months later.

day, salazosulfapyridine 1000 mg/day, iguratimod 25 mg/day, bucillamine 200 mg/day, and denosumab 60 mg every 6 months.

Patient 2

This patient was a 63-year-old woman seropositive for RA (RF 24 IU/mL and anti-CCP antibody > 500 U/mL) who was diagnosed with RA at the age of 37 years and underwent left wrist surgery at the age of 38 years. She was subsequently treated with PSL 2.5 mg/day and auranofin 6 mg/day, but the control of RA was poor. At the age of 60 years, she was referred to our hospital because of severe destruction of both knee joints and a matrix metalloproteinase-3 level of 1780 ng/mL. MTX was started at 6 mg/week and increased to 16 mg/week over a 1-year period with evaluation of disease activity every few months. Concomitant total knee arthroplasty was performed sequentially for both knees. Two months after the patient received MTX 16 mg/week, multiple shadows were seen in the left lung, and deterioration of pleural effusion was noted in the right lung (Fig. 3a, b and Fig. 4a, b). The patient underwent bronchoscopy. There were no signs of infection or metastatic tumors. Therefore, the patient received a high-dose steroid consisting of PSL at 30 mg/day and continued receiving MTX at 16 mg/week. One month after the start of treatment, the pleural effusion had decreased, and it disappeared completely at 9 months (Fig. 4c, d). The multiple shadows were considered rheumatoid nodules. It was considered a pathological condition (rheumatic lung) that was directly related to inflammation of rheumatoid arthritis and was caused by an autoimmune reaction. Biologics were considered to reduce the amount of steroid, while tight control was needed to suppress rheumatoid lung activity. Abatacept, which inhibits T cell activation, was selected because it is known to have relatively few complications among the biologics[4]. Clinical remission was obtained (disease activity score[DAS]28-CRP 1.64) after a subcutaneous injection of abatacept 125 mg/week was introduced, and the PSL was then reduced to 10 mg/day.

At the age of 63 years, 3 years after the introduction of MTX and 1 year after the introduction of abatacept, the patient experienced cough and a fever of 38 degrees, and multiple lung shadows appeared (Fig. 3c and Fig. 4e). Bronchoscopic biopsy revealed Epstein-Barr

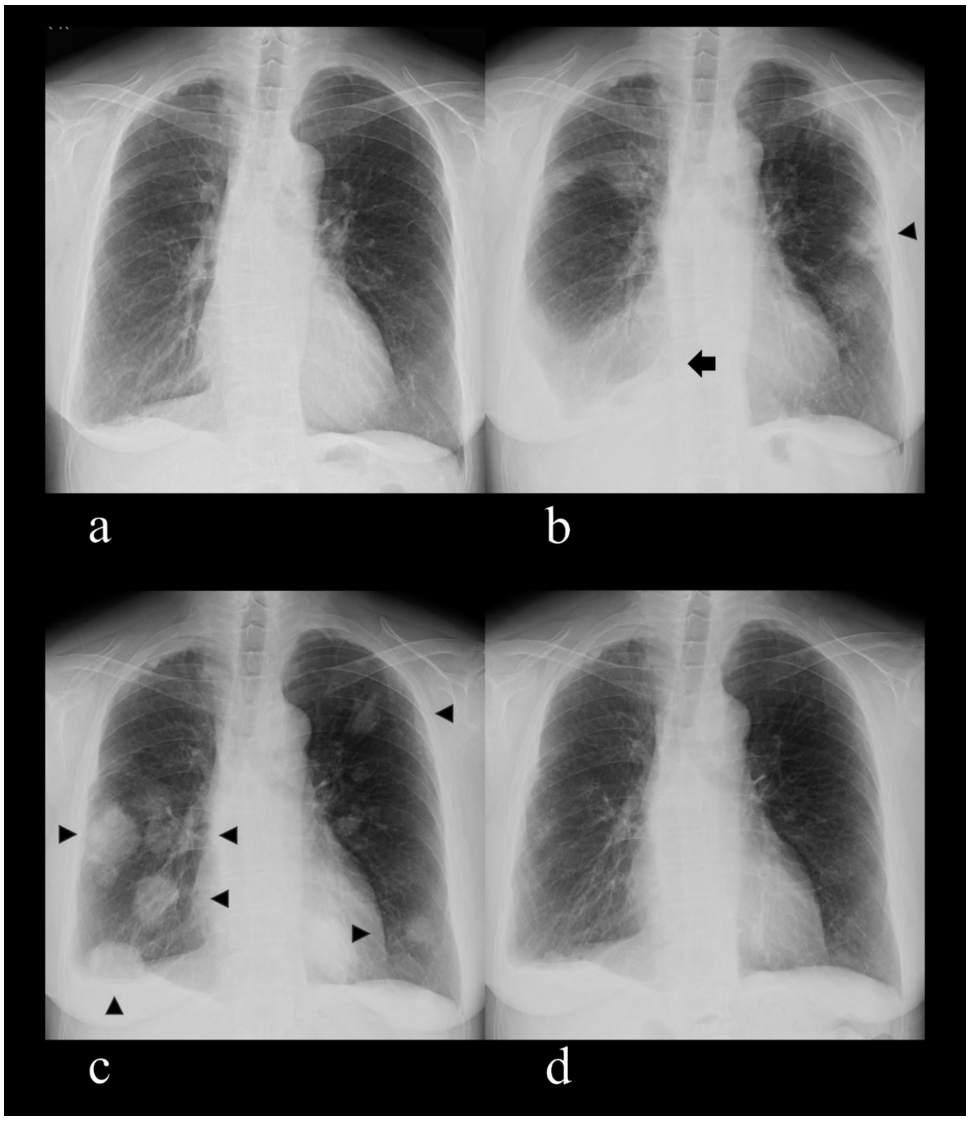

Fig. 3 Changes in chest X-rays of Patient 2. (**a**) Slight blunting of the costophrenic angles in the right lung at the time of the first visit to our hospital. (**b**) Worsening of right pleural effusion (arrow) and multiple shadows in the left lung (arrowhead) due to inflammation of rheumatoid arthritis. (**c**) Multiple nodules in both lungs at the diagnosis of LPD (arrowheads). (**d**) The nodules disappeared 5 months after discontinuation of MTX.

virus-positivity and MTX-LPD (Fig. 5), and MTX and abatacept were discontinued. Lymphadenopathy disappeared 5 months later (Fig. 3d and Fig. 4f). Six months after the resolution of LPD, there was recurrence of pain in multiple joints, and tight control was needed again to suppress the high disease activity. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), was selected (Fig. 4g), because it was thought to be relatively safe, even after MTX-LPD[5]. Denosumab was also started because of bony destruction in both the elbows and ankles.

Four and a half years after the discontinuation of MTX, the 67-year-old patient remains in clinical remission from RA and without recurrence of LPD (Fig. 4h). She is receiving monotherapy with a subcutaneous injection of tocilizumab 162 mg every 2 weeks with PSL 8 mg/day, salazosulfapyridine 1000 mg/day, a subcutaneous injection of denosumab 60 mg every 6 months, sulfamethoxazole 400 mg/day and trimethoprim 80 mg/day.

Patient 3

This patient was a 44-year-old woman seropositive for RA (RF 412 IU/mL and anti-CCP antibody 71.0

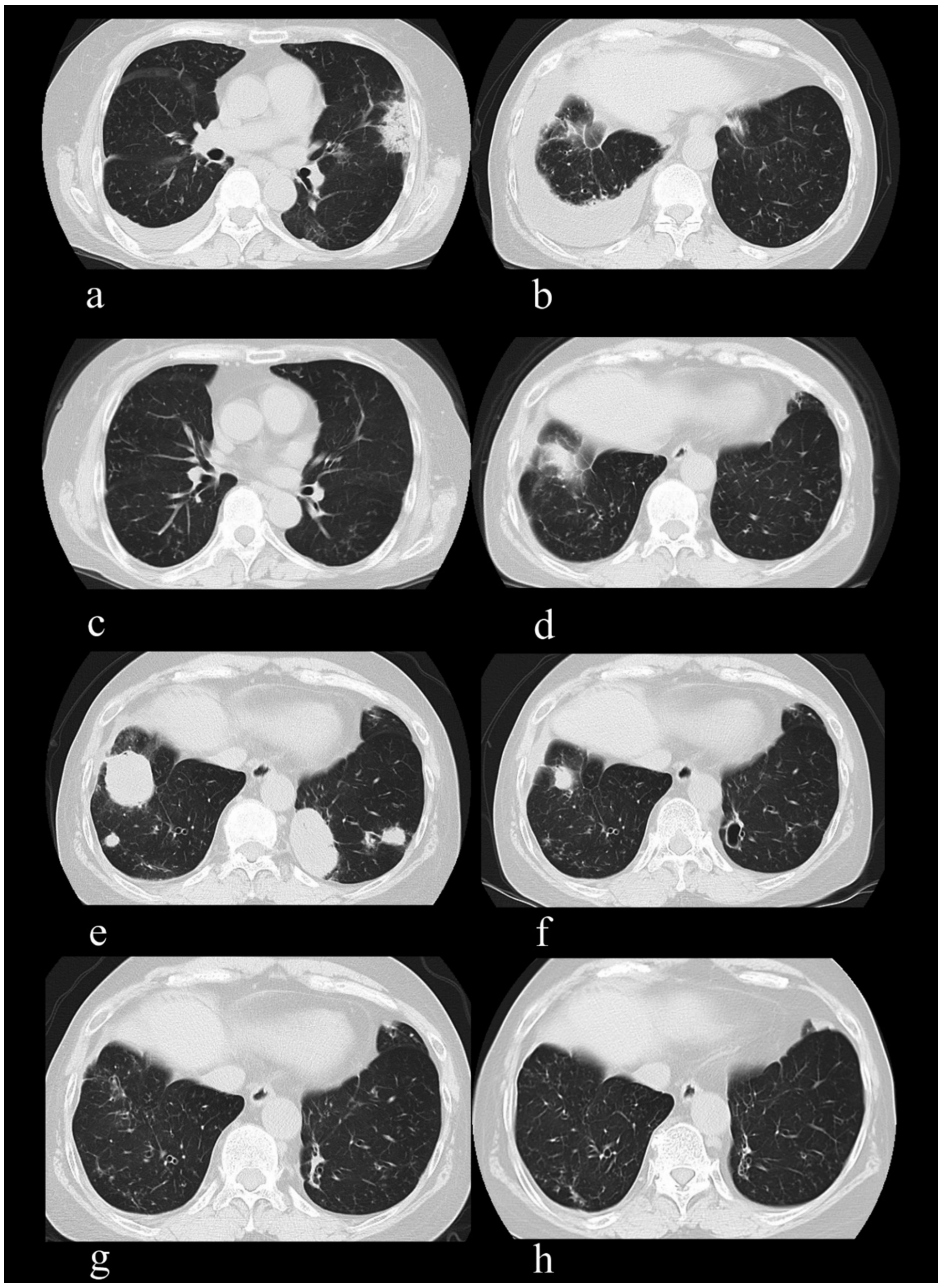

Fig. 4 Changes in chest CT images of Patient 2. (**a**) Axial image at the level of the arrowhead in Figure 3b. Right lung pleural effusion and left lung showing shadow. (**b**) Axial image at the level of the arrow in Figure 3b. Marked pleural effusion in the right lung. (**c**) Pleural effusion seen in (**a**), and (**d**) shadow seen in (**b**) have disappeared 9 months after high-dose steroid treatment. (**e**) Multiple nodules in both lungs at the time of the diagnosis of LPD. (**f**) The nodular shadows in both lungs were markedly reduced 5 months after discontinuation of MTX. The large para-aortic nodule in the left lung formed a cavity. (**g**) The nodular shadows had almost disappeared 11 months later. (**h**) LPD has not recurred during 51 months of follow-up.

U/mL) who was diagnosed at the age of 20 years and had been treated with PSL 6 mg/day and bucillamine 300 mg/day. She had a past medical history of hyperthyroidism, asthma, and hypertension. At the age of 38 years, she had severe, painful destruction of the joints in her left hip and right knee, which interfered with her activities of daily living. The destroyed joints were replaced by total hip and knee arthroplasties, but due to the high disease activity of RA, tight control was required to prevent the progression of bone destruction to the remaining joints. MTX was started at 6 mg/week and then increased to 8 mg/week, which was combined with infliximab 160 mg every 8 weeks. She achieved clinical remission at the age of 42 years. She was able

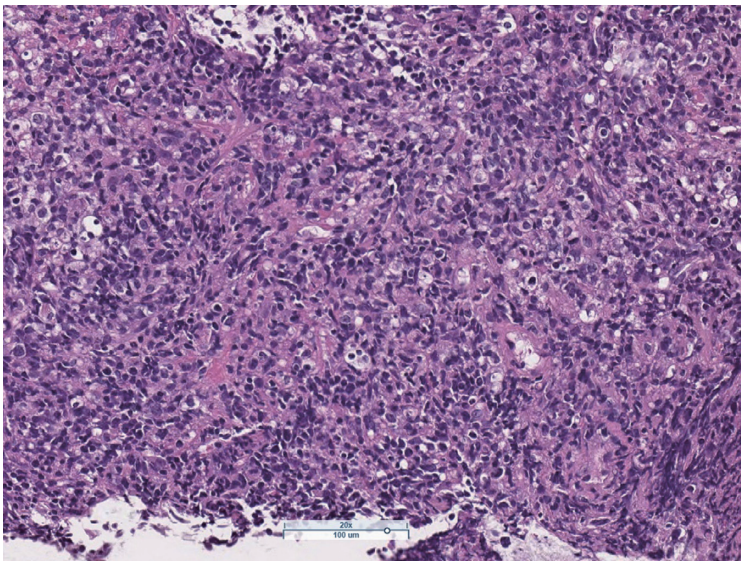

Fig. 5 Histopathological findings of a lung biopsy specimen. Nodule-like tissue with a high degree of lymphocytic infiltration in the bronchial tissue. Lymphocytic proliferation in the parenchyma of the lung and alveolar spaces.（Hematoxylin and eosin stain, 20 × magnification）.

to work after changing from an intravenous drip of infliximab to a subcutaneous injection of golimumab 50 mg every 4 weeks.

At the age of 44 years, the patient discontinued treatment with biologics for economic reasons, and symptoms recurred 2 months later. Therefore, MTX was increased to 12 mg/week, and a biosimilar of infliximab was administered. During the second administration of the infliximab biosimilar, she developed chills and anaphylactic shock, which required steroids and hospitalization. Chest CT showed bilateral axillary lymphadenopathy（Fig. 6a, d）and an elevated level of soluble IL-2 receptor（sIL-2R）（6,076 U/mL）, which suggested MTX-LPD. MTX was discontinued immediately. One month later, positron emission tomography（PET）-CT showed accumulation of fluorine 18-labeled fluorodeoxyglucose in bilateral axillary lymph nodes, which appeared to be getting smaller（Fig. 6b, e）. Since the lymph nodes were rapidly decreasing in size, the swollen lymph nodes were thought to be reactive instead of tumor-related. A hematologist did not perform a lymph node biopsy. Seven months after discontinuation of MTX, CT showed that the lymph node swelling had completely disappeared（Fig. 6c, f）, and the sIL-2R level decreased to normal. However, the patient complained of pain in the joints of her ankles, wrists, right shoulder, and right elbow from a 10-minute walk, which hindered work with DAS28-CRP 4.16. Tocilizumab was started, and clinical remission was achieved. Two years later, for economic reasons, tocilizumab administration was extended from 2-week intervals to 3-week intervals, resulting in general malaise and pain in the left knee joint, and RA flared. Tocilizumab administration was returned to the 2-week interval, but the symptoms did not improve. In addition, the dose was increased to a weekly dose, but it was ineffective. Therefore, a switch to a Janus kinase（JAK）inhibitor, baricitinib 4 mg/day, was required.

At the age of 49 years, 5 years after discontinuation of the MTX, the patient remains in clinical remission from RA and free of the recurrence of LPD. She is receiving PSL 4 mg/day, salazosulfapyridine 1000 mg/day, baricitinib 4 mg/day, and denosumab 60 mg every 6 months.

Ⅲ. Discussion

MTX-LPD is a lymphoproliferative disease that occurs in patients receiving MTX and has received attention because it resolves naturally when MTX is discontinued[2]. The frequency of lymphoma has

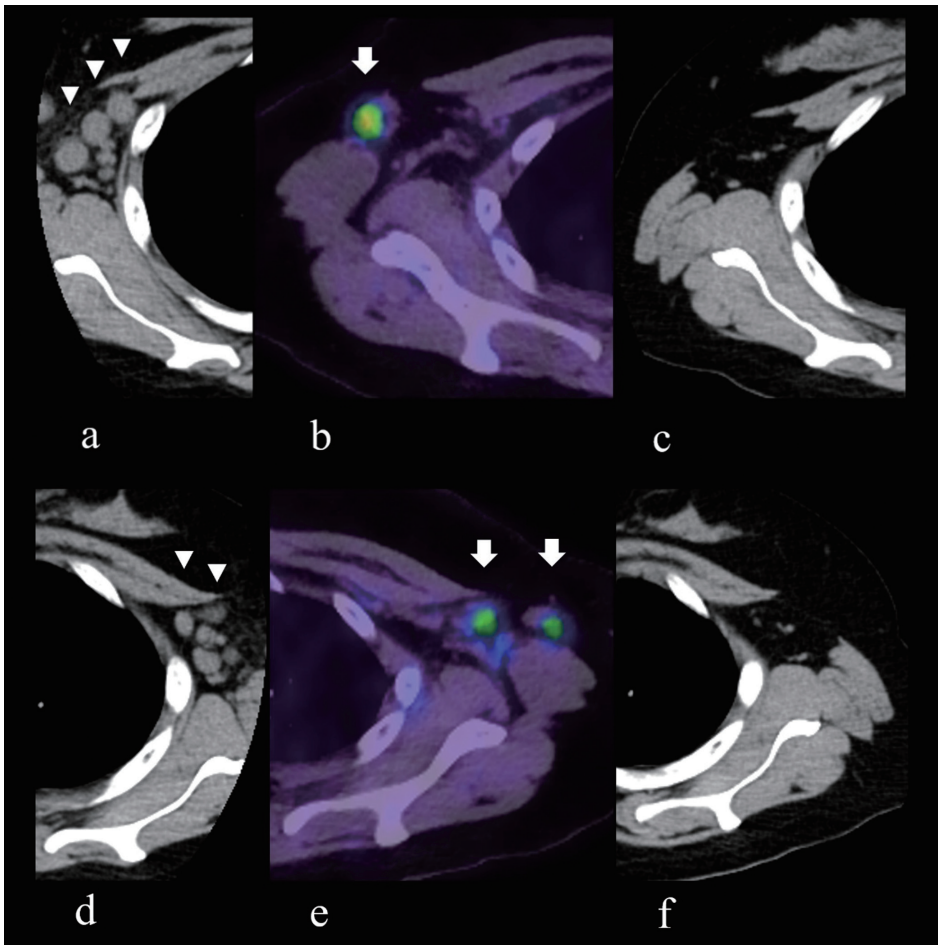

Fig. 6 Changes in CT and positron emission tomography (PET)/CT images of axillary lymph nodes in Patient 3. (**a**) Multiple enlarged lymph nodes in the right axilla (arrowheads) at the time of diagnosis of LPD. (**b**) Increased accumulation of fluorine 18-labeled fluorodeoxyglucose in the right axillary lymph node (arrow), but smaller size than 10 days prior. (**c**) The lymphadenopathy in the right lung has completely disappeared 7 months after discontinuation of MTX. (**d**) Multiple enlarged lymph nodes in the left axilla (arrowheads) at the time of diagnosis of LPD. (**e**) Increased accumulation of fluorine 18-labeled fluorodeoxyglucose in the left axillary lymph nodes (arrows), but smaller size than 10 days prior. (**f**) Lymphadenopathy in the left lung has completely disappeared 7 months after discontinuation of MTX.

been reported to be approximately 2-fold higher among patients with RA than among the general population[3]. Thus, information on the risk, prognosis, and mortality of LPD in patients with RA is of clinical importance.

Five Japanese multi-institutional retrospective studies on LPD in RA patients have been reported[5-9]. These nationwide cohort studies enrolled 9,815 patients between April 2011 and July 2011 who were aged > 20 years and had RA. Honda et al.[6]reported that 0.69% of the RA patients developed LPD over a 3-year observation period. The significant risk factors of LPD were older age (1.47-fold increased risk for every 10 years) and higher doses of MTX at baseline (2.35-fold increased risk for < 8mg/week, 4.39-fold increased risk for > 8 mg/week versus non-use)[6]. Kuramoto et al.[7]reported that among 232 patients with RA who had LPD between 2000 and 2017, 216 were treated with MTX at the onset of LPD and 144 of the 216 (66.7%) patients achieved spontaneous regression (SR) of LPD as early as 2 weeks after the discontinuation of MTX. The proportion of patients with high titers of anti-CCP antibodies (> 13.5 IU/mL) was significantly higher in the patients achieving SR than in those not achieving SR[7]. The median level of sIL-2R was higher than the upper limit of normal in both the patients achieving and not achieving SR; however, the level was significantly lower in the patients achieving than in those not achieving SR (sIL-2R 842 vs. 1,570 U/

mL, respectively; $p < 0.001$) [7]. While the MTX dose at the diagnosis of LPD was slightly but significantly higher in the patients achieving than in the patients not achieving SR (9.0 vs. 8.0 mg/week, respectively; $p = .0049$), the differences between the duration of MTX use and the cumulative amount of MTX administered were not significant [7]. Compared to findings reported previously in the literature [5-9], all three of our patients had high titers of anti-CCP antibodies and took MTX ≥ 12 mg/week, achieving SR a few weeks after MTX discontinuation. Two patients had high titers of SIL-2R, but one patient had a normal value.

Among the clinicopathological characteristics of LPD in patients with RA, lymphadenopathy and extra-nodal involvement were present in 77.1% and 51.9%, respectively [8]. The lungs and oral/oropharyngeal mucosa were the major extra-nodal sites. The most common pathological subtypes of LPD were diffuse large B-cell lymphoma (40.5%), followed by classical Hodgkin lymphoma (10.8%), Epstein-Barr virus-positive mucocutaneous ulcer (7.7%), and reactive lymphoid hyperplasia (6.2%) [8]. Clinical LPD without pathological diagnosis was defined when an attending physician deemed that a patient without pathological examination had a possibility of lymphoma or LPD other than lymphoma considering his/her clinical symptoms, laboratory data, and imaging findings [6]. In our report, Patient 2 with a histopathological diagnosis of LPD, and Patients 1 and 3 were considered to be clinical LPD without a histopathological diagnosis. Patients 1 and 2 had lung lesions, and Patient 3 only had deep lymph nodes that appeared to be affected (bilateral axillae).

In one study, the 1-, 2- and 5-year overall survival rates of LPD in patients with RA in Japan were 89.5%, 86.1%, and 78.2%, respectively [9]. The survival rates were lower in patients > 70 years of age (hazard ratio [HR]0.26) and patients with classical histology for Hodgkin lymphoma (HR 0.30). The 2- and 5-year post-SR relapse rates were 14.2% and 24.9%, respectively [9]. In our report, all three patients were < 70 years of age, and LPD did not recur.

In the same study population as Sato et al. [9], treatment of RA was resumed in 190 (82%) of 232 patients after LPD for exacerbation of arthritis [5]. LPD relapses occurred in 40 patients (21%), and classical Hodgkin lymphoma was the only factor associated with the relapse of LPD (odds ratio, 3.81) [5]. In 88 RA patients treated with biologic DMARDs, tocilizumab showed the highest retention rate (1 year, 76.3%; 2 years, 65.2%), particularly in diffuse large B cell lymphoma [5]. In our report, Patient 2 and Patient 3 resumed RA treatment with tocilizumab because of worsening arthritis. Patient 3 is being treated with a JAK inhibitor, because tocilizumab had become ineffective. Fortunately, the LPD disappeared after the discontinuation of MTX in all 3 cases and has not recurred for up to 5 years of follow-up.

In conclusion, the clinical management of MTX-LPD and RA treatment after discontinuation of MTX was reported as follows:

1) RA was able to be controlled with csDMARDs other than MTX in one of the three cases.
2) RA was unable to be controlled with csDMARDs other than MTX and required biologics in two of the three cases. Tocilizumab was chosen as the biologic.
3) In one of the two cases that required biologics, the biologic became ineffective and required a switch to a JAK inhibitor.
4) No recurrence of MTX-LPD was observed up to 5 years after discontinuation of MTX.

Contributors

JM, JN and KN contributed to the concept and design of the study and to manuscript preparation. SH, YK and KI contributed to data acquisition. SO1, YE, KI, YS, SO2 and KI revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Conflict of interest

The corresponding author, JN, is the chief executive officer of Calm Lana Inc. SO2 is an editorial board member of this journal. The other authors have no conflicts of interest.

Ethical approval

Written informed consent was obtained from the patients for publication of the present report. This is not human research. This is not animal research.

Data availability

Not applicable.

Acknowledgements

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