Methotrexate-associated Lymphoproliferative Disease with Multiple Pulmonary Nodules in a Patient with Rheumatoid Arthritis

Koichiro Suemori, Hitoshi Hasegawa, Jun Ishizaki, Takuya Matsumoto, Sachiko Onishi, Eiji Sada, Atsuro Sugita and Masaki Yasukawa

Abstract

Patients with rheumatoid arthritis (RA) treated with methotrexate (MTX) sometimes develop lymphoproliferative disease (LPD). MTX-associated LPD can affect nodal or extranodal sites, including the gastrointestinal tract, skin, lungs, kidneys and soft tissues, at almost equal frequency. However, it is very rare for MTX-associated LPD to manifest as multiple nodules in the lungs. We herein report the case of a RA patient who developed MTX-associated LPD with multiple pulmonary nodules during a 5-year course of MTX therapy.

Key words: methotrexate-associated lymphoproliferative disease, rheumatoid arthritis, multiple pulmonary nodules


Introduction

Methotrexate (MTX) is a key drug for the treatment of rheumatoid arthritis (RA), and the long-term use of MTX at an average dose of 10.7 mg/week in patients with RA has been shown to be safe (1). However, lymphoproliferative disease (LPD) is a rare complication of MTX therapy that has received attention since Ellman’s first report of lymphoma in a patient with RA who received low-dose MTX (2-5). In addition, interstitial pneumonitis is known to be a pulmonary side effect of MTX therapy for RA, and pulmonary lesions of LPD are relatively rare (6-9). In particular, the manifestation of LPD in the form of multiple pulmonary nodules is exceptional. To our knowledge, only one case of MTX-associated LPD in the form of multiple pulmonary nodules has previously been described (8). The LPD in that case involved multiple nodal and extranodal lesions in the cervical lymph nodes, both kidneys and lung. The onset of LPD with multiple pulmonary nodules only, as observed in the present patient, is very rare. In addition, making the differential diagnosis between lung cancer, fungal infection, tuberculosis, sarcoidosis and pneumonia is difficult based on clinical symptoms, laboratory data and imaging findings.

In this report, we describe the case of a patient with RA who developed MTX-associated LPD with multiple pulmonary nodules during a 5-year course of MTX therapy. Withdrawal of the MTX treatment resulted in complete remission. This case suggests that LPD should be considered as a cause of multiple pulmonary nodules.

Case Report

A 79-year-old Japanese woman was admitted to our hospital due to a low-grade fever and fatigue. She had been diagnosed as having RA at 75 years of age and had been receiving MTX (8 mg/week), prednisolone (PSL) (2 mg/day) and sulfasalazine (SASP) (1,000 mg/day) for five years (functional class II, radiographic stage II). The RA activity had been well controlled with these drugs. She had also been diagnosed with RA-associated interstitial pneumonia that had remained unchanged for five years and had a history of pulmonary aspergillosis that had been cured with an-
tiful fungal agents five years previously. She presented with a 3-week history of low-grade fever that was not responsive to antibiotics, although no weight loss or night sweats were observed. A physical examination revealed a body temperature of 37.6°C, blood pressure of 115/63 mmHg, pulse of 93/min, oxygen saturation of 98% on room air and slightly fine crackles in the lower bilateral lungs. Neither hepatosplenomegaly nor superficial lymphadenopathy were observed. No joints exhibited an RA activity.

The laboratory data showed a hemoglobin value of 11.0 g/dL, with a normal mean corpuscular volume, leukocyte count of 7,900/μL and platelet count of 19.9×10^4/μL. Hepatic and renal function tests were normal. The serum albumin level was 3.2 g/dL (normal: 3.9-4.9 g/dL), the C-reactive protein level was 2.7 mg/dL and the erythrocyte sedimentation rate was 26.9 mm/h. The titers of serum immunoglobulins (IgG, IgA, IgM) were within the normal ranges, while the level of soluble interleukin-2 receptor was 7,900 U/mL and the KL-6 activity was 811 U/mL (normal: <500 U/mL) without exacerbation. Examinations for infection, procalcitonin, (1,3)-beta-D-glucan, Aspergillus galactomannan antigens, cryptococcal antigens, a QuantiFERON-TB Gold In-Tube assay (QFT-TB) and cultures of sputum and blood all yielded negative results. However, serological tests to determine the Epstein-Barr virus (EBV) antibody titer indicated a previous infection. EBV detection using polymerase chain reaction (PCR) was detected on serum samples. Thereafter, no lung lesions recurred for two years. Based on the overall clinical data, the multiple pulmonary nodules were diagnosed as MTX-associated LPD.

Following the withdrawal of MTX, the RA activity was found to have progressed gradually at four weeks, and we therefore added low-dose tacrolimus (TAC: 1.5 mg/day) to the patient’s medication regimen. This therapy with low-dose TAC subsequently resulted in a low disease activity and treatment retention.

### Discussion

The relationship between RA and the development of LPD has been a topic of discussion for many years. Although the underlying mechanisms responsible for LPD have not been clarified, several factors, including chronic stimulation of B cells, genomic aberrations, viral infection and drug-induced immunodeficiency, have been considered (4, 5, 8-14). Among agents possibly implicated in the onset of immunodeficiency-associated LPD, MTX is the most representative. As the number of patients treated with MTX has increased, so too has the incidence of MTX-associated LPD (4).

According to the recent World Health Organization (WHO) classification of lymphoid neoplasms, MTX-associated LPD is categorized as either iatrogenic or immunodeficiency-associated (15). Iatrogenic LPD includes lymphoid proliferation or lymphomas in patients treated with immunosuppressive drugs for autoimmune disease. These lesions comprise a spectrum ranging from sites of polymorphic proliferation resembling post-transplant lymphoproliferative disorders to cases fulfilling the criteria for diffuse large B-cell lymphoma or other B-cell lymphomas as well as peripheral T/NK-cell lymphoma or classical Hodgkin’s lymphoma (3).

EBV is associated with a variety of LPDs and malignant lymphomas (13). A previous study demonstrated that MTX directly induces the reactivation of EBV infection with the release of infectious virions (16). In fact, many reports have suggested that EBV contributes to the development of MTX-associated LPD and that MTX-associated LPD regresses spontaneously after the withdrawal of MTX (2-5, 8, 12, 15). Hoshida et al. reported that the rate of EBV positivity in cases of LPD showing spontaneous regression (54.5%) is higher than that observed in cases without spontaneous regression (21.1%) (4). On the other hand, it is unknown why MTX-associated LPD regresses in EBV-negative patients after withdrawing the dose of MTX. This observation appears to be consistent with the hypothesis that MTX influences local tumor immunity, thus retarding LPD progression (14). Although EBV can be detected using various methods, EBV-encoded RNA (EBER) in situ hybridization...
Figure 1. a: Chest CT performed on admission showing nodules in the right upper and left lower lung fields. Note the mild surrounding linear opacity indicating focal lymphangitic extension. The arrowhead shows the site of the lesions. The arrow highlights a part of the liver. b: CT scan obtained 1.5 months after the cessation of MTX showing regression of the tumor.

Figure 2. Histopathology of a biopsied pulmonary nodule in the left lower lung field showing diffuse monotonous lymphoid cell infiltration (Hematoxylin and Eosin staining).

(ISH) and LMP-1 immunohistochemistry are widely used clinically (17). In particular, EBER ISH is a straightforward and rapid procedure that provides unequivocal results and, when used in the appropriate clinicopathological setting, is a highly useful ancillary diagnostic tool (18).

Sites primarily affected by MTX-associated LPD are nodal and extranodal at almost equal frequency, as is the case for sporadic LPD (4, 19). In addition, extranodal LPD may occur at various sites, including the lungs, gastrointestinal tract, spleen, oral cavity, kidneys, skin and soft tissue. However, the manifestations include only multiple pulmonary lesions, as LPD is very rare. Recently, Hare et al. reviewed the radiological spectrum of pulmonary LPD (20) and characterized it as the abnormal proliferation of indigenous cell lines or infiltration of the lung parenchyma by lymphoid cells. Pulmonary LPD encompasses a wide spec-
trum of focal and/or diffuse abnormalities, which may be
classified as reactive or neoplastic based on the cellular
morphology and degree of clonality. Reactive LPD is associated
with immunological disturbances and commonly seen in pa-
tients with immunodeficiency or autoimmune disorders. The
spectrum of reactive disorders results primarily from the an-
tigenic stimulation of bronchial mucosa-associated lymphoid
tissue (MALT) and comprises three main entities: follicular
bronchiolitis, lymphoid interstitial pneumonia and (more
rarely) nodular lymphoid hyperplasia (NLH). NLH is a be-
nign, localized, reactive polyclonal lymphoproliferative le-
sion. CT imaging usually shows a discrete nodular mass
(around 2-3 cm in diameter) and mild focal lymphangitic
extension. NLH is usually asymptomatic and found incident-
ally on imaging studies. Occasionally, however, it can in-
duce shortness of breath, coughing and/or pleuritic chest
pain.

Our patient had been treated with weekly low-dose MTX
and exhibited a controlled RA activity before suddenly de-
veloping multiple pulmonary nodules. The only clinical
manifestations were a slight fever and fatigue, with no B
symptoms (high fever, weight loss, night sweats) and no res-
piratory symptoms, such as coughing, shortness of breath or
chest pain. The CT imaging findings were consistent with a
pattern of nodular lymphoid hyperplasia, as described by
Hare et al. The biopsy specimen of the pulmonary nodule
showed a diffuse monotonous pattern of lymphoid cells
without typical lymphoma. Immunohistological studies
showed that these cells were predominantly B lymphocytes
with T lymphocytes exhibiting clonal rearrangement of the
immunoglobulin heavy chain JH gene on a PCR analysis.
These results strongly suggest that the pulmonary nodules
represented B lymphoid proliferation, thus indicating a diag-
nosis of LPD. However, the association between LPD and
EBV infection remained undetermined, as confirmation with
EBER ISH was not obtained. However, the increase in the
blood EBV DNA load implies an association between LPD
and EBV.

Recently, two reports have been published indicating that
MTX-associated LPD appears to have a better prognosis
than previously assumed (21, 22). In particular, Ichikawa et
al. reported that the spontaneous regression of LPD is asso-
ciated with EBV positivity and non-diffuse large B-cell lym-
phoma (non-DLBCL) and that IgH rearrangement in cases
of non-DLBCL is not associated with the progression or re-
gression of LPD (21). Tokuhira et al. reported that various
drugs have been given to patients after the onset of LPD, al-
though no cases of recurrence have been documented (22).
These reports are consistent with the clinical data and course
observed in the present case.

In this case, MTX-associated LPD occurred in the form
of multiple pulmonary lesions only, which subsequently dis-
appeared almost completely within one month after MTX
withdrawal, with no recurrence for two years following the
resumption of RA treatment. To our knowledge, only very
rare reports have documented MTX-associated LPD involv-
ing only multiple pulmonary lesions with spontaneous re-
mission of pulmonary MTX-associated LPD within such a
short period following the discontinuation of MTX therapy
and a long period of remission after resuming RA treatment.
Increased awareness of the possible occurrence of multi-
ple pulmonary LPD in RA patients treated with MTX is ad-
visable. In order to avoid overdiagnosis and overtreatment,
we emphasize the need for close attention to clinical and
laboratory findings as well as morphological features.

The authors state that they have no Conflict of Interest (COI).

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