Case report

A case of spontaneous regression of pulmonary mucosa-associated lymphoid tissue (MALT) type lymphoma with Sjögren’s syndrome treated with methotrexate for rheumatoid arthritis

Hideki Yasui a, Yutaro Nakamura a,*, Hirotsgu Hasegawa b, Tomoyuki Fujisawa a, Noriyuki Enomoto a, Naoki Inui a, Junya Fukuoka c, Takafumi Suda a

a Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan
b Department of Respiratory Medicine, Seirei Mikatahara General Hospital, Hamamatsu, Japan
c Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Keywords:
Rheumatoid arthritis
Sjögren’s syndrome
Methotrexate
Pulmonary mucosa-associated lymphoid tissue type lymphoma
Spontaneous regression

A B S T R A C T

A 72-year-old man who had suffered from rheumatoid arthritis (RA) and Sjögren’s syndrome (Sjs) since he was 66 years of age had been treated with methotrexate (MTX) for six years. He presented with a cough, sputum and dyspnea on exertion, and computed tomography findings showed multiple ground-glass opacities in both of his lungs. A biopsy of the lungs revealed low-grade mucosa-associated lymphoid tissue (MALT) type B-cell non-Hodgkin’s lymphoma. Spontaneous complete remission of the lymphoma was achieved six months after withdrawing immune suppression with MTX. To our knowledge, no previous cases of spontaneous regression of pulmonary MALT-type lymphoma with Sjs treated with MTX for RA have been reported. Patients on MTX who are being treated for RA should be carefully monitored, especially when they have been diagnosed with coexistent Sjs.

Introduction

Several studies have suggested an increased risk of lymphoma in patients with rheumatoid arthritis (RA). It has also been shown that RA patients treated with methotrexate (MTX) can develop lymphoproliferative disorders that share characteristics with lymphomas occurring in immunosuppressed patients. Similarly, patients with Sjögren’s syndrome (Sjs) also have a markedly increased risk for developing non-Hodgkin’s lymphoma (NHL), especially with mucosa-associated lymphoid tissue (MALT)-type lymphoma [1].

Herein, we describe a case of MALT-type lymphoma in a patient with both RA and Sjs who had been treated with MTX. Interestingly spontaneous remission of the lymphoma was achieved after withdrawing MTX. The oncogenic potential of MTX in the setting of both RA and Sjs is discussed.

Case report

A 72-year-old man with a history of RA, Sjs, and nephrosclerosis was referred to our institution with a cough, sputum, and dyspnea on exertion. He had a smoking history of two packs of cigarettes/day, but he had stopped smoking 20 years ago. He was treated with MTX at a dose of 4 mg/week for six years for treatment of his RA. Chest computed tomography (CT) showed multiple cysts with thin wall, bilateral multiple ground-glass opacities, multiple nodules, and interlobular septal thickening in the middle and lingular segments (Fig. 1A). Serum and bronchoalveolar lavage fluid (BAL) testing for bacterial, viral, fungal, and mycobacterial infections were negative. There were no atypical cells in the BAL fluid. BAL cell analysis revealed that a subset of lymphocytes was elevated...
(% lymphocytes = 47.8%) and that the patient had CD8⁺-predomi-
nant lymphocytic alveolitis (% CD4:CD8 = 0.52). With a presum-
tive diagnosis of a MTX-related lung complication, MTX was
discontinued. To reach a definite diagnosis, video assisted thoracic
surgery was performed and samples were taken from S5 and S8 of
the right lung. Histopathological evaluation and immunohisto-
chemistry led to the diagnosis of an extranodal marginal zone
lymphoma of the MALT-type (Fig. 2). No metastasis was detected by
bone marrow aspiration or CT scans evaluating from neck to pelvis,
and gastroscopy was negative. Interestingly, the multiple ground-
glass opacities and interlobular septal thickening that were
observed on CT images underwent spontaneous regression six
months after the discontinuation of MTX (Fig. 1B). To date, he re-
mains in complete remission, and his rheumatoid symptoms are
well controlled with non-steroidal anti-inflammatory drugs.

**Discussion**

Baecklund et al. reported that the risk of lymphoma is increased
in a subset of patients with very severe RA [2]. Elevated inflam-
matory activity is a major risk determinant; however, no causal link
has been established. MTX is commonly used as a disease-
modifying agent in patients with RA, in whom it interferes with
gene synthesis, repair, and replication [3,4]. It inhibits hydrofolate
reductase, interrupting purine biosynthesis, and it may have
immunosuppressive and anti-inflammatory effects. Although the
association of MTX with the development of lymphoma in RA
patients is controversial, more than seventy cases of lymphoma
occurring in patients with RA taking MTX have been reported,
suggesting that in RA, a relationship between MTX and the devel-
opment of lymphoma in some patients appears highly probable.
Salloum et al. [5] reviewed 16 patients with rheumatoid arthritis
whose methotrexate treatment was withdrawn after a diagnosis of
NHL; six (37.5%) had spontaneous complete remission, three (19%)
had partial remission, six (37.5%) had no response and one (6%) had
a minimal response. These data highlight that MTX withdrawal has
resulted in the regression of lymphoma in multiple patients.
Several reports support their data [3,6]; however, no studies
describe an increased risk of developing lymphoma in patients with
RA associated with MTX use in a prospective study. Further studies
are necessary in order to conclude a causal association between
MTX use for RA and lymphoma.

In Sjs, NHL commonly occurs; the prevalence of NHL was found
to be 4.3% in Sjs in a large multicenter European study [7]. Ekstrom
et al. also reported that Sjs was associated with a 6.6-fold increased
risk of NHL [8], and secondary Sjs yielded a higher risk than the

![Fig. 1. Chest computed tomography (CT) scan revealed ground-glass opacities and interlobular septal thickening (A). Multiple ground-glass opacities and interlobular septal thickening on CT showed spontaneous regression six months after the discontinuation of methotrexate (B).](image)

![Fig. 2. The cellular infiltrate is present along the alveolar septa and the interlobular septum and onto the pleura. Formation of lymphoid follicles is scant. The inset is a higher magnification showing predominantly small lymphoid cells in the infiltrate (A). The immunohistochemical study revealed aggregates of those cells showed restricted staining for immunoglobulin λ light chains (B).](image)
primary form [9]. Furthermore, it has been reported that Sjs patients are also at a dramatically increased risk of parotid gland MALT lymphoma [9]. Although pulmonary lymphoma is relatively rare, it is often reported in patients with Sjs [10,11]. Interestingly, low-grade NHL accounts for 58–87% of cases of primary pulmonary lymphoma [12–15], and two-thirds of these cases correspond to MALT-type NHL [16]. To date, no triggering antigens have been identified in the lung, but chronic antigenic stimulation in certain autoimmune disorders, such as Sjs, are considered to affect the onset of pulmonary MALT lymphoma [17].

In our case, it is considered that the disease conditions both of RA with MTX treatment and the presence of Sjs with RA triggered the development of lymphoma. Importantly, MTX withdrawal has resulted in the regression of the lymphoma in this patient, suggesting that MTX is associated with MALT lymphoma. Although MTX is an anchor drug in RA, it is not generally used for primary Sjs. Hence, there are no data demonstrating the relationship between MTX and Sjs. We conclude that patients on MTX treatment for RA should be carefully monitored, especially when concomitant Sjs is present.

References