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

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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.
(\% lymphocytes = 47.8\%) and that the patient had CD8^{+}-predomi-
nant lymphocytic alveolitis (\% CD4:CD8 = 0.52). With a presump-
tive diagnosis of a MTX-related lung complication, MTX was dis-
continued. 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
DNA 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

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**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).

**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 \(\lambda\) light chains (B).
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