



## 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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## A B S T R A C T

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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.

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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.

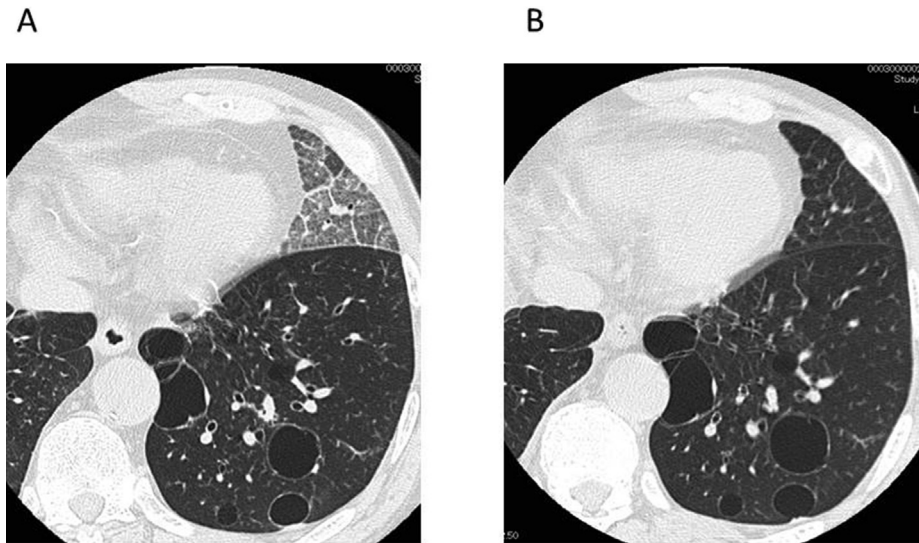
## Case report

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

*Abbreviation list:* RA, rheumatoid arthritis; MTX, methotrexate; Sjs, Sjögren's syndrome; NHL, non-Hodgkin's lymphoma; MALT, mucosa-associated lymphoid tissue; BAL, bronchoalveolar lavage fluid.

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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).

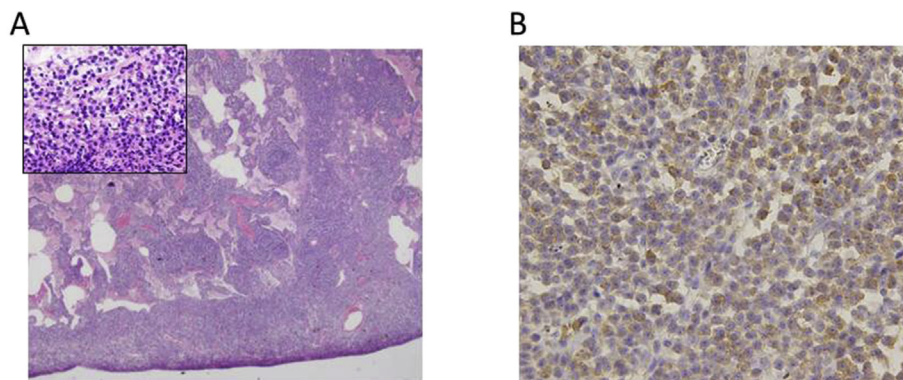
(% lymphocytes = 47.8%) and that the patient had CD8<sup>+</sup>-predominant lymphocytic alveolitis (% CD4:CD8 = 0.52). With a presumptive diagnosis of a MTX-related lung complication, MTX was discontinued. To reach a definite diagnosis, video assisted thoracic surgery was performed and samples were taken from S5 and S8 of the right lung. Histopathological evaluation and immunohistochemistry 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 remains 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 inflammatory 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 development 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. 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

- [1] Sutcliffe N, Inanc M, Speight P, Isenberg D. Predictors of lymphoma development in primary Sjogren's syndrome. *Semin Arthritis Rheum* 1998;28(2):80–7.
- [2] Baecklund E, Iliadou A, Askling J, Ekblom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006;54(3):692–701.
- [3] Moder KG, Tefferi A, Cohen MD, Menke DM, Luthra HS. Hematologic malignancies and the use of methotrexate in rheumatoid arthritis: a retrospective study. *Am J Med* 1995;99(3):276–81.
- [4] Georgescu L, Quinn GC, Schwartzman S, Paget SA. Lymphoma in patients with rheumatoid arthritis: association with the disease state or methotrexate treatment. *Semin Arthritis Rheum* 1997;26(6):794–804.
- [5] Salloum E, Cooper DL, Howe G, Lacy J, Tallini G, Crouch J, et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. *J Clin Oncol* 1996;14(6):1943–9.
- [6] Kamel OW, Holly EA, van de Rijn M, Lele C, Sah A. A population based, case control study of non-Hodgkin's lymphoma in patients with rheumatoid arthritis. *J Rheumatol* 1999;26(8):1676–80.
- [7] Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjogren's Syndrome. *Arthritis Rheum* 1999;42(8):1765–72.
- [8] Anderson LA, Gadalla S, Morton LM, Landgren O, Pfeiffer R, Warren JL, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. *Int J Cancer* 2009;125(2):398–405.
- [9] Ekstrom Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008;111(8):4029–38.
- [10] Pathak V, Resnick JM, Islam T. Bilateral pulmonary nodules and mediastinal lymphadenopathy in a patient with Sjogren's syndrome. *WMJ* 2014;113(1):32–4.
- [11] Kluka EM, Bauer PR, Aubry MC, Ryu JH. Enlarging lung nodules and cysts in a 53-year-old woman with primary Sjogren syndrome. *Chest* 2013;143(1):258–61.
- [12] L'Hoste Jr RJ, Filippa DA, Lieberman PH, Bretsky S. Primary pulmonary lymphomas. A clinicopathologic analysis of 36 cases. *Cancer* 1984;54(7):1397–406.
- [13] Fiche M, Caprons F, Berger F, Galateau F, Cordier JF, Loire R, et al. Primary pulmonary non-Hodgkin's lymphomas. *Histopathology* 1995;26(6):529–37.
- [14] Li G, Hansmann ML, Zwingers T, Lennert K. Primary lymphomas of the lung: morphological, immunohistochemical and clinical features. *Histopathology* 1990;16(6):519–31.
- [15] Nicholson AG, Wotherspoon AC, Diss TC, Butcher DN, Sheppard MN, Isaacson PG, et al. Pulmonary B-cell non-Hodgkin's lymphomas. The value of immunohistochemistry and gene analysis in diagnosis. *Histopathology* 1995;26(5):395–403.
- [16] Ahmed S, Kussick SJ, Siddiqui AK, Bhuiya TA, Khan A, Sarewitz S, et al. Bronchial-associated lymphoid tissue lymphoma: a clinical study of a rare disease. *Eur J Cancer* 2004;40(9):1320–6.
- [17] Isaacson PG. Mucosa-associated lymphoid tissue lymphoma. *Semin Hematol* 1999;36(2):139–47.