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# A Case of Methotrexate-Associated Lymphoproliferative Disorder After Resection of an Accidentally Detected Enlarged Thyroid Tumor

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## 1. Abstract

**Introduction:** We herein present a case of methotrexate-asso-ciated lymphoproliferative disorder (MTX-LPD) with a diagnosisof an 8-mm thyroid tumor of class III cytology that grew three times larger during 2 years 8 months before resection.

**Case Presentation:** The patient was a 71-year-old woman who was receiving methotrexate treatment for rheumatoid arthri- tis. A thyroid tumor was identified on computed tomography scans taken to closely examine the abnormal shadows observed on chestradiographs taken during a routine health checkup. She was then referred to our department. Ultrasound of the thyroid confirmed an 8-mm tumor in the right lobe of the thyroid, and the patient was considered for a class III cytology diagnosis. Owing to the enlarge-ment of the tumor at 2 years 8 months after the first examination, the patient underwent surgery. Histopathological examination revealed that the tumor was a diffuse large B-cell lymphoma; given the patient's use of methotrexate, it was conceived as MTX-LPD. Discontinuing MTX treatment and observing the patient's clinicalcourse is considered the first course of action to be taken for MTX-LPD.

**Conclusion:** This is a rare case of MTX-LPD that was confirmed while monitoring a microthyroid tumor discovered accidentally and operated on before the manifestation of MTX-LPD symptoms. Radical excisional biopsy could be performed even before the patient shows symptoms such as neck swelling.

## 2. Introduction

Methotrexate (MTX) is a drug that is often administered to patients with rheumatoid arthritis. At times, patients develop lymph- oproliferative disorder during the course of treatment, and the condition is referred to as MTX-associated lymphoproliferative disorder (MTX-LPD). Here we describe a case of MTX-LPD in- volving an 8-mm thyroid tumor of class III cytological diagnosis, and this tumor grew three times larger during 2 years 8 months before resection.

## 3. Case Report

A 71-year-old woman was receiving methotrexate treatment for rheumatoid arthritis. Chest radiographs were taken during a routine health checkup. Later, she was referred to our department andcomputed tomography (CT) scans were performed to closely ex- amine the abnormal shadows observed on the chest radiographs,

which revealed a thyroid tumor. There were no palpable masses in the thyroid or cervical lymph nodes. Ultrasound examination revealed an 8-mm hypoechoic tumor in the right lobe of the thyroid (Figure 1). Fine needle aspiration cytology revealed a Betheda category III finding. Therefore we decided to follow up the tumor. Two years eight months after the first examination, the tumor grew threefold, to a size of 24 mm over (Figure 2). We elected to perform surgery as a suspicion of malignancy. Then she underwent surgery (right-sided hemithyroidectomy) and was discharged on postoperative day 7 on account of a favorable clinical course. Histopathological examinations were performed on a tumor specimen with dimensions of 25X20X20mm. Hematoxylin-eosin (HE) staining showed proliferation of lymphoma cells with multiple nucleoli in a large nucleus. There were multiple mitotic presentations, and the cells lacked cytoplasm (Figure. 3). Immunostaining showed CD20 positivity, CD3 negativity, and an MIB-1 index of approximately 50% (Figure. 4). The histopathological presentations of the tumor specimen were similar to those of diffuse large B-cell lymphoma. We surmised that she had developed MTX-LPD due to her use of MTX for treating chronic rheumatoid arthritis. After a 2-year follow-up, local recurrence was not detected.

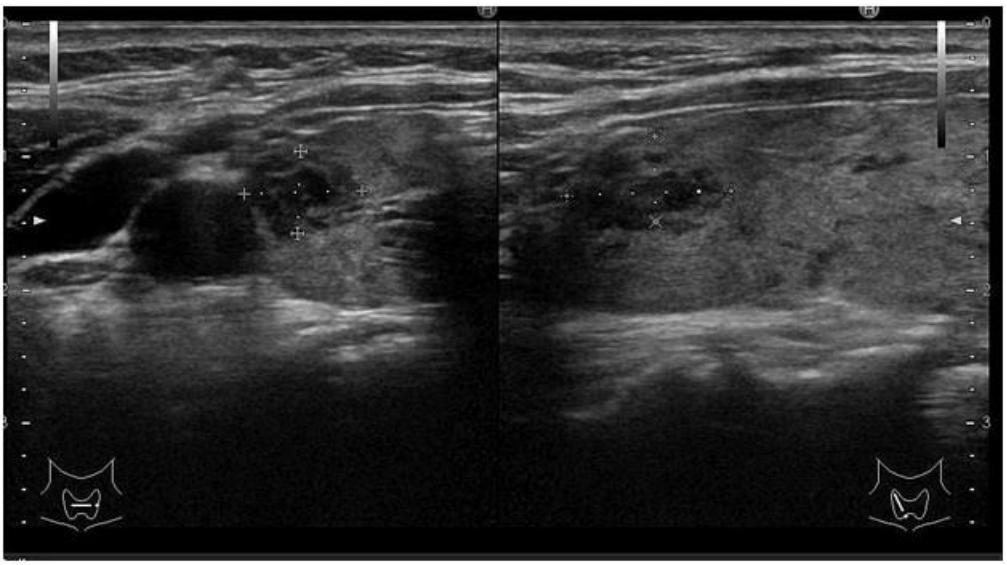


**Figure 1**: Thyroid ultrasonography image showing an 8-mm hypoechoic tumor in the right lobe of the thyroid.

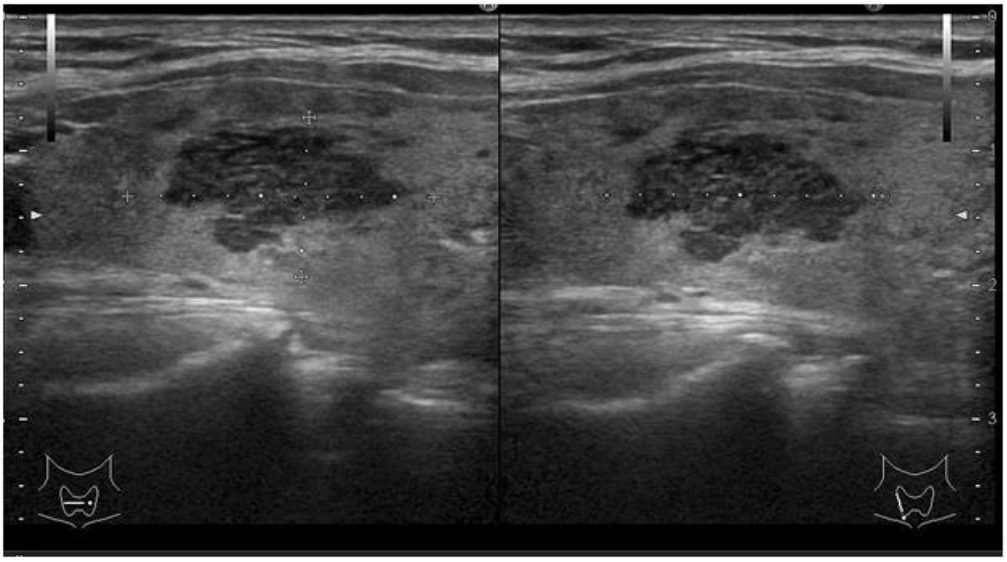
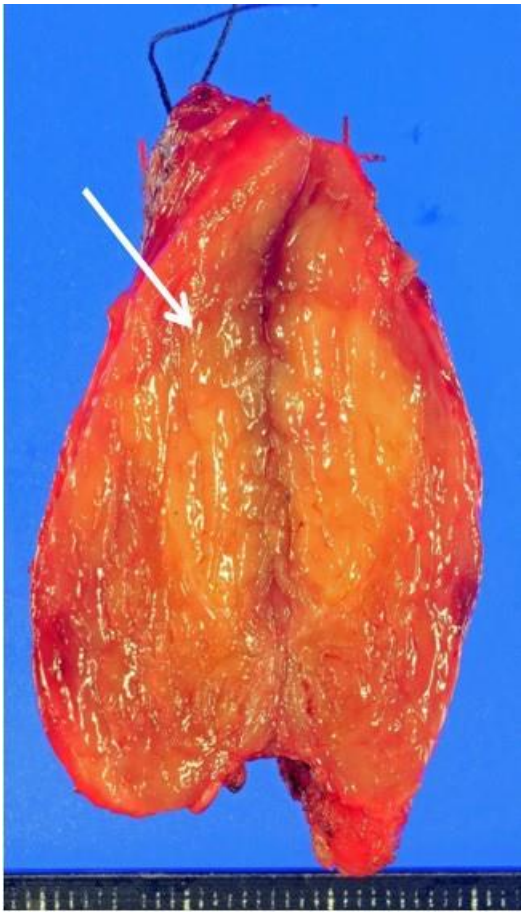


**Figure 2**: Image showing the threefold growth of the tumor, from 8 mm to 24 mm, over 2 years 8 months since the initial examination.



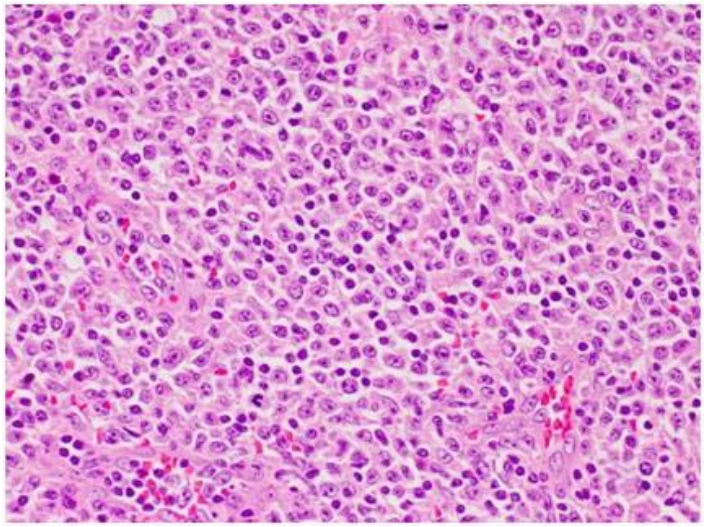
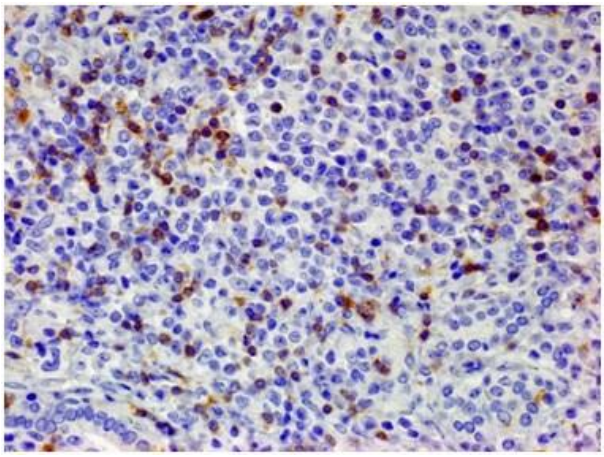
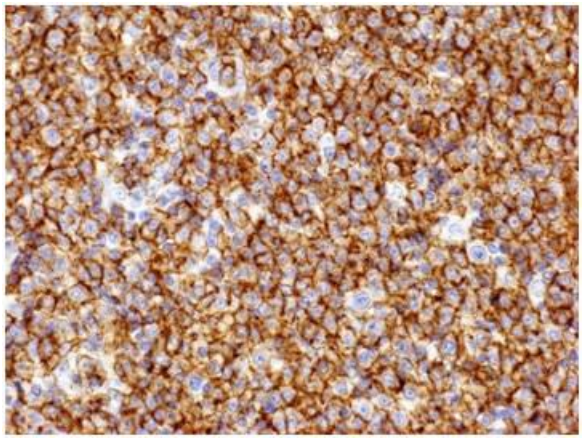


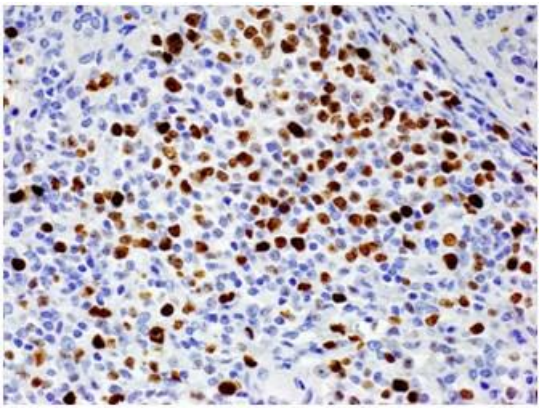
**Figure 3**: Image of the resected tumor specimen with dimensions of 25X20X20mm (A). Hematoxylin-eosin staining image showing the proliferation of lymphoma cells with multiple nucleoli in a large nucleus. There are multiple mitotic presentations and the cells lack cytoplasm. (B).



CD3



CD20



MIB-1

**Figure 4**: Immunostaining image showing CD20 positivity, CD3 negativity, and the MIB-1 index was approximately 50%.

## 4. Discussion and Conclusion

MTX has been administered as an anticancer drug for various types of carcinomas such as leukemia and breast cancer. It is also administered as an immunosuppressant for autoimmune disease such as rheumatoid arthritis and dermatomyositis. MTX-LPD was first reported in 1991 by Ellman et al. based on their experience with a patient with rheumatoid arthritis who was taking oral

MTX and who developed lymphoma and their report discussed the possibility of immunosuppression by MTX contributing to the development of lymphoma [1]. In 1993, Kamel et al. reported two cases of lymphoma that developed during oral MTX treatment [2], and this report was supported by multiple similar reports in the following years [3-6]. Currently, the World Health Organization classifies MTX-LPD as an "immunodeficiency-associated lymphoproliferative disease" and considers it as a pathology caused by immunodeficiency [7]. Hoshida et al. reported that the median age at onset of MTX-LPD diagnosis was 67 years, the male-to-female ratio of patients with this condition was approximately 1:2 the mean duration from RA onset to MTX-LPD onset was 11 years, and the mean duration of MTX treatment was 5 years [3]. Furthermore Yoshihara et al. reported that the mean age at MTX-LPD onset was 71 years, the mean duration of MTX treatment was 9 years. However, the duration of treatment was not necessarily long, with an even distribution across patients from 0.3 years to 17 years [4]. Kameda et al. analyzed several clinical parameters and reported that the dose of MTX used is a risk factor [8]. Yoshihara et al. strongly suspected a link between high-dose MTX and the number of MTX-LPD cases [4]. However, no clear risk factor for MTX-LPD is yet to be reported. It is said that the duration of MTX treatments, total dose of MTX used, or severity of RA cannot be considered risk factors [4]. Compared to other lymphomas, lymphomas due to MTX-LPD tend to manifest more frequently as extranodal lesions and are common in the gastrointestinal tract, skin, lungs, and soft tissues. In the head and neck regions, such lymphomas are seen in the cervical lymph nodes and tonsils; as extranodal lesions, they have been seen in the salivary glands, thyroid glands, and tooth buds [3, 6, 9-12]. The histopathological presentations of MTX-LPD are diverse, with the most common diffuse large B-cell lymphoma accounting for 35%-60% of cases, followed by Hodgikin lymphoma and follicular lymphoma, which account for 12%-25% and 5%-10%, respectively [3-6, 10, 13]. There are reports suggesting the involvement of the Epstein-Barr (EB) virus as a cause of the disease, with 32%-71% of MTX-LPD cases tested positive for EB virus [2, 14, 15]. According to the disease type, it has been reported that approximately 80% of Hodgkin lymphoma cases and approximately 20% of diffuse large B-cell lymphoma cases are positive for EB virus [5]. Rheumatoid arthritis patients are reported to have a 2- to 20-fold increased risk of developing lymphoma even without MTX treatment [16]. Patients treated with MTX are reported to be at an even higher risk of developing lymphoma, as the treatment changes the balance between EB virus load and the host [17]. Discontinuing MTX treatment and observing the patient's clinical course is considered the first course of action to be taken for MTX-LPD, after confirming its histological diagnosis [4, 6, 18-20]. If there is tumor regression, the patient's condition needs to be monitored carefully. However, discontinuation of MTX treatment alone after MTX-LPD onset lead to complete remission in 11 out of 48 cases as reported Hoshida et al. [3], in 3 out of 8 cases as reported by Mariette et al. [5], and in 3 out of 13 cases as reported by Kojima et al [10]. If discontinuing MTX treatment is not enough on its own to see clinical remission, patients should be provided treatment according the type of malignant lymphomas [4]. The five-year survival rate of MTX-LPD is reportedly more than 70%, but patient's age of more than 70 years old and pathological subtype of DLBCL are known to be indicators of a poor prognosis [21-22]. Our patients had an 8-mm thyroid tumor with a class III cytological diagnosis that was detected accidentally, and we decided to observe the patient's clinical course. The tumor grew in size by three times during the course (2 years 8 months) after the initial examination. Histopathological examination of the tumor specimen after hemithyroidectomy suggested a diagnosis of MTX-LPD. This is a rare case for which radical excisional biopsy could be performed even before the patient shows symptoms such as neck swelling. After a 2-year follow-up, local recurrence was not detected. It would be necessary to keep the patient under careful observation.

If a thyroid tumor is identified in a patient who is treated with oral MTX, then the possibility of MTX-LPD should be taken into consideration. It is also important to monitor the patient for the presence of nodules in the thyroid gland, even if it is so small.

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