



Methotrexate-Associated Lymphoproliferative Disorder in the Nasopharynx: A Case Report

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비인두에 발생한 메토트렉세이트 연관 림프증식성 질환 1예

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Methotrexate (MTX) is widely used in the treatment of autoimmune diseases, including Crohn's disease, but may be associated with the development of MTX-associated lymphoproliferative disorder (MTX-LPD). Although MTX-LPD frequently involves extranodal sites, involvement of the nasopharynx is rare. We report a case of MTX-LPD involving the nasopharynx in a 19-year-old male with Crohn's disease. The patient presented with right ear fullness, and endoscopic examination revealed a large polypoid mass in the nasopharynx. Imaging demonstrated a symmetric striated lesion suggestive of adenoid hypertrophy; however, lymphoma could not be excluded. Histopathologic evaluation confirmed MTX-LPD. Following the discontinuation of MTX, the lesion showed gradual regression without additional therapy, and the patient's symptoms were completely resolved. This case highlights that MTX-LPD may mimic benign lymphoid hypertrophy in the nasopharynx, and emphasizes the importance of histologic confirmation in immunosuppressed patients, as withdrawal of MTX alone may lead to spontaneous regression and help avoid unnecessary aggressive treatment.

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Introduction

Methotrexate (MTX) is widely used as a first-line immunosuppressant in the treatment of rheumatic diseases and autoimmune disorders, including Crohn's disease.^{1,2)} Although it is generally considered safe and effective, long-term MTX administration is associated with the development of MTX-associated lymphoproliferative disorder (MTX-LPD). MTX-LPD is classified as an "other iatrogenic immunodeficiency-associated lymphoproliferative disorder" and encompasses a

broad spectrum of lymphoid proliferations ranging from reactive polyclonal lymphoid hyperplasia to overt malignant lymphoma. Among the malignant subtypes, diffuse large B-cell lymphoma is reported as the most common histologic type.¹⁻³⁾

Epstein-Barr virus (EBV) is thought to play an important role in MTX-LPD pathogenesis, although approximately half of the reported cases are EBV-negative.^{3,4)} The incidence of MTX-LPD has gradually increased with the increasing use of MTX in autoimmune diseases, and optimal management strategies have been actively debated. Spontaneous regression following MTX withdrawal has been reported in approximately 50% of cases. However, lesions that persist or relapse after MTX discontinuation may require chemotherapy

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or other oncologic treatment.⁵⁻⁷⁾

MTX-LPD may present as a solitary mass or multiple masses, with approximately 40%–50% of the cases occurring at extranodal sites, including the gastrointestinal tract, skin, lung, kidney, oral cavity, and soft tissues.^{1,3)} However, involvement of the nasopharynx is rare.^{3,4)} Here, we report a rare case of nasopharynx-involving MTX-LPD that showed clinical and radiologic improvement after MTX discontinuation.

Case

A 19-year-old male presented to the otolaryngology clinic with right ear fullness. He had undergone adenoidectomy 10 years earlier and had a history of Wolff–Parkinson–White syndrome. He had initially been evaluated at a local clinic, where otitis media with effusion and a nasopharyngeal mass were identified. After ventilation tube insertion, he was referred to our institution for further evaluation.

The patient had been recently diagnosed with Crohn's disease and was initially treated with steroids, followed by MTX. At the time of presentation, he was receiving MTX, mesalazine, and folic acid. MTX had been administered at a dose of 12.5 mg weekly for approximately 10 months.

Nasopharyngoscopy revealed a large polypoid mass occupying the nasopharynx. Contrast-enhanced computed tomography and magnetic resonance imaging revealed a symmetric striated soft tissue mass in the nasopharynx, a pattern suggestive of adenoid hypertrophy; however, lymphoma could not be completely excluded (Fig. 1). Additionally, bilateral reactive cervical lymph node enlargement and palatine and lingual tonsil hypertrophy were identified.

Given the patient's history of MTX use and the nasopharyngeal mass, a punch biopsy was performed. Histopathologic examination revealed diffuse infiltration by atypical lymphoid cells with a polymorphous inflammatory background. Immunohistochemical analysis demonstrated a mixed population of CD20-positive B cells and CD3-positive T cells. The Ki-67 labeling index was approximately 40%, arguing against high-grade lymphoma such as diffuse large B-cell lymphoma. In situ hybridization demonstrated EBV positivity predominantly in CD30-positive immunoblasts, while the absence of EBV expression in NK or T cells, together with negative CD56 staining, excluded extranodal NK/T-cell lymphoma (Fig. 2). Polymerase chain reaction analysis did not demonstrate clonal gene rearrangement, supporting a polyclonal lymphoproliferative process. Taken together, these findings were consistent

with a polymorphous, polyclonal lymphoproliferative disorder. In the context of MTX use, MTX-LPD was diagnosed.

During further evaluation, comprehensive laboratory investigations, including complete blood count, biochemical profiles, lactate dehydrogenase, and C-reactive protein, were within normal limits. EBV DNA titer in peripheral blood was also within normal limits, suggesting the absence of systemic viral reactivation despite EBV positivity in the tissue. Additional staging evaluation, including chest and abdominopelvic computed tomography, revealed no evidence of systemic lymphoproliferative disease.

MTX was discontinued, and mesalazine monotherapy (2000 mg twice daily) was continued. Follow-up evaluation demonstrated gradual regression of the lesion. Endoscopy at approximately 4 months showed slight improvement, and subsequent imaging confirmed further reduction. Concomitantly, palatine and lingual tonsillar hypertrophy showed mild interval improvement, and bilateral cervical lymphadenopathy showed slight interval decrease on follow-up imaging (Fig. 1A). At approximately 1 year, marked regression of about 50% was observed (Fig. 1C), and the patient's symptoms had completely resolved. The patient remained clinically stable without evidence of disease progression and continues follow-up in the gastroenterology department.

This study was reviewed and approved for exemption by the Institutional Review Board of Asan Medical Center (IRB No. 2026-0220).

Discussion

MTX-LPD represents a heterogeneous group of lymphoid proliferations arising in the setting of immunosuppression. Its clinical and pathologic presentations are highly variable, ranging from reactive lesions to overt malignant lymphoma, which often makes diagnosis challenging in clinical practice.

MTX-LPD frequently involves extranodal sites such as the gastrointestinal tract, skin, and lungs. In the head and neck region, the oral cavity, salivary glands, and cervical lymph nodes are more commonly affected.^{3,4)} In contrast, involvement of the nasopharynx is rare.^{3,4)} Because the nasopharynx contains abundant lymphoid tissue as part of Waldeyer's ring, MTX-LPD in this location may closely mimic benign lymphoid hyperplasia, particularly in younger patients.

In the present case, the lesion demonstrated a symmetric, striated pattern suggestive of adenoid hypertrophy on imaging, which made differentiation from benign lymphoid hy-

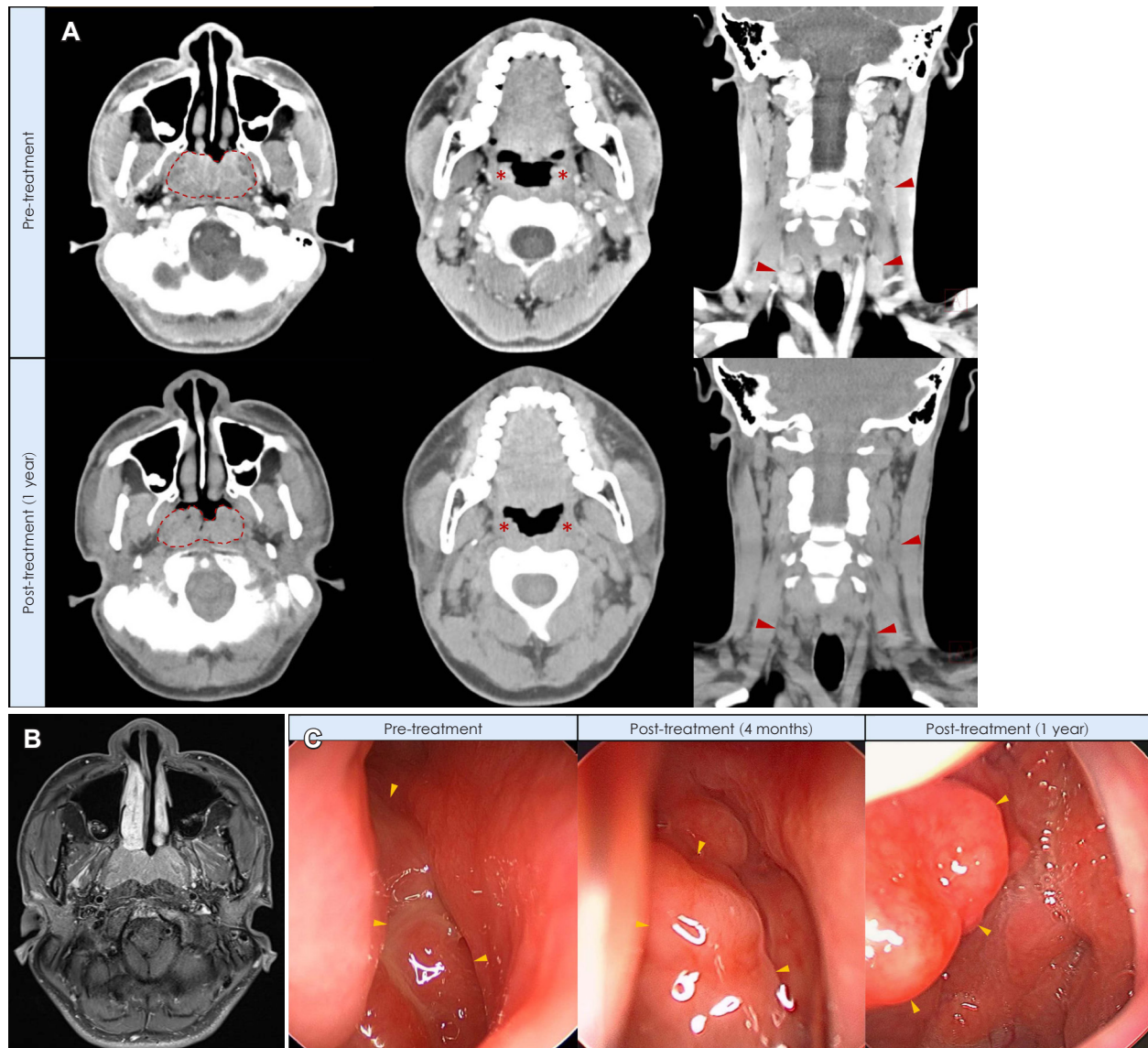


Fig. 1. Radiologic and endoscopic findings of the nasopharyngeal lesion before and after methotrexate withdrawal. A: Axial contrast-enhanced CT at initial presentation shows a symmetric nasopharyngeal mass (dashed outline), accompanied by bilateral palatine tonsillar hypertrophy (asterisks) and multiple reactive cervical lymph nodes (arrowheads). Coronal CT images demonstrate bilateral cervical lymphadenopathy at multiple cervical levels. Comparison of axial CT images at baseline (upper row) and follow-up (lower row) demonstrates regression of the nasopharyngeal lesion, improvement of tonsillar hypertrophy, and decreased cervical lymphadenopathy. B: Axial contrast-enhanced T1-weighted MRI at initial presentation demonstrates heterogeneous enhancement of the nasopharyngeal lesion. C: Endoscopic findings showing a large polypoid mass occupying the nasopharynx (arrowheads). Serial endoscopic images demonstrate progressive regression of the lesion from baseline (left) to approximately 4 months (middle) and 1 year (right) after methotrexate discontinuation.

pertrophy challenging. Recent studies have further highlighted the heterogeneous clinical presentation and variable clinical course of MTX-LPD, including its potential to mimic benign conditions and its capacity for spontaneous regression following withdrawal of immunosuppressive therapy.^{7,8)}

There are no pathognomonic histopathologic features that distinguish MTX-LPD from other lymphoproliferative disorders. Therefore, clinical context, especially a history of MTX use, is essential for accurate diagnosis. In this case, histopath-

ologic examination revealed a polymorphous, polyclonal lymphoid proliferation with EBV-positive immunoblasts, while high-grade lymphoma and extranodal NK/T-cell lymphoma were excluded based on immunohistochemical findings and molecular analysis. These findings, together with the clinical history, supported the diagnosis of MTX-LPD.

Discontinuation of MTX is the first-line management strategy for MTX-LPD, and spontaneous regression has been reported in approximately 50% of cases.⁵⁻⁷⁾ However, some pa-

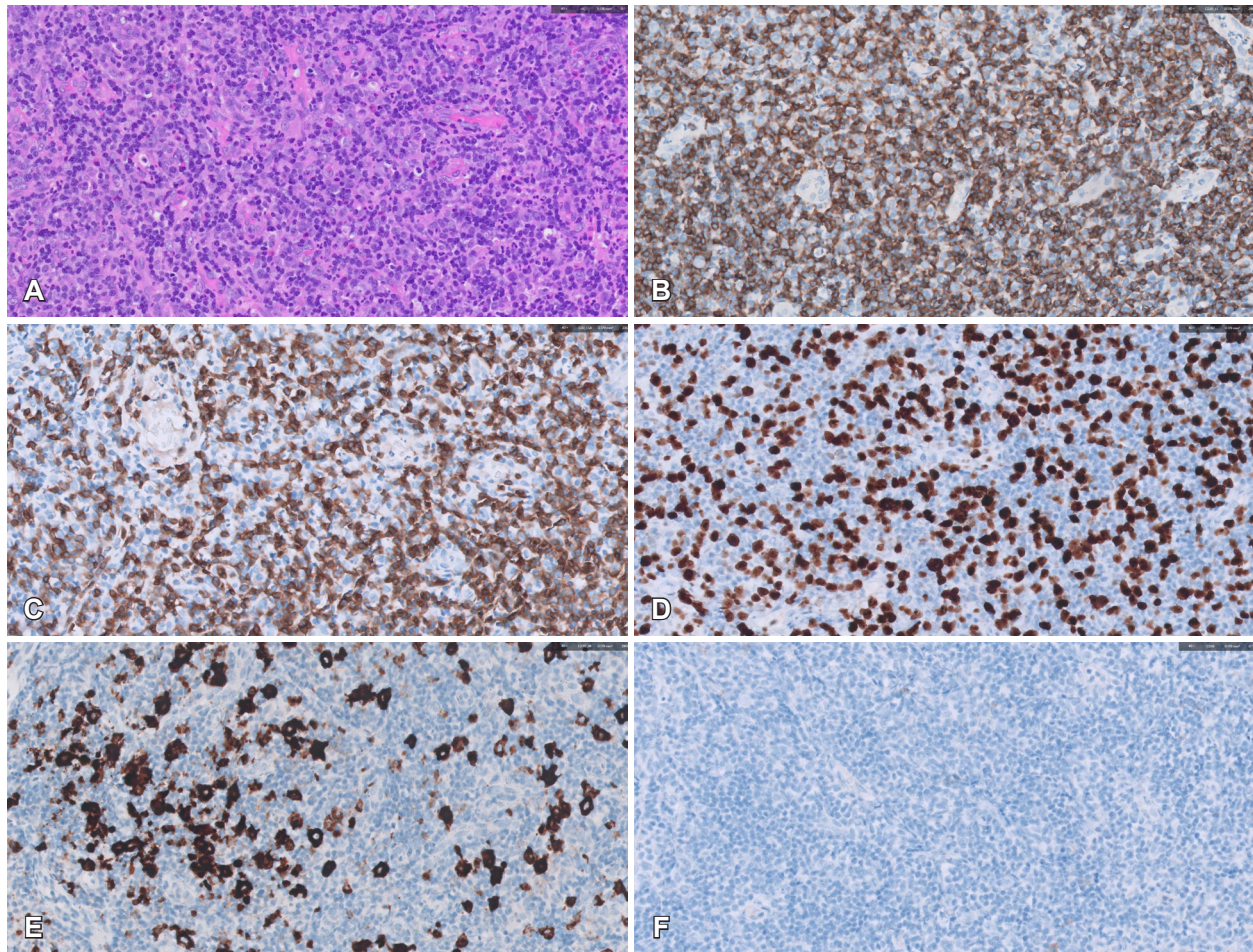


Fig. 2. Histopathologic and immunohistochemical findings of the nasopharyngeal lesion (original magnification $\times 400$). A: Hematoxylin and eosin staining shows diffuse infiltration by atypical lymphoid cells within a polymorphous inflammatory background. B: Immunohistochemical staining shows CD20 positivity in large lymphoid cells. C: Immunohistochemical staining shows CD3 positivity in several lymphoid cells. D: Immunohistochemical staining demonstrates scattered CD30-positive large immunoblasts. E: The Ki-67 index is approximately 40%, indicating relatively low proliferation. F: CD56 staining is negative, supporting exclusion of extranodal NK/T-cell lymphoma.

tients may show incomplete regression or experience relapse, requiring systemic chemotherapy or other oncologic treatment. In the present case, gradual regression of the nasopharyngeal lesion, along with improvement of associated lymphoid hypertrophy, was observed following MTX withdrawal without the need for additional therapy. Notably, although residual lesion persisted radiologically, the patient's symptoms completely resolved, and he remained clinically stable during follow-up.

This case underscores the diagnostic challenge of MTX-LPD in the nasopharynx, where the lesion may closely resemble benign lymphoid hypertrophy, particularly in immunosuppressed patients. Given this overlap, histologic confirmation is essential when evaluating nasopharyngeal masses, even when imaging findings appear suggestive of a benign process. Importantly, accurate recognition of MTX-LPD has sig-

nificant clinical implications, as withdrawal of MTX alone may lead to spontaneous regression and help avoid unnecessary aggressive treatment.

Author Contribution

Conceptualization: Gayoung Lee, Myeong Sang Yu. Data curation: Gayoung Lee, Se Eun Yi, Ji Hyun Oh. Investigation: all authors. Supervision: Myeong Sang Yu. Writing—original draft: Gayoung Lee. Writing—review & editing: Gayoung Lee, Myeong Sang Yu, Se Eun Yi.

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