

v1: 30 August 2024

## Case Report

# Methotrexate Induced Lymphadenitis: A Case Report

Peer-approved: 30 August 2024

© The Author(s) 2024. This is an Open Access article under the CC BY 4.0 license.

Qeios, Vol. 6 (2024)  
ISSN: 2632-3834

Indrani Sarma<sup>1</sup>, Bhupen Barman<sup>2</sup>, Phulen Sarma<sup>2</sup>, Dibyajyoti Saikia<sup>2</sup>

1. Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Guwahati, Changsari, India;  
2. Department of General Medicine, All India Institute of Medical Sciences (AIIMS), Guwahati, Changsari, India

**Introduction:** Methotrexate-induced lymphadenitis (MILA), a rare adverse effect of methotrexate treatment, occurs in a small percentage of patients using the drug for autoimmune diseases like rheumatoid arthritis and psoriasis. The prevalence of MILA varies, with some studies suggesting higher incidence in rheumatoid arthritis cases. The exact mechanisms are not fully understood but involve direct toxic effects on lymphoid tissue and methotrexate's immunomodulatory actions. MILA may occur early or after prolonged use, presenting as localized or generalized lymph node enlargement. Here, we are presenting a case where the patient developed lymphadenitis following methotrexate therapy for rheumatoid arthritis.

**Case report:** In this case, a 39-year-old woman with a history of Rheumatoid Arthritis, undergoing methotrexate treatment presented with complaint of swelling in the neck, joint pain, and local rise of temperature. She was admitted for further investigation. Routine tests were normal, but Fine Needle Aspiration Cytology (FNAC) revealed reactive lymphadenitis. Methotrexate was stopped on admission. The patient was kept under observation. Hydroxychloroquine along with other medications were continued. Remarkably, neck swelling regressed within 36 hours. The patient was discharged next day without any further complications. Causality assessment showed a possible relation between methotrexate and lymphadenitis.

**Conclusion:** The association between lymphadenitis and methotrexate is complicated and requires further evaluation. This patient presented with a small swelling in the cervical region which regressed completely on withholding the medication. Such complications can be avoided with routine follow up if a definitive association can be established between the two. Further studies are required in this regard.

**Corresponding author:** Indrani Sarma,  
[i.sarma17@gmail.com](mailto:i.sarma17@gmail.com)

## Introduction

Methotrexate-induced lymphadenitis (MILA) is considered a relatively rare adverse effect of methotrexate therapy, occurring in a small percentage of patients. Methotrexate is commonly used in the treatment of various autoimmune diseases, including rheumatoid arthritis, psoriasis, and inflammatory

bowel disease. All individuals on methotrexate do not develop lymphadenitis<sup>[1]</sup>.

The prevalence of MILA varies across different studies and populations. Some research suggests that the incidence may be higher in patients with rheumatoid arthritis compared to other conditions<sup>[2]</sup>. The exact mechanisms underlying the development of methotrexate-induced lymphadenitis are not fully understood, but it is believed to involve a combination

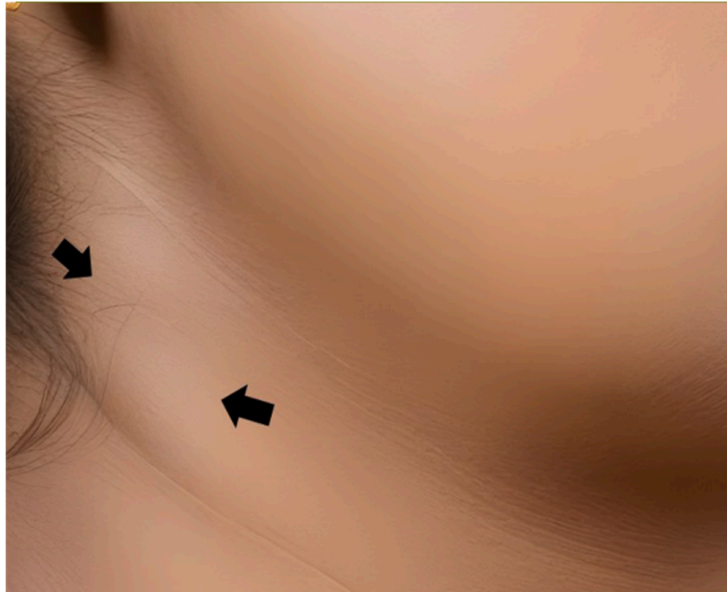
of direct toxic effects on lymphoid tissue and immunomodulatory actions of methotrexate.

Despite its relatively low frequency, healthcare providers have to be aware of the possibility of methotrexate-induced lymphadenitis in patients undergoing methotrexate therapy. Monitoring for signs and symptoms of lymphadenopathy, particularly in the cervical region, is important during routine follow-ups<sup>[3]</sup>.

In some cases, lymphadenitis may occur early in the course of methotrexate treatment, while in others, it may develop after prolonged use<sup>[4]</sup>. The lymphadenopathy associated with methotrexate can manifest in various ways, ranging from localized to generalized lymph node enlargement, particularly in the cervical region<sup>[5]</sup>.

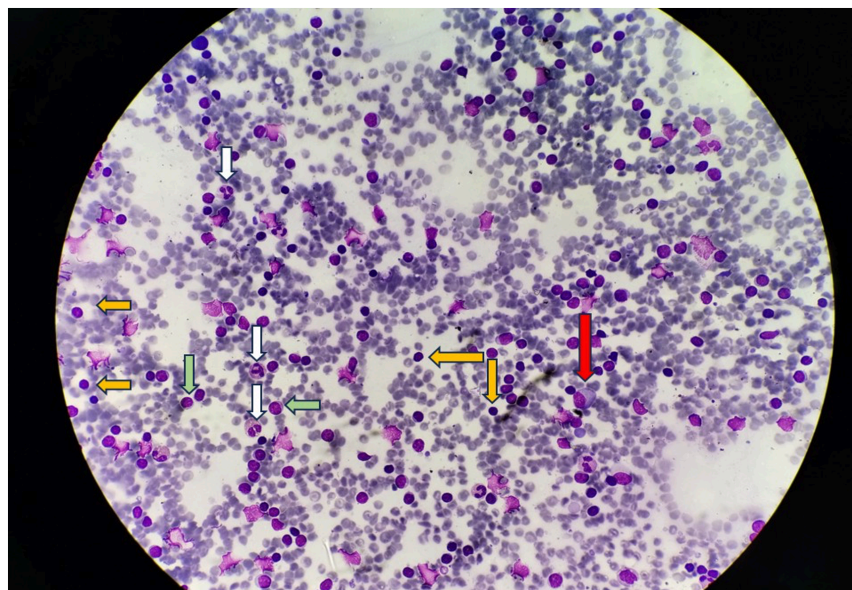
## Case report

In this case discussion, we explore the scenario of a 39-year-old female with a history of seropositive Rheumatoid Arthritis currently undergoing methotrexate(7.5mg once weekly) treatment. Diagnosed with rheumatoid arthritis seven years ago, she initially responded well to methotrexate, experiencing a notable reduction in pain. However, one month prior to the present examination, she developed pain and swelling in her left wrist joint, accompanied by an enlarging swelling on the left side of her neck. Her disease activity score (DAS 28) was 2.5. Seeking medical attention at the outpatient department, she presented with neck swelling and joint pain, accompanied by a localized temperature increase. While there were no additional symptoms or signs of fever, the patient was admitted for thorough investigation.



**Fig. 1.** Arrows indicate swelling of the neck on the right side.

Upon admission, routine tests, including Complete Blood Count, ECG, RBS, and Uric Acid, were conducted. An ultrasound-guided Fine Needle Aspiration Cytology (FNAC) was also performed. While her other test results fell within normal ranges, the FNAC revealed reactive lymphadenitis.



**Fig. 2.** Polymorphous population of lymphocytes(yellow arrow), centrocytes(green arrow), neutrophils(white arrow) and plasma cells(red arrow) in a background of lymphoglandular bodies and blood.

## Management

Given the findings, methotrexate was immediately discontinued. The patient was admitted for observation and continued on hydroxychloroquine and other supportive medications. Over the next 36 hours, the neck swelling showed significant regression, and the patient reported a decrease in pain and discomfort. The patient was discharged the following day with instructions for close follow-up. At the follow-up visit one week later, the neck swelling had completely resolved, and the patient remained asymptomatic. A causality assessment by WHO-UMC scale suggested a probable link between methotrexate and the development of lymphadenitis.

## Conclusion

In conclusion, the presented case highlights the importance of prompt intervention and monitoring in patients with rheumatoid arthritis under methotrexate therapy<sup>[6]</sup>. The emergence of pain, swelling in the left wrist joint, and the subsequent development of reactive lymphadenitis, particularly in the context of methotrexate use, necessitated a careful reassessment of the patient's treatment plan<sup>[7]</sup>. This case emphasizes the dynamic nature of autoimmune disease

management, necessitating a nuanced approach to medication regimens and close attention to emerging clinical manifestations. The successful resolution of symptoms following therapeutic adjustments shows the importance of individualized patient care and ongoing vigilance in the management of rheumatoid arthritis and its complications<sup>[8]</sup>.

Methotrexate induced lymphadenitis is a rare adverse effect of the drug. Diagnosis and early detection plays a major role in this regard. The causality assessment by WHO-UMC criteria showed a probable relation between the drug and the condition which is evidenced by spontaneous and early regression of the swelling. As the actual pathophysiology for methotrexate induced lymphadenitis is not known, further studies are needed for establishing a definitive relationship between the two.

## Statements and Declarations

### *Conflict of interest*

The authors declare that there are no conflicts of interest to disclose. All authors have no financial or personal relationships that could be perceived as influencing the content of this manuscript.

## Funding

This study received no funding from any sources. The research was conducted independently, without financial support or external contributions.

## Author contribution

IDS was responsible for the conception of the case report and the initial drafting of the manuscript. BB provided clinical insights, conducted the literature review, and contributed to the analysis of the case. PS assisted with data collection, helped in the interpretation of clinical findings, and reviewed the manuscript for critical content. DS offered substantial revisions to the manuscript, ensuring accuracy and clarity. All authors reviewed and approved the final version of the manuscript and are accountable for all aspects of the report.

## Acknowledgements

We would like to express our gratitude to Dr. Pakesh Baishya and Dr. Mridul Singh for their support and contributions to this work. This research was conducted independently, with no external funding.

## References

1. <sup>△</sup>Kaito S, Goto M, Iguchi M, Okuno Y, Moriyoshi K, Koyama H. Methotrexate-associated lymphoproliferative disorder with histopathological features of histiocytic

necrotizing lymphadenitis. *Mod Rheumatol Case Rep.* 2021;5(1):141-144.

2. <sup>△</sup>Lai WF, Chin YP, Liu CW, Tsai CY. Methotrexate-associated lymphoproliferative disease with multiple pulmonary nodules in a patient with rheumatoid arthritis. *BMJ Case Rep.* 2017;2017:bcr-2017-221778.
3. <sup>△</sup>Methotrexate Induced Muco-Cutaneous Ulcer: A Case Report. *Int J Pharm Sci Rev Res.* 2021;84(5):12-15.
4. <sup>△</sup>Sato K, Takahashi K, Takahashi H, et al. Methotrexate-induced lymphoproliferative disorder in a patient with rheumatoid arthritis: A case report and review of the literature. *Oncol Lett.* 2016;11(1):123-126.
5. <sup>△</sup>Hoshida Y, Tomita Y, Zhiming D, et al. Lymphoproliferative disorders in rheumatoid arthritis patients treated with methotrexate: Clinicopathological analysis of 26 cases. *Pathol Int.* 2007;57(9):575-583.
6. <sup>△</sup>Ichikawa A, Arakawa F, Kiyasu J, et al. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: Histology and immunophenotype of Hodgkin lymphoma-like lesions. *Pathol Int.* 2012;62(10):633-641.
7. <sup>△</sup>Kameda T, Dobashi H, Miyatake N, et al. Methotrexate-induced lymphoproliferative disorder in a patient with rheumatoid arthritis: A case report and review of the literature. *Intern Med.* 2014;53(7):707-710.
8. <sup>△</sup>Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med.* 1993;328(18):1317-1321.

## Declarations

**Funding:** No specific funding was received for this work.

**Potential competing interests:** No potential competing interests to declare.