# *Case study*

Hodgkin lymphoma in an elderly Rheumatoid patient on long term Methotrexate therapy :A Case report

**Abstract**

Methotrexate associated lymphoproliferative disorders (MTX-LPD)arelymphomas that develop after administration of methotrexate. Here, we report a case of MTX-LPD in a 58-year-old femalewith Rheumatoid arthritis(RA)for10 yearsand isonmethotrexate since then. She presentedwith complaint of cough for 1 month with noB symptoms.Chest and abdomen computed tomography showed hilar, mediastinal and abdominallymphadenopathy. Biopsy and immunohistochemistry confirmed involvement with classical Hodgkin lymphoma. She was advised to stop methotrexate which resulted in complete regression of her lesions on PET CT within 1 month. For patients who are taking MTX for long time,MTX associated LPD should be considered in differential diagnosis in patients presenting with diffuse lymphadenopathyto avoid unnecessary treatment as manyof these casescan be cured with discontinuation of methotrexate alone.

Keywords : methotrexate , hodgkin lymphoma

**Introduction**

Incidence of malignant lymphoma in patients with rheumatoid arthritis or other autoimmune diseasesis higher, with many studies reporting 2-5.5 times more prevalence in patients with RA than in healthy individuals (1-2).

Methotrexate, an antimetabolite and immunosuppressive drug, despitebeing highly effective inthe treatment of rheumatoid arthritis, has been shown to be associated with serious adverse effects including myelosuppression, liver toxicity and interstitial pneumonia. MTX was the first drug found to be associated with lymphoproliferative disorder. Ellman et al. first reported lymphoma in patient with RA treated with low dose MTX in 1991 (3). Since then,there have been various reports of benign or malignant lymphomas occurringafterMTX administration; but few cases have been reported from India.

WHO categorizes immunodeficiency- associated LPD(IA-LPD) into 4 subclasses: LPD associated with primary immune disorders, Lymphomas associated with HIV infection, post-transplant lymphoproliferative disorder(PTLD) and other Iatrogenic Immunodeficiency-associated Lymphoproliferative Disorder(OIIA-LPD). MTX-LPD falls under the OIIA-LPD class which typically develops in patients of autoimmune diseases receiving methotrexate and other biological immunosuppressive drugslike anti TNF inhibitors (anti-tumour necrosis factor inhibitors). (4)

Pathogenesis of MTX-LPD is still uncertain andappears to be multifactorial and related to hyper immune statein RA, chronic immunosuppressive state associated with MTX and reactivation of EBV ~~virus.MTX~~virus. TX-LPD consists mainly of diffuse large B-cell lymphoma (DLBCL; 35–60% of cases) and classical Hodgkin's lymphoma (12–25% of cases) [5].

Approximately 40–50% of MTX-LPD cases occur at extra-nodalsites, such as the skin, salivary glands,oropharynx, lungs, digestivetract, liver, and spine.

Although spontaneous remissionof MTX-LPD after MTX withdrawal can be seenin approximately50% of cases [6], chemotherapy may be needed totreat lymphoma recurring or persisting after stoppingMTX treatment.

**Case presentation**

A 58 year oldfemale with RA and hypertensionsince 10 years presented to our clinic with complaints of dry cough and fatigue since last 1 month. She was onmethotrexate 7.5mg twice/week (cumulative dose= 7800 mg) for RA since last 2012 and atenolol and amlodipine for hypertension. She did not complain of fever, weight loss, ~~anorexia,night~~anorexia, night sweats or hemoptysis. She did nothavedyspnoea, palpitation or pedal edema. There was no history of any swelling in body. Physical examination did not show any lymphadenopathy or hepatosplenomegaly. Laboratory tests showed LDH-228u/l, ESR- 120 mm/hr with a normal renal or liver functiontests. Lymphocyte count was 12% (2008/dl).

Plain radiography was suggestive of asymmetric bulkiness in right hilum (figure 1). Computed tomography of chest revealed asymmetric hypo-enhancing soft tissue density in right infra-hilar and perihilar region measuring 4.4×3.4×3.9cm and encasing the right main pulmonary artery(MPA), right bronchus and pulmonary vein abutting mediastinum with diffuse septal thickening in right lower lobe. Multiple mediastinal lymph nodes were also seen (Figure 2).Abdominal CTrevealed enlarged lymphnodes involving gastro-esophageal junction, gastro-hepatic region, retroperitoneum and common iliac region.

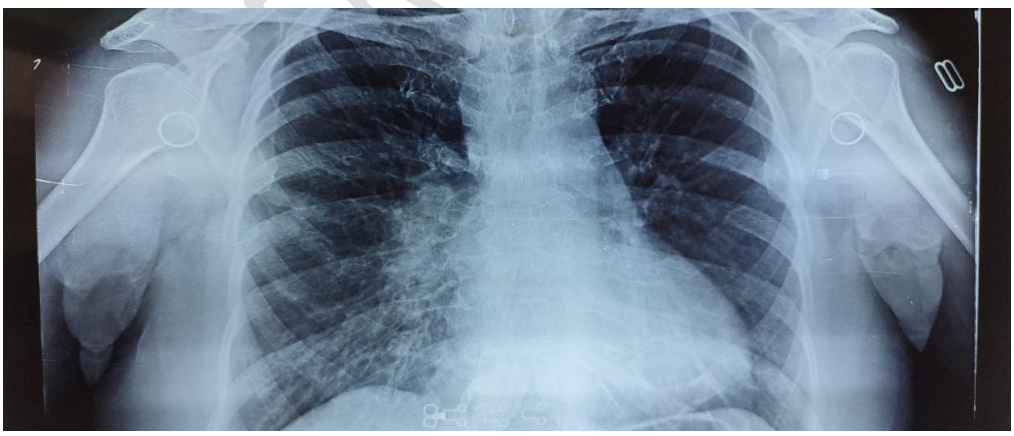


*Figure 1:CXR showing bulky right hilum*

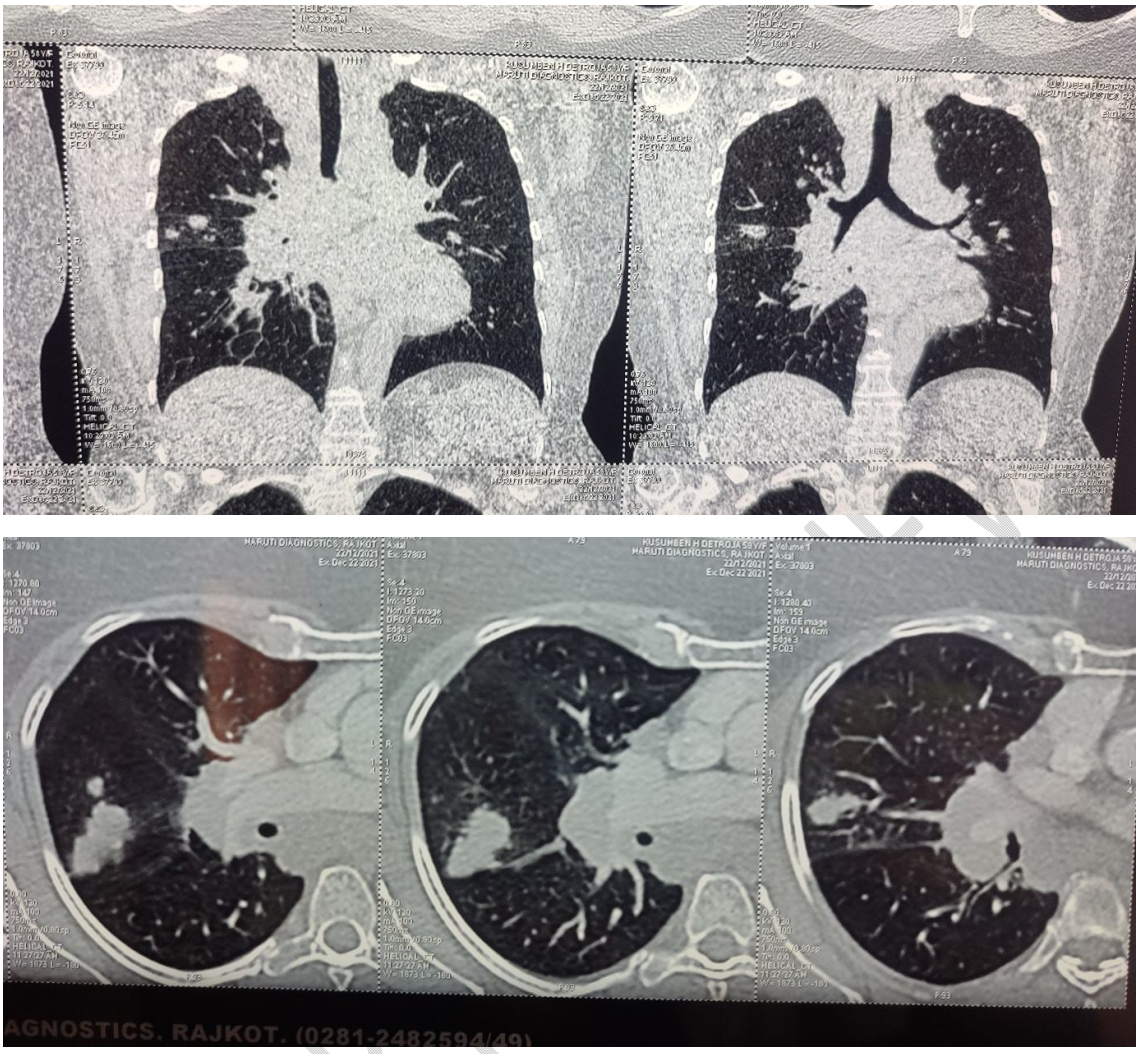


*Fig.2: right hilar STD with involvement of right MPA, right bronchus and pulmonary vein*

Based ontheradiological findings, differential diagnoses included disseminatedKochs, malignant lymphoma andmetastaticCarcinomalung. CT guided biopsy was doneand histopathological evaluation revealed fibrous tissue with admixed lymphoplasmacytic cells with histiocytes, eosinophils and occasional multinucleated giant cells. Few mononuclear and occasional binucleate large cells werealso evident with prominent nucleoli. An impression of Hodgkin lymphoma was made (figure 3). IHC showed CD30 and PAX5 positive, CD15 and CD20 negative atypical cells. Based on these findings, and along with the patient's history of RA treated with MTX, she was diagnosed as a case ofMTX-LPD showing features of stage IIIE Classical Hodgkin lymphoma (Lugano classification).

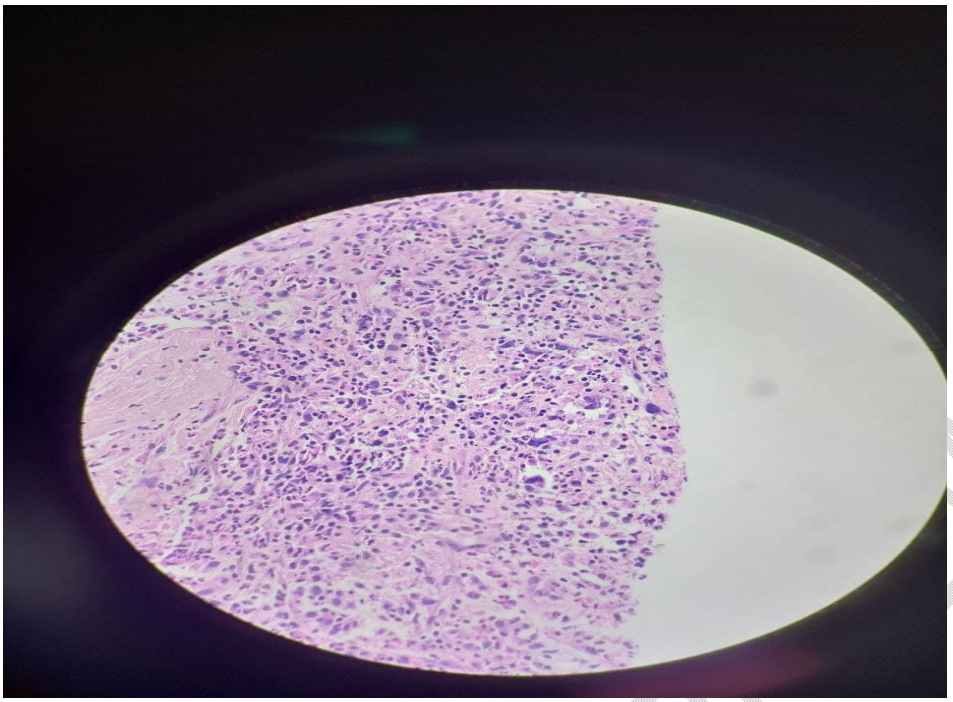


*Figure 3: HPE*

Patient was initially managed with discontinuation of methotrexate which resulted in significant improvement in symptoms within 4 weeks. PET-CT done after 4 weeks showed complete response with no metabolic abnormality related to primary disease. 9 weeks after MTX withdrawal, lymphocyte increased from 12% to 30% (2008/uL to 3684/uL). CT done after 10 weeks was suggestive of sub centimetric few lymph nodes in mediastinum and abdomen with resolution of primary lesion. (Figure 4)

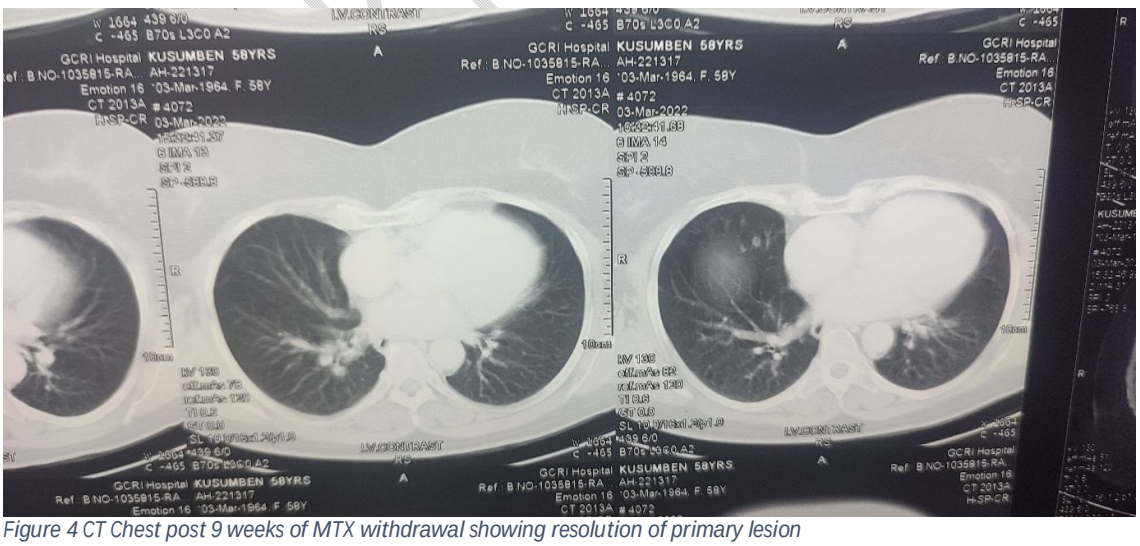



*Figure 4 CT Chest post 9 weeks of MTX withdrawal showing resolution of primary lesion*

PET CT done after 6 months showed ametabolic to low grade metabolically active nodes in mediastinum and retroperitoneum (Deauville score=3) suggestive of good response to MTX withdrawal. Patient was last followed up in November 2022 when PET-CT was still suggestive of ametabolic active nodes(Deauville Score=3).

After discontinuation of MTX, patient did complain of aggravation in joint pain which was managed with NSAIDS conservatively. Rheumatologist opinion was taken who advised to switch to alternate immunosuppressant other than MTX after 3 months of observation.

## Discussion

MTX- LPD is aserious and uncommon complication in patients of various autoimmune disorders including RA, psoriasis,dermatomyositis,and inflammatory bowel disease who are onMTX for their chronic condition(7-10).The rising incidence of MTX-LPD is related partly to the increased use of MTX as an anchor drug in the management of RA .

Pathogenesis of MTX- LPD is poorly understood: combination of immunodeficiency as a result of RA and the immunosuppressive effect of MTX has been implicated in the pathogenesis of MTX-LPD (11,12).Chronic MTX administration leads to suppression of immune system reactivating viral infections like EBV, including subclinical infections, leading to clonal proliferation of cells (13).Activation of EBV is identified in the majority of MTX-LPD cases, including the present case, which was characterized by the presence of positive EBV viral DNA(845.35 copies/ml) detected on RTPCR.

Clinically MTX-LPD is seen predominantly in females with median age of60-70years and usually develops after 5-10years of MTX administration. MTX-LPD is characterised by diffuse lymphadenopathy with or without B symptoms. Involvement of extra lymphatic tissue is relatively high (11,12,13)with approximately 40–50% of MTX-LPD cases occurring at extra nodal sites, such as the skin, salivary glands, lungs, digestive tract, liver, and spine.In the present case, lung lesions with mediastinal and abdomen lymphadenopathy were seen.

MTX-LPD can originate from different cell types, including B cells, T cells and NK cells. Histologically, MTX-LPD can be diverse: but most common finding is diffuse large B-cell lymphoma accounting 50% of cases, followed by Hodgkin lymphoma (20-35%)(11,14).Other rare phenotypes like peripheral T-cell lymphoma, Hodgkin like lesions, EBV positive mucocutaneous ulcer or polymorphic/lymphoplasmacytic infiltrates have also been reported (14). The patient in present case had Hodgkin lymphoma (MTX-HD).

Most MTX-DLBCL are activated B cell type (ABC).MTX- HD is a rare disease. MTX-HD is more frequently found to be mixed cellularity subtype (61% in one study (15) and more commonly associated with EBV infection (83% vs 45% in sporadic CHL (16).MTX-HD is less frequently CD 20 positive compared to sporadic type. Clinically, in contrast to sporadic HD, MTX-HDmore commonly presents in advanced stage and is often associated with extra nodal disease in 40-70% of cases. (15,16).

The duration and dose of MTX treatment leading to MTX-LPD has varied across studies.Duration ranges from 2-131 months (12)with cases reports even after 20yrs.

Cumulative dose observedvaries from 24 to 4785 (median 940) mg (12). Inone case–control study conducted by Kameda et al, higher mean MTX dose was found to be an independent risk factor for LPD development in RA patients.[11] In our patient HD developed after 10yrs with cumulative dose of 7800mg.

Three clinical courses following MTX withdrawal has been suggested:

- LPD regression after ISD withdrawal without relapse/regrowth
- LPD regression after ISD withdrawal with relapse/regrowth
- Persistent LPD

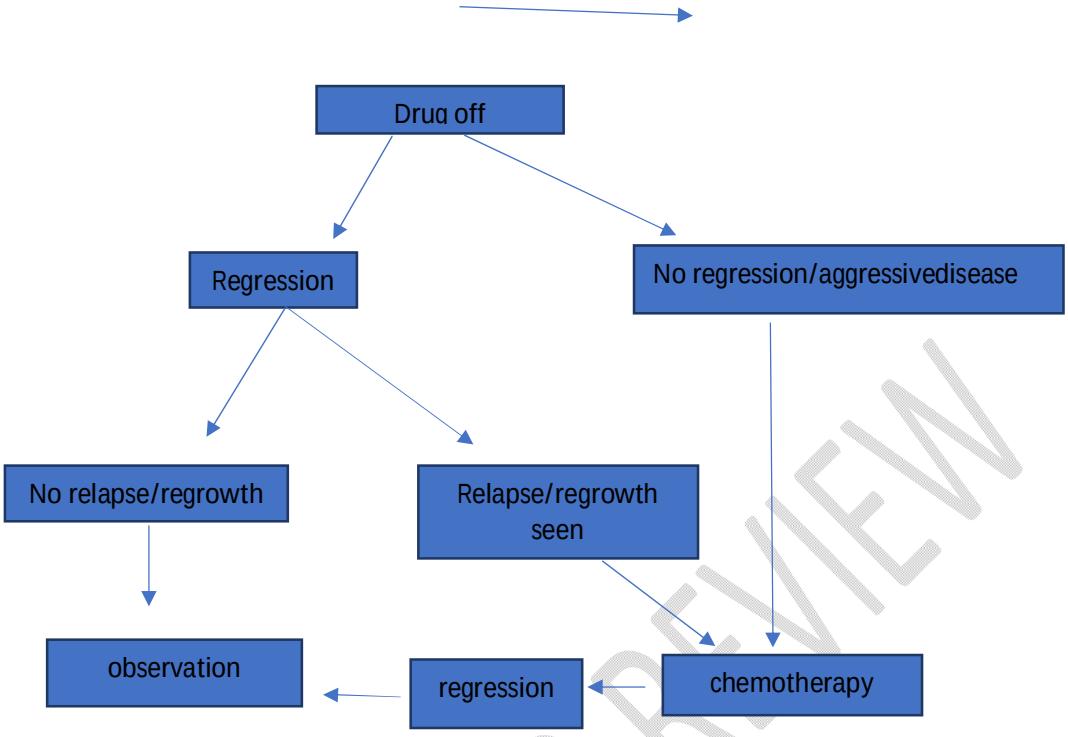
Spontaneous resolution of LPD after withdrawal of MTX treatment is observed in ~50% of all affected patients (14,17). In one of the studies,76.7% had regression of LPD by MTX withdrawal (18). In another study, the majority of DLBCL-type MTX-LPD patients (81%) achieved remission with MTX discontinuation alone.Thus, the first choice of treatment of MTX-LPD is rapid cessation of MTX (14,17,18). However, subsequent recurrence of MTX-LPD has been reported in 18–45% of patients, and chemotherapy is indicated in cases of recurrence, aggressive LPD and in those notreaching remission after > 3 months [17,19). OS is better in patients with LPD regression without relapse regrowth compared to those with persistent LPD or those who relapse following regression.MTX- DLBCL requiring chemotherapy has better prognosis than sporadic DLBCL after receiving rituximab-basedtherapy (19). As opposed to MTX-DLBCL, rate of spontaneous regression following MTX withdrawal is lower with MTX-HD and roughly 3/4$^{th}$ require additional chemotherapy (15) but have similar PFS and OS compared to sporadic HD following treatment.



Clinical MTX- LPD

Differential diagnosis

- Lab inv ( LDH, ALC, sIL2R)
- PET-CT, CT
- Bone marrow
- EBV RTPCR




**Flowchart 1 : Treatment analytical procedure for Pathogenesis of MTX- LPD**

Increase in lymphocyte count following withdrawal of MTX has been shown to be a marker of higher rate of spontaneous regression of MTX-LPD (20).As reported by Saito et al., lymphocyte count increased more than 220/µl in the regressive group compared to less than 150/µl in the persistent group at 2 weeks afterwithdrawal of MTX (20). This finding wasconsistent with our case too as the lymphocyte count increased from 12% to 30% (2008/uL to 3684/uL), though the recovery was seen at nine weeks.

EBV positivity in MTX-LPD has been proved to be an important prognostic factor. Prevalence of EBV in RA patients with LPD has been reported to be significantly higher than that in sporadic LPD (27.6% vs. 9.9%) (12). Patients with EBV DNA positivity in peripheral blood have a better outcome with higher rate of spontaneous regression compared to those who are negative (18).This finding is also consistent with our experience, as the patient in the present case was EBV-positive and has not developed any recurrence.

Use of alternative immunosuppressant drug after development of MTX-LPD is poorly defined. Generally,it is recommended to not use MTX and anti TNFi.

Although the treatment of RA has changedover the years with the use of high efficacy drugs such as the biological agents, MTX, being cost effective and highly efficacious - will remain the first-line drug. Hence, studies should be conductedto elucidate the pathogenesis of MTX-LPD. To summarize, MTX-LPD should be suspected in patients who are on MTX and presents with clinical features of Lymphoma. First-line therapy is the withdrawal of MTX. Even after the remission of MTX-LPD, close observation is important, and if the disease recurs, chemotherapy should be started promptly.

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