

Case Report

Leflunamide Induced Pneumonitis in Rheumatoid Arthritis - A Case Report and Review of Literature

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Abstract

A 51 year old woman while treated on methotrexate (MTX) and leflunomide (LEF) for rheumatoid arthritis (RA), developed exertional breathlessness and undue tiredness followed by fever and cough, at her 11 years of suffering. Her respiratory symptoms developed around 12 weeks after leflunomide intake. She improved with steroid treatment. The Leflunomide (LEF) induced interstitial pneumonitis is an uncommon condition in absence of prior lung disease but potentially fatal. We report a case of Leflunomide (LEF) induced interstitial pneumonitis.

Key words: Rheumatoid arthritis, drug induced pneumonitis, methotrexate, leflunomide

INTRODUCTION:

Methotrexate (MTX) is the most commonly used disease modifying anti-rheumatic drug (DMARD) in RA.¹ At low dose (<30mg), MTX has immunosuppressive and anti-inflammatory properties. ² Other than therapeutic effect and well tolerability, one of the most serious infrequent side effects of this agent is MTX induced pneumonitis.³ Leflunomide (LEF) is another DMARD that have immunomodulatory effect had clinical outcome similar to MTX. It is also prescribed to manage RA since 1998.⁴ It has good safety profile but it can cause some side effects and

pneumonitis is one of the reported one.⁵ We discuss here a patient who developed leflunomide induced pneumonitis. Who was on MTX for nine years.

CASE REPORT:

A 51-year-old woman has been suffering from RA since 2005. She was in remission for nine years with MTX at a dose of only 10 mg/week. At 10th year she experienced a mild flare of RA and went into remission after escalation of MTX at 12.5 mg weekly but failed to maintain remission and MTX doses was raised in subsequent flare gradually up to 25 mg but complete remission could not be achieved. To achieve target 20 mg leflunomide was added to MTX. After 3 months of MTX and leflunomide combination she again achieved remission (CDAI-2) and was relatively well until early May, 2016. But she suddenly developed fever, dry cough, progressive exertional shortness of breath and marked tiredness. Her physical findings were unremarkable. Few days later she got herself admitted in hospital for progressive deteriorations. Her respiratory rate was 30 breaths /minute, temperature was normal, pulse was 88 beats /minutes, BP was 120/80 mm Hg and oxygen saturation was 90%. She was evaluated with the clinical consideration of Pneumonia, acute asthma, pneumonitis, DPLD and/or pulmonary hypertension. Asthma, pneumonia, pulmonary hypertension were excluded after both clinical and laboratory evaluation.

Following investigations were done (table 1).

Table 1: Baseline investigations

Hb	11.4 gm/dl
Total WBC	6890/mm ³
Eosinophilia	13%
ESR	96 mm in 1st hour
CRP	7.13 mg/dl
X-ray chest P/A view	Bilateral interstitial and alveolar opacities in mid and basal region

Hb = Haemoglobin, WBC= white blood cell count, ESR= Erythrocyte sedimentation rate, CRP= C - reactive protein, P/A= posterior/ anterior

Her hematological, renal and liver function tests were normal with normal blood and urine culture. ECG, Echocardiography, spirometry and DLCO were normal. X-ray

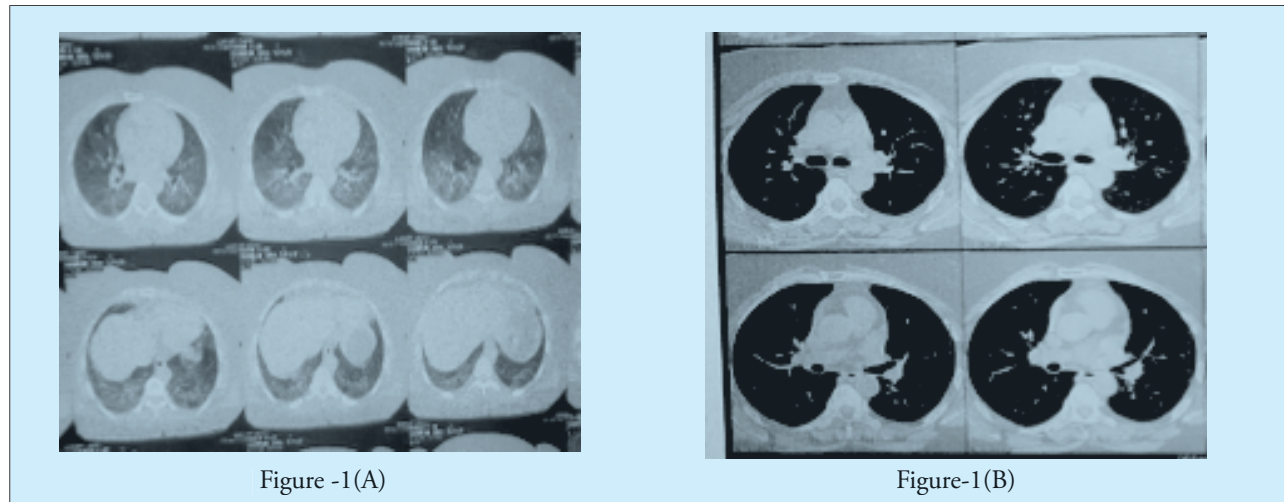
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chest P/A view showed bilateral interstitial and alveolar opacities in mid and basal region. HRCT of chest showed diffuse hyper attenuated areas with interstitial fine septal thickening intermixed with ground glass opacities in all segments of both lung fields predominantly in basal segments. (Figure-1A)

With that drug induced pneumonitis (most probably leflunomide) was suspected and both MTX and LEF were stopped. Prednisolone 40mg/day was started with other supportive treatments. Her fever started settling down and she symptomatically started to improve with lesser cough and breathlessness.

Figure- 1: HRCT of chest before (A) and after treatment (B) with steroid.



During first follow up after one month, she had no breathlessness or cough but complained of generalized weakness. Physical examination was unremarkable. Serum electrolytes, RBS and Serum creatinine were normal.

After two months of treatment there only was generalized weakness. Physical examination was unremarkable. Investigation reports revealed normalization of eosinophilia (01%) and ESR (26 mm in 1st hour). Repeat HRCT showed few calcified foci with marked improvement of previous shadow. (Figure-1B)

DISCUSSION:

The active metabolite of Leflunomide is A77 1726 which inhibits dehydroorotate dehydrogenase.⁶ In previous trials, LEF was proved to be as effective as MTX in improving joint symptoms and to halt the radiological progression of RA patients.⁷ The relation between onset of pneumonitis and the initiation of LEF makes the strong possibility for the diagnosis of leflunomide induced pneumonitis (LEIP). Most LEIP patients had previous exposure with MTX and it is not surprising because LEF is used as second line therapy after MTX; but LEIP was also reported in MTX naïve patients.⁸ Both MTX and LEF can induce pneumonitis either as monotherapy or in combination. In most of the cases the LEIP and MTX-P are indistinguishable. Currently, there is no available established clinical criteria that can distinguish LEIP from MTX-P but there are some differences in presentation between MTX-P and LEIP. LEIP symptoms usually

appear acutely (median duration is 3 days and the range is 1–10 days), but in MTX-P symptoms appear sub-acutely (median duration is 14 days and the range is 1–56 days).⁹ MTX-P occurs within first twelve months of therapy but LEIP commonly occur within the first five months of starting treatment.¹⁰ In our patient, though she was on methotrexate but pneumonitis developed 3 months after starting leflunamide which suggest, according to this literature review, pneumonitis was due to leflunamide.

Many patients were on methotrexate prior to leflunomide, and methotrexate can be presumed as the cause of DPLD. While a patient is on methotrexate, development of pneumonitis soon after adding leflunomide suggests that leflunomide is responsible for pneumonitis and this are similar reports.¹¹

LEIP incidence varies from 0.08% to 0.49% with a mortality of 0.7%.¹² LEIP can occur while treated with leflunomide alone or combined with MTX.¹³ Some author claimed that previous treatment with MTX augment the development of LEIP.¹⁴ Ground glass appearance, bilateral interstitial nodular pattern, alveolar consolidation and honeycomb appearances are common findings in HRCT in LEIP.¹³ Which is consistent with our patient. Higher dose (100mg), age, body weight <40 kg male sex, presence of previous lung injury, genetic predisposition, treatment history with MTX are the risk factors for LEIP.¹⁶

In this case, there was diffuse alveolar consolidation, ground glass densities, and septal thickenings, consistent with the

findings reported in the literature. Especially discontinuation of LEF and MTX, faster clinical and radiological regression after steroid justified the diagnosis of LEIP in this case and plasma exchange could be an alternative method to clear the active metabolites.¹⁵

CONCLUSIONS:

During the treatment period with leflunomide, we suggest for giving importance to the nonspecific pulmonary symptoms even in absence of physical signs as high index of suspicion and a prompt treatment with steroid might bring successful outcome in LEIP.

REFERENCES:

1. Chan V, Tett SE. Changes in use of disease-modifying antirheumatic drugs in Australia over the period 1992-2004. *Pharmacoepidemiol Drug Saf* 2006; 15: 462-8.
2. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; 39: 655-65.
3. Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. *Rheumatology* 2005; 44: 61.
4. Cohen S, Cannon GW, Schiff M et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. *Arthritis Rheum* 2001; 44:1984-92.
5. Sakai F, Noma S, Kurihara Y, Yamada H, Azuma A, Kudoh S, et al. Leflunomide-related lung injury in patients with rheumatoid arthritis. *Mod Rheumatol* 2005; 15:173-9.
6. Chong AS, Huang W, Liu W et al. In vivo activity of leflunomide: pharmacokinetic analyses and mechanism of immunosuppression. *Transplantation* 1999; 68:100-9.
7. Cohen S, Cannon GW, Schiff M et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. *Arthritis Rheum* 2001; 44:1984-92.
8. Otsuka T, Koyama T, Ohtani R et al. Leflunomide-induced lung injury that developed after its withdrawal, coinciding with peripheral blood lymphocyte count decrease. *Mod Rheumatol* 2008; 18:96-9.
9. Chikura B, Sathi N, Lane S, Dawson JK. Variation of immunological response in methotrexate-induced pneumonitis. *Rheumatology* 2008; 47:1647-50.
10. Savage RL, Highton J, Boyd IW, Chapman P. Pneumo-

nititis associated with leflunomide: a profile of New Zealand and Australian reports. *Intern Med J* 2006; 36:162-9.

11. Savage RL, Highton J, Boyd IW, Chapman P. Pneumonitis associated with leflunomide: A profile of new Zealand and Australian reports. *Intern Med J* 2006;36:162-169.
12. Kelly C. Leflunomide and the lung. *Rheumatology (Oxford)* 2009; 48:1017-8.
13. Carloni A, Piciucchi S, Giannakakis K, Nori G, Zobel BB, Poletti V. Diffuse alveolar hemorrhage after leflunomide therapy in a patient with rheumatoid arthritis. *J Thorac Imaging* 2008; 23: 57-9.
14. Chikura B, Lane S, Dawson JK. Clinical expression of leflunomide-induced pneumonitis. *Rheumatology (Oxford)* 2009; 48: 1065-8.
15. Inokuma S, Sato T, Sagawa A, Matsuda T, Takemura T, Ohtsuka T, Saeki Y, Takeuchi T, Sawada T. Proposals for leflunomide use to avoid lung injury in patients with rheumatoid arthritis. *Mod Rheumatol* 2008;18:442-446.
16. Güzel, A., Köksal, N., Gök, A., & Elmalı, M. Leflunomide-Induced Interstitial Lung Disease: A Case Report. *Eurasian J Pulmonol* 2015; 17: 67-9.