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**Review Article**



# Histopathological Features of Methotrexate Induced Pulmonary Lesions in Rheumatoid Arthritis Patients: A Systematic Review of Case Reports

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## Abstract

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**BACKGROUND:** Methotrexate (MTX) is the most commonly used disease-modifying drug in the treatment of rheumatoid arthritis (RA); however, it causes many side effects, including pulmonary lesions. In this review, we characterised the histopathological features of MTX-induced pulmonary lesions in RA patients.

**AIM:** We carried out an electronic search of the relevant literature published during the period from 1990 to 2016. We included only the cases with definitive histo-pathological findings caused by MTX therapy.

**MATERIAL AND METHODS:** The total number of cases is 27. Male: female ratio was 1:3, and ages ranged from 48 to 87 years old, with a mean (SD) = 65.7 (1.0). The cases were originally from Asia (55%), Europe (41%), and America (4%). The major complications of methotrexate therapy were lymphoproliferative disorders (42%) followed by interstitial fibrosis (33), and infections (25%). The incidence of these complications significantly increases with the duration of MTX treatment ( $p = 0.044$ ). Among the infections, the most common causative organism was pneumocystis jiroveci. The majority of patients who developed infections following methotrexate therapy were from Europe whereas the majority of those who developed lymphoproliferative disorders were from Asia ( $p = 0.003$ ).

**CONCLUSION:** In conclusion, methotrexate therapy in rheumatoid arthritis patients causes different types pulmonary complications.

## Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disorder with articular and extra-articular manifestations. The pulmonary complications are a well-recognized extra-articular manifestation of RA and important cause of morbidity and mortality [1]. They include interstitial lung disease, pleural thickening, pleural effusions, airways obstruction, pulmonary vasculitis and pulmonary hypertension. Post-mortem evaluation in RA patients showed a possibility of 50% prevalence of pleural involvement [2].

The lung involvement in these patients is not always due to the systemic effects of the disease; the therapeutic agents, as well as other causes, are also contributing to the pulmonary parenchymal damage

as adverse side effects. Methotrexate (MTX) is one of the widely used drugs in many autoimmune diseases, holds a first line drug status in the management of rheumatoid arthritis patients, and holds the longest duration of a therapeutic segment [3, 4]. In many clinical trials, methotrexate has been found as an effective immunosuppressive agent that efficiently slows the progression of the disease; however, it causes many side effects such as alopecia, stomatitis, gastrointestinal toxicity, liver function abnormalities, and pulmonary lesions [4].

About 2-7% pulmonary involvement has been reported in previous literature, even with a low dose of MTX. The reported incidence of pulmonary toxicity with methotrexate in RA patients is higher than that of liver toxicity. The most prevalent induced MTX pulmonary complication is the acute hypersensitivity pneumonitis [5]. It is estimated that acute pulmonary

toxicity develops in about 12.5% of patients on methotrexate therapy for all rheumatic conditions, including rheumatoid arthritis, but other studies suggest an incidence as high as 33% [6, 7]. Table 1 lists the major and the minor criteria for the diagnosis of MTX-induced pulmonary complication in rheumatoid arthritis patients, and how definite or probable cases are diagnosed [8]. In correlation with clinical features, the histopathological features can be valuable in diagnosing drug-induced lung toxicity and in guiding treatment interventions. Although the surgical lung biopsy is usually large enough to allow the pathologist to give a complete description of the pulmonary process, a minimally invasive procedure, such as bronchoscopic biopsy or Broncho-alveolar Lavage (BAL), can provide valuable data [9, 10]. The histopathological features of MTX-induced pulmonary lesions vary from patient to patient, and the present evidence provide no definite characteristic for pulmonary involvement in these patients [11]. In this review of case reports, the main objective is to characterise the histo-pathological features of MTX-induced pulmonary lesions in RA patients and to investigate the association with the demographic features and the duration of treatment.

**Table 1: Diagnostic criteria for the adverse pulmonary events associated with methotrexate treatment in rheumatoid arthritis patients [8]**

#### Major

1. Hypersensitivity pneumonitis by histo-pathologic examination (and without evidence of pathogenic organisms)
2. Radiologic evidences of pulmonary interstitial or alveolar infiltrates
3. Blood (if febrile) and initial sputum (if produced) cultures negative for pathogenic organisms

#### Minor

1. Shortness of breath of <8weeks duration
2. Non-productive cough
3. O<sub>2</sub> saturation ≤ 90% at the time of initial evaluation on room air
4. DLCO (Diffusing capacity of carbon monoxide) ≤ 70% of that predicted for age
5. WBC (White blood cell count) ≤ 15000 per mm<sup>3</sup>
  - Definite cases were defined as the presence of major criteria 1, or major 2 and 3 and 3 of 5 minor criteria
  - Probable cases: Presence of major criteria 2 and 3 and 2 minor criteria

## Methodology

An electronic search is carried out for the relevant literature published during the period from 1990 to 2016 in the databases of COCHRANE Review, MEDLINE Ovid (from 1990 to 2015 November 25), CINAHL PLUS, Scopus and EMBASE. The following search terms “methotrexate” “rheumatoid arthritis” “lung lesions” “lung complications” “pulmonary lesions” and „pulmonary complications” were used along with appropriate Boolean operators such as AND or OR. The further search criteria were the articles in English language and human adults. Also, we used forward as well as backwards chaining for the relevant articles cited in retrieved publications to get relevant results. We included the case reports of adult rheumatoid arthritis patients on methotrexate

treatment and with findings on histopathology of lung lesions. The excluded articles were those reporting pulmonary complications due to pulmonary toxic agents other than methotrexate. Two authors independently searched and retrieved the articles for the second stage selection process of reading the title and abstract to avoid duplication. During second stage evaluation, the same authors analysed for the availability of required data in the evidence.

### Inclusion criteria

1. Case reports on adult rheumatoid arthritis patients on methotrexate treatment;
2. Case reports with data on histopathology of lung lesions;
3. Articles on both seropositive and negative rheumatoid arthritis patients

### Exclusion criteria

1. The use of pulmonary toxic agents other than methotrexate and
2. Articles without a description of histo-pathological features of lesions.

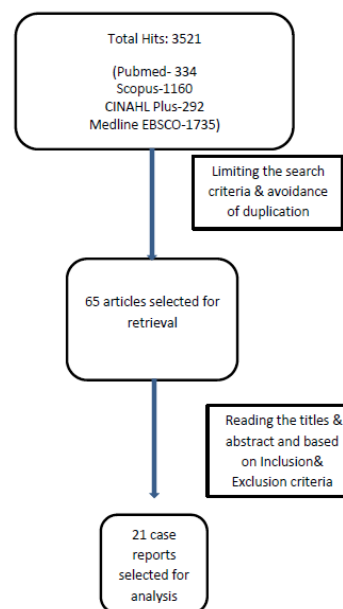


Figure 1: Flow chart of events in literature search

After removing duplication and reading abstracts of retrieved articles, the relevant evidence were selected based on the above inclusion and exclusion criteria. The data extracted from the selected articles were the type of study, year of publication, population studied (country), the number of patients, age and gender of patients, dose and duration of MTX treatment, and pathological characters/ features of the lesions. The relevant data were analysed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) version 20.

**Table 2: Descriptions of evidence selected for analysis**

Author /Year/Reference	Country	Gender	Age	MTX Dose	Duration	Type of infection
Cormelissen, et al., 1991 [12]	England	Female	71	Low	9	Nocardia Infections
Hilliquin & Menkes, 1991 [13]	France	*		Low	*	E.coli Infections
Hilliquin & Menkes, 1991 [13]	France	*		Low	*	Pneumocystis jiroveci
Hilliquin & Menkes, 1991 [13]	France	*		Low	*	Pneumocystis jiroveci I
Wollner et al., 1991 [14]	England	Female	59	Low	*	Pneumocystis jiroveci
Okuda et al., 1995 [15]	Japan	Female	70	Low	2.5	Pneumocystis jiroveci
Roux et al., 1996 [16]	France	Female	62	Low	7	Pneumocystis jiroveci
Roux et al., 1996 [16]	France	Female	85	Low	8	Pneumocystis jiroveci
Schnabel et al., 1997 [17]	England	Female	59	High	*	Pneumocystis jiroveci
Schnabel et al., 1997 [17]	England	Female	66	Low	*	Interstitial Pneumonitis
Schnabel et al., 1997 [17]	England	Female	60	Low	*	Interstitial Pneumonitis
Schnabel et al., 1997 [17]	England	Male	57	Low	*	Interstitial Pneumonitis
Eboe et al., 2003 [18]	USA	Male	54	Low	60	Lymphoproliferative
Hsu et al., 2003 [19]	Taiwan	Female	55	Low	54	Interstitial fibrosis
Shimada et al., 2004 [20]	Japan	Male	64	Low		Interstitial fibrosis
Cho et al., 2007 [9]	Japan	Male	66	Low	5	Interstitial fibrosis
Kameda et al., 2007 [21]	Japan	Male	71	Low	24	Lymphoproliferative
Shimada et al., 2007 [22]	Japan	Female	54	Low	120	Lymphoproliferative
Minagawa et al., 2008 [23]	Japan	Female	62	Low	*	Interstitial fibrosis
Inaba et al., 2011 [24]	Japan	Male	76	Low	*	Lymphoproliferative
Kudoh et al., 2014 [25]	Japan	Female	75	Low	60	Lymphoproliferative
Sakai et al., 2014 [26]	Japan	Female	87	Low	120	Lymphoproliferative
Tokuyama et al., 2014 [27]	Japan	Female	68	Low	18	Lymphoproliferative
Yamakawa et al., 2014 [28]	Japan	Male	78	Low	*	Lymphoproliferative
Tajima et al., 2015 [29]	Japan	Female	64	Low	142	Lymphoproliferative
Akiyama et al., 2015 [30]	Japan	Female	56	Low	24	Lymphoproliferative
Koji et al., 2016 [31]	Japan	Female	48	Low	572	Lymphoproliferative

\* Not Mentioned

## Results

The initial total number of search hits was 3521 articles. After removing duplications and irrelevant results, the number was reduced to 64 articles. Then after revision of the contents and application of the inclusion and exclusion criteria, a total of 21 pieces of evidence were selected for analysis (Fig 1).

Twelve pieces of evidence (44%) were published during 1990-2000 and 15(56%) evidence during 2001-2016. Three pieces of evidence presented data of more than one patient, and the total number of cases reached 27 (Table 2).

Male: female ratio was 1:3, ages ranged from 48 to 87 years old, with a mean (SD) = 65.7 (1.0). The cases were originally from Asia (55%), Europe (41%), and America (4%) (Fig. 2).

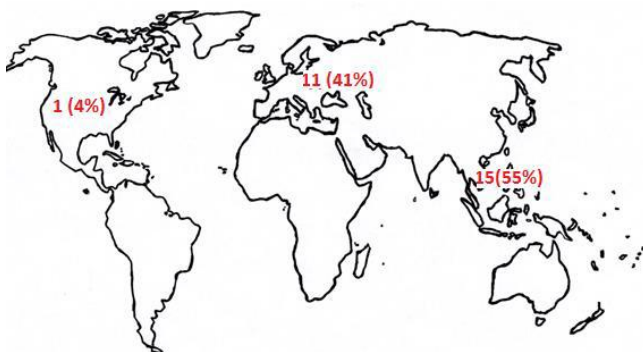


Figure 2: Regional distribution of the case reports

Table 3 shows that the major complications of methotrexate therapy were the lymphoproliferative

disorders (42%) followed by interstitial fibrosis (33), and infections (25%), with the insignificant difference between the male and female cases ( $p = 0.191$ ).

**Table 3: Pulmonary Complications of methotrexate therapy about gender of the reported cases**

Complication	Male	Female	Total
Infections	0 (0%)	6 (25%)	6 (25%)
Interstitial fibrosis	3 (13%)	5 (21%)	8 (33%)
Lymphoproliferative disorders	4 (17%)	6 (25%)	10 (42%)

$P = 0.191$ .

After exclusion of the missing values, the duration of treatment had a significant effect on the type of pulmonary complications ( $P = 0.044$ ), Table 4.

**Table 4: Complications of methotrexate therapy in relation to duration of treatment**

Complication	< 6 month	6 – 18 month	> 18 month
Infections	1 (7%)	3 (21%)	0 (0%)
Interstitial fibrosis	1 (7%)	0 (0%)	2 (14%)
Lymphoproliferative disorders	0 (0%)	1 (7%)	6 (43%)

$P = 0.044$ .

The majority of patients who developed infections following methotrexate therapy were from Europe whereas the majority of those who developed lymphoproliferative disorders were from Asia (Table 5). The regional distribution of these lesions was statistically significant ( $P = 0.003$ ).

**Table 5: Regional incidence of MTX induced pulmonary complications**

Complication	Europe	Asia	America	Total
Infections	8 (30%)	1 (4%)	0 (0%)	9 (33%)
Interstitial fibrosis	3 (11%)	5 (18%)	0 (0%)	8 (30%)
Lymphoproliferative disorders	0 (0%)	9 (33%)	1 (4%)	10 (37%)

$P = 0.003$ .

## Discussion

Methotrexate (MTX) is the most common disease modifying anti-rheumatoid drug (DMARD) used in the treatment of RA patients. It is metabolised intracellularly to polyglutamate, which inhibit dihydro folate reductase enzyme and other folate-dependent enzymes and ultimately causes inhibition of chemotaxis and pro-inflammatory cytokine activity such as IL-1, IL-2 and IL-6 [32]. It exerts both an anti-inflammatory and immune-modulating effects for the management of rheumatoid arthritis [33]. The lung biopsy performed in patients with MTX pneumonitis has demonstrated interstitial inflammation, fibrosis, granulomas, giant cells, tissue eosinophils, type II pneumocyte hyperplasia and increased intra-alveolar macrophages [34]. The lung injury induced by methotrexate are due to several factors such as interference in folate metabolism by methotrexate, hypersensitivity reaction to the drug, and impaired immunity which predisposes to infection [8, 35].

In this review, the authors identified 21 articles on case reports describing the details of 27 patients who developed pulmonary lesions while receiving methotrexate for the treatment of rheumatoid arthritis. The case reports of 12 patients were reported during 1990-2000, and the remaining cases were reported during the period between 2001 and 2016. The majority of evidence (55%) are published from the Asian continent, followed by Europe. Among the nations, the Japanese patients are the most dominant. However, this distribution does not reflect the geographical prevalence of RA. With the exclusion of 3 unmentioned data about the gender of some patients, a higher rate of pulmonary complications are reported among the females compared to the males. This gender variation in MTX-induced pulmonary lesions is most probably due to the higher prevalence of RA among the females compared to the males [36].

We found an insignificant age-related difference in the development of pulmonary complications due to MTX therapy. The histopathological examinations of lung biopsy samples in this review revealed three major categories of pulmonary lesions: infections (25%), interstitial fibrosis (33%) and lymphoproliferative disorders (42%). The high incidence of lymphoproliferative disorders may be due to the propensity of RA Patients to develop Epstein Barr viral infection, secondary to methotrexate induced iatrogenic immunodeficiency [35]. The incidence of these disorders significantly increases with the duration of MTX treatment. However, there is no significant gender-related difference for these lesions. Among the infections, the most common causative organism was *pneumocystis jiroveci*, which affected seven patients of the infection group. The superimposed pulmonary infection attributed to the

immunosuppressive status with opportunistic infectious agents, notably pneumocystis and nocardia, is one of the prime notified complication associated with MTX therapy [34]. The incidence of infection is higher in European region when compared to other regions whereas the incidence of lymphoproliferative disorders is higher among the Asian patients.

In this study, we could not exclude the pulmonary effects of the other medications that were used in combination with the MTX, and not excluded because they are not known to be pulmo-toxic. On the other hand, the exclusion of the patients who received known pulmo-toxic agents in addition to methotrexate caused a large reduction in the number of our cases. Another limitation of this study are the direct effects of rheumatoid arthritis on the pleura and lung parenchyma. Also, the impure preparation of methotrexate in some laboratories is a recognised cause of toxicity [33].

In conclusion, methotrexate therapy in rheumatoid arthritis patients causes three categories of pulmonary lesions: lymphoproliferative disorders (42%), interstitial fibrosis (33), and infections (25%). The incidence of these complications significantly increases with the duration of MTX treatment. Among the infections, the most common causative organism was pneumocystis jiroveci. Further reviews are recommended to evaluate its side effects in comparison with the side effects of the other immunosuppressive agents.

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