Italian Journal of Medicine

https://www.italjmed.org/ijm

eISSN 1877-9352

Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. The Early Access service lets users access peer-reviewed articles well before print/regular issue publication, significantly reducing the time it takes for critical findings to reach the research community.
These articles are searchable and citable by their DOI (Digital Object Identifier).

The Italian Journal of Medicine is, therefore, E-publishing PDF files of an early version of manuscripts that have undergone a regular peer review and have been accepted for publication, but have not been through the copyediting, typesetting, pagination, and proofreading processes, which may lead to differences between this version and the final one.

The final version of the manuscript will then appear in a regular issue of the journal.

The E-publishing of this PDF file has been approved by the authors.

Please cite this article as:

Mancini GS, Rampini S, Freguia S, et al. **Pulmonary nodules in rheumatoid arthritis: the case of leflunomide**. *Ital J Med* doi: 10.4081/itjm.2025.1964

Submitted: 01-03-2025
Accepted: 23-04-2025

Pulmonary nodules in rheumatoid arthritis: the case of leflunomide

Giovanni Simone Mancini,[1]* Silvia Rampini,[2]* Stefania Freguia,[3] Clara Valsecchi,[4] Domenico Cozzo,[5] Anna Lou Christe,[2,6] Adam Ogna[2,6,7]

[1]Department of Internal Medicine, Ente Ospedaliero Cantonale, Regional Hospital of Mendrisio; [2]Department of Internal Medicine, Ente Ospedaliero Cantonale, Regional Hospital of Locarno; [3]Cantonal Institute of Pathology, Ente Ospedaliero Cantonale, Locarno; [4]Institute of Imaging of Italian Switzerland, Ente Ospedaliero Cantonale, Locarno; [5]Division of Nephrology and Hypertension, Department of Medicine, Geneva University Hospitals; [6]Department of Pulmonology, Ente Ospedaliero Cantonale, Regional Hospital of Locarno; [7]Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland

*These authors contributed equally to this work and should be considered as first authors

Correspondence: Domenico Cozzo, Division of Nephrology and Hypertension, Department of Medicine, Geneva University Hospitals, Rue Gabrielle-Perret Gentil 4, 1205 Geneva, Switzerland. E-mail: cozzo.domenico@gmail.com

Key words: rheumatoid arthritis, pulmonary nodules, leflunomide.

Contributions: all the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: informed consent for publication was obtained from the patient.

Availability of data and materials: data available from the corresponding author upon request.

Funding: none.

Abstract
Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily affecting joints. Extra-articular manifestations, including pulmonary involvement, significantly contribute to morbidity and mortality. Disease-modifying antirheumatic drugs are crucial for RA treatment but may also have pulmonary side effects. The differentiation between pulmonary RA manifestations, infection in the immunosuppressed patient, and drug-induced pulmonary toxicity remains a diagnostic and therapeutic challenge. This report presents a rare case of accelerated pulmonary nodulosis associated with leflunomide therapy, emphasizing the need for careful differential diagnosis in immunosuppressed patients.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by joint inflammation and progressive joint damage, with an estimated prevalence of 0.24% globally.[1] Its pulmonary manifestations are the most important extra-articular manifestations in terms of frequency and morbidity. These include interstitial lung disease, pulmonary hypertension, pleural involvement, and, in a minority of the patients, asymptomatic pulmonary nodules (0.2-4%).[2] Risk factors for rheumatoid pulmonary nodules include rheumatoid factor positivity, the presence of subcutaneous rheumatoid nodules, long disease duration, smoking, and male sex.[3]

The mainstay of RA treatment is represented by the disease-modifying antirheumatic drugs (DMARDs). However, DMARDs have also been associated with lung toxicity, particularly methotrexate, but even hydroxychloroquine, leflunomide, infliximab, etanercept, adalimumab, and rituximab.[2] A rare but noteworthy side effect of DMARDs is the emergence of pulmonary nodules. We focus on the effects of leflunomide. This complication is particularly challenging to address, as it may be difficult to distinguish from the progression of rheumatological disease and opportunistic infection in immunosuppressed patients.

This case report details the clinical course of a 74-year-old patient with seropositive RA who developed accelerated pulmonary nodulosis following leflunomide therapy. The findings highlight the importance of timely recognition and management of drug-induced pulmonary toxicity.

Case Report

A 74-year-old male with a known history of seropositive RA presented to the emergency department with severe fatigue lasting several weeks, associated with exertional dyspnea, but without cough or sputum production. The patient reported no articular complaints. RA had previously been managed with methotrexate, which was discontinued due to inefficacy, and subsequently with leflunomide, initiated approximately 6 months before presentation, with a dosage that has been gradually increased. Concurrently, long-term corticosteroid therapy had been gradually tapered. One month before the current episode, the patient had been hospitalized for community-acquired pneumonia without an identified causative pathogen.

Upon admission, the patient appeared in preserved general condition. Vital signs were within normal limits, and pulmonary auscultation was unremarkable. There were no clinical signs of active arthritis. Hematologic workup revealed elevated inflammatory markers (C-reactive protein: 201 mg/L, leukocytosis at 11.4 G/L with neutrophilia, erythrocyte sedimentation rate 110 mm/h) and anemia (hemoglobin: 101 g/L). Renal and hepatic function tests were normal.

During the following hospitalization, the patient developed a febrile state. Blood cultures were sterile, and thoracic computed tomography (CT) imaging revealed consolidation in the left lower lobe and multiple pulmonary nodules distributed across all lung lobes, some with early cavitation. Comparing these images with a prior CT scan performed during the pneumonia episode one month earlier, the nodules appeared to have developed from small ground-glass opacities initially attributed to infection (Figure 1).

Empiric antibiotic therapy with piperacillin/tazobactam was initiated, suspecting nosocomial pneumonia. Given the rapid progression of lesions in an immunosuppressed patient, bronchoscopy with bronchoalveolar lavage was performed 6 days after antibiotic initiation. Microbiological analyses, including cultures and polymerase chain reaction (PCR) for respiratory viruses, atypical bacteria, and opportunistic pathogens, were negative except for a PCR result positive for rhinovirus, deemed clinically insignificant (Table 1). Autoimmune testing, including antineutrophil cytoplasmic antibody, was also negative.

Due to worsening clinical and radiological findings despite antibiotic therapy, a surgical lung biopsy was performed. Histopathological examination of one of the nodules excluded malignancy and vasculitis. No pathogens were identified *via* direct examination or microbiological tests (Table 1). The biopsy revealed multiple foci of peribronchial fibrinous pneumonia with organizing features and granulomatous changes, with central necrosis. In the absence of histological findings consistent with

rheumatoid nodules, the lesions were considered drug-induced pulmonary changes (Figure 2).
A presumptive diagnosis of accelerated pulmonary nodulosis of drug-induced origin was made, reposing on the clinical and radiological evolution, with rapidly developing nodules following Leflunomide initiation, and supported by histological findings.

Management and follow-up

Leflunomide was discontinued, and prednisone doses were increased to prevent a flare of RA. Cholestyramine therapy was introduced to accelerate leflunomide plasma clearance,[4,5] but this was poorly tolerated. Following leflunomide discontinuation, the patient showed progressive clinical improvement, notably resolution of the febrile state. Inflammatory markers decreased, and subsequent thoracic CT scans demonstrated partial regression of nodules (Figure 2), with cavitation of several lesions and development of bronchiectasis in the left lower lobe.

Discussion

We report here a rare case of accelerated pulmonary nodulosis associated with treatment with leflunomide.
The presence of pulmonary nodules in patients with RA poses a diagnostic challenge due to the wide range of differential diagnoses that must be considered. The immunosuppressed state induced by DMARDs increases the risk of fungal and bacterial infections, which may manifest as nodules. The disease itself can induce the formation of pulmonary nodules, and finally, the nodules may be of neoplastic origin.
Extensive examinations, including a biopsy by thoracoscopy, were carried out on our patient, allowing us to exclude an infective or neoplastic etiology of the nodules.
The probable causal link between leflunomide and the pulmonary nodulosis of our patient is substantiated by the compliance with all the recommended diagnostic criteria for drug-induced interstitial lung disease:[6] i) clinical, physiological, and radiological findings were consistent with interstitial lung disease (in our case, diffuse nodules); ii) a temporal relationship was observed between the onset of the pulmonary manifestation and drug exposure in a patient with longstanding RA without previous pulmonary involvement; iii) other potential causes, such as infection and malignancy, were excluded through comprehensive investigations, including a lung biopsy, which suggested drug toxicity; iv) the nodules showed an improvement upon withdrawal of the suspected causative agent.
Leflunomide-induced pulmonary toxicity is highly variable. Cases of iatrogenic pulmonary hypertension, hypersensitivity pneumonitis, and interstitial lung disease have been reported in the literature.[7-9] Pulmonary nodules have occasionally been reported in the literature in association with leflunomide therapy,[10-13] with a higher prevalence observed in patients of Japanese ethnicity.[14]
This phenomenon seems to be more pronounced in patients previously exposed to methotrexate.[15]
Unlike interstitial disease, the appearance of pulmonary nodules during treatment with leflunomide appears to be even rarer and is described sporadically in the literature.[9,11,12] On the other hand, the appearance of elbow joint nodules has been clearly described with leflunomide treatment,[16] as well as an increase in the size and number of pre-existing rheumatic pulmonary nodules.[15]
The pathophysiological mechanism underlying this drug toxicity is unclear, but it could be related to its immunomodulatory effects. By reducing monocyte migration and tissue macrophage activation, leflunomide may disrupt local immune surveillance and cytokine signaling pathways, particularly involving tumor necrosis factor-α and interferon-γ. These cytokines are critical mediators in granuloma formation, as they regulate macrophage activation and the coordination of immune cells within granulomatous tissue.[17] Some authors postulate that the reduction in macrophage function reduces the elimination of rheumatoid factor, leading to accumulation in the alveolar space, which would be a factor in activating the inflammation underlying nodule formation.[11]

Conclusions

This case highlights the importance of differentiating drug-induced pulmonary nodulosis from other potential etiologies, such as malignancy, infection, or progressive RA, and raises the need for heightened awareness among clinicians regarding potential pulmonary toxicities of DMARDs and the importance of post-marketing surveillance to better characterize rare adverse effects. Early imaging and invasive sampling should be rapidly evaluated, given the urgent need to introduce appropriate treatment.

References

1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73:1316-22.
2. Tashfeen M, Jose C, Isham I, Kenneth N. The effect of disease modifying drugs on the lung in patients with rheumatoid arthritis. Southwest Respir Crit Care Chron 2016;4:3-11.
3. Spagnolo P, Lee JS, Sverzellati N, et al. The lung in rheumatoid arthritis: focus on interstitial lung disease. Arthritis Rheumatol. 2018;70(10):1544-54.
4. ARAVA® (leflunomide) prescribing information. Bridgewater, NJ: Sanofi-Aventis; 2010. Food and Drug Administration. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020905s020lbl.pdf.
5. Wong SPY, Chu CM, Kan CH, et al. Successful treatment of leflunomide-induced acute pneumonitis with cholestyramine wash-out therapy. J Clin Rheumatol 2009;15:389-92.
6. Skeoch S, Weatherley N, Swift AJ, et al. Drug-induced interstitial lung disease: a systematic review. J Clin Med 2018;7:356.
7. Lacoste-Palasset T, Chaumais MC, Weatherald J, et al. Association between Leflunomide and Pulmonary Hypertension. Ann Am Thorac Soc 2021;18:1306-15.
8. Martin N, Innes JA, Lambert CM, et al. Hypersensitivity pneumonitis associated with leflunomide therapy. J Rheumatol 2007;34:1934-7.
9. Raj R, Nugent K. Leflunomide-induced interstitial lung disease: a systematic review. Sarcoidosis Vasc Diffuse Lung Dis 2013;30:167-76.
10. Sakai F, Noma S, Kurihara Y, et al. Leflunomide-related lung injury in patients with rheumatoid arthritis: imaging features. Mod Rheumatol 2005;15:173-9.
11. Rozin A, Yigla M, Guralnik L, et al. Rheumatoid lung nodulosis and osteopathy associated with leflunomide therapy. Clin Rheumatol 2006;25:384-8.
12. Abiyarghamsari M, Ahmadzadeh A. Pulmonary nodules after leflunomide therapy in rheumatoid arthritis: a case report. Clin Case Rep 2024;13:e9615.
13. Karadag F, Polatli M, Senturk T, et al. Cavitary necrobiotic nodule imitating malignant lung disease in a patient without articular manifestations of rheumatoid arthritis. J Clin Rheumatol 2003;9:246-52.
14. McCurry J. Japan deaths spark concerns over arthritis drug. Lancet 2004;363:461.
15. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum 2006;54:1435-9.
16. Braun MG, van Rhee R, Becker-Capeller D. Neuauftreten und/oder Zunahme von Rheumaknoten unter Leflunomidtherapie bei RA-Patienten. Z Rheumatol 2004;63:84-7.
17. Grisar J. Leflunomide inhibits transendothelial migration of peripheral blood mononuclear cells. Ann Rheum Dis 2004;63:1632-7.

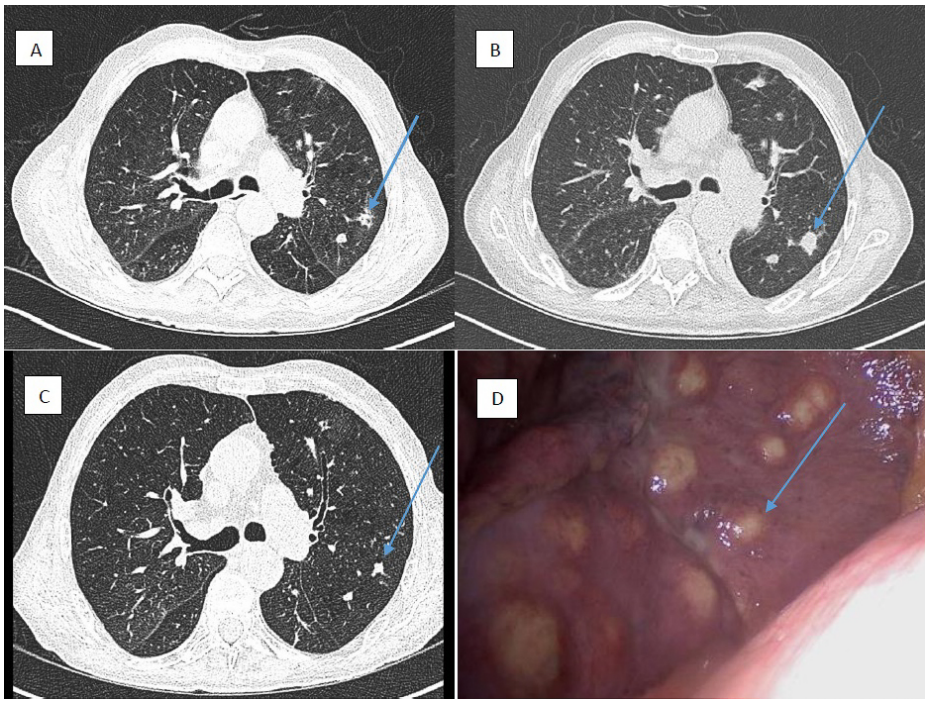

Figure 1. A) 1 month before hospitalization, under Prednisone 2.5 mg/day and leflunomide; B) worsening of nodular lesions at admission; C) evolution after discontinuation of leflunomide and increased prednisone dosage; D) thoracoscopic image (surgical lung biopsy).

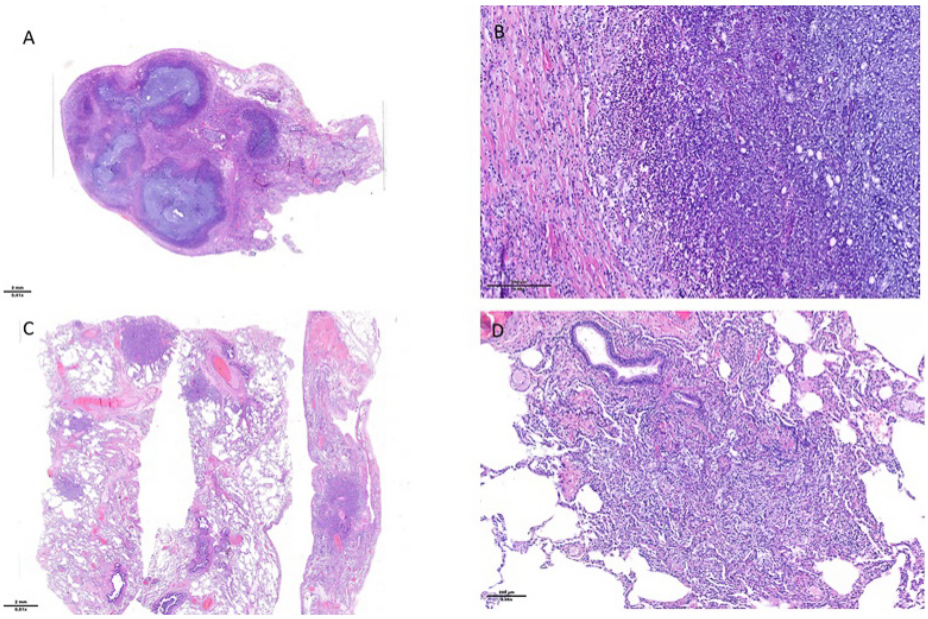

Figure 2. Pulmonary parenchyma with confluent nodules featuring a necrotic center (A), surrounded by neutrophil granulocytes, resembling an abscess (B). The lesions are distributed peribronchially. Silver Methenamine, PAS, and Ziehl-Neelsen staining did not reveal any microorganisms. The pulmonary parenchyma distant from the lesions (C) is characterized by multiple foci of fibrinous pneumonia, with signs of organization and granulomatous features, predominantly peribronchial (D). No evidence of capillaritis. *(Hematoxylin-eosin, low magnification [A and C] x100, [B] x60, [D]).*

Table 1. Comprehensive microbiological assessment.

Microbiological assessment	
Blood cultures	4 negative pairs
Serological tests	*C. burnetiid* (IgG, IgM): negative *Brucella* (polyagglutinins): negative *Cryptococcus* antigen: negative PCR *Bartonella* spp.: negative
Bronchoalveolar lavage	Direct examination: negative PCR respiratory viruses: positive for rhinovirus PCR *Aspergillus fumigatus*: negative PCR *Pneumocystis jirovecii*: negative PCR *M. tuberculosis* and *Mycobacterium* spp.: negative *Aspergillus* galactomannan detection: negative General bacteriology cultures: *Enterococcus faecium* 10^2 CFU/mL Fungal culture: *Candida albicans* Actinomycetes culture: negative
Bronchial aspiration	PCR *Aspergillus fumigatus*: negative PCR and cultures for *Legionella*: negative Fungal cultures: *Candida albicans* General bacteriology culture: physiological flora Mycobacteria direct examination and cultures: negative
Pulmonary biopsies	Panfungal PCR: negative Panbacterial PCR: negative PCR *M. tuberculosis* and *Mycobacterium* spp.: negative PCR *Bartonella*: negative

PCR, polymerase chain reaction; IgG, immunoglobulin G; IgM, immunoglobulin M.