

Recurrent Pneumothorax In A Patient With Rheumatoid Arthritis On Leflunomide Treatment: Case Report And Overview Of The Literature

D Hilling, P van den Berg, A Makkus, F van der Straaten, P Plaisier

Citation

D Hilling, P van den Berg, A Makkus, F van der Straaten, P Plaisier. *Recurrent Pneumothorax In A Patient With Rheumatoid Arthritis On Leflunomide Treatment: Case Report And Overview Of The Literature*. The Internet Journal of Rheumatology. 2006 Volume 3 Number 1.

Abstract

Rheumatoid arthritis is a multi-system disease. One of the most common extra-articular manifestations of RA is the rheumatoid nodule. Pulmonary rheumatoid nodules can result in spontaneous pneumothorax. We present the complicated course of a patient with rheumatoid arthritis on leflunomide treatment who developed recurrent pneumothorax. An overview of literature is also given.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the synovial membrane, leading to bone damage and joint destruction. One of the most common extra-articular manifestations of RA is the rheumatoid nodule, which is found in approximately 25% of patients with this disease. Nodules are usually subcutaneous but can be found elsewhere. This is usually the case on pressure points, such as the olecranon process, but nodules may also occur at other sites including internal organs, such as the lung ¹.

Pneumothorax secondary to rheumatoid lung disease is rare ^{1,2,3,4,5}. We present a 53-year-old woman with RA, who developed recurrent spontaneous pneumothorax during treatment with leflunomide (Arava®).

CASE REPORT

A 53-year-old woman presented in January 2005 at our pulmonary outpatient clinic with a 4 week history of progressive dyspnoea. She had seropositive RA for 13 years and further history revealed hypertension and several orthopaedic procedures for the RA (i.e. arthrodesis of both ankles and left wrist). She smoked 5-10 cigarettes a day. She had been treated with prednisone (7.5 mg/day) for several years. Three years before this event, leflunomide 20 mg/day had been added to this regimen. Chest X-ray showed a pneumothorax of the left lung. Laboratory data are shown in Table 1. She was admitted and chest tube drainage was performed. Recovery was uneventful and the patient was

discharged without any signs of pneumothorax 5 days after she was admitted.

Figure 1

Table 1: Laboratory data

	January 2005	April 2005	Normal values
Erythrocyte Sedimentation Rate (ESR)	34	37	0 – 30 mm at 1 hour
Eosinophil count	0.8	-	0-0.7 x 10 ⁹ /l
Haemoglobin	7.1	7.5	7.5 – 10.0 mmol/l
White blood cells	11.5	13.3	4.3 – 10.0 x 10 ⁹ /l
Thrombocytes	407	545	150 – 400 x 10 ⁹ /l

All other laboratory data were within normal values

Within two days she was re-admitted for recurrent, progressive, dyspnoea. Chest X-ray showed a new left pneumothorax, this time with evident subcutaneous emphysema. A Chest CT was in accordance with the plain film and, moreover, showed multiple noduli in both lungs. (Figure 1 and 2) Again chest tube drainage was performed, followed by thoracoscopic bullectomy and pleurectomy. Recovery was uneventful and the patient was discharged without dyspnoea. Histology of the excised pleura showed signs of chronic, mildly active inflammation.

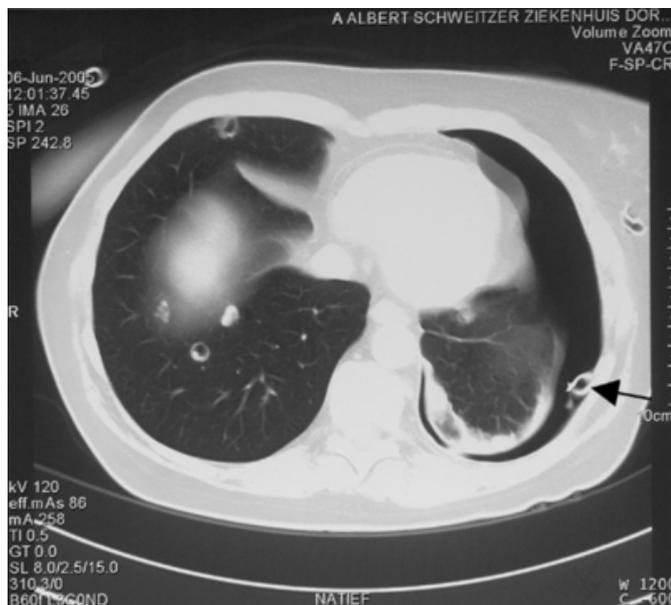
Figure 2

Figure 1 : necrobiotic rheumatoid nodules in the right lung and pneumothorax of the left; thorax drain 'in situ'.



Figure 3

Figure 2 : subpleural necrobiotic nodule in the left lung and pneumothorax; thorax drain 'in situ'.



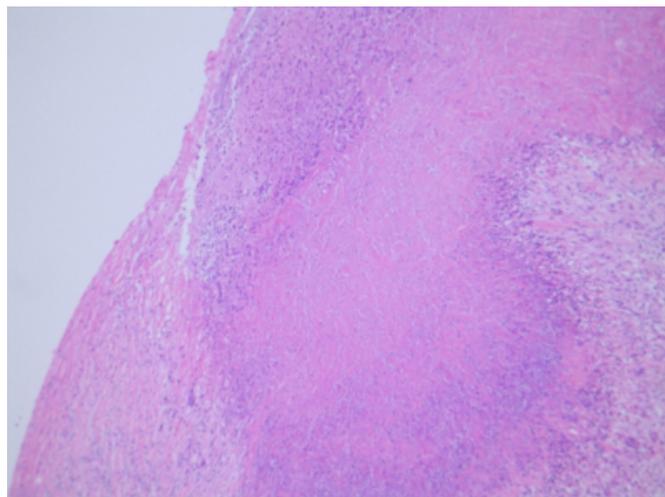
Three days after discharge she was admitted for a third time with subcutaneous emphysema again based on a minor pneumothorax left. Subcutaneous emphysema was present in the whole thorax and extended to the upper abdomen and the mediastinum. Again chest tube drainage was performed and again she recovered uneventfully.

In April 2005, she was admitted for the fourth time when she

felt movement of air in the left chest during attacks of cough. There was increased production of white sputum and only little dyspnoea. Laboratory data are shown in Table 1. Chest X-ray showed again a large pneumothorax left. Now, she was scheduled for pleurectomy by classical thoracotomy. Post-operatively, she developed empyema and was shortly admitted to the ICU for treatment of mild septic shock. The empyema was treated by re-thoracotomy, antibiotics, and drainage and irrigation. Further recovery was complicated by positive stains of the drainage fluid for *Staphylococcus aureus* and a new pneumothorax in the top of the left lung. Therefore, a second re-thoracotomy was performed, the leakage was closed and an irrigation system was applied. Histology of the excised tissue showed a cavitary lesion of 0.6 cm in diameter, containing several granulomas with central necrosis consistent with rheumatoid lung node (Figure 3). There were also signs of focal vasculitis and a bronchopleural fistula was found, which could be an explanation for the persisting air leakage. Although there still was a small pneumothorax present at the top of the left lung, which was treated conservatively, she recovered well. Additionally, leflunomide was stopped considering the negative effect this drug could have on the patient's recovery.

Figure 4

Figure 3 : Subpleural, ruptured, nodule consisting of a necrotizing granuloma surrounded by palissading histiocytes consistent with a rheumatoid nodule by exclusion of other causes, most notably tuberculosis.



Finally, she presented again with dyspnoea. Moreover, after stopping leflunomide she had had more complaints of the RA. Chest X-ray showed a pneumothorax on the basis and top of the left lung, with little pleural effusion. Because of

the persistence of the pneumothorax, a Heimlich-valve was placed.

DISCUSSION

Pulmonary nodules are a rare manifestation of RA. They occur in less than 0.5% of patients with RA. Usually they are associated with the presence of subcutaneous nodules and appear mainly in men with long-standing seropositive RA. The nodules can cavitate and depending on their location, may cause haemoptysis, if they are close to a main bronchus, or may cause pneumothorax if they are situated adjacent to the pleura^{1, 3}. Such spontaneous pneumothorax may even occur before developing arthritic symptoms⁶.

Pneumothorax in RA may be associated with eosinophilia, high ESR and other pulmonary manifestations of RA, such as pulmonary fibrosis and vasculitis^{4, 5}. Crisp and co-authors conclude that the appearance of eosinophilia in rheumatoid disease may indicate a more aggressive course with extra-articular complications⁴. Our patient only had a mild elevation of ESR and a slightly elevated eosinophil count. Although she had no signs of pulmonary fibrosis, histology did show signs of focal vasculitis.

Recurrent pneumothorax rates after thoracoscopic and 'open' bullectomy/pleurectomy vary respectively from 3 – 10.3% and 0 – 7.7%^{7,8,9,10}. We have excellent results after thoracoscopic bullectomy and pleurectomy¹¹ and have, therefore, no other explanation for the complicated course for the (re-)recurrence of the pneumothorax other than the underlying disease or, perhaps, its treatment.

Leflunomide is a disease-modifying anti-rheumatic drug that inhibits the enzyme dihydroorotate dehydrogenase, responsible for de novo synthesis of pyridine-containing ribonucleotides. Activated T cells are particularly dependent on this de novo synthesis. Leflunomide thus induces a stop of the cell division of activated T cells, which play a crucial part in the pathogenesis of RA^{12,13,14}. It was launched in the USA in 1998 and in Europe the following year^{12, 14}. Several trials have evaluated the efficacy and safety of leflunomide in patients with RA. The most common adverse events reported are nausea, diarrhoea, vomiting, skin rash, hepatotoxicity, upper respiratory tract infections and hypertension^{12, 15}. Also several pulmonologic side effects have been reported. Ulusoy et al. reported a patient with RA who developed a pulmonary abscess due to leflunomide¹⁴. Fatal interstitial lung disease has been reported during treatment of RA with leflunomide in Japan¹⁶. Rozin et al

described lung nodulosis as complication of successful leflunomide therapy for RA¹⁷. If nodulosis and growth of existing nodules is indeed due to leflunomide treatment, we postulate here that the complicated course in our patient may be attributed to this treatment and the location of the nodules, i.e. adjacent to the pleura. However, it must be noted that this observation must be treated with caution since clinical trials so far did not suggest that leflunomide causes excess of pulmonary adverse effects¹⁸.

CONCLUSION

Pulmonary nodules are a rare manifestation of RA. They may cause spontaneous pneumothorax depending on their location. Lung nodulosis is previously described as an adverse effect of leflunomide therapy. We have no other explanation for the re-recurrences and complicated course in our patient other than the underlying disease and perhaps medication (prednisone and leflunomide).

CORRESPONDENCE TO

Dr. P.W. Plaisier Department of Surgery Albert Schweitzer Hospital PO Box 444 NL-3300 AK Dordrecht The Netherlands Tel: +31 (0)78 6541111 Fax : +31 (0)78 6542264 E-mail address: p.w.plaisier@asz.nl

References

1. Adelman H, Dupont E, Flannery M, Wallach P. Case report: recurrent pneumothorax in a patient with rheumatoid arthritis. *Am J Med Sci* 1994; 308:171-2.
2. Kobayashi T, Satoh K, Ohkawa M, Satoh A. Multiple rheumatoid nodules with rapid thin-walled cavity formation producing pneumothorax. *J Thorac Imaging* 2005; 20:47-9.
3. Gotsman I, Goral A, Nusair S. Secondary spontaneous pneumothorax in a patient with pulmonary rheumatoid nodules during treatment with methotrexate. *Rheumatology (Oxford)* 2001; 40:350-1.
4. Crisp A, Armstrong R, Grahame R, Dussek J. Rheumatoid lung disease, pneumothorax, and eosinophilia. *Ann Rheum Dis* 1982; 41:137-40.
5. Portner M, Gracie WJ. Rheumatoid lung disease with cavitary nodules, pneumothorax and eosinophilia. *N Engl J Med* 1966; 275:697-700.
6. Saravana S, Gillott T, Abourawi F, Peters M, Campbell A, Griffith S. Spontaneous pneumothorax: an unusual presentation of rheumatoid arthritis. *Rheumatology (Oxford)* 2003; 42:1415-6.
7. Sawada S, Watanabe Y, Moriyama S. Video-Assisted Thoracoscopic Surgery for Primary Spontaneous Pneumothorax: Evaluation of Indications and Long-term Outcome Compared With Conservative Treatment and Open Thoracotomy. *Chest* 2005; 127:2226-30.
8. Ben-Nun A, Soudack M, Best L. Video-assisted thoracoscopic surgery for recurrent spontaneous pneumothorax: the long-term benefit. *World J Surg* 2006; 30:285-90.
9. Cardillo G, Facciolo F, Regal M, et al. Recurrences following videothoracoscopic treatment of primary

- spontaneous pneumothorax: the role of redo-videothoracoscopy. *Eur J Cardiothorac Surg* 2001; 19:396-9.
10. Chan P, Clarke P, Daniel F, Knight S, Seevanayagam S. Efficacy study of video-assisted thoracoscopic surgery pleurodesis for spontaneous pneumothorax. *Ann Thorac Surg* 2001; 71:452-4.
11. Schutte P, Oostenbroek R, Tan K, Eland M. Surgical thoracoscopy; initial results in 13 patients. *Ned Tijdschr Geneesk* 1993; 137:960-3.
12. Cohen S, Igbal I. Leflunomide. *Int J Clin Pract* 2003; 57:115-20.
13. Fox R. Mechanism of action of leflunomide in rheumatoid arthritis. *J Rheumatol Suppl* 1998; 53:20-6.
14. Ulusoy H, Bilgici A, Kuru O, Celenk C. Pulmonary abscess due to leflunomide use in rheumatoid arthritis: a case report. *Rheumatol Int* 2005; 25:139-42.
15. Li E, Tam L, Tomsilon B. Leflunomide in the treatment of rheumatoid arthritis. *Clin Ther* 2004; 26:447-59.
16. McCurry J. Japan death spark concerns over arthritis drug. *Lancet* 2004; 363:461.
17. Rozin A, Yigla M, Guralnik L, et al. Rheumatoid lung nodulosis and osteopathy associated with leflunomide therapy. *Clin Rheumatol* 2006; 25:384-8.
18. Kalden J, Schattenkirchner M, Sorensen H, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. *Arthritis Rheum* 2003; 48:1513-20.

Author Information

D. E. Hilling

Department of Surgery, Albert Schweitzer Hospital

P. M. van den Berg

Department of Pulmonology, Albert Schweitzer Hospital

A. C.F. Makkus

Department of Pathology, Albert Schweitzer Hospital

F. van der Straaten

Department of Radiology, Albert Schweitzer Hospital

P. W. Plaisier

Department of Surgery, Albert Schweitzer Hospital