Pathol. Oncol. Res. (2008) 14:101–104
DOI 10.1007/s12253-008-9003-6

ORIGINAL PAPER

Intrapulmonary Rheumatoid Nodules in a Patient with Long-Standing Rheumatoid Arthritis Treated with Leflunomide

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Received: 8 May 2007 / Accepted: 25 June 2007 / Published online: 8 April 2008

Abstract Rheumatoid nodules are well established manifestations of rheumatoid arthritis but in the lungs they are very rare according to the literature. In our study we present the case of a 34-year-old woman with rheumatoid arthritis and secondary Sjögren's syndrome who developed multiplex rheumatoid nodules in the lungs 3 years after initiating leflunomide therapy. During leflunomide therapy we did not detect inflammation in the joints. Surprisingly, in November 2005 she started to cough, had low grade fever and low back pain. On the chest X-ray there were multiplex necrobiotic nodules in the lungs. All bacteriological, viral and fungal investigations including tuberculosis, serological tests and cytology were negative. The X-ray, video-associated thoracoscopy and repeated biopsy of the lung followed by histology of the samples proved intrapulmonary rheumatoid nodules, caused by leflunomide.

Keywords Intrapulmonary rheumatoid nodules · Leflunomide · Video-associated thoracoscopy · Histological findings

Abbreviations

anti-CCP	anti citrullinated vimentin
anti-SS-A and anti-SS-B	specific autoantibodies of Sjögren's syndrome
CA with various numbers	tumor markers
CEA	carcino-embrionic antigen
DMARDs	disease-modifying-anti-rheumatic drugs
ILD	interstitial lung diseases
MCH	mean cell haemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
RA	rheumatoid arthritis
RF	rheumatoid factor
VATS	video-assisted thoracoscopy

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Introduction

The presence of rheumatoid nodules in dermal or subcutaneous tissues, although is indicative of rheumatoid arthritis, is a rare entity. It is even less common to identify these rheumatoid nodules by biopsy from the lung tissue and can represent a difficult diagnostic problem [1–8]. These nodules are generally located subpleurally, and may involve the pleura itself. They are usually multiple, 1–2 cm in diameter, may cavitate with a necrotic central part. They may lead to pneumothorax, hydro-, or even pyopneumothorax, and in several cases pleural effusions and subpleural or pleural nodules co-exist. These necrobiotic nodules have characteristic histological structure, with a central zone of fibrinoid necrosis, an intermediate zone of histiocytes and fibroblasts with palisade formation, and a peripheral zone of connective tissue with lymphoplasmocytic infiltration. Pulmonary rheumatoid nodules in patients with rheumatoid arthritis treated with immunosuppressive drugs (e.g. methotrexate), have been recently reported, but none with leflunomide [9–11]. Merely 5 case reports have been presented [12, 13]. Leflunomide is one of the newly

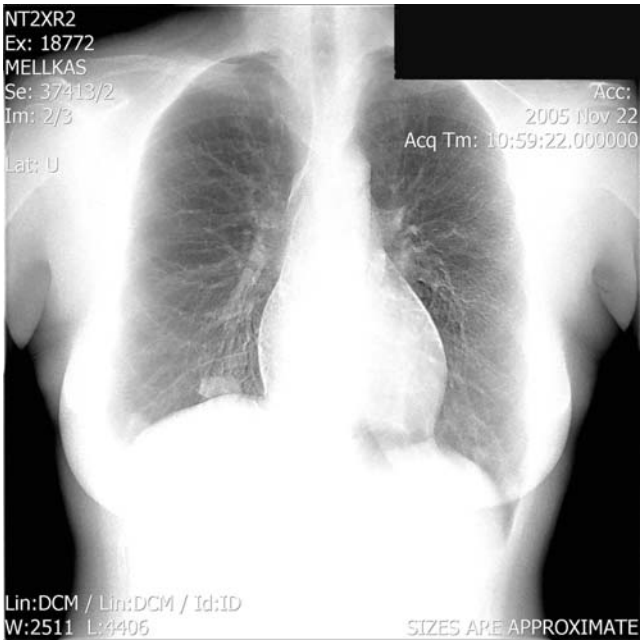

Fig. 1 Multiple rheumatoid nodules in the right lower lobe of the lung, near the diaphragmal surface (chest X-ray)

developed disease-modifying-anti-rheumatic drugs, which inhibit the key enzyme of the pyrimidine synthesis in activated lymphocytes and there are strong evidences that this drug is successful in the regression of joint manifestations of rheumatoid arthritis. During the clinical trials with leflunomide, lung toxicity was rare [14–19]. In this report, we described the case of a young woman with rheumatoid arthritis association with multiplex necrobiotic nodules in almost all lung fields during leflunomide therapy.

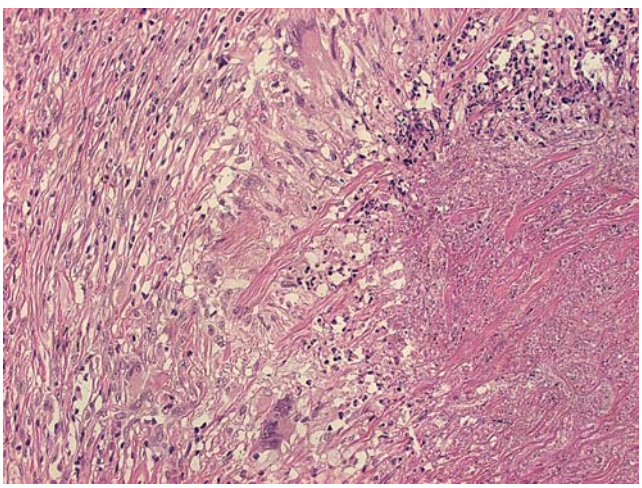

Fig. 2 Histological characteristic of rheumatoid nodule: typical structure of palisading granulomas with necrotizing granuloma, in which the mononuclear phagocytes at the periphery have elongated or spindle-shaped nuclei that are palisaded and arranged roughly parallel to each other and roughly perpendicular to the edge of the central necrotic zone (H&E stain, 20×)

Case Description

A 34-year old woman with a 9-year history of seropositive rheumatoid arthritis and secondary Sjögren's syndrome, without subcutaneous nodules developed respiratory manifestations (upper and lower back pain, nonproductive cough and fever). Her first symptoms appeared in 1987, with polyarthritis affecting the left hip, bilateral wrists and proximal metacarpophalangeal joints. From the immunoserological markers rheumatoid factor, SS-A and SS-B were positive at the beginning. The patient has fulfilled the diagnostic criteria for rheumatoid arthritis (RA) and secondary Sjögren's syndrome in 1996 according to the corresponding diagnostic criteria [20, 21]. After diagnosis she was treated sequentially with corticosteroids, salasosulfapyridine and methotrexate, but due to the side-effects such as photosensitivity or elevated liver enzymes, the medications had to be changed. In addition in June, 2002 metothrexate was replaced by 20 mg/day of leflunomide. Subsequently alternating steroid therapy was used. The patient reached complete remission of RA for 3 years. In November, 2005 she complained of shortness of breath, nonproductive cough and back pain, and she exhibited a fever of 38°C. The patient was not smoking or has not been exposed to noxious dust. The initial physical examination showed pleural friction in all lung fields, the chest radiograph revealed the signs of oxidative pleuritis and multiplex ground-glass opacities in the left and right lower lobes (Fig. 1). The diameter of these consolidations was 10–27 mm and they did not show tendency to form a cavity. Laboratory findings included mild hypochrom, microcyter anemia (hemoglobin of 10.7 g/dL [normal value:12.0–16.0 g/dL], mean cell volume: 85.5 fL [normal value: 80.0–99.0 fL], mean cell haemoglobin: 25.9 pg [normal value: 27.0–31.0 pg], mean cell hemoglobin concentration: 30.3 g/L [normal value: 30.5–35.5 pg]), elevated titer of D-dimer (normal value: 0–0.5 FEU/L) a

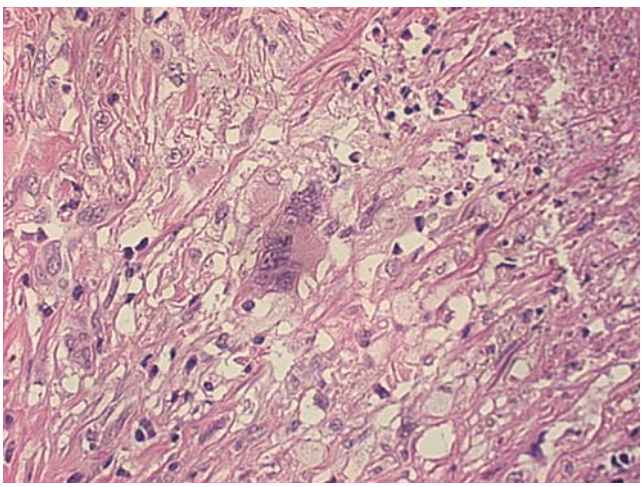

Fig. 3 Langerhans-giant cell in the sample (H&E stain, 40×)

tendency to hypoglycemia, but normal leuko- and thrombocyte counts and normal liver and renal function. The anti citrullinated vimentin (anti-CCP) titer was high (1,252.9 IU/mL, [normal value: 0–25 IU/mL]). To confirm the diagnosis, the patient was screened for solid tumors or metastases, Boeck-sarcoidosis and infective agents. The cultures and serological tests for bacterial, viral or fungal infections were negative as well as the repeated Mantoux cutan test. The Koch tests of sputum were also found negative. Repeated biopsies by bronchoscopy and 3 months later by video-assisted thoracoscopy were performed. Histological evaluation of these samples and cytological evaluation of sputum and samples of broncoalveolar lavage did not show malignant cells. Microscopic assessment revealed the typical structure of palisading granulomas with necrotizing granuloma, in which the mononuclear phagocytes at the periphery have elongated or spindle-shaped nuclei that are arranged in palisades and roughly parallel to each other and roughly perpendicular to the edge of the central necrotic zone (Figs. 2 and 3). After the diagnosis leflunomide therapy was ceased and methyl-prednisolone was administered for 2 months. Since this monotherapy was ineffective, and in order to prevent the recidive polyarthritis, biological therapy, adalimumab was administered. Although adalimumab is known to have a side-effect of rheumatic nodule formation in the lung, but by considering the risk/benefit ratio, we decided to initiate adalimumab therapy [22]. The soft pulmonary nodules gradually became smaller on the chest X-rays and disappeared 6 months after the leflunomide treatment stopped. Throughout the subsequent regular follow-up we have not experienced signs of relapse.

Discussion

There are many reports showing that the disease-modifying-anti-rheumatic drugs (e.g. methotrexate, azathioprine, etanercept and cyclosporine A) can cause accelerated growth of rheumatoid nodules, but generally in typical sites [9–11, 23, 24]. However they are prone to trigger potential pulmonary side-effects, e.g. interstitial lung diseases. 5 cases have been published recently in which during leflunomide therapy multiplex rheumatoid nodules have been developed [12, 13]. All patients had sustained remission of their joint disease. In these cases the appearance of nodules occured 6 or 7 months after leflunomide therapy was initiated. Leflunomide is an effective drug of rheumatoid arthritis, which inhibits the key enzyme of pyrimidine synthesis, the dehydroorotate dehydrogenase. The main function of leflunomide is exhibiting antiproliferative activity on activated T lymphocytes, macrophages and monocytes. In addition, it decreases the production of many cytokines and adhesion molecules. There are well-established side-effects of leflunomide [14–19]. It may cause diarrhea and other gastrointestinal disturbances, mucositis, hepatotoxicity with elevated titers of aminotransferase enzymes and often various infections. In our patient the first complaints of lung side effect of leflunomide therapy were shortness of breath, nonproductive cough and back pain, subsequently fever, after 3 years of the therapy initiated. The diagnostic bronchoscopy, and the repeated biopsies from the lung failed to demonstrate the presence of any infectious agents including Mycoplasma tuberculosis. Based on radiological images and laboratory findings including tumor markers (carcino-embrionic antigen, CA19–9, CA 72–4, CA-125, CA15–3, AFP) we could exclude the presence of malignancies. We have measured high level of anti-CCP antibody, but according to a widespread measurement there was no correlation with extra-articular manifestations of RA including rheumatoid nodules [25]. There are several mechanisms, different for each medication, proposed to potentate accelerated development of rheumatoid nodules. These susceptible factors are monocytopenia for other causes, deteriorative tissue oxygenisation and long-term smoking. Patients with long-standing seropositive RA are prone to have intrapulmonary nodules compared to seronegative or newly diagnosed cases. Herein, we have presented a rare case exhibiting large numbers of rheumatoid nodules throughout the lungs, interestingly the multiplex opacities on the chest radiograph developed after 3 years treated with leflunomide. We emphasize that clinicians should be vigilant for new complaints of patients during immunosuppressive therapy, chest imaging should be considered every 6 months for each patient to achieve early diagnosis, and initiate a change in the treatment if necessary.

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