JCEI /
Journal of Clinical and Experimental Investigations

2016; 7 (1): 98-102
doi: 10.5799/ahinjs.01.2016.01.0579

CASE REPORT

Pulmonary Nodulosis Associated with Leflunomide Therapy in Rheumatoid Arthritis: Report of Four Cases and Review of the Literature

Ayse Balkarli[1], Veli Cobankara[2]

ABSTRACT

Rheumatoid arthritis (RA) is a multisystem inflammatory disease characterized by destructive synovitis and systemic extra-articular involvement. Leflunomide is a disease-modifying anti-rheumatic drug with anti-inflammatory and anti-proliferative features. Leflunomide is an isoxazole immunomodulatory agent, which inhibits dihydroorotate dehydrogenase enzyme involved in de novo pyrimidine synthesis. It was shown that leflunomide can reduce signs and symptoms of rheumatoid arthritis (RA) with regression in structural damage. Pulmonary involvement is one of the extra-articular manifestations of rheumatoid arthritis and it can occur due to either disease itself or medications used in the treatment. We presented 4 cases with rheumatoid arthritis which developed pulmonary nodules with leflunomide therapy and reviewed literature. *J Clin Exp Invest 2016; 7 (1): 98-102*

Key words: Rheumatoid arthritis, leflunomide, pulmonary nodule

Romatoid Artitte Leflunomid Tedavisi ile İlişkili Pulmoner Nodülozis: 4 Vaka Sunumu ve Literatürün Gözden Geçirilmesi

ÖZET

Romatoid artrit destrüktif sinovit ve sistemik ekstraartiküler tutulumla karakterize inflamatuar multisistemik bir hastalıktır. Leflunomid antienflamatuar ve antiproliferatif özellikleri olan, hastalığı modifiye edici bir antiromatizmal ajandır. Leflunomid dihidroorotat dehidrogenaz enzimini (novo pirimidin sentezinde yer alan bir enzim) inhibe eden bir izoksazol immün modülatör ajandır. Leflunomid romatoid artrit belirti ve bulgularını azalttığı ve yapısal hasarı gerilettiği gösterilmiştir. Pulmoner tutulum romatoid artritin eklem dışı tablolarından biridir ve hastalığın kendisine bağlı veya tedavide kullanılan ilaçlara sekonder olarak gelişebilir. Biz leflunomide tedavisi altında pulmoner nodül gelişen dört romatoid artrit hastasını sunduk ve literatürü gözden geçirdik.

Anahtar kelimeler: Romatoid artrit, leflunomid, pulmoner nodül

INTRODUCTION

Rheumatoid Arthritis (RA) is a multisystem inflammatory disease characterized by destructive synovitis and systemic extra-articular involvement [1]. The presence of peripheral rheumatoid nodules is highly specific. However, rheumatoid pulmonary nodules are rare. The cytological analyses of a rheumatoid pulmonary nodule are similar to those of peripheral rheumatoid nodules. Histologically, rheumatoid nodules have a core consisting from collagen fibrils, non-collagen filaments, and necrotic material parts including cellular residue; a middle layer including macrophages which form palisades; and an external layer consisting from granulation tissue. Pulmonary nodules are generally asymptomatic. However, these nodules may lead to pleural effusion and broncho-pleural fistulas by forming cavities [2].

Leflunomide is used in treatment of RA. It inhibits de novo pyrimidine synthesis by blocking dihydroorotate dehydrogenase (a mitochondrial enzyme), resulting diminished lymphocyte proliferation. It also inhibits kinase activity that is essential in immune system and inflammatory process; in addition, it suppresses gene expression. Besides, it also affects B cell prolif-

[1] *Antalya Education and Research Hospital, Division of Rheumatology, Antalya, Turkey*
[2] *Pamukkale University Medical School, Division of Rheumatology, Denizli, Turkey*

Correspondence: Ayşe Balkarli,
Antalya Education and Research Hospital, Division of Rheumatology, Antalya, Turkey Email: draysebalkarli@gmail.com

Received: 27.01.2016, Accepted: 29.02.2016

eration, neutrophil chemotaxis and immunoglobulin formation [3,4]. In a study on Japanese patients treated with leflunomide, fatal interstitial lung disease was reported as a rare side effect of leflunomide [5,6]. However, other studies failed to confirm this side effect of leflunomide [7]. It was reported that peripheral nodule development and an increase in the number of nodules were observed in patients with RA received leflunomide therapy [8]. Recently, it was reported that there was an increase in pulmonary nodule development and number of manifestations associated with leflunomide treatment [2,9-13]. In this case report, we presented 4 cases in which multiple pulmonary nodules were found during leflunomide treatment. Our aim was to emphasize that leflunomide therapy may lead pulmonary nodules in addition to known side effects.

CASE 1

A 60-years old female patient who had been followed over 5 years with a diagnosis of seropositive RA was admitted to our hospital on the month 20 of leflunomide treatment. She had progressive cough over one month. The patient was receiving medical therapy including sulphasalazine, leflunomide, hydroxchloroquine and low-dose prednisolone treatment. In history, it was found that she had diabetes mellitus, coronary artery disease and smoking (35 packages per year). In addition, it was found out that the patient was admitted to hospital due to mucositis and bone marrow suppression during methotrexate therapy. Chest radiograph was found to be normal in that admission. Methotrexate was withdrawn and leflunomide (20 mg/day) was initiated after clinical recovery. The patient was receiving leflunomide over 20 months when she presented to our clinic. No pathologic finding was found in physical examination. In chest radiograph, nodular lesions were seen in basal zone at right side. Computerized tomography scan confirmed multiple parenchymal nodules in lower basal segment of right lung, as largest nodule being 13 mm in diameter. In the bronchoscopy, it was found that right main bronchia were intact, and that opening of superior segment was edematous and fragile. Brush sample and bronchoalveolar lavage fluid were obtained during bronchoscopic evaluation. No pathologic finding found. The patient underwent mini thoracotomy for diagnostic purposes and multiple biopsy samples were taken during thoracotomy. Biopsy samples were reported as rheumatoid nodule by pathology department.

CASE 2

A 42-year-old female patient presented to our rheumatology outpatient clinic with complaints of progressive swelling and pain in hand joints over three months, fatigue, coughing and sputum. In history, it was found out that she was diagnosed as RA 20 years ago and receiving medical therapy with a diagnosis of seropositive RA. She was considered to be resistant to disease modifying drugs (DMARDs) (DAS28>5.1); thus, an anti-TNF treatment was planned. Before anti-TNF therapy, it was required to eliminate other reasons of acute phase response including tuberculosis. On chest X-Ray, it was seen that costophrenic recess was obscured with pulmonary infiltration. The patient was receiving leflunomide (20 mg/day, over 13 months), methyl prednisolone (4 mg/day, hydroxychloroquine (200 mg/day). There was no pathological finding on the chest radiography obtained for thyroid surgery before initiation of leflunomide therapy. She had no history of allergy, smoking or alcohol consumption. In laboratory evaluations it was found that leukocyte count, erythrocyte sedimentation rate (79 mm/h) and C-reactive protein (CRP) levels were elevated. Microscopic urine analysis revealed 9 red blood cells (RBCs) and 13 white blood cells (WBCs) in each field. In tuberculin skin test there was no induration, and empiric antibiotic therapy was prescribed for respiratory system infection. After one week of therapy, there was marked improvement in the complaints of patients. However, leukocyte count, sedimentation and CRP levels remained to be high. As an infiltration was seen on chest radiograph, a thorax computerized tomography (CT) scan was obtained for differential diagnosis. On CT scan, pleural effusion was seen at right side and there were bilateral multiple nodules at posterior basal and laterobasal segments. Most nodules were cavitary lesions and 4x3 cm in size. In the left upper anterior segment, there was a peripheral cavitary nodule (11x7 mm in size), and another nodule in the left lung apex with similar nature. No pathological lymph nodule was observed. Perinuclear anti-neutrophil cytoplasmic antibody (pANCA), cytoplasmic anti-neutrophil cytoplasmic antibody (cANCA), anti-nuclear antibody (ANA) and anti-ds DNA tests were found to be negative, which was performed to exclude Wegener granulomatosis. Acid resistant bacteria (ARB) was also negative in 3 occasions. It was decided that the patient should receive an anti-TNF drug, and a lung biopsy should be performed to establish definitive di-

agnosis since diagnoses of tuberculosis and Wegener granulomatosis could not be clearly excluded. Thus, the patient underwent mini thoracotomy and wedge resection. Surgical specimen was reported as rheumatoid nodule by pathology department.

CASE 3

A 42 years-old female patient was diagnosed as RA 9 years ago. In history, it was found out that she was receiving methotrexate (10 mg per week), sulphasalazine (2 g/day), leflunomide (20 mg/day) and non-steroid anti-inflammatory drug (NSAI). She was admitted to the hospital on month 15 after initiation of leflunomide therapy with complaints of cough and shortness of breath. In physical examination, it was found that there was dullness in percussion and decreased breathing sound on the right lower lobe. On chest radiograph, there was remarkable effusion in right sinus. Clarithromycin was prescribed to the patient based on clinical presentation and elevated ESR, CRP level and leukocyte count. Ultrasound-guided thoracentesis confirmed exudate. Malignancy and infection was excluded by cytological and microbiological examination of pleural fluid. Cytological and microbiological evaluation of bronchoscopic endobronchial lavage specimen showed no abnormal finding. In acido-resistant bacilli (ARB) screening and Ziehl-Neelsen culture test, no mycobacterium tuberculosis was detected. ANA, ANCA, and anti-ds DNA tests were negative. Viral, bacterial, and parasitic antibodies were within normal limits. On thoracic CT scan, pleural effusion and 4 cavitary nodular lesions below the posterior peripheral segment were found at right lung as largest being 16x16 mm in size. For diagnostic purposes, wedge resection was performed in the right lower lobe. The pathologic findings were reported to be compatible with rheumatoid nodule.

CASE 4

A 65-years old male patient presented to our clinic with pain and swelling at hand, knee and foot joints. In history, it was found that he had RA over 14 years and was receiving methotrexate, hydroxychloroquine, methyl prednisolone and NSAID. Chest radiograph obtained at presentation was found to be normal. As the patient had active RA, leflunomide (20 mg/day) was added to therapy. On the control visit after initiation of leflunomide, biological agent was planned due to active disease. The patient was consulted to chest disease department for tuberculosis prophylaxis. A cavitary nodule was seen in the right lobe on chest radiograph. A high-resolution CT scan revealed a thin-walled cavitary nodule (18x12 mm in size) at interested area. Besides, minimal interlobular and intralobular septal thickening were found in bilateral anterior segments of upper lobe and posterobasal segments of lower lobe. In laboratory evaluations, ESR and CRP were 29 mm/h and CRP was 2.93 mg/dl, respectively. In microscopic urinary examination, 4 RBCs and WBC were observed in each field. The ARB-PCR was negative in 3 occasions. ANCA, ANA (IFA), anti-DNA, myeloperoxidase (MPO) and proteinase 3 (PR3) Elisa tests were also negative. Pulmonary wedge resection was performed in the patient. In histopathological examination, it was seen that there was epithelioid histiocyts having a palisadic sequence surrounding necrotic areas in the middle parts. Besides, there were granulomas which accompanied by several giant cells having characteristics of multinuclear foreign bodies. Both were reported to be compatible with rheumatoid pulmonary nodule.

Table 1. Patients' characteristics

Case	Age (year)	Gender	Duration of disease (year)	Rheumatoid factor	Smoking	Presence of subcutaneous nodule	Leflunomide Duration (days)	Pulmonary nodule
1	60	F	5	+	+	-	20	Multiple
2	42	F	20	+	-	-	13	Multiple
3	44	F	9	+	-	-	15	Multiple
4	65	M	14	+	-	-	10	Multiple

F: Female, M: Male

DISCUSSION

RA is a chronic disease with unknown etiology, which is characterized by progressive, degenerative articular involvement and systemic manifestations. Pulmonary involvement is among the systemic findings in RA and could be seen as pleural effusion, bronchiolitis obliterans, pulmonary hypertension, interstitial lung disease, bronchiolitis obliterans- organized pneumonia and necrobiotic nodules [14,15].

Pulmonary nodules are relatively rare form of extra-articular RA. Given that RA has a progressive nature, risk factors include male sex, longer disease duration, presence of subcutaneous rheumatoid nodules, rheumatoid factor positivity and smoking [16].

Rheumatoid pulmonary nodules are generally asymptomatic. However, depending on localization, they may cause hemoptysis, bronchopleural fistula or pneumothorax. Pulmonary abscess, pneumonia and fatal interstitial lung diseases have been reported rarely during leflunomide treatment [17-19]. Leflunomide is an effective disease-modifying drug in the treatment of rheumatoid arthritis. Leflunomide inhibits dihydroorotate dehydrogenase, a key enzyme of the pyrimidine synthesis in activated lymphocytes. It was shown that leflunomide reduces signs and symptoms of RA with regression in structural damage [7].

It is known that an increase in the number of peripheral rheumatoid nodules or de novo nodule formation can be seen during methotrexate and leflunomide treatment. It has been recently reported that pulmonary nodules were seen in 3 patients who achieved clinical remission with leflunomide therapy [2,9-13], including one woman (34 years old) and two men (77 and 66 years old, respectively). All three were seropositive and had no subcutaneous nodules. Disease duration was relatively long in all patients (mean: 4.5 years). Pulmonary nodules were found in these patients at median 18 months. Kim and Yoo reported a RA patient in whom recurrent pneumothorax related to pulmonary nodule was developed after leflunomide therapy [2].

The prevalence is variable for pulmonary nodules. Pulmonary nodules are detected in only 1% of RA patients by chest radiograps while they are detected in 20-22% of RA patients by chest HRCT and in 32% of RA patients by open lung biopsy [21]. The presentation of pulmonary nodules in RA patients comprises a diagnostic problem. Malignancy, bacterial infection, fungal infection, vasculitis and tuberculosis can also present with pulmonary nodule. Thus, differential diagnosis should have to include above-mentioned diseases. We assessed our cass for potential diseases in the differential diagnosis and detected no pathology. Biopsy results were also compatible with rheumatoid pulmonary nodule.

In our report, 3 of 4 patients, who developed pulmonary nodules during leflunomide treatment, were women. All had seropositive rheumatoid arthritis with a mean disease duration of 12 years. The mean age was 52.75 years and one patient (woman) had a history of smoking for 35 years. Daily dosage was the same in all patients (20 mg/daily). Mean duration of leflunomide use was 15 months. Table 1 presents characteristic of the patient.

Case 3 and 4 but not case 1 and 2 received methotrexate treatment. In case 3, we had no information about chest radiograph findings before initiation of leflunomide treatment. Chest radiographs were normal in remaining 3 cases. We think that pulmonary nodules detected in case 1, 2 and 4 are related to leflunomide treatment. However, it is difficult to draw a definitive conclusion in case 3 as we had no information about chest radiograph before initiation of leflunomide treatment. In this patient, pulmonary nodule could be related both methotrexate and leflunomide treatment. It is difficult to propose a direct link between leflunomide treatment and pulmonary nodule development. Leflunomide could be directly related to pulmonary nodule or it facilitated pulmonary nodulosis related to methotrexate treatment.

It has been long known that methotrexate therapy facilitates formation of peripheral rheumatoid nodules. There are 3 in vitro studies on mechanisms underlying nodule formation with methotrexate. In these studies, it was shown that differentiation to multi-nuclear giant cells in human monocyte cultures via cell fusion is a process that is associated to adenosine receptor 1 (A 1). Thus, it was concluded that methotrexate enhances adenosine release from culture cells without changing the A1 expression in cells undergoing fusion [21]. Given the known effect on adenosine metabolism, different pathogenetic mechanisms might be involved in the induction of nodulosis by leflunomide. However, it also proposed that effect of leflunomide on monocytes play role in pathogenesis of this rare complication of leflunomide therapy [2].

In conclusion, we presented four RA patients developed pulmonary nodules during leflunomide therapy. Clinicians should be kept in mind that multiple

pulmonary nodules can develop during leflunomide therapy.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received.

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