Cavitary pulmonary nodules in rheumatoid arthritis: case reports and review of the literature

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Abstract

Rheumatoid nodules are the most common pulmonary manifestations of rheumatoid arthritis (RA) and are usually asymptomatic. In rare cases, they progress cavitary formation and cause severe clinical symptoms because of disease activity, infectious diseases, and other etiologies. The determination of clinical and histopathological features may be helpful for differential diagnosis in patients with RA with cavitary pulmonary nodules. Herein, we report two female patients with RA with cavitary pulmonary nodules and aim to obtain more detail data by means of reviewing previously reported cases.

Keywords: Cavitary pulmonary nodules, rheumatoid arthritis, leflunomide

Introduction

Rheumatoid arthritis (RA), primarily affecting joints, is a systemic chronic inflammatory disorder. Respiratory complications with the involvement of pleura, airway, pulmonary vascular system, and parenchymal lung might be seen in RA (1). Drug toxicity and opportunistic infection also might cause pulmonary system symptoms in patients with RA. Pulmonary rheumatoid nodules have been reported in up to 32% of individuals with RA and require a more detailed evaluation to exclude neoplasms, tuberculosis (TB), and fungal infection (2). They usually tend to be asymptomatic and 1–3 cm in size. In rare cases, they can progress to cavitary lesions, potentially causing difficulty in differential diagnosis and more severe pulmonary symptoms. We report two patients with RA with large cavitary pulmonary nodules and provide a review of the literature based on published cases.

Case Presentations

Case 1

A 55-year-old woman with RA, diagnosed 20 years ago, was initially treated with methotrexate (MTX) 15 mg/week, hydroxychloroquine (HCO) 200 mg/day, and prednisolone (P) 5 mg/days. After 5 years of treatment, MTX and HCO were withdrawn due to vomiting and retinal toxicity and then leflunomide (LEF) 20 mg/day was started as a monotherapy. There was no other significant disease in her and her family's history.

She was admitted to our outpatient clinic complaining of fatigue, weight loss, cough, and chest pain for 2 months. In her physical examination, the tender and the swollen joint counts were 2 and 1, respectively. The 28-joint disease activity score (DAS28) was calculated to be 4.8. Serum biochemical test was normal, except for the increase in acute-phase reactants [erythrocyte sedimentation rate (ESR): 71 mm/h; C-reactive protein: 4 mg/dL; normal range <0.5]. Rheumatoid factor (RF) was found positive (143 IU/mL; normal value: <20), whereas anti-CCP, ANA, and ANCA were negative. Radiography of extremities showed erosions of the hands. Computed tomography (CT) of the chest revealed bilateral multiple nodular lesions with extensive cavitary areas in especially lower zones (Figure 1). The three negative sputum tests for acid-fast bacillus were obtained and culture examination of bronchoalveolar lavage for TB was also negative. Histopathological evaluation of pulmonary tissue obtained with transbronchial needle biopsy revealed central necrosis surrounded by granulomatous inflammation and perivascular lymphoplasmacytic infiltration with the destruction of medium-sized vessels (Figure 2a, b). Anti-TB therapy with isoniazid (5 mg/kg), rifampin (10 mg/kg), ethambutol (15 mg/kg), and pyrazinamide (20 mg/kg) was given as an empirical treatment after LEF was stopped. Anti-TB therapy was interrupted in the second month of treatment because the progression of pulmonary lesions was detected with control; the chest...
Histopathologic specimens

Large number of macrophages, multinucleated giant cells, and epithelioid histiocytes surrounded by fibrinoid necrosis (a) and dense lymphoplasmacytic infiltrates which cause vascular wall damage (b) (H&E, original magnification ×100, ×200, respectively)

Discussion

Rheumatoid pulmonary nodules contained central necrosis surrounded by epithelioid histiocytes, lymphocytes, plasma cells, and proliferating fibroblasts. They are observed more frequently in smokers, males, and patients with advanced seropositive RA (3). The necrotic central zone may develop into cavitation as a result of the resolution of necrosis and consequent inflammation due to airflow (4). In this case, more severe symptoms could be seen, and the differentiation of RV, AAV, and/or pulmonary TB in patients with RA may be difficult with regards to similar histopathological findings. The detection of caseous necrosis or mycobacteria with specific microbiological tests is diagnostic for TB. In our first case, we started anti-TB therapy empirically because TB infection was not clinically excluded. We thought that pulmonary lesions may be associated with RA due to the progression of pulmonary lesions observed under the anti-TB therapy. The differential diagnosis was also difficult for the second patient with RA, with vasculitic findings in histopathological evaluation and anti-MPO positivity. According to RA cohorts, the rate of ANCA positivity in ELISA is up to 32% (5). Other studies reported that ANCA and anti-CCP positive antibodies were present in about 40% of RA patients at the time of diagnosis (6).

Case 2

A 61-year-old female patient was admitted to our clinic with complaints of cough and pain and swelling of the wrists and small joints of the hands, shoulders, and knees. She also showed fatigue, weight loss, and loss of appetite. Joint symptoms started 2 years ago, and she was treated with LEF 20 mg/day and HCO 200 mg/day for 10 months with the diagnosis of RA. There was no comorbidity. Physical examination showed severe polyarthritis (DAS28 score was 7.2) and necrotic skin lesions in the breast (Figure 3). Laboratory examination revealed an increase of the acute-phase reactant (ESR: 88 mm/h; C-reactive protein: 17 mg/dL; normal range <0.5). The other serum biochemical test was in normal range. RF, anti-CCP, and anti-MPO were found positive [569 IU/mL (<20), 201 IU/mL (<12), and 93 IU/mL (<18), respectively]. Periarticular osteopenia and few lytic lesions were detected in X-ray of the hands. Chest CT indicated cavitary pulmonary nodules (Figure 4). Skin biopsy revealed dermal lymphocyte and neutrophil infiltration. A percutaneous transthoracic needle biopsy was performed, and the subcutaneous nodule disclosed a necrotizing area surrounded by a palisade of histiocytes and chronic inflammatory cells and lymphoplasmacytic inflammation in all layers of vessels (Figure 5a, b). There were no laboratories or histopathological findings to support infectious diseases, including fungal diseases and TB. It was not possible to make an exact diagnosis between ANCA-associated vasculitis (AAV) and RA vasculitis (RV) because the findings of the former coincide with the latter. Since corticosteroid and immunosuppressive treatment could have been effective in both conditions, we started pulse methylprednisolone (1 gm’3 days) and cyclophosphamide (15 mg/kg/day) intravenously after excluding infective etiologies. Pneumothorax was observed in the second week of treatment. In follow-up, all symptoms resolved. Methylprednisolone dose was continued 1 mg/kg/day and diminished 10% daily dose per week.
double-positive patients with RA may more frequently present with pulmonary nodules (6, 7). Histopathological findings of pulmonary nodules may not be helpful enough at differentiating RV from AAV in RA. Necrotizing granulomatosis inflammation and perivascular lymphocyte infiltration might be seen in both diagnoses. Therefore, we could not be sure that the diagnosis was RV or AAV in our second patient.

We searched case reports and case series published in the last 30 years with keywords including “rheumatoid arthritis,” “cavitary pulmonary nodules,” and “vasculitis” in the PubMed database (8-15). Case reports diagnosed with diseases other than RA and suspicions of infectious disease which can cause cavitary pulmonary nodules were excluded. Consequently, clinical and histopathological features of 11 patients with RA (7 female) and two female patients with RA with cavitary pulmonary nodules are seen in Table 1. The disease duration ranged 2–20 years, and seven of the patients were older than 60 years. Skin ulcers were detected in two patients. Five cases were complicated with pneumothorax. Eleven of 12 patients with RA were seropositive. ANCA was positive in one of nine patients. There was...
Leflunomide was a remarkable anti-rheumatic drug in the treatment of 10 patients. LEF inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which plays a key role in the de novo synthesis of pyridine-containing ribonucleotides (rUMP). This agent targets the activated T cells and suppresses inflammatory reaction on synovium in RA (16). Although LEF therapy was reportedly less than other anti-rheumatic drugs such as MTX, TNF-alpha inhibitors in patients with RA with pulmonary non-cavitary nodules and fatal interstitial lung disease in this review, the high frequency of LEF therapy in patients with RA with cavitary pulmonary nodules should be emphasized (17-19). However, the underlying mechanism for the association between LEF therapy and the pulmonary cavitary lesion is not known at present.

In conclusion, patients with RA with cavitary pulmonary nodules tend to present with sero-positive, long disease duration, and more severe pulmonary findings compared with non-cavitary lesions. Anti-rheumatic drugs, especially LEF, may play a role in the development of this clinical presentation. On the other hand, the vasculitic course in RA might be responsible for the development of cavitary pulmonary lesions. In literature, there is insufficient data about evaluations of vasculitis in such patients. We need to collect more information from new studies designed with descriptive clinical, laboratory, and histopathological perspective to manage these challenging patients. Written informed consent was obtained from the patients.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.