J Microbiol Immunol Infect
2001;34:76-78

Legionnaires' disease in a patient with rheumatoid arthritis

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Received: October 18,1999 Revised: January 15, 2000 Accepted: May 9, 2000

A 62-year-old male with rheumatoid arthritis (RA) who was taking nonsteroid anti-inflammatory drug for controlling synovitis developed a flare of his arthritis, hepatitis, and pneumonia due to infection with *Legionella pneumophila* serotype 1. Adult respiratory distress syndrome (ARDS) occurred following the development of pneumonia. After the introduction of erythromycin and ventilator support with positive end expiratory pressure (PEEP), his condition stabilized and he recovered gradually. We suggest that *L. pneumophila* should be considered early in the differential diagnosis of pneumonia in RA patients due to their immunocompromised status.

Key words: Adult respiratory distress syndrome, *Legionella pneumophila*, rheumatoid arthritis

Legionellaceae cause a variable spectrum of disease manifestations which tends to occur opportunistically in immunosuppressed individuals, including patients with systemic lupus erythematosus [1,2], acquired immunodeficiency syndrome [3] and renal transplant [4]. Since 1983 there have been increased reports of the opportunistic infection with *Pneumocystis carinii* pneumonia in rheumatoid arthritis (RA) patients receiving low dose methotrexate (MTX) therapy [5-7]. Legionnaires' disease is rare in RA, and only three cases have been reported [8-10]. Herein we report a case of pneumonia due to *Legionella pneumophila* in a patient with RA.

Case Report

A 62-year-old man with RA whose condition had been previously stable developed fever, chills and polyarthralgia with general malaise 3 days before admission. Two days before admission a dry cough developed. RA had been diagnosed about 1 year prior to admission after the patient complained of morning stiffness (lasted for more than 60 min) and multiple symmetrical joint arthritis. The joints involved bilateral metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist, elbow and knee joints. X-ray film of both hands revealed juxta-articular osteoporosis over the MCP joints. At that time, the laboratory data showed serum rheumatoid factor was positive and erythrocyte sedimentation rate (ESR) was raised to 102 mm/h (normal < 20 mm/h). The diagnosis of RA was made according to the 1987 American Rheumatism Association criteria. He was treated with non-steroid anti-inflammatory drug for relief of articular pain.

On admission the temperature was 39.5 °C, pulse was 106/min, and respirations were 22/min, and blood pressure was 96/60 mmHg. On examination the patient appeared well despite intermittent chills and fever. No rash or evidence of sepsis was observed. The head was normal, and the neck was supple and showed no signs of lymphadenopathy. Examination of the lungs showed a few rales over bilateral lower lung fields. The heart was normal. The liver and spleen were not palpable. There was symmetrical painful swelling of the joints including PIP, MCP, wrist and knee joints. Neurological examination disclosed that motor function was limited by arthralgia.

The white blood cell (WBC) count was 11400/mm^3 with 85% neutrophils, 11% lymphocytes and 4% monocytes. Hemoglobin was 10.8 g/dL and platelet count 182,000/mm^3. The ESR was 118 mm/h and C-reactive protein (CRP) was 24 mg/L. Serum chemistry disclosed aspartate aminotransferase (AST) 125 U/L and alanine aminotransferase (ALT) 77 U/L and normal values of other parameters. Immunological data were antinuclear antibody 1:640, speckle pattern, anti-DNA (-), anti-Ro(+), anti-La(-), anti-RNP(-), C3: 136 mg/dL, C4: 34mg/dL and rheumatoid factor 42 IU/mL (normal, < 40 IU/mL). Electrocardiogram demonstrated sinus tachycardia at a rate of 104/min. Chest film showed infiltration over both lower lung fields. Sputum examination disclosed a few neutrophils with moderate numbers of gram-positive and gram-negative bacteria. No acid-fast bacilli or malignant cells were found on three occasions. Specimens of blood, urine and sputum

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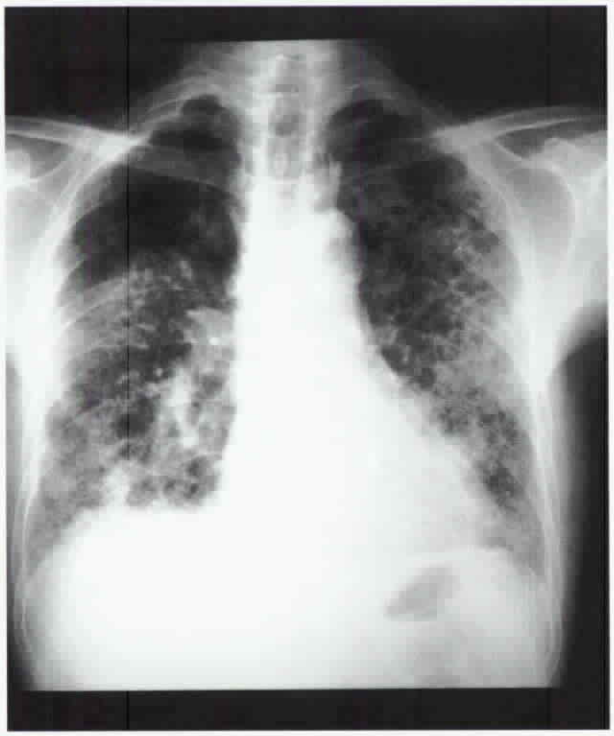

Fig.1 Chest film showed extensive alveolar infiltration over both lower lung fields.

were obtained for culture. The patient was given intravenously cefuroxime. On the third hospital day he was still febrile and had symptoms of dyspnea. Chest film showed more extensive alveolar infiltration over both lower lung fields (Fig. 1). Because of suspicion of *Mycoplasma* or *Legionella* pneumonia, oral erythromycin 500 mg every 6 h was added. However, his fever still persisted and he developed acute respiratory failure. Chest film showed further progressive change over both lung fields. Arterial blood gas revealed severe hypoxemia resistant to high inspired oxygen concentration. Adult respiratory distress syndrome (ARDS) was diagnosed. He was transferred to the intensive care unit and mechanical ventilation and intravenous erythromycin were started. All bacteriologic cultures remained negative. An open lung biopsy was performed and was negative for fungi, acid fast bacilli and *P. carinii*. On the ninth hospital day, *L. pneumophila* serotype 1 was identified by direct fluorescent antibody (DFA) and cultures from the sputum and blood [11] collected on admission. Indirect fluorescent antibody for *L. pneumophila* serotype 1-6 showed at titer of 1:256. Four weeks after the introduction of intravenous erythromycin 4 gm/day and ventilator support with positive end expiratory pressure (PEEP), recovery of clinical conditions was achieved. He was discharged without fever and his arthritis was quiescent.

Discussion

Legionnaires' disease is rare in RA and only three previous cases of *Legionella* pneumonia in patients with RA have been reported. The clinical characteristics of the patients in these cases are shown in the Table 1 [8-10].

Infections due to *Legionella* are transmitted from contaminated aqueous site, such as air-conditioning cooling towers, evaporative condensers, shower heads and nebulizers. *Legionella* infection can be either in community or hospital-acquired. Usually, immunocompromised patients are most likely to develop pneumonia due to an outbreak of *Legionella* infection [1].

Our patient had unequivocal evidence of infection with *L. pneumophila* based on the pure culture of sputum and blood. The occurrence of *Legionella*

Table 1. Reports of occurrence of *Legionella* pneumonia in patients with RA

Sex/age	DMARD	Prednisolone	NSAID	Duration	Outcome	References
M/64	NA	10 mg	Aspirin	5 years	Death	[8]
F/55	Hydroxychloroquine /sulfasalazine	10 mg	Piroxicam	4 years	Death	[9]
F/54	Hydroxychloroquine /sodium aurothiomalate /penicillamine /azathioprine /methotrexate /cyclosporine	5-10 mg	Aspirin /naproxen	11 years	Recovery	[10]
M/62	NA	NA	Diclofenac	1 year	Recovery	[This case]

Abbreviations: DMARD = Disease Modifying Anti-Rheumatic Drug; NSAID = non-steroid anti-inflammatory drug; NA = not available

pneumonia in patients with RA raises the question of an increased susceptibility to the infection due to RA or due to associated immune abnormalities. There have been some hypotheses on the relation of the occurrence of *L. pneumophila* to RA. First of all, RA is associated with an increased frequency of infection. Patients with RA display defects in both humoral and the cellular immunity. Examination of tissue from patients with RA shows a marked increase in the numbers of infiltrating lymphocyte, functional T-cell abnormalities, diminished neutrophil chemotaxis and alteration of complement metabolism [12]. This combination of factors puts RA patients at increased risk for infection. It also explains why Legionnaires' disease tends to occur as an opportunistic infection in patients with systemic lupus erythematosus [2], acquired immunodeficiency syndrome [3] and organ transplant [4].

Secondly, because the most important host defense system against this organism is cellular immune system [8], the immunosuppressed state resulting from treatment with corticosteroids and Disease-Modifying-Anti-Rheumatic-Drugs (DMARDs) may contribute to greater virulence of this infection when it occurs in these patients. The concomitant use of immunosuppressive therapy in the reported cases of Legionnaires' disease in RA patients is shown in the Table 1. At the time of *L. pneumophila* infection, two of the previously reported patients were taking DMARDs and prednisolone. Although our patient was not treated with immunosuppressive drugs, the mechanism by which steroid and DMARDs impair host resistance against *L. pneumophila* remains unknown.

Erythromycin 4 gm daily for 3 weeks is the recommended therapy for moderate to severe infections caused by *L. pneumophila* [13]. The drug should be given intravenously until a clinical response becomes evident, followed by oral therapy. Two of the three previously reported RA patients with *Legionella* pneumonia died as a result of the infection. Death in these cases appeared to have been associated with one of the following situations: (1) late initiation of therapy; (2) lack of specific anti-*L. pneumophila* therapy; or (3) premature discontinuation of erythromycin.

The present case demonstrates the importance of suspecting the diagnosis of *Legionella* infection in a patient with RA who develops pneumonia. Early diagnosis and institution of the appropriate treatment will improve the likelihood of recovery.

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