Seminars in
Arthritis and
Rheumatism

Rheumatoid Pleural Effusion

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OBJECTIVES To describe the clinical and laboratory features of rheumatoid pleural effusion (RPE) and the diagnostic and therapeutic approaches to this condition.
METHODS The review is based on a MEDLINE (PubMed) search of the English literature from 1964 to 2005, using the keywords "rheumatoid arthritis" (RA), "pulmonary complication", "pleural effusion", and "empyema".
RESULTS Pleural effusion is common in middle-aged men with RA and positive rheumatoid factor (RF). It has features of an exudate and a high RF titer. Underlying lung pathology is common. Generally RPE is small and resolves spontaneously but symptomatic RPE may require thoracocentesis. Rarely, RPE has features of a sterile empyematous exudate with high lipids and lactate dehydrogenase, and very low glucose and pH levels. This type of effusion eventually leads to fibrothorax and lung restriction. Superimposed infective empyema often complicates RPE. Oral, parenteral, and intrapleural corticosteroids, pleurodesis and decortication, have been used for the treatment of sterile RPE. Infected empyema is treated with drainage and antibiotics.
CONCLUSIONS RPE may evolve into a sterile empyematous exudate with the development of fibrothorax. Symptomatic effusions or suspicion of other causes of exudate (infection, malignancy) require thoracocentesis. The "rheumatoid" nature of the pleural exudate in patients without arthritis mandates a pleural biopsy to exclude tuberculosis or malignancy. The optimal therapy of RPE has yet to be established. The role of cytokines in the course of RPE and the possible usefulness of cytokine blockade in the treatment of this RA complication require further evaluation.

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KEYWORDS pleural effusion, pleural empyema, pulmonary complications, rheumatoid arthritis, TNF-α

Rheumatoid arthritis (RA) is the most common inflammatory joint disease, affecting about 1% of the adult population (1). The main feature of RA is chronic progressive inflammation of multiple joints with erosion formation, progressive cartilage damage, joint destruction, and functional disability. At least 70% of patients with RA have positive rheumatoid factor (RF)—autoantibodies directed against antigenic determinants on the Fc fragment of immunoglobulin (Ig) G. In some patients the course of RA is complicated by extra-articular manifestations. A high titer of RF is a predictor of more severe joint damage as well as of extra-articular complications (2).

A variety of systemic manifestations have been described in RA patients: rheumatoid nodules, pleuropulmonary complications, rheumatoid vasculitis, sicca syndrome, Felty's syndrome, amyloidosis, and ocular, nervous, and skeletal involvement (3-6). A list of rheumatoid pleuropulmonary complications is presented in Table 1. Lung involvement in RA can be primary or secondary to drugs and/or infections. Pulmonary disorders induced by antirheumatic drugs are well recognized. Cigarette smoking may negatively influence RA-related lung disease (7). Patients with RA are prone to

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Table 1 Pleuropulmonary Complications of Rheumatoid Arthritis

A. Noninfective complications
Parenchymal involvement
• Pulmonary nodules
• Necrobiotic nodules
• Pulmonary fibrosis
• Cryptogenic organizing pneumonia (COP)
• Caplan's syndrome
• Aspiration pneumonia
Airway involvement
• Upper airway obstruction
• Bullous emphysema
• Bronchiolitis obliterans (BO)
• Bronchiolitis
• Bronchiectasis
Vascular involvement
• Pulmonary arterial hypertension (without significant underlying lung fibrosis)
• Pulmonary vasculitis
• Diffuse alveolar hemorrhage
Pleural involvement
• Pleurisy
• Pleural effusion
• Pleural nodules
• Pneumothorax
• Fibrothorax
B. Infective complications
Common bacterial agents
• Parenchymal (pneumonias, abscess) infections
• Airway infections (bronchitis, bronchiectasis)
• Pleural—empyema
Uncommon agents
• Tuberculosis (lung, pleural, thoracic vertebral involvement)
• Bullous aspergillosis
• Other organisms (opportunistic infections: *Pneumocystis carinii*, viral infections, Nocardia, Candida)
C. Drug-related complications
Methotrexate-induced
• Pneumonitis
• Pulmonary fibrosis
• Pulmonary nodules
• Pleural effusion
• Opportunistic infection
Gold-induced
• Pneumonitis
• COP
• Pulmonary fibrosis
• Irreversible BO
Sulfasalazine-induced
• Pneumonitis
• Pulmonary fibrosis
• Diffuse alveolar hemorrhage
• Pleural effusion
Azathioprine-induced
• Pneumonitis
• Diffuse alveolar hemorrhage
Minocycline-induced
• Pneumonitis
• COP
• Pulmonary nodules
• Pleural effusion
• Mediastinal lymphadenopathy
D-Penicillamine-induced
• Pneumonitis
• COP
• Pulmonary fibrosis
• Diffuse alveolar hemorrhage
• Goodpasture-like syndrome
• Irreversible BO
• Bronchospasm
• Pleural effusion

pulmonary infections because of an impaired immune system due to the disease itself or to drug-induced immune suppression. In some cases the respiratory tract infection is an independent problem, but generally it is superimposed on existing pleuropulmonary RA complications (pleuritis, pneumothorax, interstitial lung disease, cavitating pulmonary nodules) (3-8). Among the various pleuropulmonary complications, rheumatoid pleuritis is the most commonly observed (8,9). The purpose of this review is to describe the clinical and laboratory features of rheumatoid pleural involvement, with a focus on "rheumatoid empyematous exudate" and its pathogenesis, including the role of different proinflammatory cytokines, diagnostic tools, and therapeutic approaches.

Abbreviations

RA	rheumatoid arthritis
RPE	rheumatoid pleural effusion
LDH	lactate dehydrogenase
TNF-α	tumor necrosis factor-alpha
RF	rheumatoid factor
Ig	immunoglobulin
MTX	methotrexate
US	ultrasound
CT	computed tomography
MRI	magnetic resonance imaging
WBC	white blood cells
TB	tuberculosis
IL	interleukin
SLE	systemic lupus erythematosus
CHF	congestive heart failure
ANA	antinuclear antibodies
MCTD	mixed connective tissue disease
SSc	systemic sclerosis
IFN-γ	interferon-γ
CS	corticosteroids
BO	bronchiolitis obliterans
COP	cryptogenic organizing pneumonia