Concomitant Large Loculated Pleural and Pericardial Effusions in a Patient with Rheumatoid Arthritis on Methotrexate

Nakiya Whitfield, PharmD; Anne Krasniak, PharmD; Hien Nguyen, MD

ABSTRACT

Rheumatoid arthritis (RA) is the most common multisystemic autoimmune inflammatory joint disorder, affecting nearly 1.3 million adults in the US. RA has high economic and social burdens. Functional disability may arise in RA from the characteristic chronic progressive inflammation and the erosion of multiple joints and cartilage damage. Systemic manifestations of RA include rheumatoid nodules, pleuropulmonary complications, pericarditis, rheumatoid vasculitis, Felty’s syndrome (the rare triad of rheumatoid arthritis, splenomegaly, and neutropenia), amyloidosis, and neurological complications. We present the diagnostic challenges of differentiating pleuropulmonary and pericardial complications of rheumatoid arthritis from side effects of therapy (rheumatoid pleural and pericardial effusions vs immune suppression associated side effects and infections). We use the Naranjo score to facilitate this decision-making process. A 52-year-old man with a history of RA, chronic small right pleural effusion, and hypertension on long-term oral methotrexate and corticosteroid therapy presented to the emergency room after 1 week of worsening respiratory symptoms. A chest radiograph demonstrated a large pleural effusion and pneumonia. Intravenous methylprednisolone and antibiotics were administered. A video-assisted thoracoscopic procedure was performed, chest tubes were inserted, and abatacept was eventually initiated as adjunctive therapy to methotrexate and corticosteroid therapy for the rheumatoid arthritis and lung condition. Abatacept is an immunosuppressive fusion protein composed of the Fc region of immunoglobulin G1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4, which interferes with the immune activity of T cells.

INTRODUCTION

Pleural disease and pericardial effusion are established systemic manifestations of rheumatoid arthritis (RA) that can further complicate the disease. Pleural disease in RA is typically subclinical and can be primary or secondary to antirheumatic drugs or infections. Methotrexate (MTX) is an immunosuppressive folate antagonist that is used to treat malignancies and autoimmune diseases. High-dose MTX is used in cancer patients, and low-dose MTX is used in RA. Pleuropulmonary disease occurs in 3 to 4% of patients who receive high-dose MTX but may also occur with low-dose MTX. We present a case of suspected MTX-induced pleural and pericardial effusions in a patient with RA.

CASE PRESENTATION

Presenting Concerns

A 52-year-old, nonsmoking man with a several-year history of RA on long-term MTX (20 mg orally weekly) and prednisone (20 mg orally daily) and hypertension was followed in the pulmonary clinic for chronic right pleural effusion. He had been diagnosed with rheumatoid arthritis 3 years prior after complaining of symmetric swelling and stiffness in his hand, elbow, and knee joints. At this initial presentation for RA, antinuclear antibody was present and homogenous 1:320, SSA/SSB was negative, rheumatoid factor was 34, and anti-CCP was 468. On this admission, he presented to the emergency room with a 1-week history of increased cough, shortness of breath, fever, and an acute flare of symmetric swelling in his hands and feet.

Therapeutic Intervention and Treatment

A chest radiograph demonstrated a large right pleural effusion and pneumonia. The differential diagnosis of his respiratory distress and pleural effusion included pulmonary embolism, pneumonias, congestive heart failure, autoimmune connective tissue disease, drug reaction, and cyclophosphamide. A differential diagnosis of his pericardial effusion included acute pericarditis, cardiac tamponade, cardiogenic pulmonary edema, dilated cardiomyopathy, and pulmonary embolism. He was started on methylprednisolone therapy (125 mg intravenously daily for 5 days), antimicrobial therapy with ceftriaxone (2 g intravenous for 10 days), and azithromycin (500 mg intravenously for 7 days). Computed tomography scan of the chest excluded pulmonary embolism and demonstrated a small pericardial effusion and a large right pleural effusion (Figure 1). An echocardiogram revealed a left ventricular ejection fraction of 50%, mild left ventricular hypertrophy, and a small circumferential pericardial effusion without tamponade. A thoracentesis was attempted but was not successful due to the presence of a loculated effusion. The patient was taken to the operating room, where a video-assisted thoracoscopic decortication procedure and pericardial window and pericardiocentesis were performed. A volume of 500 mL of pericardial fluid was drained, and 2,000 mL of pleural fluid was removed from the right pleural cavity.

Pleural fluid studies revealed clear yellow pleural exudate, with 1% red blood cells, 2% eosinophils, 8% lymphocytes,
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6% monocytes, 84% neutrophils, 540 nucleated cells, specific gravity 1.031, protein 5.2 gm/dL, lactate dehydrogenase (LDH) 736 U/L, glucose 81 mg/dL, and amylase 36 U/L. The differential diagnosis of this patient’s exudative pleural and pericardial effusions was narrowed to malignancy, connective tissue disease, infections (pneumonia, tuberculosis, fungal disease, viral), and drug reaction. The noneosinophilic result of his effusion argued against a medication side effect. Hence, glucarpidase, an antidote for MTX toxicity, was not considered due to the patient’s presentation and the low likelihood of drug-induced pulmonary disease. The pericardial and pleural samples did not demonstrate malignant cells, tuberculosis, or bacterial growth, and pathology on the pleural and pericardial sacs showed acute and chronic inflammation. Subsequently, 2 chest tubes were placed to water seal without air leak and were removed 8 days later following radiographic resolution of the pleural effusions.

Follow-up and Outcomes

A repeat chest radiograph at the patient’s pulmonary clinic 10 days after hospital discharge revealed a small right pleural effusion and post-surgical changes. MTX was continued at a dosage of 10 mg orally weekly because the patient’s presentation was more consistent with a systemic complication of his RA rather than a medication side effect. This is supported by the onset of an acute rheumatoid joint flare with his effusions and the noneosinophilic nature of his effusions. A course of prednisone was tapered over 3 weeks to his regular 20 mg daily dosage, and a weekly abatacept (125 mg intravenous infusion) was initiated for further immunosuppressive therapy for his rheumatoid arthritis and autoimmune pleural and pericardial disease.

DISCUSSION

Rheumatoid Pleural Effusions and Diagnostic Approach

Rheumatoid pleural effusion (RPE) is the most common pleuropulmonary manifestation. Characteristic symptoms of RPE are fever, pleuritic chest pain, and dyspnea; cough is generally absent unless there is a concomitant parenchymal lung disease. Clinical symptoms of RPE arise from irritation and inflammation of the pleura, from underlying coexisting pulmonary pathology, or from compromised respiratory function. Physical examination findings include change in tactile fremitus, dullness of chest percussion, and decreased breath sounds. The formation of RPE is postulated to occur from impaired fluid resorption in inflamed pleura, necrosis of subpleural rheumatoid nodules, and endothelial injury and capillary permeability from cytokines and immune complexes.

Small pleural effusions are noted in up to 70% of patients with RA on autopsy studies, although only 3 to 5% of RA patients in their lifetime are symptomatic with pleurisy. Risk factors for RPE include age over 35 years, male sex, and those with rheumatoid nodules. Seventy percent of rheumatoid pleural effusions are unilateral; the other 30% are bilateral. In about one-quarter of RA patients, the onset of RPE preceded or occurred at the same time as the onset of joint disease. In the majority of other cases, RPE occurs several years after established RA diagnosis, such as in our patient. However, case reports have described RPE occurring 3 decades after RA diagnosis. The duration of RPE is also variable, and in various case series RPE has been described as lasting from several months to years.

Other pulmonary involvements by RA include pulmonary parenchymal disease (interstitial lung disease) and disease of the airways and pulmonary vasculature (pulmonary hypertension and vasculitis). Smoking may adversely affect the course of RA-related lung diseases. There are proposed mechanisms for pulmonary pathogenesis, including chronic immune activation, increased susceptibility to infection due to direct toxicity, or immunomodulation from disease modifying drugs or biologic therapy. In some patients with RA, respiratory symptoms from these pulmonary involvements may precede articular symptoms. This is supported by studies of a subgroup of patients who are anti-CCP with lung disease who later developed articular symptoms of rheumatoid disease.

Chest radiograph is the initial diagnostic test of choice for evaluation of pleural disease. Other imaging modalities may include ultrasound, computerized tomography, and magnetic resonance imaging. Thoracentesis should be performed for any effusion with 1 cm of layering on decubitus films. The typical RPE is sterile, exudative, and yellow-green straw colored. Other characteristics include low pH <7.2, glucose <40, elevated LDH >700, and cholesterol >65. Low pleural fluid pH occurs because of lactate and carbon dioxide production from enhanced glucose metabolism in the inflamed pleural space. High levels of pleural fluid lactate may suggest an alternate diagnosis, such as tuberculosis or malignancy. High pleural fluid LDH levels in RPE reliably correlate with the degree of pleural inflammation from activated white cells in the pleural fluid. Pleural fluid glucose may be similar to serum glucose at the onset of RPE but typically falls to very low levels (10-30 g/dL) in chronic RPE. Pleural fluid glucose in RPE lowers as a result of pleural thickening, which prevents the entry of glucose into the pleural space or alternatively from consumption of glucose in the inflamed pleura. Infection or empyema should always be excluded in the diagnostic workup of RPE due to the similar low pleural fluid pH, low glucose, and high LDH.

The approach to the differential diagnosis of pleural or pericardial effusion starts out with confirmation of these
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Methotrexate and Pleuropulmonary Toxicities

In general, MTX is used in the therapy of various malignancies, psoriasis, and autoimmune diseases. MTX is first-line therapy for initial treatment of active RA and typically serves as an anchor for the most commonly used disease-modifying antirheumatic drug combinations. 20 MTX is an antimetabolite and folate antagonist that inhibits DNA synthesis. Both the absorption and bioavailability of MTX are highly variable, are dose dependent, and decrease at higher doses. At higher oral doses of MTX, there is decreased bioavailability. In a study comparing the 7.5-mg weekly dose and the 15- to 20-mg weekly dose, there was better absorption with the smaller dose. Subsequently, as the dose of MTX was increased from the starting dose of 7.5 mg to typical maintenance doses, the bioavailability was shown to drop off by a mean of 13.5%.21,22 The variable absorption and bioavailability of MTX can lead to unpredictable serum levels. Adverse effects to MTX can be dose dependent or idiosyncratic in nature.23

Drug-induced pleural disease occurs rarely, and manifestations include asymptomatic pleural effusion, acute pleuritis, or symptomatic pleural thickening. Although the precise mechanisms of most drug-induced pleural diseases are largely unknown, potential pathogenic processes are speculated, such as 1) hypersensitivity or allergic reaction, 2) a direct toxic effect, 3) increased oxygen free radical production, 4) suppression of antioxidant defenses, and 5) chemical induced inflammation.22 Pleural fluid eosinophilia is described by more than 10% of nucleated cells and is a nonspecific finding that is supportive for drug-induced pleural disease. Drugs proven to cause pleural disease include MTX, valproic acid, propylthiouracil, isotretinoin, nitrofurantoin, dantrolene, and gliclazide.23 Pleuropulmonary toxicity occurs in 3% to 4% of patients who receive high-dose MTX, but these medication effects may also occur with low-dose MTX treatment.23 These medication effects are fever, cough, and dyspnea, which are identical symptoms found in pleuropulmonary complications of RA. Risk factors for the development of lung injury from MTX include age greater than 60 years, rheumatoid pleuropulmonary involvement, previous use of disease-modifying antirheumatic drugs, higher-dose MTX therapy, and diabetes.23-25

Concurrent Pericardial and Pleural Effusions Attributed Directly to MTX Reported in only Two Prior Case Reports and Naranjo Score

To the best of our knowledge, there are only 2 prior cases in the medical literature that attribute the concurrent development of pericardial and pleural disease directly to MTX use.24,25 Cudzilo et al19 described eosinophilic effusions in the setting of MTX therapy for psoriatic arthritis, but Savoia et al26 described noneosinophilic effusions in the setting of MTX for plaque psoriasis. In contrast, Judge et al27 presented a 54-year-old woman whose initial presentation for rheumatoid arthritis was fever, pleural effusion, pericardial effusion, and ascites. Collectively, these cases illustrate how pleural and pericardial effusions may arise directly from medication effects or conversely signify the onset of RA.

The Naranjo score is an algorithm that is used to validate the probabilities for adverse drug reactions (ie, the existence of prior conclusive reports, temporal occurrence of an adverse drug event relative to time of drug administration, improvement of drug reaction after cessation of the drug, alternative causes of reaction, existence of toxic concentrations of the drug, similar reaction to same or similar drugs with prior exposure, and objective evidence that confirmed adverse drug event).27 We arrived at a Naranjo score of 3 (possible side effect) (Table 1). Our patient’s pleural fluid...
Moreover, elevated levels of eosinophils in the effusions, which both support RPE, are secondary to medications in any previous exposure. Our patient presented with acute pericardial joint symptoms at the time of presentation for therapy such as abatacept may be considered.20

**CONCLUSION**

Medication-induced effects should always be considered in the setting of therapy for autoimmune conditions to avoid potentially unnecessary medical and surgical interventions and patient discomfort. Our patient presented with acute rheumatoid joint symptoms at the time of presentation for the pericardial and pleural effusions, and he had non-eosinophilic exudative effusions, which both support RPE. On the other hand, elevated levels of eosinophils in the effusion and recurrence with reexposure to MTX are much more suggestive of a drug-induced effusion. Interestingly, our patient’s pleural fluid glucose was normal, which is unlike the characteristic low pleural fluid glucose levels in RPE. Thus, sometimes not all possibilities can be resolved, especially when a therapy side effect can mimic the manifestations of the condition. Further, rheumatoid arthritis or other connective tissue diseases should be considered in any patient presenting with pericardial or pleural effusion at any point because extraarticular manifestations of an autoimmune disease may precede or occur concurrently with articular manifestations. In refractory cases of chronic RPE, such as occurred in our patient after repeated thoracentesis and corticosteroid therapy, second-line immunosuppressive therapy such as abatacept may be considered.20

**Disclosure Statement**
The author(s) have no conflicts of interest to disclose.

**Authors’ Contributions**
All authors conceptualized this paper, drafted the initial manuscript, and revised the final submission. All authors have given final approval to the manuscript.

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