62-Year-Old Woman With Fever, Dyspnea, Pleuritic Chest Pain, and Weight Loss

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A 62-year-old woman with rheumatoid arthritis (RA) presented for evaluation of chronic pleuritic chest pain, dyspnea, cough, odynophagia, fatigue, weight loss of 16.6 kg (30 lb), and migratory joint pains. Ten years earlier, RA had been diagnosed on the basis of polyarticular inflammatory arthritis. Rheumatoid factor (RF) had subsequently been positive and anticyclic citrullinated peptide (anti-CCP) antibodies negative. No signs or symptoms of underlying connective tissue disease (CTD) had been reported, and no serologic testing for CTD performed. For the past 6 years, the patient had been taking etanercept, methotrexate, and prednisone. Five months before presentation, findings on computed tomography (CT) of the chest reportedly were consistent with RA-associated interstitial lung disease (RA-ILD) or methotrexate-induced lung injury. Pulmonary function testing displayed a restrictive pattern. Methotrexate use was discontinued. One month before presentation, use of etanercept was discontinued because of leukopenia and perioral "fever blisters," presumed to be adverse effects of medication. On arrival to our institution, her medication regimen was prednisone at 7.5 mg/d, sitagliptin-metformin, levothyroxine, lisinopril, pantoprazole, and simvastatin, as well as nonsteroidal anti-inflammatory drugs as needed.

Outpatient evaluation revealed an elevated erythrocyte sedimentation rate and C-reactive protein value, high RF, and negative anti-CCP antibodies. Chest CT showed bilateral pleural effusions (possibly loculated on the right) and a small pericardial effusion, but no lymphadenopathy or pulmonary infiltrates. During outpatient evaluation, the patient developed worsening dyspnea and pleuritic chest pain. Her temperature was 38.7°C and heart rate was 120 beats/min. Laboratory testing revealed mild hyponatremia and anemia. She was admitted for further evaluation.

1. Which <u>one</u> of the following diagnoses is <u>most crucial</u> to rule out immediately?

a. *Empyema*
b. *RA-ILD*
c. Pneumocystis jirovecii *pneumonia*
d. *Methotrexate-induced lung injury*
e. *Aspiration pneumonia*

Empyema typically presents with fever, pleuritic chest pain, dyspnea, and productive cough, with loculated pleural effusion on imaging. Treatment may require immediate drainage.[1] This condition is important to rule out given our patient's symptoms and imaging findings. Dyspnea on exertion and nonproductive cough due to RA-ILD usually have an insidious onset. Chest pain and fever are less common. Parenchymal findings on chest CT may resemble usual interstitial pneumonia or nonspecific interstitial pneumonia.[2] Although underlying RA-ILD is possible, our patient's presentation suggested a more acute process. *P jirovecii* pneumonia occurs in immunocompromised hosts. In patients without human immunodeficiency virus infection, *P jirovecii* pneumonia causes fever, dry cough, and fulminant respiratory failure, with bilateral interstitial infiltrates seen on imaging. The presentation of methotrexate-induced lung injury is usually subacute and progressive and may include fever, cough, malaise, dyspnea, or chest pain. Symptoms typically improve shortly after use of methotrexate is discontinued. Pleural effusions are not common.[3] Our patient had stopped taking methotrexate months earlier, so methotrexate-induced lung injury is unlikely. Aspiration pneumonia often has a relatively indolent course. Cough, fever, purulent sputum production, dyspnea, and weight loss may evolve over weeks. A predisposing condition, such as dysphagia, is often apparent. Imaging may reveal evidence of necrosis.[4]

Cultures of blood and urine were obtained, and broad-spectrum antimicrobial therapy was initiated. Diagnostic thoracentesis was performed. Pleural fluid was serous, and analysis revealed the following: total nucleated cells, 747/μL (82% neutrophils); glucose, 128 mg/dL; lactate dehydrogenase (LDH), 168 U/L; total protein, 3.4 g/dL; and pH, 8.2. Cytologic testing, Gram stain, and culture were negative. Concurrent serum studies revealed a total protein value of 7.2 g/dL (reference ranges shown parenthetically) (6.3-7.9 mg/dL) and LDH of 300 U/L (122-222 U/L).

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See end of article for correct answers to questions.

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2. Which one of the following conclusions is the most appropriate to make based on the pleural fluid analysis?

a. *The patient's pleural effusions are due to rheumatoid pleurisy*
b. *The gross appearance of the pleural fluid confirms a transudative effusion*
c. *An empyema is unlikely*
d. *The cytologic profile is indicative of a chronic effusion*
e. *Malignancy is relatively likely*

Patients with pleural effusions due to rheumatoid pleurisy often have high LDH (>1000 U/L), low pH (<7.30), and low glucose (<60 mg/dL) values.[5] Serous pale yellow or straw-colored effusions are usually transudative but may occur in paucicellular exudates. Gross appearance cannot distinguish between the two.[5] An empyema, generally defined as a pleural effusion with positive Gram stain or gross pus, does not have universally accepted diagnostic criteria. However, a pH of less than 7.20 typically portends the need for pleural space drainage.[1] Our patient had serous effusions with negative Gram stain and a pH of 8.2; thus, an empyema is unlikely. Cytologic response to acute pleural injury is neutrophil-predominant. In the absence of ongoing injury, cytologic predominance becomes mononuclear with chronic effusions.[5] Malignant pleural effusions typically present with low glucose (<60 mg/dL), low cell count (<5000 /μL), and positive cytologic results. Eosinophilia and grossly visible blood are common.[5]

Although empyema was ruled out, broad-spectrum antimicrobial agents were continued empirically. Bronchoscopy was not performed because of lack of pulmonary parenchymal findings. Subsequent work-up included transthoracic echocardiography, which revealed circumferential pericardial effusion without tamponade, and CT of the abdomen and pelvis, which showed only diffuse jejunal thickening. Because of scleral injection, ophthalmology was consulted; corticosteroid eyedrops were initiated for bilateral scleritis and dry eye syndrome. The patient began to note asymmetric, migratory joint pain. Objective findings of arthritis were intermittent, and radiography of the hands, wrists, and feet showed no synovitis or bony erosions. Development of leukopenia was normalized with an increase in the dose of prednisone. Esophagogastroduodenoscopy, performed because the patient had odynophagia and weight loss, revealed gastritis, suspected to be induced by nonsteroidal anti-inflammatory drugs. All cultures remained negative, and use of antimicrobial agents was discontinued.

On hospital day 8, the patient developed sharp, nonradiating, pleuritic left anterior chest pain with dyspnea. All vital signs were within normal limits, although she required 2 L of oxygen. Cardiac auscultation revealed a soft, coarse sound over the left sternal border with systolic and diastolic components. Examination of the lungs revealed coarse inspiratory crackles and dullness to percussion in the lower fields. Chest radiography showed stable pleural effusions and atelectasis.

3. Which one of the following etiologies is the most likely cause of this patient's worsening chest pain?

a. *Eosinophilic esophagitis*
b. *Pericarditis*
c. *Myocardial infarction*
d. *Aortic dissection*
e. *Pulmonary embolism (PE)*

Eosinophilic esophagitis typically presents with dysphagia. Diagnosis requires intraepithelial eosinophils on esophageal biopsy.[6] Pericarditis usually presents with acute onset of sharp anterior pleuritic chest pain, although pain may be dull and vague. Leaning forward may provide relief. Common signs include pericardial effusion, cardiac friction rub, and changes on electrocardiography (widespread ST-segment elevation or PR depression).[7] Although electrocardiography was not performed in our patient, the clinical findings were highly suggestive of pericarditis. Myocardial infarction often presents with crushing substernal chest pain that may radiate into either the shoulder or arm. Common accompanying symptoms include dyspnea, diaphoresis, and nausea/vomiting. Pain is typically nonpleuritic.[8] Aortic dissection presents with sudden onset of sharp or "tearing" nonpleuritic pain; it may be in the anterior chest, posterior chest, or back. Hypertension, either previously or at presentation, is common. Chest radiography may show mediastinal widening.[9] The most common symptoms of PE are dyspnea and pleuritic pain. Evidence of lower extremity deep venous thrombosis is present in approximately half of patients.[10] Although PE is a diagnostic consideration, pericarditis was more likely given our patient's new pericardial rub.

Becasue of suspicion for worsening pericarditis, another echocardiogram was obtained; it revealed increased pericardial effusion, with signs of early tamponade. Pericardiocentesis yielded 370 mL of cloudy serous fluid. Cultures were negative. The patient's symptoms improved, and the dose of prednisone was again increased. Shortly thereafter, the patient developed an erythematous, maculopapular, mildly pruritic gluteal rash. Biopsy revealed palisaded neutrophilic and granulomatous dermatitis, an uncommon condition that can accompany autoimmune or vasculitic diseases.[11]

Given the lack of evidence for infection or malignancy, the clinical picture was thought to be consistent with autoimmune disease, although elements were not consistent with RA. Autoimmune serologies were obtained, revealing positive RF, negative anti-CCP antibodies, and positive anti-nuclear antibodies (ANAs). Total complement was 23 U/mL (30-75 U/mL).

4. Which one of the following serologic studies will most likely confirm the suspected diagnosis in this patient?

a. *Anti-centromere antibodies*
b. *Anti-RNP antibodies*
c. *Anti-Ro/Sjögren syndrome antigen A (SSA) and anti-La/Sjögren syndrome antigen B (SSB) antibodies*
d. *Anti-double-stranded DNA (anti-dsDNA) antibodies*
e. *Anti-proteinase (PR3) and anti-myeloperoxidase (MPO) antibodies*

Anti-centromere antibodies are highly specific for limited scleroderma, which is characterized by calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias (CREST syndrome), along with sclerosis of the hands, face, and neck.[12] High titers of anti-RNP antibodies are required for diagnosis of mixed CTD, a syndrome with overlapping features of systemic lupus erythematosus (SLE), RA, polymyositis, and scleroderma.[13] One or both of anti-Ro/SSA and anti-La/SSB antibodies are often positive in primary Sjögren syndrome, a non-CTD–associated illness that presents with xerophthalmia and xerostomia.[14] Anti-dsDNA antibodies are highly specific for SLE. Connective tissue disease can be classified as SLE when a patient fulfills 4 of the following 11 criteria: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleuritis or pericarditis), renal disorder (proteinuria or casts), neurologic disorder (seizures or psychosis), hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia), immunologic disorder (positive lupus erythematosus cell preparation, anti-DNA antibodies, anti-Smith antibodies, false-positive serologic test results for syphilis), and ANAs.[15] Our patient met 5 of the 11 criteria (arthritis, leukopenia, serositis, anti-DNA antibodies, and ANAs). Leukopenia in SLE is most often accompanied by lymphopenia, which our patient had throughout her hospitalization. Her "fever blisters" before presentation may have represented oral ulcers. Anti-PR3 and anti-MPO antibodies are often positive in patients with active Wegener granulomatosis or microscopic polyangiitis.[16] Hypocomplementemia is not characteristic.

Further serologic testing revealed positive anti-dsDNA antibodies. Anti-Ro/SSA and anti-La/SSB antibodies, anti-RNP antibodies, anti-Jo 1 antibodies, anti-Smith antibodies, anti-Scl 70 antibodies, anti-PR3 antibodies, and anti-MPO antibodies were all negative. A clinical diagnosis of SLE was made. Our suspicion was that SLE had been the appropriate diagnosis all along; however, we had no record of past serologic studies other than RF and anti-CCP antibodies, so this could not be confirmed. In addition, we noted that one of her current medications has been associated with drug-induced lupus.

5. Which one of the following medications is most likely to have been associated with an anti-dsDNA–positive lupus-like syndrome in this patient?

a. *Lisinopril*
b. *Methotrexate*
c. *Simvastatin*
d. *Infliximab*
e. *Etanercept*

Although rare, multiple angiotensin-converting enzyme inhibitors have been associated with drug-induced lupus erythematosus (DILE). Captopril is more commonly implicated, with very few reports implicating enalapril and lisinopril.[17] When lisinopril has caused DILE, it has presented with positive antihistone antibodies, negative anti-dsDNA antibodies, and normal complement levels.[18] Methotrexate has not been reported to cause DILE. Statins have rarely been reported to cause DILE. Anti-dsDNA antibodies are almost universally negative.[19] Tumor necrosis factor (TNF) α inhibitors have been associated with DILE that is antihistone antibody–negative and anti-dsDNA antibody–positive.[20-23] Our patient had been taking etanercept until approximately 1 month before presentation. This medication could have been associated with her syndrome. However, etanercept use had been discontinued with subsequent worsening of symptoms, so this was thought to be unlikely.

After addition of azathioprine with prednisone, our patient improved. She was discharged on hospital day 12.

DISCUSSION

Clinical overlap between SLE and RA can be substantial. The most common symptoms of active SLE are fatigue, arthritis/arthralgia, fever, Raynaud phenomenon, alopecia, weight loss, photosensitivity, lymphadenopathy, butterfly rash, mucous membrane lesions, and psychosis. Common signs include pleurisy, pleural effusions, pericarditis, and various gastrointestinal manifestations.[24] Our patient had many of these characteristics and fulfilled the classification criteria for SLE.

The American College of Rheumatology (ACR) classification criteria for RA include the following: morning joint stiffness persisting at least 1 hour; arthritis of 3 or more joint areas; arthritis of the proximal interphalangeal, metacarpophalangeal, and wrist joints; symmetric arthritis; rheumatoid nodules; positive RF; and erosions or periarticular osteopenia in hand/wrist joints. The first 4 criteria must be present for at least 6 weeks. Four of 7 criteria are required for classification as RA.[25] Retrospectively, our patient fulfilled only 3 of these criteria. In addition to the symptoms and signs included in the ACR classification

criteria for RA, extra-articular manifestations can occur. These include anemia, fatigue, pleuropericarditis, neuropathy, episcleritis, scleritis, splenomegaly, secondary Sjögren syndrome, vasculitis, and renal disease. Our patient had a number of these. Furthermore, a clinical diagnosis of RA is sometimes made even when full classification criteria are not fulfilled (as in our patient). Her presentation could have easily been attributed to either SLE or RA.

Distinguishing between SLE and RA requires careful clinical evaluation and complete serologic testing. Positive RF has only 79% specificity for RA.[26] Many other conditions, including SLE, infections, malignancy, and old age, can cause RF positivity.[27] Positive RF should prompt further testing to confirm a suspected diagnosis of RA, particularly when the ACR classification criteria are not fulfilled. Anti-CCP antibodies provide 96% to 98% specificity for RA with newer assays.[28] In our patient, who had a positive RF and negative anti-CCP antibodies and who did not fulfill the ACR classification criteria, RA was an unlikely diagnosis. Evaluation for other syndromes, including SLE, was warranted.

Classic DILE is associated most commonly with procainamide, hydralazine, isoniazid, quinidine, and chlorpromazine and is characterized by positive antihistone antibodies and negative anti-dsDNA antibodies. Anti-TNF agents can cause DILE that is antihistone antibody–negative and anti-dsDNA antibody–positive, serologically more consistent with SLE. Hypocomplementemia is more commonly associated with DILE due to TNF-α inhibitors.[23] Anecdotally, the cornerstone of treatment is discontinuation of the offending agent, after which symptoms typically improve within weeks to months. However, systemic corticosteroids may be required.[20-23] Infliximab is the most common culprit, with etanercept and adalimumab being less commonly implicated.[23] Allthough it was ultimately unclear whether our patient had SLE, DILE due to etanercept, or both, we thought, given her failure to improve after discontinuation of etanercept, that her syndrome most likely represented SLE.

Symptoms and signs of RA, SLE, and DILE overlap considerably. DILE may be induced by medications used to treat RA, such as anti-TNF agents. Determining the underlying etiology of clinical signs and symptoms in such cases requires a careful review of the clinical history, serologic data, and response to immunomodulatory agents.

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Correct answers: 1. *a*, 2. *c*, 3. *b*, 4. *d*, 5. *e*