A Triad of Pericarditis, Pericardial Effusion, and Pleural Effusion as the Predominant Presentation of Rheumatoid Arthritis—A Case Report

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ABSTRACT

We describe a case of a 67-year-old African American man who presented to the emergency department with a sharp, pleuritic chest pain and shortness of breath. After several admissions and extensive workup, he ultimately was diagnosed with a persistent pleural effusion, pericardial effusion, and secondary constrictive pericarditis due to rheumatoid arthritis. By highlighting immunological disorders such as rheumatoid arthritis in the differential diagnosis, in the setting of a refractory pericardial effusion and serositis, this case report addresses key aspects of the presentation both in the emergency and inpatient settings, reviews the criteria for a rheumatoid arthritis diagnosis, and emphasizes areas of importance in predominantly cardiopulmonary extra-articular manifestations of a typically musculoskeletal disease.

CASE REPORT

A 67-year-old African American man with a significant past medical history for chronic obstructive pulmonary disease, paroxysmal atrial fibrillation, chronic kidney disease stage 1, gastroesophageal reflux disease (GERD), esophageal dysmotility, and peptic ulcer disease presented to the emergency department (ED) with sharp, pleuritic chest pain and shortness of breath.

On his first admission, the evaluation for his first episode of chest pain revealed nonspecific ST-T wave changes on 12-lead electrocardiogram (ECG) and nondiagnostic elevations in high-sensitivity troponin levels, which were attributed to poor renal clearance from his chronic kidney disease (Figure 1). An initial transthoracic echocardiogram (TTE) was performed in the ED and was unremarkable. With a history of GERD, antacids were administered with partial improvement of his chest pain. Given the presenting history, unremarkable TTE, lack of friction rub, cardiac biomarkers, and ECG nonsuggestive of ischemia or pericarditis, his chest pain was defined as noncardiac. Further gastroesophageal workup revealed a presumed etiology of his symptoms, as esophagram displayed esophageal dysmotility, intraesophageal reflux, and poor clearance on marshmallow challenge without esophageal dilatation. Clinical suspicion at this time was highest for a primary or idiopathic motility disorder as cause of presentation, and no further laboratory or serological studies were conducted for secondary disorders. He was discharged with conservative GERD management.

The patient was admitted for the second time 3 days later for evaluation and management of persistent, sharp pleuritic chest pain, worsened when lying supine and improved with leaning forward. He denied any recent trauma, cardiothoracic surgeries, radiation exposure, or myocardial infarctions. On examination, he was afebrile and without audible friction rub. ECG showed diffuse ST-elevations in anterior and inferior leads and PR depressions in leads II, III, AVF, V5, and V6, with concern for pericarditis (Figure 2A). High-sensitivity troponin levels were elevated but stable from previous admission. Posterior-anterior (PA) chest x-ray showed a small left-sided pleural effusion. Repeat TTE depicted a new small, circumferential pericardial effusion measuring up to 7 mm in depth, without any echocardiographic indications of cardiac tamponade and normal cardiac function. There was also a 20% respiratory phasic variation in the mitral valve inflow velocity (<25% considered normal). The pericardial effusion was further described on computed tomography (CT) angiogram of the chest with contrast (Figure 2B). With pericarditis suspected, a detailed

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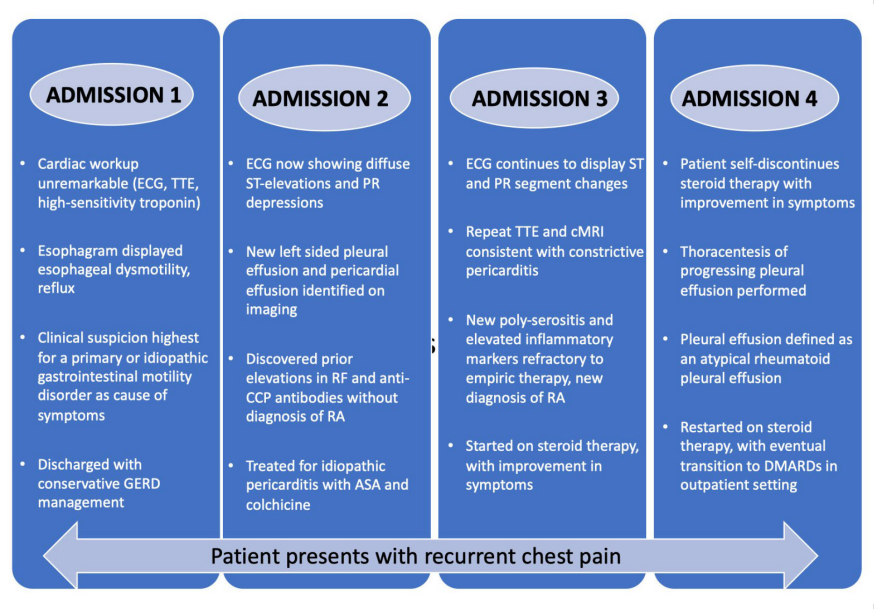
workup for the causes of pericarditis was pursued.

Rheumatological origins were then considered, as the c-reactive protein (CRP) was elevated at 7.4mg/dL and erythrocyte sedimentation rate (ESR) was elevated at 78 mm/hr. There was low suspicion for infectious etiology as the patient was without leukocytosis, and his blood, urine, and sputum cultures returned negative. Uremic pericarditis was ruled out with blood urea nitrogen within normal limits. Medication review included no potential causative agents, such as minoxidil or hydralazine. Medical record review revealed a positive rheumatoid factor (RF) of 356 IU/mL and an elevated anticyclic citrullinated peptide (anti-CCP) antibody IgG/IgA >250 IU/mL five years prior, which was drawn for workup of back pain. At that time, anti-C3, anti-C4, and anti-dsDNA antibodies were normal. After finding these positive serologies, subsequent physical exams were unremarkable for inflammatory joint deformities, synovitis, or joint effusions. Furthermore, subsequent radiographic pursuits revealed no bony erosions or rheumatoid changes. Without clinical correlation of positive high titer RF and CCP antibodies, he did not meet diagnostic criteria for rheumatoid arthritis (RA), and there was no indication for initiation of medical therapies. Rheumatology recommended close follow-up for monitoring, but the patient elected to discontinue care due to lack of development of typical RA symptoms.

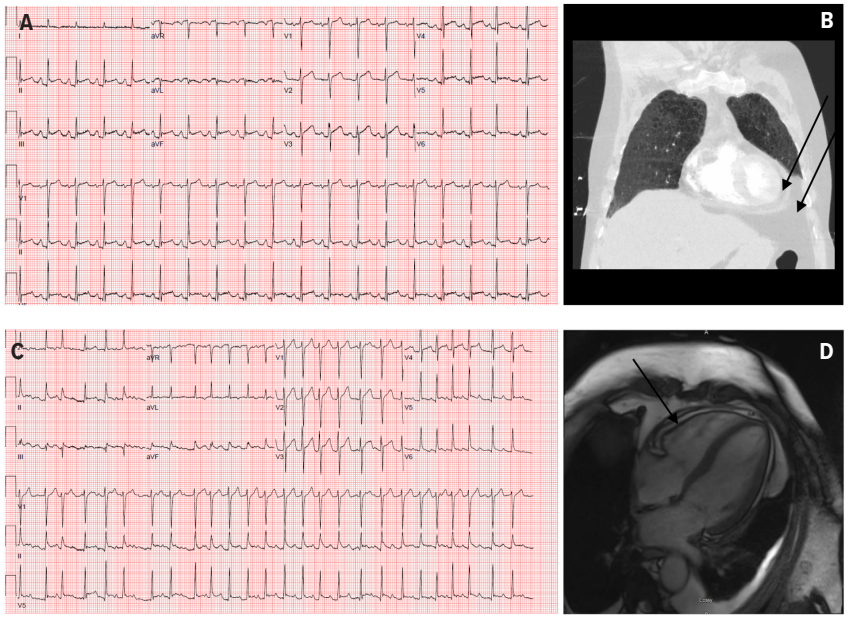
During this second admission, the patient continued to show neither synovitis nor evidence of inflammatory arthritis on a physical exam. He was treated with high-dose aspirin and colchicine for idiopathic pericarditis. Typical nonsteroidal anti-inflammatory drugs, which are recommended in combination therapy for idiopathic pericarditis, were avoided due to his history of peptic ulcer disease. Notwithstanding the clinical signs of pericarditis, a pleural effusion, and a pericardial effusion, there remained concern of an underlying rheumatological disease, as

Figure 1. Pictorial Summarization of Each Admission in Chronological Order



Abbreviations: ECG, electrocardiogram; TTE, transthoracic echocardiogram; GERD, gastroesophageal reflux disease; RF, rheumatoid factor; RA, rheumatoid arthritis; ASA, aspirin; cMRI, cardiac magnetic resonance imaging; DMARD, disease modifying antirheumatic drugs.

Figure 2. Patient's Electrocardiogram, Computed Tomographic Angiogram of Chest, and Cardiac Magnetic Resonance Imaging



A and B: Electrocardiograms from second (A) and third (B) admissions depicting the presence of diffuse ST-elevations in anterior and inferior leads, with PR depressions in leads II, III, aVF, V5, and V6.

C: Computed tomography angiogram of chest (coronal view) with contrast depicting pericardial effusion and pleural effusion.

D: Cardiac MRI demonstrating a clear demarcated circumferential rim of delayed enhancement in the pericardium.

Table. Relevant Laboratory Values Throughout Hospitalizations

	LDH (unit/L)	Protein (g/dL)	Glucose (mg/dL)	pH	WBC (unit/L)	Gram Stain Culture	CRP (mg/dL)	ESR (mm/hr)	RF (IU/mL)	CCP Antibody (IU/mL)
Pleural Fluid	600	4.4	257	8.0	10,200	No Growth	-	-	-	-
Serum	2047	7.7	-	-	-	-	7.4	78	356	>250

Abbreviations: LDH, lactate dehydrogenase; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; CCP antibody, anticyclic citrullinated peptide antibody IgG/IgA.

the aforementioned cardiopulmonary and infectious workup was unrevealing thus far. As the patient was medically stable on aspirin and colchicine, his predischarge plan included continuing medical management for a 4-week period, acknowledging the smaller—though still present—risk of gastrointestinal complications.

In spite of outpatient treatment and adherence to prescribed colchicine and aspirin, the patient was admitted for a third time 5 days later for relapsing persistent sharp, pleuritic chest pain and unresolving shortness of breath. ECG showed persistent, diffuse ST-elevations in anterior and inferior leads, with resolving PR depressions in leads II, III, AVF, and V6. He also was noted to be in atrial fibrillation with rapid ventricular response (Figure 2C). TTE revealed small-to-moderate circumferential stable pericardial effusion, unchanged from prior study but now notable for a rise in respiratory phasic variation in mitral valve inflow velocity to 35%, suggesting clinical correlation of constrictive pericarditis. The PA chest x-ray showed progression of the left-sided pleural effusion. Cardiac magnetic resonance imaging demonstrated a clear demarcated circumferential rim of delayed enhancement in the pericardium consistent with pericarditis and free breathing sequences showing respirophasic septal shift (Figure 2D), consistent with constrictive pericarditis.

Based on prior elevation of RF and CCP antibodies, now in the setting of constrictive pericarditis and polyserositis, refractory to aspirin and colchicine with elevated CRP and ESR, the impression of the inpatient rheumatology team was that the patient's pericarditis was secondary to a new diagnosis of RA. There was no indication to repeat RF or CCP serologies, given his history of highly RA specific, positive high titers. The patient was then started on prednisone 40 mg daily, in addition to aspirin and colchicine. After only 2 days, he reported significant improvement in symptoms. Pericardiocentesis or pericardiotomy were considered in treatment of constrictive pericarditis but ultimately not pursued with clinical improvement on prednisone and a formal diagnosis of RA.

Unfortunately, the patient self-discontinued medical therapy with initial improvement in symptoms and again presented to the ED with acute hypoxic respiratory failure shortly after medical therapy cessation. On initial evaluation, he was afebrile but now required 4L of supplemental oxygen. Arterial blood gas showed oxygen saturation of 89.1%, pH of 7.40, PaCO2 of 33 mmHg, and HCO3- of 20. ECG would show no ST-elevations or PR-depressions (Figure 2C). CT angiogram showed significant progression of the known left pleural effusion, with new development of potential areas of loculation and near-complete collapse of the left lower lobe. There was no evidence of interstitial lung disease. Based on these findings, infectious etiologies were thoroughly explored, yet workup with blood, urine, and sputum cultures were negative. Nucleic acid amplification tests for *Chlamydia pneumoniae, Legionella pneumoniae,* and *Mycoplasma pneumoniae* were negative. *Streptococcus pneumoniae* antigen and viral respiratory panel were negative as well. Procalcitonin was within normal limits. A diagnostic and therapeutic thoracentesis with chest tube placement was then pursued, which removed 1.4 L. The pleural exudate showed 10,200 unit/liter white blood cells (WBC) (ref: <1000 unit/liter), lactate dehydrogenase (LDH) of 600 unit/L (ref: <50% serum concentration), glucose of 257 mg/dL (ref: 40-70 mg/dL), pH of 8.0 (ref: 7.6-7.64), and protein of 4.4 g/dL (ref: 1-2 g/dL). His serum total protein was 7.7 g/dL and LDH 2047 unit/L (Table). The exudative effusion was classified most probably secondary to RA. With infection ruled out, prednisone was restarted and he was continued on steroid therapy with a taper. He would eventually transition to azathioprine, a steroid-sparing agent, in the outpatient setting. Azathioprine was chosen over typical first-line disease modifying antirheumatic drugs (DMARD), like methotrexate, as the patient lacked typical articular and peripheral symptoms. It was, therefore, an anecdotal opinion that, with primarily extra-articular manifestations, azathioprine may be a superior agent in targeting his symptoms. After a 6-month follow-up period, he maintained adherence to azathioprine therapy and showed no traditional signs of rheumatoid disease or recurrence of cardiopulmonary symptoms.

DISCUSSION

RA is a systemic inflammatory disease primarily affecting joints. The clinical manifestations of RA are diverse and depend on the pattern of joint involvement, degree of joint destruction, and level of functional impairment. The clinical diagnosis of RA is based on a composite of characteristic clinical symptoms and diagnostic evaluation. Extra-articular manifestations are common in rheumatoid arthritis, although uncommon to be the presenting clinical feature without articular manifestations.[1]

There are several aspects from a patient's historical, physical, and laboratory standpoint that promote a clinician's suspicion for RA, yet typically we follow the diagnostic criteria from the

American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) for a formal diagnosis for RA. The ACR/EULAR outline criteria that must be met for diagnosis, the first of which is the presence of synovitis involving 3 or more joints for at least 6 weeks.[2] The more joints that are inflamed—especially in symmetric, small-joint involvement—the higher likelihood that RA is the underlying etiology.[3] In addition to these clinical findings, laboratory assessment via serologies and inflammatory markers also are incorporated in the diagnostic algorithm, specifically RF, anti-CCP antibody, ESR, and CRP.[2] Lastly, all other etiologies of synovitis should be excluded.[2]

Despite longstanding established guidelines to the diagnosis of RA, there are currently no diagnostic criteria for patients who present with predominant cardiopulmonary symptoms, as manifested in this case. Diagnostic criteria have yet to be fully developed for patients with primarily cardiopulmonary objective clinical results, suggesting that such predominant presentation may be due to the rarity of the presentation. However, it warrants the question of whether cardiopulmonary objective clinical results should be included in the diagnosis criteria of RA. Only 4 cases in the literature have reported pericarditis and pericardial effusions as predominant presentations of RA.[4-6] In all 4 cases, the patients presented with substernal chest pain.[4-6] In 2 of those cases, the patients eventually developed wrist and other joint pain within 3 to 6 months of the initial cardiac presentation requiring continued treatment.[4-6] Typically RA manifests with musculoskeletal symptoms or, if not initially, will progress to evolve into an inflammatory arthritis. In this case, the patient never objectively displayed signs of polyarthritis per physical exam or radiographic workup.

Notwithstanding the predominant presentation, there is no evidence to suggest the treatment of RA should differ from typical predominant presentations. DMARDs are considered first-line in the treatment of RA.[7] Glucocorticoids can be used for symptom control and are often used as a bridge therapy to DMARDs during high disease activity.[7]

Rheumatoid pleural effusions (RPE) typically affect 3% to 5% of patients with RA.[8] Diagnosis of an RPE can be confirmed in an RA patient with a pleural fluid sample that will characteristically show a low pH (<7.2), low glucose level (<60 mg/dL), negative gram stain and culture of the fluid, and WBC elevated above 3000 unit/liter.[9] The exudative effusion from this patient exhibited a glucose of 257 mg/dL, pH of 8.0, and WBC count of 10,200 unit/liter. Thorough investigation of exudative etiologies was ruled out via laboratory analysis.[10] Per extensive literature review, there is no other RPE documented to show a pH this alkalotic, alongside glucose and WBC count as elevated. However, for definitive diagnosis of RPE in patients who display no signs of arthritis, as in the case with this patient, a pleural biopsy must be completed.[9] Although the etiology of the exudative effusion was not confirmed, clinical context suggests a high likelihood of an atypical RPE as a consequence of RA. This is supported by the lack of regression and actual improvement with steroids and that the patient had no relapses after a DMARD was introduced, suggestive of underlying rheumatologic origin, specifically RA.

CONCLUSIONS

This report presents a patient diagnosed with probable nonerosive, seropositive RA with only cardiopulmonary extra-articular features consistent with constrictive pericarditis, pericardial effusion, and a pleural effusion. In spite of this cardiopulmonary presentation, the patient was still treated as a traditional articular RA patient with good initial clinical response. While cardiopulmonary manifestations are rare predominant presentations, a high index of clinical suspicion is essential when there is a paucity of classical diagnostic criteria for cardiopulmonary symptoms, warranting evaluation of current guidelines.

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