Rheumatoid arthritis and atypical cardiovascular disease

Inflammation changing the clinical presentation

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Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 1% of the population, with a standardized mortality rate ranging from 1.28 to 3.0, according to literature review.[1] The morbidity and mortality of patients with RA are increased by their elevated risk of cardiovascular disease (CVD): a meta-analysis of observational studies showed CVD-associated death could be 50% higher in patients with RA[2]; a study using electron-beam computed tomography of patients with RA showed an odds ratio of 3.42 for developing severe coronary artery disease relative to controls[3]; and a small study of 40 patients with RA less than 12 months after diagnosis showed increased prevalence of subclinical atherosclerotic findings.[4]

This case describes a patient with RA and atypical CVD presentation, and explains the current pathophysiology linking the 2 disorders and how to appropriately manage CVD in patients with RA.

Case

A 77-year-old woman presents to the emergency department with complaints of worsening fatigue, poor exercise tolerance, general malaise, and constant right-sided thoracic pressure without radiation. At this time her relevant past medical history includes bird-breeder's lung, poorly controlled systolic hypertension, and poorly controlled RA. The patient is not adherent to her methotrexate regimen, and she suffers from moderate RA symptoms: synovitis of the wrists, metacarpophalangeal joints, shoulders, and feet, as well as prolonged morning stiffness and pain. There is no history of left-sided or retrosternal chest pain or previous myocardial infarction (MI).

On physical examination she does not appear to be in distress. Vital signs are stable except for a respiratory rate of 24 breaths/min and blood pressure of 150/73 mm Hg. Respiratory examination shows decreased air entry bilaterally and crepitus located at the lung bases. Findings of cardiac examination are unremarkable; however, right costochondral chest pain is reproduced on palpation.

Remarkable investigation findings include an electrocardiogram showing an old inferior MI. The patient is not aware she has ever suffered an MI, and she has never experienced the typical symptoms associated with an MI. She is sent home the next day, and appropriate follow-up is arranged. Two weeks later, results of a dipyridamole nuclear scan show evidence of scarring in the left anterior descending coronary artery and right coronary artery.

There are no events in the patient's past that suggest anything remotely similar to symptoms typical of an acute coronary syndrome (ACS)—her most comparable symptoms, perhaps, are her 1-year history of worsening fatigue, general malaise, and poor exercise tolerance. Although these symptoms are brought to the attention of her care providers, no diagnosis of ACS is made. Her 2 previous ACS events within approximately the past year were either silent or presented atypically.

EDITOR'S KEY POINTS

- There is a dramatic increase in atherosclerotic disease in patients with rheumatoid arthritis (RA). Although the link between the 2 disorders is not fully understood, risk factors, family history, genetic predisposition, and pro-inflammatory states appear to play roles.
- Premature atherosclerotic changes might concurrently develop with subclinical inflammation for years before RA is clinically evident. Cardiovascular disease (CVD) often goes unrecognized in patients with RA, and therefore CVD prevention should begin shortly after the diagnosis of RA is made.
- All patients with RA should receive a cardiovascular assessment that focuses on risk factor identification, including hypertension, hyperglycemia, dyslipidemia, increased body mass index, central obesity, physical inactivity, tobacco use, and family history of CVD.

POINTS DE REPÈRE DU RÉDACTEUR

- Il y a une hausse dramatique des maladies athérosclérotiques chez les patients atteints d'arthrite rhumatoïde (AR). Quoiqu'on ne comprenne pas entièrement le lien entre les 2 affections, il semble que des facteurs de risque, les antécédents familiaux, la prédisposition génétique et des états pro-inflammatoires jouent un rôle.
- Des changements athérosclérotiques prématurés pourraient survenir concurremment pendant des années avec une inflammation sous-clinique avant que l'AR soit cliniquement évidente. Les maladies cardiovasculaires (MCV) passent souvent inaperçues chez les patients atteints d'AR et, par conséquent, la prévention des MCV devrait commencer peu après qu'on ait posé un diagnostic d'AR.
- Tous les patients atteints d'AR devraient faire l'objet d'une évaluation cardiovasculaire axée sur l'identification des facteurs de risque comme l'hypertension, l'hyperglycémie, la dyslipidémie, un indice de masse corporelle accru, une obésité centrale, l'inactivité physique, le tabagisme et des antécédents familiaux de MCV.

Although this patient has several confounding variables that might lead to atypical CVD presentation, her poorly controlled RA is a possible important determinant.

Discussion

The association between RA and CVD was researched with MEDLINE, using the key words *rheumatoid arthritis, acute coronary syndrome,* and *cardiovascular disease*. Articles were only reviewed if they were published in the past 10 years, elucidated the link between RA and CVD, or commented on effective management of CVD for patients with RA.

Although a 2005 case-control study has shown RA to be an independent risk factor for multivessel coronary artery disease,[5] the reasons for the dramatic increase in atherosclerotic disease in patients with RA are not fully understood.[1] The following are several pathogenic correlations linking RA and CVD.

Inflammatory pathogenesis. Rheumatoid arthritis and CVD share an inflammatory pathogenesis. Sattar et al suggested markers of systemic inflammation (eg, interleukin [IL]–6, IL-17, tumor necrosis factor [TNF]) have been correlated with increased risk of cardiovascular death in patients with RA[6]; these cytokines are substantially elevated in RA.[6]

Proatherogenic lipid profile. One study that compared 87 women with RA with 50 healthy women found a proatherogenic lipid profile among the women with RA: lipoprotein A was substantially increased and high-density lipoprotein cholesterol was substantially decreased in women with RA.[7]

Metabolic syndrome. In a study by Chung et al involving 154 patients with RA, there was a higher prevalence of metabolic syndrome in patients with RA for whom insulin resistance was likely due to increased systemic oxidative stress and pro-inflammatory cytokine overexpression.[8]

Genetic correlations. There are several genetic correlations linking RA to CVD, including functional polymorphisms of the major histocompatibility complex,[9] shared epitope alleles (human leukocyte antigen DRB1 genotype),[10] the IL-6-174C allele,[11] and the TNF-α-1031 T/C polymorphism.[12]

Cellular events. Cellular events can predispose patients with RA to CVD. A retrospective chart review showed patients with RA had an expanded population of $CD4^{+}CD28^{-}$ T cells, which is a similar cellular presentation to patients with atherosclerotic plaques and unstable angina.[13]

Extra-articular manifestations of RA. A population-based study showed that extra-articular manifestations of RA such as rheumatoid nodules, vasculitis, rheumatoid lung, and joint swelling were all independently associated with an increased risk of cardiovascular death in patients with RA.[14]

Traditional risk factors. Traditional risk factors for CVD still apply to patients with RA: an increased Framingham score, older age, hypertension, physical inactivity, and smoking all increase the risk of CVD in patients with RA.[1,15]

Literature review

As shown in a 2005 population-based cohort study, CVD and MI in patients with RA are either silent or present with atypical anginal symptoms.[16] Patients with RA are 6 times more likely to have experienced an unrecognized MI compared with individuals without RA.[16] This absent or atypical CVD symptomatology results in more patients with RA experiencing sudden cardiac death before getting to hospital.[16]

Table 1. Managing cardiovascular risk factors in rheumatoid arthritis

RISK FACTOR	CARDIOVASCULAR PREVENTION STRATEGIES
Smoking	Counseling, nicotine patches or gum, bupropion, varenicline
Hyperlipidemia	Diet, exercise, reducing alcohol consumption,* statins, minimizing use of corticosteroids, antimalarials*
Diabetes	Counseling, diet, exercise, oral hypoglycemic agents, insulin
Insulin resistance	Counseling, diet, controlling inflammation (DMARDs or biologics), PPAR agonists*
Obesity	Counseling, diet, exercise, minimizing use of corticosteroids
Hypertension	Frequent blood pressure monitoring, diet, exercise, stress management, antihypertensive drugs, minimizing use of NSAIDs and corticosteroids
High homocysteine level	Folic acid supplementation with methotrexate or sulfasalazine use
Inflammation	DMARDs, biologics, NSAIDs, statins,* PPAR agonists*
Thrombotic risk	Low-dose acetylsalicylic acid (consider anticoagulation when other thrombosis risk factors are present)
Family history of CVD	Counseling, monitoring risk factors

CVD—cardiovascular disease, DMARD—disease-modifying antirheumatic drug, NSAID—nonsteroidal anti-inflammatory drug, PPAR—peroxisome proliferator–activated receptor.
*Not enough evidence to suggest standard of care.
Data from Kaplan.[1]

As atherosclerosis can begin in less than 12 months after the diagnosis of RA, CVD prevention should begin shortly after the diagnosis of RA is made.[4] Sattar et al suggest universal CVD screening in all patients with RA who are older than age 40, or younger if the patients with RA have several risk factors or a strong family history of premature vascular disease.[17]

Kaplan suggests cardiovascular assessment in patients with RA should begin with risk factor identification (**Table 1**).[1] Cardiovascular disease risk factor modification should include weight control with guidance from an exercise physiologist owing to physical limitations present in RA.[15] An electrocardiogram will help discover previous silent or atypical MIs.[17] Hypertension and dyslipidemia should be treated accordingly, using guidelines as for the general population.[15] C-reactive protein (CRP) titres should be obtained.[15] When calculating the 10-year global CVD risk in patients with RA, it is recommended that the risk be multiplied by 1.5.[17]

Patients with RA with prevalent vascular disease should be urged to begin statin therapy regardless of risk factor measures.[17] The JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) study, a randomized controlled trial of 17 802 patients with high CRP levels (>2 mg/L), showed a relative risk reduction of 54% for MI, 48% for stroke, and 20% for all-cause death.[18] A retrospective review of 47 patients with RA has shown that CRP elevation correlates with accelerated atherogenesis.[19]

Treating the patient's RA will confer benefit for CVD. The QUEST-RA (Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis Program) study, which included 4363 patients from 15 countries, showed that prolonged use of treatments such as methotrexate, sulfasalazine, leflunomide, glucocorticoids, and TNF-α blockers reduced the risk of CVD in patients with RA.[20] However, Friedewald and colleagues believe TNF-α blockers should be avoided in patients with severe heart failure (classes III and IV) or recent MIs.[15] Further, Friedewald et al also suggest that the lowest possible doses of corticosteroids do not add to CVD risk and should be used to help manage RA symptomatology, while higher corticosteroid doses add to CVD risk through effects on serum lipids and blood pressure.[15]

Conclusion

There is a dramatic increase in atherosclerotic disease in patients with RA. Although the link between the 2 disorders is not fully understood, risk factors, family history, genetic predisposition, and pro-inflammatory states appear to play roles. Premature atherosclerotic changes might concurrently develop with subclinical inflammation for years before RA is clinically evident. Cardiovascular disease often goes unrecognized in patients with RA; therefore, it is prudent to carefully assess all patients with RA shortly after the diagnosis of RA is made, reduce risk factors, and ensure proper control of RA symptoms. When managing CVD in patients with RA, many shades of gray are expected, each requiring careful analysis and contemplation.

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Competing interests
None declared

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