Case Report

Reversing Myocardial Microvascular Disease in a Patient with Rheumatoid Arthritis

KARIM RAZA, MATTHEW BANKS, and GEORGE D. KITAS

ABSTRACT. Rheumatoid arthritis (RA) is associated with increased cardiovascular mortality. This is regarded as being due to accelerated coronary atherosclerosis. We describe a 62-year-old man with seropositive erosive RA and extraarticular manifestations but no history of cardiovascular disease. Noninvasive assessment of myocardial blood flow by adenosine stressed thallium scanning showed reversible ischemia and diffusely poor myocardial perfusion. Repeat assessment after intensive immunosuppression for rheumatoid vasculitis revealed resolution of the ischemic changes and generally increased myocardial perfusion. Coronary angiography revealed no significant atheroma, suggesting that myocardial microvascular disease was responsible for the ischemia. This may be an important determinant of cardiovascular outcome in RA, and this case indicated that it can be reversed with immunosuppression. (J Rheumatol 2005;32:754–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS VASCULITIS CARDIOVASCULAR DISEASE
MICROVASCULAR DISEASE IMMUNOSUPPRESSION

Rheumatoid arthritis (RA) is associated with a significantly increased cardiovascular mortality[1]; the mechanisms for this remain unclear. While lesions characteristic of rheumatoid heart disease (pericarditis, myocarditis, endocarditis, and coronary arteritis) are common pathological or echocardiographic findings, they rarely present clinically[2]. Patients with RA have an increased carotid artery intima-media thickness[3], an assessment of arterial structure that is widely used as a surrogate marker for atherosclerosis. We have reported that myocardial perfusion is significantly impaired in patients with RA and that this is not explained by traditional cardiovascular risk factors[4]. This impaired myocardial blood flow, and the excess cardiovascular mortality in RA, is usually ascribed to coronary atherosclerosis[1,4]. Several mechanisms have been proposed to explain the promotion of atheroma in RA[5]. Endothelial dysfunction, a critical early event in atherogenesis, is evidenced in RA by impaired brachial artery flow-mediated dilatation[6] and increased arterial stiffness[7]. Endothelial dysfunction is also common in patients with primary systemic vasculitis (PSV) and is seen at both the brachial artery and cutaneous microvasculature — sites often remote from those involved in the clinically apparent vascular inflammation[8,9]. Supporting these observations, increased arterial stiffness has also been reported in PSV[10]. Vasculitis is common in patients with RA, with a point prevalence of subclinical disease as high as 30%[11]. We have proposed that in patients with RA, endothelial dysfunction occurring in the coronary vasculature as a consequence of distant vascular or synovial inflammation may accelerate coronary atherosclerosis and be responsible for adverse cardiovascular outcomes[12]. However, an increase in coronary atherosclerosis has never been confirmed directly in patients with RA.

In a recent study of myocardial blood flow in hypertrophic cardiomyopathy, myocardial microvascular dysfunction was a strong independent predictor of clinical deterioration and death[13]. We describe a patient with RA with myocardial microvascular disease in the absence of coronary atheroma that was reversed with immunosuppressive therapy.

CASE REPORT

A 62-year-old man with one year history of seropositive erosive RA and recurrent episcleritis was enrolled into a research study of cardiovascular disease in RA. He was taking sulfasalazine and prednisolone (5 mg daily). He had no symptoms of ischemic heart disease, and had smoked until 10 years previously. His history and family history were otherwise unremarkable. Clinical examination revealed that he had active synovitis and was normotensive. He had a total cholesterol of 6.2 mmol/l, HDL of 1.4 mmol/l (normal range 0.8–2.5), and triglycerides of 2.4 mmol/l (normal 0.2–2.0). Inflammatory markers were significantly elevated: erythrocyte sedimentation rate (ESR) was 101 mm/h, C-reactive protein (CRP) 115 mg/l (normal

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0–8). Chest radiograph, resting 12-lead electrocardiogram, and echocardiogram were normal. Myocardial perfusion was assessed by single photon emission computed tomography (SPECT) scanning using ^{201}thallous chloride during adenosine stressing and after 4 h of rest. SPECT scanning with ^{201}thallous chloride is a very reproducible method of assessing myocardial blood flow, with little variation between serial scans in patients whose clinical conditions are stable[14]. An adenosine-stressed scan showed reversible ischemia in the septum and inferior and infero-lateral walls as well as a fixed inferior defect. The overall count was low, with low washout, suggesting diffusely poor myocardial perfusion (Figure 1A, 1B). He was given simvastatin, was intolerant of aspirin, and was referred for further cardiological assessment and coronary angiography.

One year later he developed a vasculitic leg ulcer and necrotizing scleritis. After 3 intravenous infusions of methylprednisolone (1 g each) the ulcer healed and the scleritis resolved. Remission of his arthritis and rheumatoid vasculitis was maintained with prednisolone (15 mg daily), cyclosporin A (150 mg daily), and methotrexate (MTX, 15 mg weekly). Coronary angiography performed 4 months later revealed good left ventricular function, normal unobstructed left anterior descending and right coronary arteries, and only mild atheroma in the circumflex artery. A repeat thallium scan showed persisting fixed inferior ischemia, with resolution of the previous reversible ischemic defects and a generalized increase in myocardial perfusion (Figure 1C, 1D). Investigations at the time of this second scan revealed ESR 25 mm/h, CRP 6 mg/l, total cholesterol 5.3 mmol/l, HDL 1.6 mmol/l, triglycerides 1.7 mmol/l. After 3-year followup, he continues to be well, with no evidence of active arthritis or vasculitis, no cardiovascular symptoms, and preserved normal left ventricular function on echocardiography.

DISCUSSION

While RA is associated with an increased cardiovascular mortality, the mechanisms for this remain unclear. Most cardiovascular deaths in RA appear to be due to ischemic pathologies such as myocardial infarction, congestive heart failure, or sudden death[15]. Myocardial ischemia, detected through myocardial perfusion imaging, is highly prevalent in RA[4]. This has been assumed to be largely due to accelerated atherosclerosis[1,5,15]. Indeed, endothelial dysfunction and increased arterial stiffness, important determinants of cardiovascular risk and predictors of atherosclerosis, are

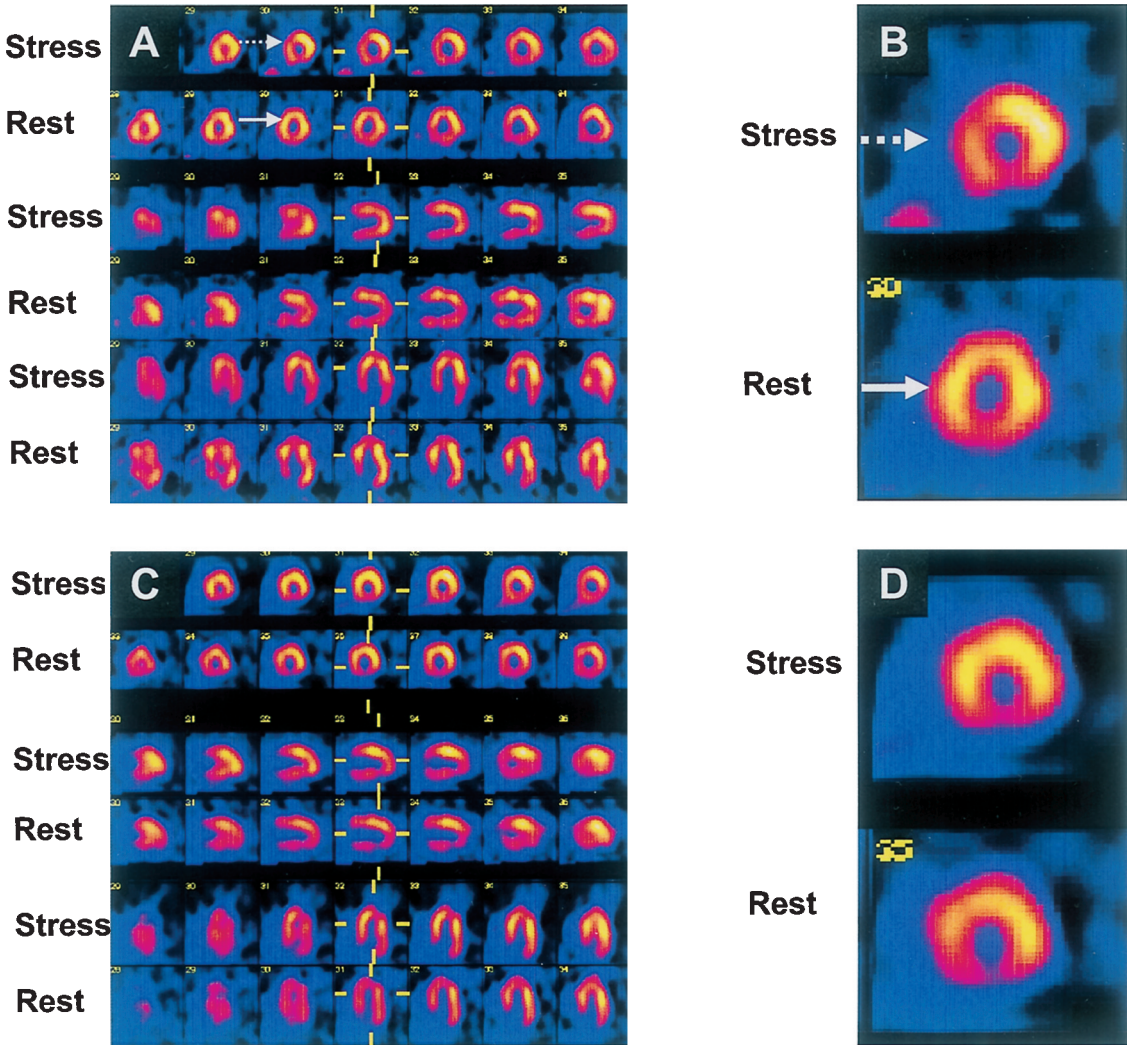

Figure 1. Myocardial perfusion was assessed by SPECT scanning using ^{201}thallous chloride during adenosine stressing and after 4 h rest. Reversible ischemia is indicated by a relative impairment of uptake during stress (dashed arrow in A, and magnified view in B), which normalizes after rest (solid arrow in A, magnified view in B). Scans were performed before [A and B (magnified view)] and after [C and D (magnified view)] therapy with intravenous methylprednisolone, cyclosporin A, and MTX for rheumatoid vasculitis.

both seen in RA. The mechanisms leading to these abnormalities in arterial function have yet to be fully elucidated. CRP, which impairs endothelial NO production[16] and accelerates atherosclerosis in a transgenic mouse model[17], has been suggested as a candidate. In addition, insulin resistance, dyslipidemia, and oxidative stress seen in RA may contribute[5]. Recent work suggests that the functional status of the vasculature, reflected by noninvasive assessments of endothelial function, and the structural status of the arteries, reflected by atherosclerotic plaque burden, are independent predictors of outcome in patients with coronary artery disease[18]. These processes may indicate involvement of different vascular beds and be the result of different pathogenic mechanisms, but may be equally important or additive in terms of eventual cardiovascular outcome.

In hypertrophic cardiomyopathy, myocardial microvascular disease predicts a worse cardiovascular outcome[13]. The mechanisms for this microvascular disease are unclear, but may also relate to endothelial dysfunction. The case we describe demonstrates that active systemic RA is associated with diffusely impaired myocardial perfusion. It is likely that this is consequent upon microvascular disease, in the absence of any significant coronary atheroma on followup angiography. Importantly, this was reversed following intensive immunosuppression and the introduction of simvastatin. This is analogous to the improvement in brachial artery endothelial function seen following treatment with steroid and cyclophosphamide in primary systemic vasculitis[8] and with anti-tumor necrosis factor-α therapy in RA[6]. As in hypertrophic cardiomyopathy, myocardial microvascular disease may be associated with a worse cardiovascular outcome in RA. The timing of the angiography in this case means that we cannot exclude the possibility that the initial perfusion defects were due to coronary atherosclerosis, which regressed with immunosuppression and statin therapy. Although an exciting possibility, such remodeling of a fixed lesion is less likely than an improvement in the functional status of the microvasculature following therapy. In addition, the separate contributions of immunosuppression (with steroid, MTX, and cyclosporin A) and statin therapy (which itself has immunomodulatory and cholesterol-lowering effects[19,20]) to the improvement in myocardial perfusion cannot be defined in an individual case such as this. There is clearly a need for a prospective study of the effect of rheumatoid disease activity on myocardial perfusion, and the ability of traditional immunosuppression or statin therapy to reverse any defect.

This case challenges the current assumption that myocardial ischemia and its adverse sequelae in RA are due solely to accelerated atherosclerosis affecting the epicardial coronary arteries, and suggests that the myocardial microvasculature may also be important. The observation that such microvascular abnormalities are reversible with immunosuppression may have therapeutic implications for chronic inflammatory rheumatic disorders associated with increased cardiovascular mortality.

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