Rheumatic Diseases
Insights Into Inflammation and Atherosclerosis
Johan Frostegård

The inflammatory nature of atherosclerosis was previously described by the Austrian pathologist Carl von Rokitansky in the 1840s and by Rudolf Virchow somewhat later. Although Rokitansky believed that the inflammation was secondary to other disease processes, Virchow promoted atherosclerosis as a primary inflammatory disease. It appears that Virchow had a point. Even in Rokitansky’s own arterial specimens, activated T cells and other inflammatory cells are present at an early stage of disease, which argues for the opinions of Virchow. On the other hand, as is demonstrated in the meta-analysis in the present issue of Arteriosclerosis, Thrombosis, and Vascular Biology, rheumatic diseases are associated with increased atherosclerosis. Thus, it is plausible that both Rokitansky and Virchow were right, that both possibilities were nonmutually exclusive.

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It is somewhat surprising that little attention was paid to the inflammatory nature of atherosclerosis in general until the 1980s. Thus, atherosclerosis is an inflammatory process in large and middle-sized arteries, characterized by infiltration of the intima by activated monocytes/macrophages and T cells. Proinflammatory cytokines are produced by immune-competent cells in the lesions. Interestingly, atherosclerosis has characteristics in common with autoimmune diseases, as indicated by studies in which adoptive transfer of β2-glycoprotein I-reactive lymphocytes enhances atherosclerosis in mice models of the disease.

Consequently, associations between atherosclerosis and rheumatic diseases were not much studied or even known, although the inflammatory nature of these latter conditions was much more established than was the case with atherosclerosis. In an early report, an association between cardiovascular disease (CVD) and a rheumatic disease (ie, systemic lupus erythematosus [SLE]) was described. A bimodal pattern of SLE was reported, indicating that in addition to early direct effects of this disease on various organ systems, a later complication was CVD.

SLE is characterized by various disease manifestations, such as nephritis, arthritis, serositis, and vasculitis. A typical feature of SLE is the occurrence of high levels of autoantibodies. The strong association between SLE and CVD has been reported in several recent articles. The risk of CVD in those with SLE is strikingly high in some patient populations: for example, in a study women aged 44 to 50 years had a 50 times increased risk of myocardial infarction. Also, an increased, albeit not so striking, CVD risk has been noted in several other studies.

Risk factors for CVD in those with SLE include those that are traditional, such as dyslipidemia (especially a high triglyceride level), hypertension, and renal disease; and those that are nontraditional, such as inflammation, antiphospholipid antibodies, and low-density lipoprotein oxidation. The increased risk of CVD in those with SLE (and in principle in those with other rheumatic diseases) is a major clinical problem that is likely to increase in importance as the possibilities to treat the underlying disease improve. Furthermore, studies on the role of atherosclerosis and CVD in rheumatic disease may also shed light on the underlying mechanisms in atherosclerosis and CVD per se.

We have reported 2 examples of this, 1 being the interaction between annexin A5 and antiphospholipid antibodies, where atheroprotective annexin A5 is outcompeted by antiphospholipid antibodies, causing a prothrombotic state. We also reported that annexin A5 is abundant in atherosclerotic plaques, especially at sites prone to plaque rupture, and we suggested that this protein may stabilize plaques, protect endothelium, and inhibit plaque rupture. We recently reported that low levels of natural IgM antibodies against phosphorylcholine (anti-PC) independently predict CVD in general and that there is a negative association between anti-PC levels and the development of human atherosclerosis. This association appears to be accentuated in stroke. Furthermore, low levels of IgM anti-PC were associated with SLE in a nested case-control SLE study and in a new SLE case-control study (unpublished); further anti-PC was anti-inflammatory, inhibiting the effects of inflammatory phospholipids. Thus, low anti-PC could predispose to both atherosclerosis and rheumatic disease, illustrating 1 possible common underlying factor that deserves further study.

The increased risk of CVD in rheumatoid arthritis (RA) has only recently become determined. However, it has become clear that CVD is a major cause of comorbidity and mortality and has been reported to be related to approximately a 60% mortality risk in RA. It has been suggested that RA is comparable to type 2 diabetes mellitus as an independent risk factor for CVD. Traditional CVD risk factors and inflammation-associated factors appear to be of major importance to explain the increased risk of CVD in those with RA, as in those with SLE.

Thus, although it appears that CVD is increased in those with RA and SLE (and other rheumatic diseases), the exact
role of atherosclerosis in rheumatic diseases has been less clear.\textsuperscript{11}

In an interesting meta-analysis, Tyrell et al\textsuperscript{2} demonstrate that atherosclerosis, as determined by the surrogate measure of intima-media thickness by ultrasonography, is indeed increased in rheumatic disease. A total of 68 comparisons from 60 different studies in which cases and matched controls were identified through systematic analysis on PubMed were reviewed: 37%, RA; 35%, SLE; 9%, systemic sclerosis; and 19%, other rheumatic diseases.

When treating patients with rheumatic disease, it is important to pay attention to the increased risk of atherosclerosis and CVD by focusing on traditional risk factors and on controlling disease symptoms, including inflammation. Further studies are needed to shed light on the risk factors and causes of the increased atherosclerosis present in patients with rheumatic diseases.

References

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