Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are autoimmune inflammatory diseases associated with juvenile atherosclerosis and thrombosis, respectively. A 44-year-old woman who had SLE with secondary APS had been treated with corticosteroid therapy, however, her inflammatory marker had never been within a normal range in her clinical course, and finally acute myocardial infarction was developed. Intra-vascular ultrasound also revealed diffuse coronary atherosclerosis progression for her age, which might result from SLE and APS, including vascular inflammation. (Circ J 2006; 70: 1082–1085)

Key Words: Coronary atherosclerosis; Intra-vascular ultrasound; Systemic lupus erythematosus; Vascular inflammation

Case Report

A 44-year-old woman was admitted to hospital because of continuous chest oppression over a period of 24h. She had been treated with a corticosteroid for 23 years since being diagnosed as having discoid lupus at the age of 21 years. Despite the therapy, her skin lesions had never completely disappeared and her serum C-reactive protein (CRP) level had never become negative throughout the clinical course. She had been admitted several times because of exacerbation of lupus. When she was 39 years old, she was diagnosed as having APS. She had been receiving anti-coagulant therapy with warfarin, and her international normalized ratio of prothrombin-time had been well controlled to approximately 2.0. Her renal function had been normal, and macro- or micro-proteinuria had never been detected. The maintenance dose of the corticosteroid, prednisolone, had been 15 mg/day. Her body mass index at admission was 23.6 kg/m². She had a smoking history of more than 20 years (Brinkman Index 300).

On admission, her blood pressure was 90/50 mmHg and her pulse rate was 70 beats/min, with regularity. A physical examination revealed no crackles (Killip class I), no heart murmur and no pretibial edema. Her electrocardiogram (ECG) showed poor R wave progression in leads V1 and V2, and ST segment depression in leads V1 to V5. A chest roentgenogram showed mild cardiomegaly but no pulmonary edema. Blood examination findings were as follows: white blood cell count, 11,600/μL; aspartic aminotransferase, 276 IU/L; lactate dehydrogenase, 1,109 IU/L; creatine kinase (CK), 2,455 IU/L; creatinine, 0.83 mg/dl; hemoglobin A1c, 5.6%; fasting plasma glucose, 117 mg/dl; total cholesterol, 156 mg/dl; triglyceride, 99 mg/dl; and high-density lipoprotein cholesterol, 47 mg/dl. Results of immunological and auto-antibody examinations were as follows: anti-nuclear antibody titer, 40 (normal reference titer, <40); lupus anticoagulant, 1.55 U/ml (normal reference, <1.4); anti-cardiolipin IgG antibody, 1.3 U/ml; CH50, 34 U/ml; anti-Sm antibody, negative; and anti-double strand DNA-IgG antibody, negative. Hematological, coagulate-fibrinolytic and other findings were as follows: platelets, 13.2×10⁴/μL; activated protein C resistance, 88.2 s; thrombin anti-thrombin III complex, 4.1 mg/ml; D-dimer, 0.5 μg/ml; and CRP, 4.4 mg/dl. Urinalysis exhibited no micro- and macro-proteinuria.

Emergency coronary angiography (CAG) was performed based upon the diagnosis of AMI. CAG revealed total occlusion in the mid site of the circumflex coronary artery (CX). There was no occlusive or stenotic lesion in right
coronary artery (RCA) and the left anterior descending artery (LAD). The proper site for mid and distal LAD originated from other independent ostium. We performed emergency percutaneous coronary intervention (PCI) for the CX lesion. A 7 French left Judkins guiding catheter was used to cross the CX lesion and then a multiple balloon (size: 2.5 mm) was inflated at the site. A subsequent CAG showed Thrombolysis In Myocardial Infarction grade 3 flow without residual stenosis in the CX. After the PCI procedure, her chest pain disappeared and an ECG showed near-complete resolution of the ST depression in leads V3–5. Her serum CK levels reached a maximum at 3,017 IU/L after reperfusion.

One month after the PCI, repeated angiography showed no restenosis in the CX lesion. The left ventricular ejection fraction was 60% with hypokinesis at the inferolateral wall. We performed IVUS in the CX and RCA at the same time to evaluate coronary arteries. IVUS showed diffuse plaque formation, such as intimal thickening, with partial calcification around the lumen from a proximal site to distal site of the CX, left main trunk (LMT) (Fig 1) and RCA (Fig 2). In addition, the maximum lumen sizes of the CX, LMT and RCA were only 2.18, 3.04 and 2.51 mm, respectively. IVUS also revealed partial eccentric plaque with low echoic lesions, which might be thought of as lipid core-like vulnerable plaque (Figs 1, 2 arrows). We did not perform IVUS in the LAD because it originated from an aberrant ostium and its lumen size was too small. She had no cardiac or other thrombotic events during her period of hospitalization and was discharged 1 month after PCI.

**Discussion**

The presence of SLE is an independent risk factor for the development of atherosclerosis and frequently causes cardiovascular events, including AMI, in young patients. Manzi et al reported that the incidence of AMI is 5-fold higher in patients with SLE than in the general population, and the relative risk of AMI in patients with SLE between the ages of 35 and 44 years was shown to be 50-times greater than that in age-matched controls.

There are various reports on evaluation of the degree of atherosclerosis in SLE. Several studies have demonstrated that plaque formation and intima-media thickness of the carotid artery were greater in patients with SLE detected by carotid ultrasonography. Asanuma et al reported that patients with SLE frequently had calcification of the coronary artery, detected by using computed tomography, compared
with control subjects. However, to the best of our knowledge, there are no reports on the evaluation of coronary atherosclerosis by IVUS in patients with SLE. In our case, IVUS clearly revealed not only diffuse intimal thickness and plaque formation in the coronary arteries but also partial vulnerable plaque formation with lipid core formation. The degree of coronary atherosclerosis in our patient was advanced for her age and compared with those in healthy middle-aged women.

The precise mechanisms of atherosclerosis in patients with SLE are unknown. Traditional risk factors of coronary artery diseases, such as hypertension, dyslipidemia, diabetes and smoking, have been implicated; but these risk factors alone cannot be enough to account for accelerated atherosclerosis in patients with SLE. Patients with SLE have endothelial dysfunction associated with inflammation, which is a marker of early atherosclerosis. A recent study has suggested that vascular endothelial dysfunction and vascular inflammation plays an important role in atherosclerosis. The prevalence of immune complex and complement activation is thought to be an important pathogenesis of SLE. Although many factors contribute to endothelial injury and dysfunction in SLE, immune complex can lead to endothelium dysfunction. Immune complex can bind to C1q, which induces adhesive molecular expression and interferes with cholesterol handling at the arterial wall. Complement activation can participate in the progression of atherosclerosis through recruitment of monocytes and enhancement of migration into the arterial wall. Asanuma et al highlighted the potential relationship in SLE between proatherogenic inflammatory cytokines, interleukin-6 and monocyte chemotactic protein-1, and atherosclerosis. In patients with SLE, the total number of circulating CD40 ligand, an immunoregulatory co-stimulatory molecule, -positive cells is increased and CD40 expression on endothelial cells is upregulated. In SLE, the binding of the CD40 ligand to CD40 on endothelial cells results in increased expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and E-selectin, and these adhesion molecules play an important role in facilitating vascular inflammation leading to atherosclerosis. Thus, SLE itself might be a risk factor of atherosclerosis, as well as the traditional risk factors.

Treatment with corticosteroids is always used for the control of SLE. It has generally been thought that a cumulative dose and duration of corticosteroid administration have adverse effects on atherosclerosis. However, recent studies have revealed that there is no relationship between the use of corticosteroids and atherosclerosis. Moreover, Roman et al reported that the average dose of corticosteroids was significantly lower in patients with SLE who had severe atherosclerosis. The CRP levels in our patient had never been negative in her clinical course in spite of corticosteroid therapy. A multiethnic US cohort study showed that an elevated serum level of CRP is an independent predictor of vascular events in SLE. A high-sensitivity CRP level might be useful for the assessment of cardiovascular risk but is not a marker of disease activity in SLE. Therefore, the dose of corticosteroids might be insufficient to control systemic inflammation, including vascular inflammation in coronary arteries, caused by SLE.

APS, which is often observed in SLE, is associated with not only venous and arterial thrombosis but also with atherosclerosis. APS remarkably increases the risk of myocardial infarction in SLE, and antiphospholipid antibodies are identified as a consequence of systemic inflammation and atherosclerosis. Anti-CLβ2-GP1 antibody enhances the accumulation of oxidized low-density lipoprotein (LDL) into macrophages, leading to an increase in foam cell proliferation. Oxidized LDL is also chemotactic and pro-inflammatory. In addition, IgG anti-CLβ2-GP1 antibodies are associated with reduced paraoxonase, an anti-oxidant enzyme to prevent the oxidation of LDL, in SLE. SLE patients with secondary APS have a higher prevalence of carotid plaque than patients with primary APS do. Our patient was also complicated with APS during the course of SLE, which might have caused the development of severe systemic inflammation and atherosclerosis.

We have reported here that findings of IVUS revealed diffuse coronary atherosclerosis in a middle-aged SLE woman complicated with secondary APS. In our case, advanced coronary atherosclerosis was attributed to accelerated atherosclerosis caused by insufficient corticosteroid therapy. However, various findings in atherosclerosis have been reported in patients with autoimmune diseases, including SLE. Further study is required to clarify the differences between findings of atherosclerosis in both autoimmune and non-autoimmune diseases.

References


