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CLINICAL RESEARCH **Coronary Artery Disease**

Angioscopic Follow-Up Study of Coronary Ruptured Plaques in Nonculprit Lesions

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OBJECTIVES Changes of ruptured plaques in nonculprit lesions were evaluated using coronary angioscopy.

BACKGROUND The concept of multiple coronary plaque ruptures has been established. However, no detailed follow-up studies of ruptured plaques in nonculprit lesions have yet been reported.

METHODS Forty-eight thrombi in 50 ruptured coronary plaques in nonculprit lesions in 30 patients were identified by angioscopy. The percent diameter stenosis (%DS) at the target plaques on quantitative coronary angiographic analysis and the serum C-reactive protein (CRP) level were measured.

RESULTS The mean angioscopic follow-up period was 13 ± 9 months. Thirty-five superimposed thrombi still remained at follow-up, and the predominant thrombus color changed from red (56%) at baseline to pinkish-white (83%) at follow-up. The healing rate increased according to the angioscopic follow-up period (23% at ≤12 months vs. 55% at >12 months, $p = 0.044$). The %DS at the healed plaque increased from baseline to follow-up (12.3 ± 5.8% vs. 22.7 ± 11.6%, respectively; $p = 0.0004$). The serum CRP level in patients with healed plaques ($n = 10$) was lower than that in those without healed plaques ($n = 19$; 0.07 ± 0.03 mg/dl vs. 0.15 ± 0.11 mg/dl, respectively; $p = 0.007$).

CONCLUSIONS The present study demonstrated that: 1) ruptured plaques in nonculprit lesions tend to heal slowly with a progression of angiographic stenosis; and 2) the serum CRP level might reflect the disease activity of the plaque ruptures. (J Am Coll Cardiol 2005;45:652–8) © 2005 by the American College of Cardiology Foundation

Atherosclerotic coronary plaque rupture (or erosion) and subsequent thrombus formation in the culprit lesion are recognized to be the major motivating factors in acute coronary syndrome (ACS) (1–5). Intravascular ultrasound (IVUS) studies recently reported that a plaque rupture occurs not only in culprit lesions but also in other atherosclerotic plaques in patients with ACS, stable angina pectoris (SAP), and silent myocardial ischemia (6–9). The concept of "pancoronaritis" or "multifocal plaque rupture" has been established. In the clinical setting, ruptured plaque in the culprit lesion is usually treated with percutaneous coronary intervention (PCI), and the natural course of ruptured plaque without PCI has not yet been reported. Previous pathologic studies have shown that healed plaques after a subclinical rupture tend to result in increased narrowing of the coronary lumen (10,11). Nevertheless, ruptured plaques in nonculprit lesions have not been well described as to whether they heal uneventfully with (or without) luminal narrowing or lead to an occurrence of acute coronary events in living patients.

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Serum C-reactive protein (CRP), a predictor of acute myocardial infarction (MI), is expressed in human atherosclerotic lesions, and most CRPs show an increased expression at sites of plaque rupture (12–14). The serial changes in the serum CRP level in patients with multiple plaque ruptures have also not yet been elucidated.

Coronary angioscopy can provide direct images of the endoluminal surface and detailed information on plaque rupture (or healing), as well as on the existence and age of a thrombus. The purpose of this study was to investigate the natural course of ruptured plaques in nonculprit lesions in living patients.

METHODS

Patient population. Between September 1998 and December 2003, 327 patients were analyzed by coronary angioscopy. Thirty consecutive patients in whom two or three de novo native coronary arteries were evaluated by repeat angioscopic procedures and who had ruptured plaque(s) at nonculprit lesions were enrolled in this study. Written, informed consent approved by our institutional review boards was obtained from all study patients before catheterization.

Clinical demographics. The patient demographics were obtained by a hospital chart review. Stable angina pectoris was defined as a positive stress test and no change in the frequency, duration, or intensity of symptoms lasting <4 weeks. Unstable angina pectoris (UAP) was new-onset

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CRP = C-reactive protein
%DS = percent diameter stenosis
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
LCx = left circumflex artery
MI = myocardial infarction
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiogram
RCA = right coronary artery
SAP = stable angina pectoris
UAP = unstable angina pectoris

severe angina, accelerated angina, or rest angina. Acute or recent MI occurred within ≤6 weeks, and a previous MI >6 weeks. Patients with UAP, acute MI, and recent MI were categorized as ACS. Blood sampling was collected in the fasting state, immediately before each angioscopic procedure, except for CRP in patients with ACS. In ACS, the serum CRP level four weeks after onset was selected as the baseline level because of exclusion of the effects of myocardial necrosis.

A culprit lesion was identified by the combination of the electrocardiographic findings, left ventricle wall motion abnormalities (left ventriculography or echocardiography), scintigraphic defects, and angiographic lesion morphology.

Angiographic analysis. All angiograms were analyzed with a computer-assisted, automated edge-detection algorithm (CMS, MEDIS, Nuenen, The Netherlands) by an angiographer blinded to the clinical and angioscopic findings, using a standard qualitative definition and quantitative coronary angiographic (QCA) measurements. The variability of the QCA measurements was analyzed repeat measurements of the target plaques. The variation in minimal lumen diameter was 0.09 ± 0.09 mm and that in %DS was 2.8 ± 2.1%. A follow-up angiogram was obtained at the same angle as that in the baseline study.

Angioscopic imaging. The coronary angioscopic procedure has been previously reported (15). The proximal segments to the culprit lesion were observed by angioscopy before PCI for avoidance of mechanical damage due to the PCI procedure. The distal segments to the culprit lesion and the other coronary arteries were examined after PCI. The angioscopic and fluoroscopic images during the angioscopic observations were recorded on digital videotape for later analysis. The exact position of the angioscopic catheter at the site of the target plaque was recorded on an angiogram to ensure a reliable comparison.

Definition and analysis of angioscopic findings. A ruptured plaque was defined as a complex plaque and/or a superimposed thrombus. A complex plaque was considered to be present when the surface of the lesion had an irregular appearance, including a fissure, flap, and ulceration. Based on the surface color, the plaque was classified as either yellow or white. A fissure was defined as a torn intima without floating into the lumen; a flap was a disrupted fragment floating into the lumen; and ulceration was a crater-like lesion suggesting a gap in the vessel wall (Fig. 1). A thrombus was defined as a coalescent red or pinkish-white, superficial, or protruding mass adhering to the vessel surface, but clearly a separate structure that remained despite being flushed with saline solution. Complete plaque healing was defined as a covering by the neointima and the disappearance of thrombus and complex plaque.

The intra-observer agreement on angioscopic images was measured by having an observer repeat assessment of 20 images (presented in random order) after one week. The inter-observer agreement was measured by comparing the assessment of 100 images by the two observers blinded to the clinical background. The intra-observer agreements for the evaluated angioscopic items (complex plaque, yellow plaque, and thrombus) were 95%, 95%, and 100%, respectively. The inter-observer agreements of those items were 93%, 98%, and 97%, respectively. The kappa values for intra-observer agreement of them were 0.94, 0.99, and 0.95, respectively. The kappa values for inter-observer agreement of them were 0.95, 0.96, and 0.94, respectively. When there was any discordance between the two observers, a third investigator read the images, and a consensus was obtained.

Percutaneous coronary intervention and clinical follow-up. The PCI was performed for only the culprit lesions using a stent. Two kinds of antiplatelet agents—ticlopidine (200 mg/day) or cilostazole (200 mg/day), added to aspirin (81 to 200 mg/day)—were administered for at least six months. Glycoprotein IIb/IIIa inhibitors have not been approved for clinical use in Japan. Repeat PCI, bypass surgery, ACS, and death were all considered to be major outcome events.

Statistical analysis. Statistical analysis was performed with StatView 5.0 (SAS Institute, Cary, North Carolina). Categorical variables are presented as frequencies and compared

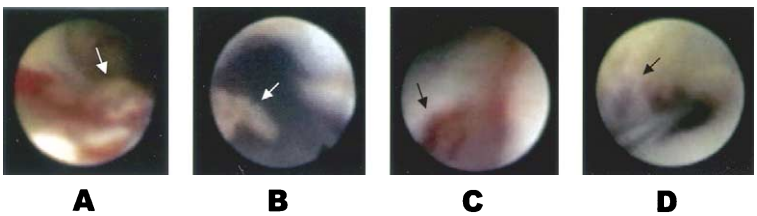

Figure 1. Angioscopic images of nonculprit ruptured plaques. **(A)** Yellow plaque with a fissure **(arrow)** and red thrombus. **(B)** Yellow plaque with a flap **(arrow)**. **(C)** Yellow plaque with an ulceration **(arrow)** and red thrombus. **(D)** Yellow plaque with a pinkish-white thrombus **(arrow)**.