2. The Role of Plaque Rupture in the Development of Acute Coronary Syndrome Evaluated by the Coronary Angioscope

Kazuhisa Kodama, Masanori Asakura, Yasunori Ueda, Osamau Yamaguchi and Atsushi Hirayama
Cardiovascular Division, Osaka Police Hospital, Osaka

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Rupture of an atherosclerotic plaque in the coronary arteries is observed in patients who died suddenly or shortly after an episode of unstable angina or myocardial infarction. This pathological finding was first reported in 1844, but its importance was focused upon nearly 150 years later with the findings of the coexistence of plaque rupture and thrombosis. These pathological findings have been studied in the clinical setting following coronary angiography performed in the acute stage of patients with unstable angina or myocardial infarction. The glittering yellow plaques have been observed in unstable coronary lesions by angioscope, and are thought to be vulnerable plaques (4).

In this article, we focused on the yellow plaque, and demonstrated the progression of the yellow plaque frequently observed in the angiographically normal coronary artery and its rupture as a cause of acute coronary syndrome based on our findings by a coronary angioscope according to the atherosclerotic process (5).

Plaque formation

The first atherosclerotic lesion consisting of fatty dots or streaks barely raised above the intimal surface, is formed by lipid-laden foam cells transformed from macrophages which take modified LDL inside through the scavenging receptors. The fatty streak is first recognized as a thin yellow plaque by angioscope in angiographically normal artery. We studied the incidence of the yellow plaques in the angiographically normal coronary arteries and found that yellow plaques were observed in 65 coronary arteries (72%) among 90 angiographically normal coronary arteries. The mean number of the isolated yellow plaques was 3 in the coronary arteries with yellow plaques. This high incidence of yellow plaques was due to the selection bias because the subjects studied were suspected to have coronary heart disease.
Advanced atherosclerotic plaque

Advance plaques have a core of extra-cellular lipid separated by smooth muscle cells inside and covered and separated from the lumen by a thick or thin fibrous cap. Much of the core lipid is thought to be derived from the death of lipid-containing macrophage form cells and the from release of their intra-cytoplasm contents. Coronary angiography could not detect these lesions, as the plaque developed directly to the outer layer and was localized in eccentric form. We examined the advanced atherosclerotic plaque in the angiographically normal coronary artery by the combination of intravascular ultrasound and coronary angioscope. The plaques which are more yellow in color might be vulnerable due to the thinner fibrous cap. On the other hand, plaques with a larger core are thought to be vulnerable. The former could be assessed by angioscope and the latter by intravascular ultrasound. The plaques will be carefully followed up and will provide important information about the plaque, and we can learn what defines a vulnerable plaque. To identify the patients with the vulnerable plaques is important to determine the high-risk subgroup for acute coronary syndrome and they should be treated intensively by the cholesterol lowering drugs. The patients with acute myocardial infarction or hyperlipidemia might belong to the high-risk group. Twenty patients with myocardial infarction one month after the onset and 13 patients with hyperlipidemia were subjected to cardiac catheterization and their angiographically normal coronary arteries were investigated by the coronary angioscope. The incidence of yellow plaques was 90.4% (19/21) of the infarct-related arteries, 95% (37/39) of the non-infarct arteries, and 77% (30/39) in angiographically normal coronary arteries of patients with hyperlipidemia. These results suggested that patients with a coronary risk factor frequently have the yellow plaques.

Plaque rupture

Rupture of the plaque surface occurs frequently during the evolution of the atherosclerotic lesions. The mechanism of plaque rupture has not been completely understood. Four major factors are suggested to contribute to plaque rupture: the presence of lipid-rich plaques, the activity of macrophages, the effect of stress on the vessel wall, and shear stress. The fissuring or rupture of the plaque with resultant intraluminal thrombosis is an important mechanism of plaque development and progression and also is the fundamental step in the development of acute coronary syndrome. The white, red, or mixed thrombus was frequently observed (94%) in the ischemia-related lesion of patients with acute coronary syndrome. Yellow glittering plaques were also frequently observed (93%) in those lesions and rupturing was also observed. The angioscopic findings of thrombus and yellow plaques clearly showed the pathophysiology of the evolving acute coronary syndrome. Yellow plaque observed frequently in the unstable lesion of patients with acute coronary syndrome, has played the fundamental role in the evolving acute coronary syndrome. The incidence of yellow plaques in the coronary arteries of 285 consecutive patients with ischemic heart disease subjected to coronary angioscopic studies was 94.7%, 92.7%, and 60.4% in unstable angina, acute myocardial infarction, and stable effort angina without prior myocardial infarction, respectively (6). Yellow plaques and thrombus were frequently observed one month after the onset. Yellow plaques were observed even 6 and 18 months after the onset, however the thrombus was not observed (7). These results indicated that the antithrombotic treatment including anti-platelet therapy should be continued for at least 6 months and the prevention of the re-rupture of the plaque must be continued from the onset.

In conclusion, the present angioscopic study demonstrated that the yellow plaques were observed in patients with coronary heart disease or risk factors and their rupture is the fundamental mechanism for acute coronary syndrome. In the future, the vulnerable plaque will be identified by both intravascular ultrasound and angioscope in asymptomatic patients with coronary risk factors, and then treated by not only the lipid lowering drugs but also plaque directed therapy for the primary prevention.

References

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3. Plaque Formation and Its Rupture

Nobuhiro Yamada
The Department of Metabolic Diseases, University of Tokyo, Tokyo

Key words: atherosclerosis, hyperlipidemia, low-density lipoprotein (LDL)

Pathophysiology of atherosclerosis

Elucidating the mechanism of the onset of atherosclerosis is indispensable to understanding the significance of treatment of hypercholesterolemia. Atherosclerotic lesions can be characterized as accumulations of cholesterol esters and pathologic reactions by various cell groups. The pathogenesis of atherosclerosis has been discussed primarily on the basis of these two phenomena. A well-known concept to explain the etiology of atherosclerosis is the theory of response to injury. According to this theory, physiologically active substances such as platelet-derived growth factor (PDGF) and macrophage colony-stimulating factor (M-CSF) are released in response to injury of the vascular wall, and these substances induce pathologic reactions by the cells constituting the vascular wall (1). Atherosclerosis is unlikely to develop if either of the two major phenomena (accumulation of cholesterol esters in the vascular wall or pathologic reactions of cellular components in the vascular wall) is absent.

Atherosclerotic lesions are composed of various types of cells, including platelets, endothelial cells, macrophages, smooth muscle cells, and T lymphocytes (Fig. 1). These cells release large amounts of cell growth factors and cytokines to maintain the homeostasis of the vascular wall exposed to risk factors (hypercholesterolemia, hypertension, smoking, and diabetes mellitus) that promote the development of atherosclerosis. This mechanism resembles inflammatory reactions to exogenous factors and the wound healing process. Dysfunction of vascular endothelial cells is thought to induce pathologic reactions of cell groups mediated by the expression of adhesion molecules, resulting in disturbed relaxation of blood vessels and promotion of thrombus formation.

If endothelial cells are activated by risk factors, adhesion molecules are expressed on endothelial cells, allowing peripheral monocytes to adhere to the surface of the endothelial cells. Peripheral monocytes invade the subendothelial tissue through the spaces between endothelial cells and subsequently mature and differentiate into macrophages under the influence of M-CSF, etc. In the presence of excessive amounts of low-density lipoprotein (LDL), denatured LDL modified by oxidation or other reactions on the vascular wall is taken up by macrophages via scavenger receptors, resulting in the formation of foam cells and the accumulation of cholesterol esters.

Atherosclerosis can develop if the formation of fatty streaks, composed of foam cells, is combined with proliferation of smooth muscle cells, growth of intercellular matrix, platelet aggregation, and calcification.

Plaque formation leading to cardiovascular events

In their early stages plaques are primarily composed of foam cells derived from macrophages. Foam cells are a characteristic of atherosclerotic lesions. It is thought that as atherosclerosis progresses, foam cells derived from smooth muscle cells that migrate from the media to the intima become involved in atherosclerotic lesions, in addition to foam cells of macrophage origin. The smooth muscle cells that constitute the media of blood vessels change character in response to stimulation by PDGF or other factors. This induces them to migrate and proliferate beyond the internal elastic membrane and to phagocytize lipids.

The smooth muscle cells that migrate from the media proliferate on the luminal side as if surrounding the plaques made up of macrophages. The superficial layers of the plaques are thus coated with a few layers of smooth muscle cells located below the endothelial cells. This can be viewed as compensation for the fragility of diseased blood vessels that occurs during the course of plaque formation. If hyperlipidemia persists, the smooth muscle cells also become foam cells, and foam cell formation progresses from the plaque towards the surface of the vascular lumen. And thus, plaques expand in this way.

More than half of all acute events of ischemic heart disease, such as angina pectoris and myocardial infarction, (as high as...