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Vulnerable atherosclerotic plaque features: findings from coronary imaging

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ABSTRACT Pathological studies have suggested that features of vulnerable atherosclerotic plaques likely to progress and lead to acute cardiovascular events have specific characteristics. Given the progress of intravascular coronary imaging technology, some large prospective studies have detected features of vulnerable atherosclerotic plaques using these imaging modalities. However, the rate of cardiovascular events, such as acute coronary syndrome, has been found to be considerably reduced in the limited follow-up period available in the statin era. Additionally, not all disrupted plaques lead to thrombus formation with clinical presentation. If sub-occlusive or occlusive thrombus formation does not occur, a thrombus on a disrupted plaque will organize without any symptoms, forming a "healed plaque". Although vulnerable plaque detection using intracoronary imaging is focused on "thin-cap fibroatheroma" leading to plaque rupture, superficial plaque erosion is increasingly recognized; however, the underlying mechanism of thrombus formation on eroded plaques is not well understood. One of intravascular imaging, optical coherence tomography (OCT) has the highest image resolution and has enabled detailed characterization of the plaque *in vivo*. Here, we reviewed the status and limitations of intravascular imaging in terms of detecting vulnerable plaque through mainly OCT studies. We suggested that vulnerable plaque should be reconsidered in terms of eroded plaque and healed plaque and that both plaque and circulating blood should be assessed in greater detail accordingly.

Acute coronary syndrome (ACS) remains a major cause of morbidity and mortality worldwide. For decades, pathological and fundamental studies have primarily focused on "vulnerable plaque" resulting in ACS. The term "vulnerable plaque", introduced in the late 1980s, refers to a coronary plaque that is most likely to result in plaque rupture.[1] Although plaque rupture is the most frequent autopsy finding in patients with sudden cardiac death,[2–4] plaque erosion or calcified nodules are reported to be other underlying mechanisms contributing to ACS.[2] In the clinical setting, optical coherence tomography (OCT), a high resolution intracoronary imaging modality, has enabled characterization of the culprit plaque that are more in line with the aforementioned diagnosis of the three pathologies in the autopsy studies.[5] Moreover, studies using OCT have demonstrated plaque erosion to be more common than previously considered.[6] The representative three types of culprit plaque on OCT images are shown in Figure 1. Naghavi, *et al*.[7] recommended that vulnerable plaque be defined in terms of morphological features to include all dangerous plaques that involve a risk of thrombosis and/or rapid progression. In addition, they suggested that not only plaque but also circulating blood plays an important role in the development of ACS.[7] However, most intracoronary imaging studies concerning vulnerable plaque as a predisposition to ACS have focused on plaque rupture, which is frequently referred to as thin-cap fibroatheroma (TCFA). Figure 2 shows a typical OCT image of TCFA. Additionally, although ACS predominantly arises from occlusive or sub-occlusive coronary thrombosis due to disrupted plaques, non-flow-limiting thrombus may heal without clinical manifestations[8] and it has been proposed that the healing process of disrupted plaques contributes to the episodic progression of coronary artery stenosis.[9–12] Herein, we review the present status and the limitations of current intracoronary imaging modalities based on ACS pathogenesis, and we reevaluate the nature of vulnerable plaque through mainly OCT studies.

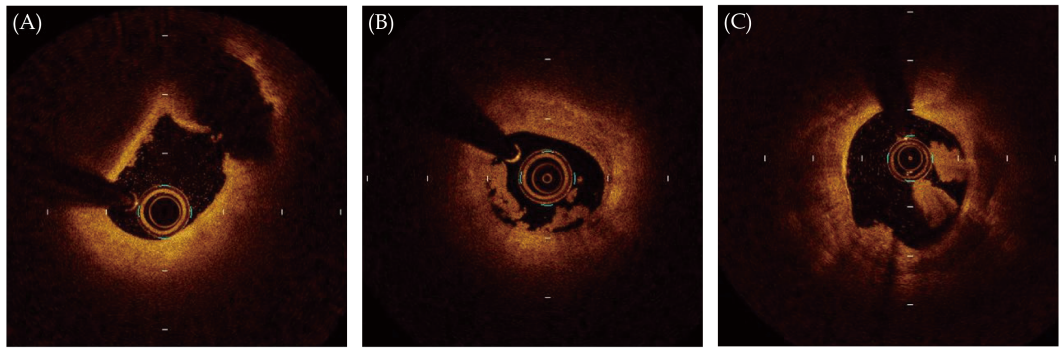

Figure 1 Representative OCT images of three types of ACS pathologies. (A): Plaque rupture was defined as the presence of fibrous cap discontinuity with a communication between the lumen and the inner core of plaque or with a cavity formation within the plaque; (B): plaque erosion was identified as the presence of an attached thrombus overlying an intact and visualized plaque, luminal surface irregularity at the culprit lesion in the absence of a thrombus, or attenuation of the underlying plaque by a thrombus without superficial lipid or calcification immediately proximal or distal to the site of the thrombus; and (C): calcified plaque was defined as the presence of superficial substantive calcium at the culprit site without evidence of a ruptured lipid plaque. ACS: acute coronary syndrome; OCT: optical coherence tomography.

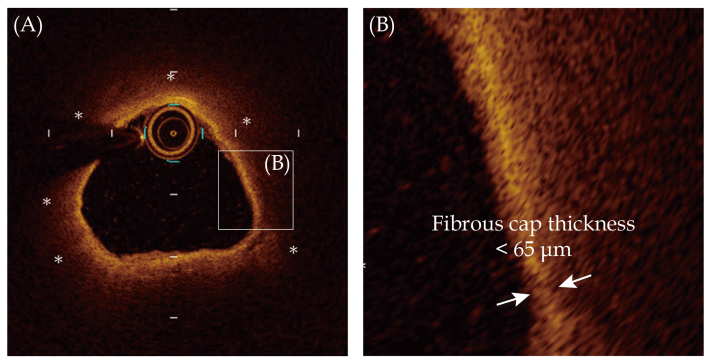

Figure 2 Representative OCT image of TCFA. (A): Lipid plaque, defined as a signal poor region with a poorly defined or diffuse border, is shown in the whole circumference (white asterisks); and (B): the minimum fibrous thickness was measured as < 65 μm (enlarged view). OCT: optical coherence tomography; TCFA: thin cap fibroatheroma.

RUPTURED PLAQUE

In plaque rupture, fibrous cap disruption exposes the thrombogenic contents in the necrotic core, including tissue factor, to circulating cellular and noncellular blood elements, causing coronary thrombosis.[13] Autopsy studies have shown an inverse relationship between the thickness of the fibrous cap covering the lipid plaque and risk of plaque rupture. Plaques at high risk of rupture with a fibrous cap thickness of < 65 μm[14] are well known as TCFA. A large plaque burden with central necrosis affects plaque vulnerability,[15] and ruptured plaque is associated with a larger necrotic core than non-ruptured plaque.[3,16] Additionally, disrupted fibrous caps have been shown to be more frequently infiltrated by foam cells originating from macrophages than those in non-ruptured TCFA.[3,17] Intravascular coronary imaging technology has made progress, and some large prospective studies concerning the detection of vulnerable plaque prone to rupture have been undertaken. In the PROSPECT study, Stone, *et al.*[18] assessed 697 patients with ACS using virtual histology (VH) intravascular ultrasound (IVUS); patients with a VH-TCFA, a minimum lumen area (MLA) < 4.0 mm^2, and a plaque burden ≥ 70% had a high 3-year risk for non-culprit major adverse cardiac events (MACEs). In the LRP study by Waksman, *et al.*,[19] 1 271 patients with coronary artery disease (CAD) were examined using near-infrared spectroscopy IVUS (NIRS-IVUS). Their results showed that a prespecified binary NIRS cutoff of a maximum 400 lipid core burden index for a 4 mm segment ($maxLCBI_{4mm}$) was a reasonable 2-year predictor of non-culprit MACEs.[19] In the CLIMA study, Prati, *et al.*[20] analyzed OCT images from 1 003 patients with CAD and found that

an MLA < 3.5 mm^2, a minimum fibrous cap thickness < 75 μm, a maximum lipid arc > 180°, and the presence of macrophages were 1-year predictors of cardiac death and myocardial infarction originating from the lesion. Representative OCT images of vulnerable features are shown in Figure 3. Based on these study findings, vulnerable features of atherosclerotic plaque *in vivo* are as follows: (1) a thin fibrous cap, (2) a large plaque or lipid burden, (3) the presence of macrophages and; (4) a small lumen area, and these features also accorded with a previous pathological study.[7]Although the observational study period and endpoints differed among the studies, the rate of non-culprit MACEs with vulnerable features was relatively low (range, 11.6% to 19.4%). Moreover, the occurrence of ACS arising from a non-culprit lesion has been reported to be relatively rare (range, 1% to 4%).[18–20] To date, no evidence has been published concerning recommended percutaneous coronary intervention for prevention against ACS based on plaque features.

Recently, advanced medical therapy has reduced cardiovascular events. Lipid-lowering statin therapy, especially, has changed the management of patients with CAD and improved their prognoses. A high plasma level of low-density lipoprotein cholesterol (LDL-C) is an important risk factor for atherosclerotic cardiovascular disease (ASCVD),[21] and the strongest risk for plaque rupture is hyperlipidemia.[14] Intravascular imaging studies have shown that a high level of plasma LDL-C is related to large plaque volume and a thin fibrous cap thickness.[22,23] Large-scale clinical trials have indicated that statin therapy reduces both the circulating levels of LDL-C and the incidence of ASCVD.[24–26] Previous imaging studies have shown that statin therapy reduces the lipid content of plaque and increases the thickness of the fibrous cap.[27–29] The prevalence of ruptured plaque appears to be higher in patients with ACS who had LDL-C levels >100 mg/dL without statin therapy than in those receiving statin therapy. Therefore, it is possible that aggressive statin therapy affects plaque stabilization and prevent rupture.[30]

Despite lipid-lowering statin therapy, many such patients remain at an elevated risk of MACE,[31] and some patients subsequently experience ACS due to plaque rupture.[30] These phenomena are commonly referred to as residual risks. Elevated non-fasting triglycerides and remnant cholesterol are considered to be risk factors for cardiovascular events,[32,33] and postprandial hypertriglyceridemia has gained attention as a residual risk. Postprandial hypertriglyceridemia is characterized as the accumulation of triglyceride-rich lipoprotein (TGRL) particles.[34–36] Recently, it has become possible to measure the number of chylomicrons based on the intestinally derived lipoprotein, apolipoprotein B-48 (apoB-48). ApoB-48 is a TGRL that acts as the primary structural component of chylomicrons.[37] Our recent study showed that impaired postprandial metabolism of TGRLs, estimated through increased levels of apoB-48 during a meal tolerance test, was associated with the presence of TCFA.[38] However, other aspects should also be considered regarding the mechanisms of ACS. In current clinical practice, the

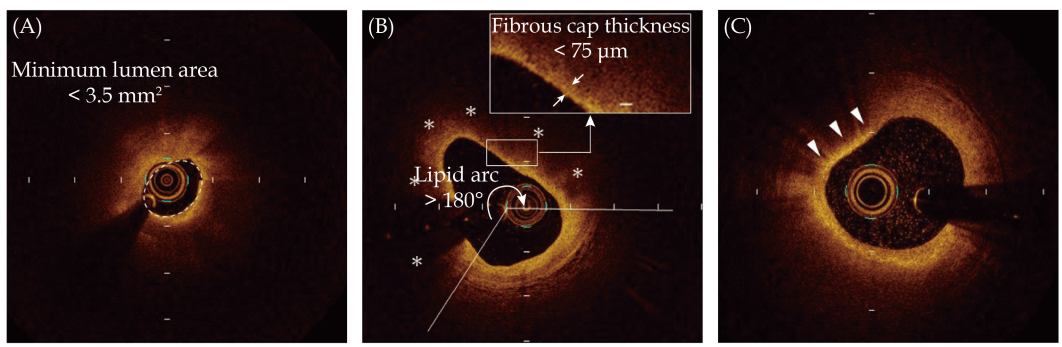

Figure 3 Vulnerable features evaluated using OCT. (A): Minimum lumen area was < 3.5 mm^2. (B): Lipid was defined as a signal poor region with a poorly defined or diffused border (white asterisks). The angle of the lipid tissue > 180° from edge to edge. Enlarged view shows that the minimum thickness of the fibrous cap was < 75 μm. (C): Macrophage infiltration was defined as a signal-rich, distinct, or confluent punctuated region that exceeded the intensity of the background speckle noise (white arrowhead). OCT: optical coherence tomography.

incidence of ST-segment elevation myocardial infarction (STEMI) has decreased, whereas the proportion of patients with non-STEMI (NSTEMI) has increased worldwide.[39] According to previous reports, the main mechanisms of STEMI and NSTEMI are plaque rupture and plaque erosion, respectively,[40,41] and previously noted preventive medicine may decrease ruptured plaque and plateau/increase eroded plaque.[39]

ERODED PLAQUE

Eroded plaque is composed of abundant smooth muscle cells within a proteoglycan matrix and is absent from the endothelium or a large lipid core.[42] A pathological study showed endothelial denudation with superficial platelet aggregation was primary vulnerable feature, alongside other features leading to plaque rupture.[7] Even when utilizing the highest image resolution, the extremely thin layer of the endothelium cannot be identified. Although the underlying mechanism of local thrombosis on eroded plaques remains unclear, local flow perturbation and changes in endothelial shear stress (ESS) may lead to upregulation of toll-like receptor 2, resulting in endothelial damage, neutrophil extracellular traps formation, and thrombosis on eroded plaque.[43]

Although plaque rupture is the principal cause of coronary thrombosis, the importance of superficial plaque erosion has gradually been recognized in recent years.[44] It is uncertain whether statin therapy affects plaque erosion, and a shift may occur from plaques being predisposed to rupture toward plaque erosion. Further investigations are required to evaluate the influence of statin therapy on superficial plaque erosion.

Although abnormally low and high ESSs are related to atherosclerotic progression and cardiovascular events, no consensus has been reached in terms of study findings.[45] A recent study using OCT-based computational fluid dynamic simulation showed that it was not ESS itself but rather that a high ESS gradient and oscillatory shear index may play critical roles in plaque erosion.[46]A retrospective registry presented five independent clinical and laboratory parameters associated with plaque erosion: age < 68 years, anterior ischemia, no diabetes mellitus, a hemoglobin level > 15.0 g/dL, and normal renal function.[47] These parameters were determined through comparing mainly patients with plaque rupture rather than healthy individuals. Recently, we reported seasonal variations in the pathogenesis of ACS, and that plaque erosion was found to be highest during summer.[48]Furthermore, plaque erosion has been found to be related to smoking,[2] and a recent study showed smoking to be independently associated with fibrin-rich thrombi in plaque erosion.[49] Smoking creates an imbalance of thrombotic and fibrinolytic factors resulting in the initiation and propagation of thrombosis.[50] Thrombogenicity in relation not only to plaque but also to circulating blood modified due to hemoconcentration and smoking, for example, may affect ACS onset in plaque erosion. Presently, data relating to risk factors for plaque erosion comparing affected patients with healthy individuals are unavailable, and a diagnostic tool to predict thrombus formation on eroded plaque has not been reported.

CALCIFIED PLAQUE

A pathological study reported that one mechanism contributing to ACS is a calcified nodule, which is composed of fibrocalcific plaque with luminal surface that is disrupted by nodules of dense calcium.[2,3,13] In addition to calcified nodules, a recent OCT study suggested that other characteristics of calcified plaque contribute to ACS, such as superficial calcific sheets and calcified protrusions.[51] The role of coronary calcification in plaque stabilization and cardiovascular events remains contested. Fibrocalcific plaques are mainly accompanied with calcific sheet (> 3 mm), whereas fragmented calcification and microcalcification (range, 0.5 to 15 μm) have been frequently found in ruptured plaque.[52] Spotty calcification (with an arc of < 90° and a length < 4 mm, measured using OCT) has been associated with plaque instability,[53,54] whereas larger and denser calcium structures have been found to be associated with plaque stabilization.[55–57] Small calcium deposits may play a role in plaque instability, whereas extensive calcification appears likely to be associated with plaque stabilization. Nevertheless, calcified plaques with relatively extensive calcification have been found at the culprit lesion in pa-

tients with ACS on occasion. The pathogenesis of calcified plaque leading to ACS has not been fully investigated, and further studies are warranted to investigate the mechanism of thrombus formation on calcified plaque.

HEALED PLAQUE

Not all cases of thrombi on disrupted plaques (ruptured plaque or eroded plaque) lead to a clinical event, and a non-occlusive thrombus may heal asymptomatically.[8] Recently, attention has been directed to the key role of plaque healing in the natural history of atherosclerotic disease. Flow-limiting thrombus formation on disrupted plaque causes ACS, but otherwise the thrombus will organize and plaque will begin healing.[58] Subsequent developments in terms of these plaque disruptions may depend on the balance between thrombogenicity and protective fibrinolysis mechanisms. After plaque disruption, the exposure of thrombogenic plaque components provides a stimulus for platelet activation and aggregation,[59,60] triggering endogenous fibrinolysis to preserve vessel lumen.[61]Although an effective endogenous fibrinolytic system is required for preventing occlusive thrombus formation,[58,62] it is unclear how to measure this healing capacity and how to intervene in patients who are impaired in terms of this capacity. A histology validation study reported that healed plaque can be reliably identified using OCT as plaque with layers of different optical density,[63] which has been described in terms of "layered plaque". Representative images of layered plaque are shown in Figure 4.

The clinical significance of healed plaque remains unclear and continues to be controversial.[64,65] One recent study reported that healed plaque was found to be infrequent in patients with a history of multiple recurrences of ACS compared with that in patients with long-term CAD stability. These findings suggest that healed plaque is a representative marker of long-term clinical stability.[66] In other studies, healed plaque has been found to be a predictor of subsequent rapid plaque progression,[67] and patients with healed plaque in the culprit vessel had a higher incidence of revascularization than patients without healed plaque.[68] These results suggest that plaque healing may protect patients from ACS, and also may lead to stenotic plaque progression without acute events.[66,68]

Serial OCT observation of thrombus on disrupted plaques showed that the smooth contours of the layered appearance were blurred and that the healed plaque was integrated into the preexisting plaque.[69] In a pathological analysis of patients who had experienced sudden death due to CAD, most thrombi on disrupted plaques were in varied phases of healing.[11] However, in another OCT study of patients with ACS, < 30% of patients had healed plaque at the culprit lesion.[64] Distinguishing fresh thrombi from old thrombi is often challenging using OCT, and the appearance of healed plaque may change depending on the time elapsed from disruption. Further studies are required to improve the methods for detecting healed plaque and clarify how intervention should be undertaken in patients with healed plaque.

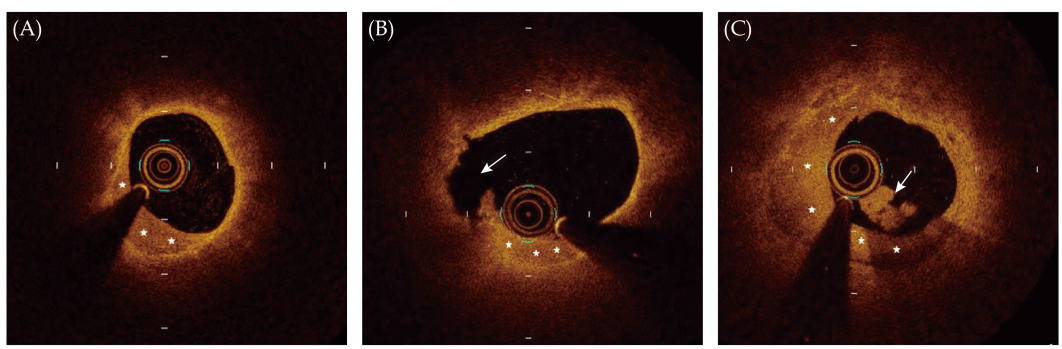

Figure 4 Representative OCT images of the layered plaque. (A): Layered plaque: a layer with different optical density is evident in the lower left section of the vessel between 5 and 9 on a clock face (white stars); (B): layered plaque is evident in the lowest section between 5 and 7 on a clock face (white stars), next to the ruptured plaque (white arrow); (C): layered plaque is evident in most of the lower and left sides between 4 and 12 on a clock face in plaque erosion (white stars), with a white thrombus (white arrow). OCT; optical coherence tomography.

CONCLUSION

It remains difficult to precisely detect even the main vulnerable plaque that might lead to plaque rupture in the near future. Additionally, it is currently not possible to predict thrombus formation on eroded plaque, and plaque healing. Thrombogenicity and/or fibrinolysis not only of plaque but also of circulating blood may affect thrombus formation on eroded plaque and the healing process of disrupted plaque. Due to limitations concerning current intravascular imaging, in addition to challenges in assessing vulnerable plaque, circulating blood needs to be studied in greater detail for an enhanced understanding of CAD.

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