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【 CASE REPORT 】

Acute Coronary Syndrome Due to Intraplaque Hemorrhage in a Post-gastrectomy Patient with a Latent Severe Glycemic Disorder

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Abstract:
Glycemic disorders involving large glucose fluctuations and recurrent hypoglycemia may lead to adverse cardiovascular events, including acute coronary syndrome (ACS). Flash glucose monitoring (FGM) has reportedly been useful for detecting latent glycemic disorders. However, only a few studies have so far reported latent glycemic disorders in coronary artery disease. Thus, we herein present a unique case of ACS due to intraplaque hemorrhage in a post-gastrectomy patient who had no apparent coronary risk, except for a latent severe glycemic disorder detected via FGM. This masked etiology should be considered in ACS patients who have no apparent cardiovascular risks in order to improve their cardiovascular outcomes.

Key words: acute coronary syndrome, directional coronary atherectomy, flush glucose monitoring, glucose fluctuation, hypoglycemia, intraplaque hemorrhage

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Introduction

Glycemic disorders with large glucose fluctuations (GFs) and recurrent hypoglycemia are reportedly among the residual cardiovascular risk factors, even after optimal interventions, including lipid-lowering therapy for dyslipidemia (1, 2). It has recently been reported that continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) methods could be used to provide daily glucose profiles (3). Several studies have so far investigated the association between coronary plaque characteristics on intracoronary imaging and the daily glucose profile by CGM. They demonstrated that large GFs with hypoglycemia were significantly associated with the prevalence of vulnerable coronary plaques, regardless of whether the patient had acute coronary syndrome (ACS) or chronic coronary syndrome (4, 5). However, the histopathological perspective of these relationships has not yet been investigated thoroughly due to the difficulty in collecting atheroma samples.

Directional coronary atherectomy (DCA) is a unique transcatheter technique used to collect *in vivo* coronary plaques during percutaneous coronary intervention (PCI). Recently, an improved novel DCA catheter (Atherocut™, NIPRO, Osaka, Japan) has become commercially available in Japan, while a combined therapy, including DCA and subsequent drug-coated balloon (DCB) angioplasty, has been reported to be effective for achieving complete revascularization with stent-less PCI. The effectiveness of this approach is attributable to the advantages provided by DCA and DCBs in reducing plaque volume and also in suppressing post-PCI neointimal proliferation, respectively (6, 7).

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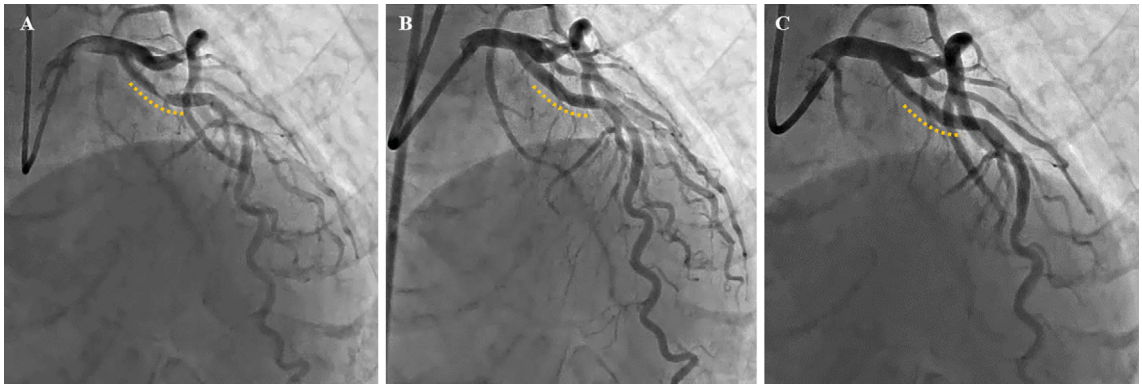

Figure 1. **The initial coronary angiogram (A) obtained from the patient showed severe stenosis in the proximal left anterior descending artery, which resolved after administering combination treatment consisting of directional coronary atherectomy and balloon angioplasty (B). A coronary angiogram taken 8 months after treatment (C) showed no stenosis in the treated legion.**

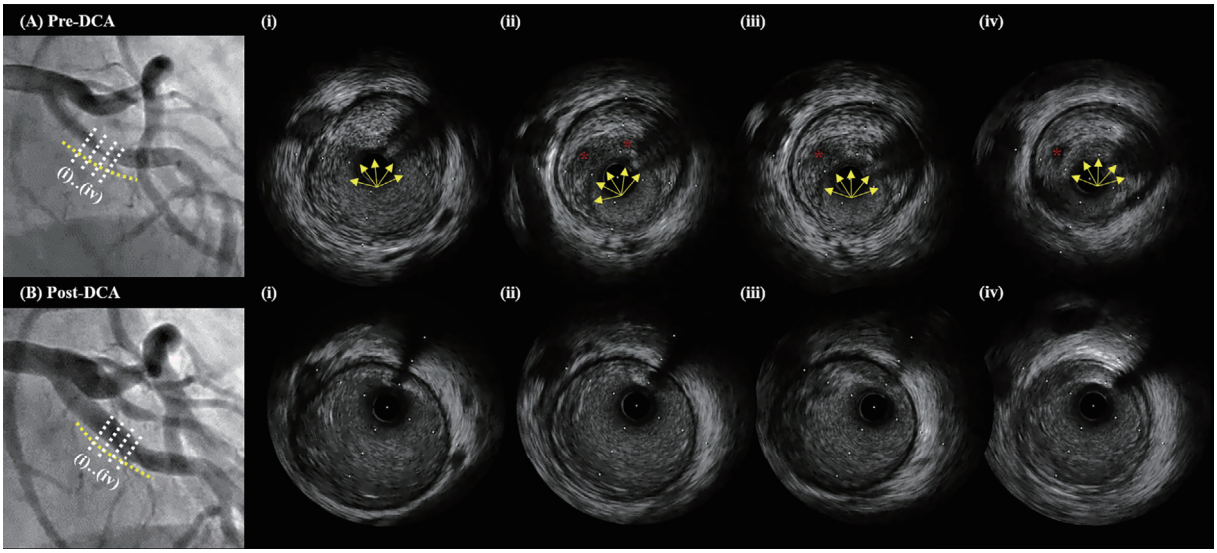

Figure 2. **Comparison of the intravascular ultrasound (IVUS) images in the culprit lesion between (A) pre-directional coronary atherectomy (DCA) and (B) post-DCA. The red asterisks indicate intraplaque hemorrhage. The plaque region resected by DCA was indicated by yellow arrows in the initial IVUS images.**

We herein present a unique case of ACS [unstable angina pectoris (UAP)], which was caused by histopathologically confirmed intraplaque hemorrhage (IPH) in a non-diabetic patient who had no cardiovascular risks except for a latent severe glycemic disorder, which was detected via FGM.

Case Report

A 65-year-old non-obese male patient without any apparent conventional cardiovascular risks and with no history of cardiovascular events presented with intermittent chest discomfort, which radiated to the neck bilaterally during the night and at post-prandial periods for 1 week prior to admission. The patient had a history of distal gastrectomy with Billroth I reconstruction (subtotal gastrectomy involving more than two thirds of the stomach) for gastric cancer more than 1 year prior to admission. There were no ischemic findings on exercise stress electrocardiography (ECG). On arrival to our emergency department, the ECG findings showed an inverted T-wave in leads V1-V3. Moreover, his laboratory results showed a slight elevation in the troponin-T level (0.024 ng/mL; normal range: <0.016 ng/dL). Based on the abovementioned findings, ACS was suspected. Subsequent coronary angiography (CAG) was performed, which confirmed severe stenosis in the proximal left anterior descending artery (LAD). Therefore, intravascular ultrasound (IVUS)-guided PCI was performed for the proximal LAD stenosis (Fig. 1A). IVUS showed that the culprit lesion consisted of non-lipidic plaque, including a superficial crescent-shaped echolucent region (Fig. 2A). DCA using Atherocut™ type L (NIPRO) was performed in four sessions with eight total cuts (the maximum cutting pressure: 4 atm), because it was suitable for this focal stenosis in the proximal LAD. IVUS post-DCA showed the coronary

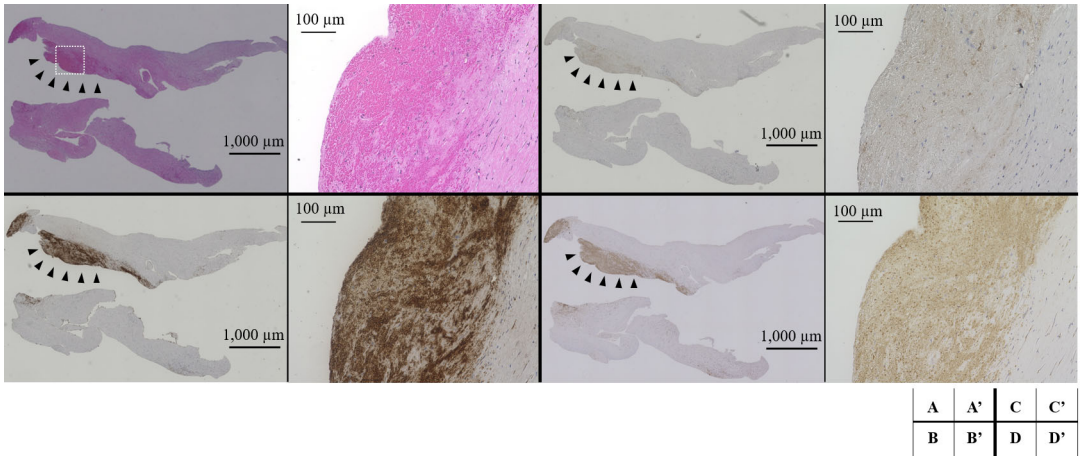

Figure 3. Histopathological findings of the specimens, including low-power images (A-D) and high-power images (A'-D') of the dotted box in the low-power images of Hematoxylin and Eosin staining, glycophorin-A staining, CD68 immunostaining, and immunostaining of matrix metalloproteinase-9 (MMP-9). The intense staining of glycophorin-A suggested the presence of intraplaque hemorrhage. Moreover, a large number of CD68-positive cells with MMP-9 expression was observed in the culprit plaque. The arrowheads in the low-power images indicate intraplaque hemorrhage, which is magnified in the high-power images.

plaque volume to significantly decrease from 89% to 43% (Fig. 2B). Additional balloon angioplasty with a scoring balloon 3.5/13 mm (Lacrosse NSE, NIPRO) enabled the elimination of the additional implantation of a stent scaffold. Although the usage of a DCB for large vessels was still off-label, a subsequent DCB 4.0/20 mm (SeQuent Please, paclitaxel-coated balloon, B. Braun, Melsungen, Germany) angioplasty was performed, which achieved an optimal result without any major coronary dissection nor coronary flow disturbance (Fig. 1B). Thereafter, a histopathological evaluation of samples obtained with DCA using glycophorin-A, CD68, and matrix metalloproteinase-9 (MMP-9) staining was performed, which showed that the culprit plaque included IPH (intense staining of glycophorin-A) with strong inflammation (CD68-positive cell with MMP-9 expression). These findings revealed that the culprit lesion consisted of IPH with macrophage accumulation and concomitant inflammatory cytokine activation within the fibrous tissue. These findings therefore indicated the presence of a vulnerable plaque (Fig. 3).

The patient was free from chest discomfort after the PCI and had an uneventful course thereafter. Although the patient had no typical hypoglycemic symptoms, we evaluated the patient's daily glycemic profile via FGM, which confirmed extremely large GFs (mean amplitude of glycemic excursion: 121.8 mg/dL) and asymptomatic hypoglycemia both post-meal and during middle of the night measurements (a latent severe glycemic disorder) (Fig. 4). These abnormal findings retrospectively suggested that the patient's chest discomfort before PCI was concordant with the timing of these glycemic disorders. Thereafter, the patient was treated with nutritional therapy for asymptomatic dumping syndrome. A follow-up CAG 8 months after the PCI showed no restenosis in the treated lesion (Fig. 1C). No further cardiovascular events, including ischemia-driven target lesion revascularization, were observed for more than 1 year.

The study was approved by the ethics review board of Hyogo Brain and Heart Center (No. 0212). Written informed consent for participation in this study and for the publication of this case along with the accompanying images were obtained from the patient.

Discussion

The main etiologies of ACS are plaque rupture, erosion, and calcified nodules (8). Additionally, IPH, associated with rapidly developing luminal narrowing, has also been reported to be a potential cause of ACS (9). To the best of our knowledge, this report is the first to demonstrate a unique case of ACS (UAP) due to IPH in a post-gastrectomy patient without any apparent conventional cardiovascular risks, who was diagnosed with a latent severe glycemic disorder upon evaluation via FGM.

Dumping syndrome is a well-known post-gastrectomy syndrome resulting in hypoglycemia following meal-induced hyperglycemia. A CGM system is useful for detecting asymptomatic hypoglycemia in post-gastrectomy patients (10). Hypoglycemia can lead to the activation of the sympathoadrenal system, causing the profuse secretion of catecholamines that exert profound hemodynamic effects, which, in turn, can result in the progression of atherosclerosis and an increased risk of cardiovascular events and mortality (11, 12). Moreover, large GFs are also associated with a poor cardiovascular prognosis in patients with coronary artery disease (2). Retrospectively, considering that the patient had chest discomfort during mid-night and post-prandial periods before PCI, myocardial ischemia via sympathetic neural activity might have been induced in accordance with the

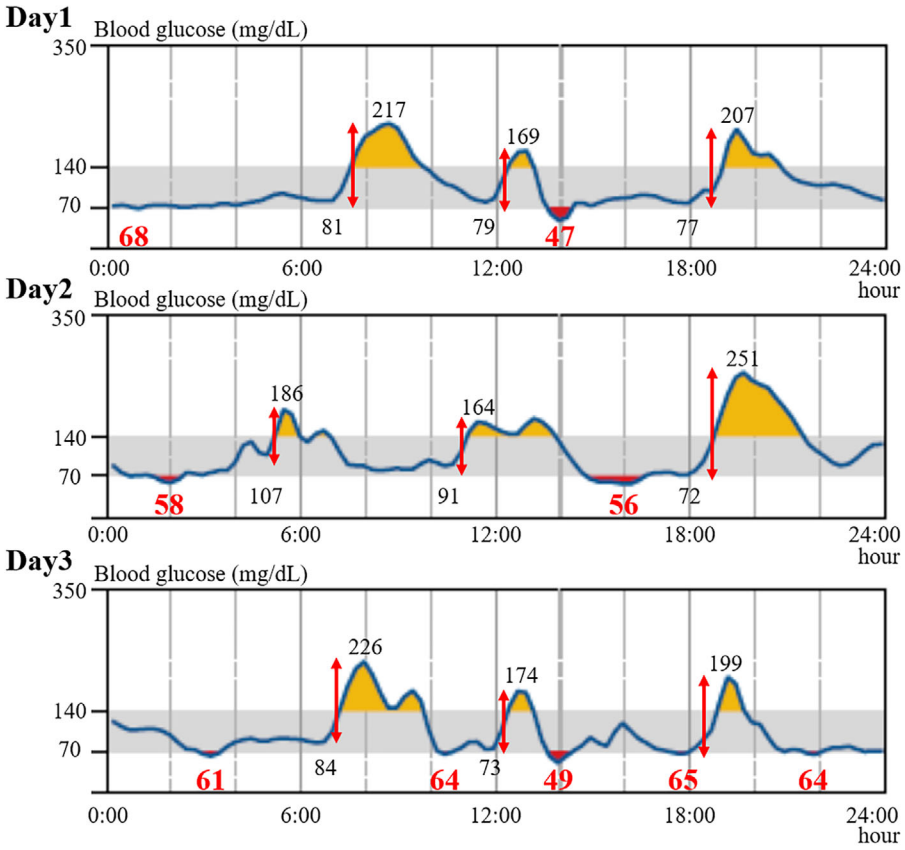

Figure 4. A flash glucose monitoring system showed large glucose fluctuations and asymptomatic hypoglycemia.

timing of asymptomatic hypoglycemia. Furthermore, considering that the patient had no ischemia before gastrectomy, the newly developed glycemic disorders could potentially be associated with coronary plaque progression, which then resulted in ACS. Since these glycemic disorders may be latent, especially in ACS patients without any apparent cardiovascular risks, careful attention should be paid to this latent etiology. For patients with glycemic disorder but without diabetes, nutritional therapy is recommended. Moreover, several randomized trials have suggested that early intervention for impaired glucose tolerance with medications, such as alfa-glucosidase inhibitors or dipeptidyl peptidase-4 inhibitor, for decreasing post-prandial hyperglycemia, may improve both plaque stability and hypoglycemia (13, 14). Future large-scale clinical trials to determine whether early intervention for glycemic disorder may improve the cardiovascular outcomes should therefore be conducted.

IPH is reportedly caused by angiogenesis via the activation of the vascular endothelial growth factor, which is more frequently observed in patients with glycemic disorders (15, 16). In this case, a histopathological evaluation confirmed that the culprit plaque mainly consisted of IPH in fibrous tissue with less lipid-rich components. Moreover, IPH included a large number of macrophages with inflammatory cytokine production, which suggested the development of vulnerable plaques. Recent *in vivo* research on animal models has demonstrated that macrophage-derived MMP-9 enhanced the progression of atherosclerosis (17). Our case supports that the presence of vulnerable plaques due to IPH with macrophage-derived MMP-9 has a strong association with ACS in a patient with latent glycemic disorder. Further investigations into the association between latent glycemic disorders and IPH-induced ACS in non-diabetic patients are warranted.

Although these findings suggested that latent glycemic disorders might contribute to the onset of IPH-induced ACS, the present case report was nevertheless associated with several limitations and speculations. It was difficult to precisely identify the cause of IPH and the impact of latent glycemic disorder on IPH due to the characteristics of the case report. The reasons why the culprit lesion consisted of fibrous plaques containing IPH rather than conventional vulnerable plaques containing lipid-rich atheromatous components were as follows: 1) the patient had no history of dyslipidemia and originally had a low level of low-density lipoprotein-cholesterol (51 mg/dL); 2) the duration for hypoglycemia/hyperglycemia in asymptomatic dumping syndrome was short compared with that in common type 2 diabetes mellitus. Although large GFs might be associated with plaque progression via an accelerating degree of endothelial dysfunction, these factors might have influenced the plaque characteristics in this case (18).

Finally, we recommend that ACS patients should be carefully screened for this masked etiology to improve future

cardiovascular outcomes.

The authors state that they have no Conflict of Interest (COI).

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