Case Report

Atheroma and Coronary Artery Spasm

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Keywords : Coronary vasospasm, ventricular fibrillation arrest, exercise induced ST segment elevation, atheroma, intravascular image study

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Received June 20, 2013.
Revision received July 5, 2013.
accepted after revision July 16, 2013.
Bangkok Med J 2013;6:30-36.
E-journal: http//www.bangkokmedjournal.com

Case Report # 1

A 47-year-old man, a heavy smoker, developed chest pain in the morning. A few minutes before arrival at our center, he collapsed in the taxi. Ventricular fibrillation (VF) was documented at the emergency room. After successful cardiopulmonary resuscitation (CPR), Electrocardiogram (ECG) showed inferior ST segment elevation (STE) so he was transferred to the cardiac catheterization laboratory. Coronary angiogram showed no significant lesion in the left main (LM), anterior descending (LAD) and circumflex (Cx) arteries. The dominant right coronary artery (RCA) had a severe vasospam (> 90% luminal diameter stenosis) in the proximal part (Figure-1A). After administration of intracoronary nitroglycerine (NTG) 300 mcg, the vasospasm disappeared (Figure 1B). The lumen of RCA was enlarged and the smooth border was suggestive of insignificant plaque burden. The inferior ST elevation pattern was also normalized without Q wave. He was pain free and discharged home on aspirin and calcium antagonist. He did well but later discontinued follow-up.

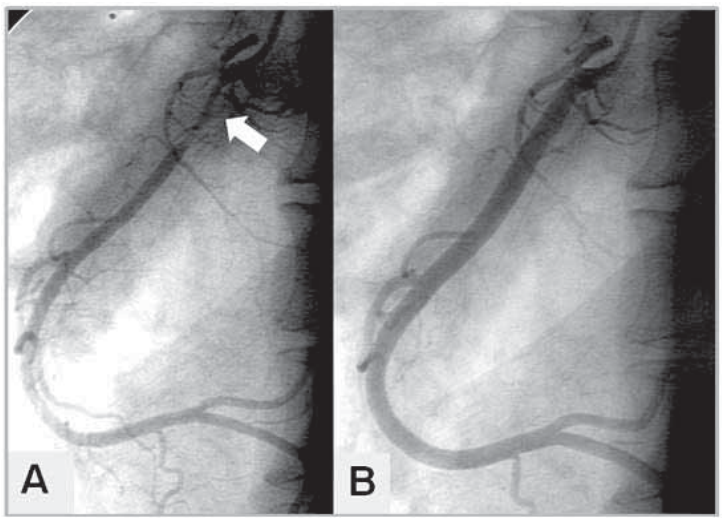

Figure 1: *A. Coronary angiogram of the right coronary artery (RCA) showed severe spasm of proximal part (white arrow). B. After administration of nitroglycerine, vasospasm disappeared. The smooth, enlarged RCA angiogram suggested no significant plaque burden.*

ISSN 2287-0237 (online)/ 2287-9674 (print)

Case Report # 2

A 54-year-old man experienced crescendo angina for a month. Chest pain started every morning, right after minimal exertion, and lasted three minutes. His known coronary risk factors included impaired fasting glucose, untreated dyslipidemia (LDL-cholesterol of 170 mg/dl) and hypertension. He had stopped smoking cigarettes 10 years before and did not use any illicit drugs.

The physical examination was unremarkable, BP was 122/88 mmHg, HR was 72 beats per minutes. Baseline ECG showed a normal sinus rhythm without ST-T changes. The echocardiogram revealed mild concentric left ventricular hypertrophy with well-preserved systolic function, ejection fraction of 0.55. Trace mitral regurgitation and mild diastolic dysfunction (grade 1) were also observed.

The Bruce protocol exercise stress test was performed. After walking three minutes, chest pain occurred. It was associated with 2-3 mm ST segment elevation (STE) in leads V1-3, aVR and 2 mm ST depression in leads II,III,F (Figure 2). These findings suggested a critical stenosis in at least one or more major coronary arteries.

A coronary angiography was then performed and showed no significant lesion in the LM trunk, Cx and RCA. There was a modest lesion (50-60% luminal stenosis) in the mid part of the LAD artery at the origin of an unobstructed diagonal branch. The lumen of mid-distal LAD artery was rather small (Figure 3A).

Since this moderate lesion could not entirely explain an ischemic exercise response at low workload, we decided to assess the functional status of this lesion. A pressure wire (St. Jude Medical Company) was passed across the lesion into the distal LAD artery. After obtaining maximal hyperemia by an intracoronary injection of Adenosine 60 cc, the measured fractional flow reserved (FFR) was in the borderline normal zone, 0.76. However, after intracoronary administration of NTG 400 mcg, FFR increased to the normal range, 0.89-0.92, therefore coronary intervention was deferred. The repeat angiogram showed a significantly enlarged luminal diameter of the whole LAD artery (Figure 3B-C) suggestive of coronary vasospasm. The mid LAD lesion persisted in the range of 50% luminal stenosis.

To study the patho-anatomy of atheromatous plaque, we examined this lesion with intravascular ultrasound (IVUS) catheter (Eagle Eye Gold, Volcano Cooperation, US). Despite the normal appearing angiogram, crescentic plaques were noted in the left main (Figure 4A) and proximal LAD (Figure 4B) arteries with an area stenosis of 30% and 54.9% respectively. The mid LAD lesion had an elliptical lumen surrounded by fibro-lipid plaque causing an area stenosis of 55.6 - 67% (Figure 4C-E). There was no significant atheroma observed in the distal LAD segment (Figure 4F). All of these findings suggested a non-hemodynamic significant plaque burden so medical treatment was administered with verapamil SR 240 mg, aspirin (300 mg/day), clopidogrel (75 mg/day) and simvastatin (40 mg/day).

After treatment, the patient had no more pain and was able to walk around as usual. The repeat exercise test after two weeks of medication showed no inducible ischemia. He walked through 9 minutes (10 mets) on standard Bruce protocol with a maximal heart rate of 130 bpm (80% of age predicted maximal heart rate), a maximal BP of 160/79 mmHg. There was no significant ST elevation observed as shown in Figure 5.

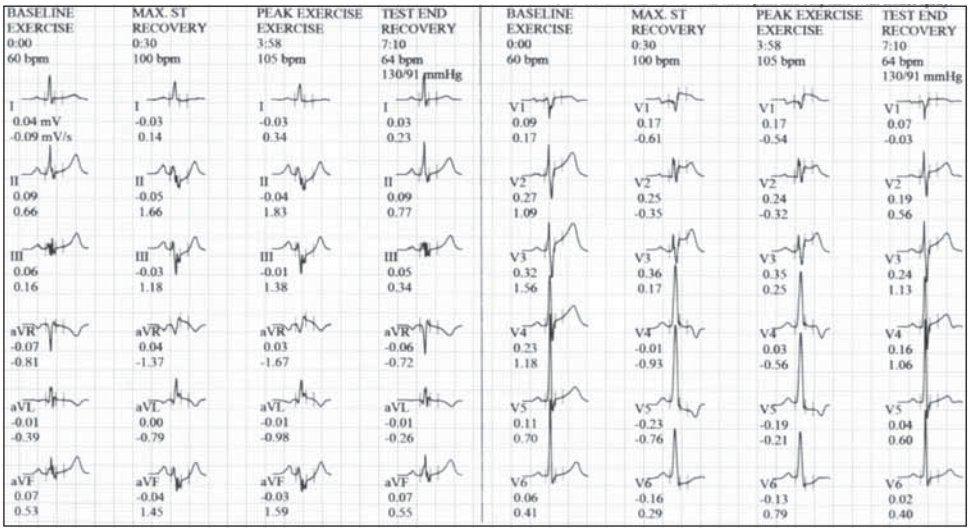

Figure 2: *ST segment elevation in leads V1-3, aVL , aVR and ST depression in leads II, III, aVF, V4-6 were documented during chest pain after exercise for 3 minutes. The maximal heart rate was only 105 bpm. His angina and ST deviation disappeared within 4 minutes.*

ISSN 2287-0237 (online)/ 2287-9674 (print)

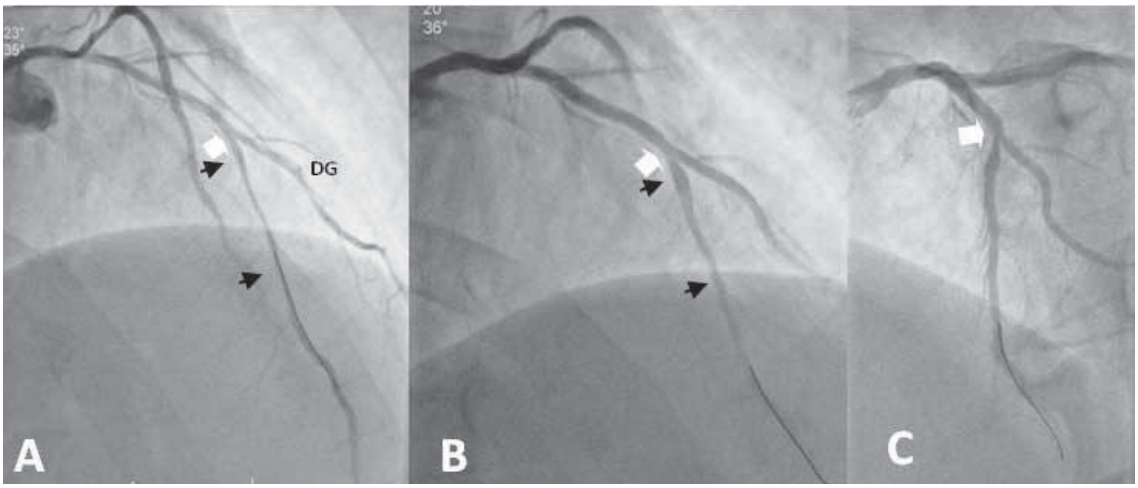

Figure 3: *A: The left coronary angiogram revealed a moderate lesion localized in the mid LAD segment (white arrow, A-C), close to the origin of an unobstructed diagonal branch (DG). The mid LAD segment had diffuse severe stenosis (black arrow).*
B-C: After administration of intra-coronary nitroglycerine, the whole LAD diameter was enlarged but the mid LAD lesion (black arrow) remained in 50-60% diameter stenosis (white arrow B,C). FFR, performed after intracoronary administration of adenosine 60 cc and 400 microgram of NTG, was in the normal range, 0.89-0.95, indicative of a non-hemodynamic significant lesion, so coronary intervention was deferred.

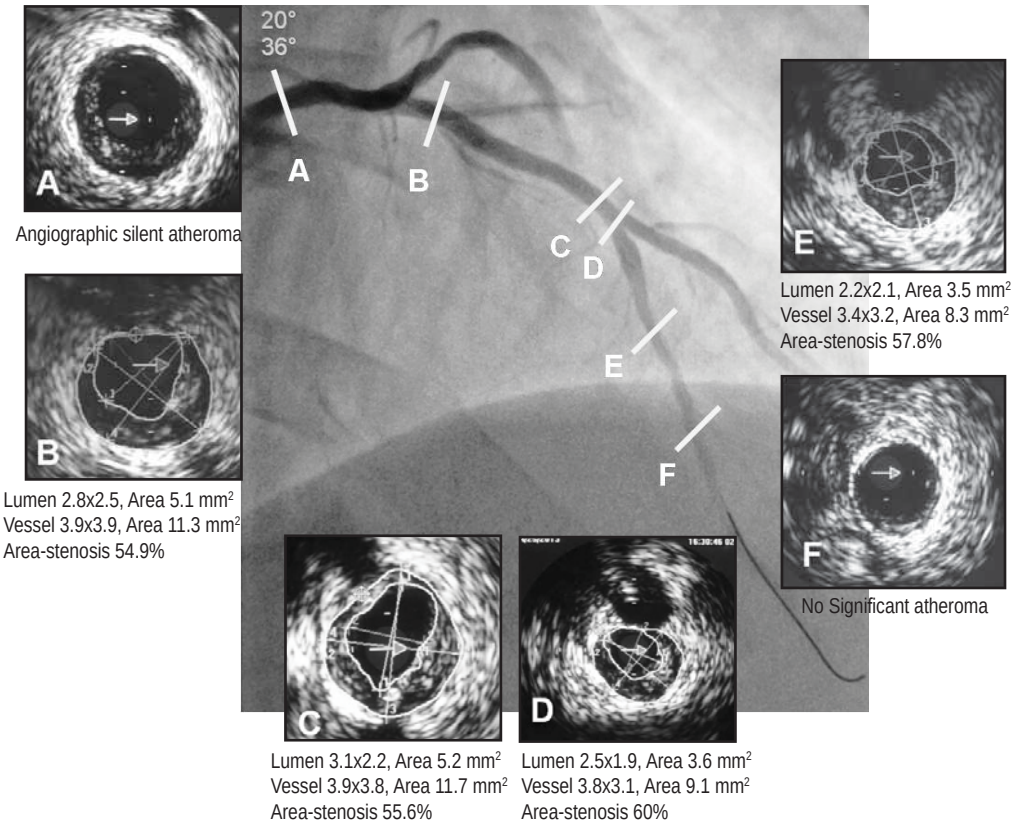

Figure 4: *Intravascular ultrasound imaging showed an angiographic silent atheroma from 2 to 12 o'clock in the left main, (A) and proximal LAD artery (B). At the mid LAD segment, the lumen (arrow sign) shape was elliptical since it was surrounded by an eccentric fibro-lipid atheroma, causing an area stenosis of 55.6% and 60% (C &D). Similar lesion was observed along the vaso-spastic segment (E). However, there was no significant plaque burden in the distal LAD (F).*

ISSN 2287-0237 (online)/ 2287-9674 (print)

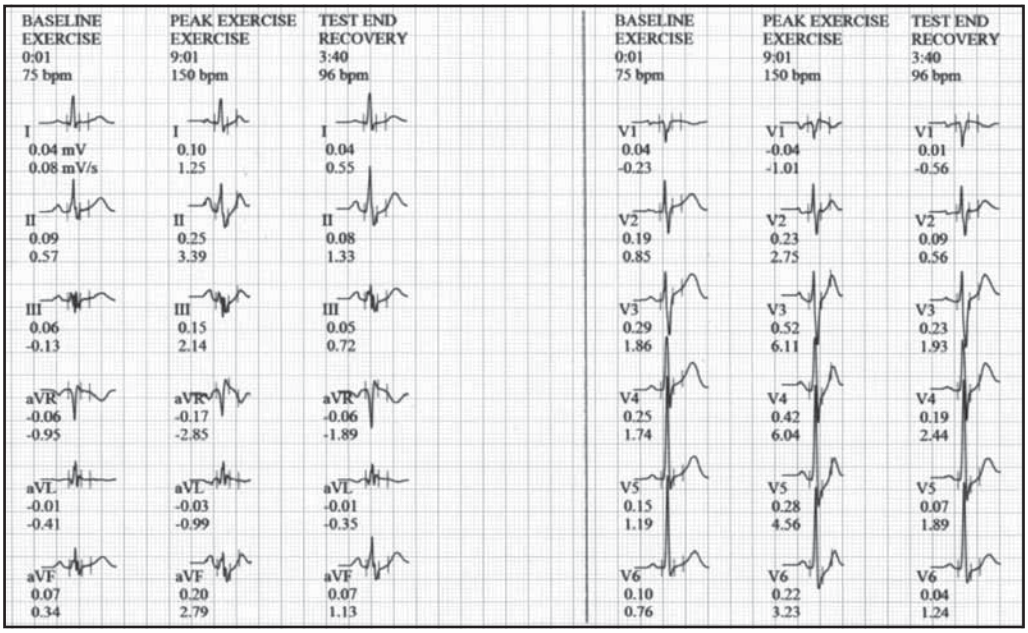

Figure 5: *After administration of slow release verapamil 240 mg for two weeks, the repeat exercise stress test showed no reproducible chest pain after walking 9 minutes on Bruce protocol (10 mets achieved). There was mild STE in aVR and J point ST depression in leads V4-6 and II, aVF but the patient had no symptoms.*

Discussion

Spectrum of coronary artery spasm

Coronary artery spasm or coronary vasospasm is defined as a transient abnormal vasoconstriction of one or more epicardial coronary arteries which results in compromising coronary blood flow and myocardial ischemia. The clinical spectrum largely depends on the degree of coronary spasm, for example in complete arterial occlusion cases, transmural myocardial ischemia, myocardial infarction (MI) and ST segment elevation (STE) would be expected.[1] If occlusion was incomplete, then patient might have angina from subendocardial ischemia and display ST depression[1]. Historically, Prinzmetal and colleagues were the first group who linked rest angina and spontaneous STE in 1959.[2] In 1962, the angiographic evidence of reversible coronary spasm was delineated by Gensini and colleagues in one patient during an angina attack as well as in animal studies.[3] In general, coronary spasm could occur either spontaneously[1-3] or after exposure to various active substances such as cocaine, marijuana, amphetamine, alcohol, anti-migraine, chemotherapeutic agents and antibiotics.[4-8] During coronary intervention, vasospasm was found in 1-5%[9] and, on rare occasions, has led to cardiogenic shock.[10] Currently, spontaneous coronary vasospasm is widely recognized as a potential cause of acute coronary syndrome (ACS) i.e. unstable angina, STE MI, non-STE-MI,[11,12] exertional angina,[13] silent myocardial ischemia with life-threatening ventricular arrhythmias,[14] advanced AV block and sudden cardiac death.[1,15,16] Although the underlying mechanism remains unclear, a recent study suggested that hyper-reactivity of the smooth muscle cell might be the pathogenic basis of coronary vasospasm.[9,18] The role of post-receptor alterations, gene mutations, autonomic triggers and vasoconstrictive stimuli has been extensively reviewed by Lanza GA and colleagues.[18] The prevalence of coronary vasospasm in the Japanese population is higher than in westerners and genetic factors are involved. For example, polymorphism of the gene associated with endothelium nitric oxide synthase (e-NOS) has been reported.[1,9,18]

Clinical presentation and risk profile

Like formerly reported cases,[14,15] the first patient presented with VF arrest on arrival. After successful defibrillation, transient inferior STE was documented before catheterization. Spasm of proximal RCA disappeared after intra-coronary administration of NTG and the RCA angiogram was completely normal (Figure 1B-C). Thus spontaneous coronary vasospasm was likely the cause of ischemic VF arrest in this particular case. In addition, smoking was the only risk he had and is a well recognized risk factor in the majority of vasospastic cases.[1,19-21] McKenna et al studied 10 cases of young (< 40 years) myocardial infarction (MI) victims who had normal coronary angiograms.[19] Interestingly, they found only one associated risk factor, heavy cigarette smoking. Sugiishi and Fumimaro compared all risk factors of 175 proven coronary spasm cases who had

ISSN 2287-0237 (online)/ 2287-9674 (print)

near normal angiogram (< 25% diameter stenosis) with the control group, comprising 176 non-vasospasm cases with normal angiogram[20]. Again, cigarette smoking was the only significant associated risk factor with the odd ratio (by multivariate logistic regression analysis) of 2.41 (95%CI = 1.5-3.8, $p < 0.05$).[20] How smoking contributed to vasospasm in the non-significant coronary stenosis was not entirely clear. Several vasoactive substances in cigarettes, such as nicotine and carbon monoxide, potentially produce lipid peroxidation products causing low grade inflammation, pro-thrombotic states and smooth muscle cell spasm.[22] In fact, high levels of inflammatory marker, C-reactive protein, has been reported in vasospastic cases during the active phase,[23] therefore, smoking cessation is mandatory.

In contrast, the second patient presented with unstable angina (increased frequency of attack on minimal exertion) which was also the common manifestation in coronary spasm cases.[1,9,12] Although he had quit smoking for more than ten years, he had all other known major coronary risk profiles: impaired fasting glucose, hypertension and a high LDL cholesterol level. Thus, it was not surprising that he had diffuse atheroma with area stenosis of 30-60%, starting from the left main to mid LAD arteries (Figure 4A-E). Similar findings were observed in McKenna's report: 30 young MI cases with obstructive coronary angiograms also had multiple risk factors.[19]

Vasospasm and lesion severity

Recent studies have focused on the hypersensitive vascular smooth muscle as a basic common mechanism in vaso-spastic cases.[17,18] While the vascular smooth muscle was scarcely left in advanced atheroma,[24] it was better preserved in mild to moderate atherosclerotic lession as reflected by mild to moderate (< 50%) stenosis or even near normal angiograms. Therefore, it was likely possible that these types of lesions (normal or no disease segment) might be the main site of the vasospasm. There was some direct and indirect evidence from both angiographic and necropsy studies to support this hypothesis. Firstly, the prevalence of acute MI victims with a normal coronary artery (by means of coronary angiographic study, necropsy or both) increased from 4-7% in the general population to almost four times in younger patients.[24-26] It suggested that either coronary spasm or other non-atherosclerotic disease could be the cause of MI in the young. Second, Ong and colleagues studied ACS patients and found that 30% of rest angina patients had a non-obstructive coronary angiogram. Nearly half of this particular group had abnormal vasoconstriction by acetylcholine test.[12] Third, in a necropsy study of 10 fatal myocardial infarction (MI) cases by Elliot et al, 60% of them had no coronary artery stenosis and the rest had only mild to moderate (< 50%) stenotic lesions.[25] In addition, McKenna et al described two fatal MI cases from coronary thrombosis in whom no atheromatous disease was found.[19] Fourth, the link between coronary spasm and subsequent thrombosis was reported in one post-mortem case and other two angiographic studies by Maseri and colleagues.[27] Recently, Reynolds et al studied multi-modalities of cardiac imaging in MI women who had non-obstructive lesions (< 50% diameter stenosis by angiogram). Half of the patients had either normal (30%) or minimal lesions (median diameter stenosis of only 20%) on angiogram. By intravascular ultrasound study (IVUS) imaging, plaque disruption was detected in 38% of the study group.[28] Although our first patient did not have an IVUS examination, it was less likely that he would have significant atheroma as evidenced by his absolutely normal angiogram. In addition, the distal LAD segment of our second case, which also contributed to vasospasm (Figure 3A), was free of atheroma by IVUS, (Figure 4F). All of this evidence suggests that severe fatal coronary spasm required an active muscle cell located in the non-obstructive lesion where the vascular media was well preserved. Severe vasospasm could lead to plaque rupture and fatal coronary thrombosis.

Vasospasm and more advanced atheroma

To study lesion characteristics requires more sophisticated tools than the angiogram, which reflects only the silhouette of contrast filling lumen, so-called luminogram. In fact, the angiogram provides no detail of the arterial wall where the atheroma originated. In contrast, IVUS imaging delineates the cross sectional anatomy of the arterial lumen and its wall component. Thus, in angiographically normal segments, like in the LM and proximal LAD artery of the second case, the silent atheroma was depicted by IVUS images, (Figure 4A-B). By IVUS imaging, various stages of atheroma had been shown at the site of the vasospasm.[1] In contrast to minimal lesions, more advanced atheroma have been reported in fatal vasospastic cases.[16,29,30] As shown in the mid LAD of our second patient (Figure 4D-E), the more advanced atherosclerotic plaques after bifurcation were mostly eccentric in distribution (lumen was out of center).[29,30] In necropsy cases, the disease-free segment (opposite to the plaque) was observed between 2.3 - 32% and vascular media in this segment remained intact.[30] Since the media behind the advanced atherosclerotic wall was thin or absent, it has been postulated that this spared segment might be the responsible site of vasospasm in this type of lesion.[29, 30] How the plaque severity contributes to various degrees of vasospasm remains unknown at the present time and further study is mandatory.

Another way to assess functional severity of the stenotic lesion is by measuring blood flow within the coronary artery by Fractional Flow Reserve (FFR) technique. FFR refers to the proportion of achievable blood flow through the stenotic lesion at baseline compared with the flow during maximal hyperemia.[31] Since the resistant vessels were maximally a dilated, the flow and pressure were well-correlated in a linear curve. This technique had been clinically validated in functional assessments of intermediate coronary lesions and the acceptable ratio was 0.75-0.80.[32] In a DEFER study,

ISSN 2287-0237 (online)/ 2287-9674 (print)

coronary disease patients who had a FFR > 0.75 had the same rate of cardiac death or acute MI between the medical therapy group and the coronary intervention arm.[32] Owing to the normal FFR, 0.76 (baseline) and 0.92 (after adenosine and NTG), coronary intervention was then deferred.

Therapeutic options

The prevention of angina attacks with calcium antagonists and long-acting nitrates has been well established in coronary vasospasm cases[1,9] and both patients responded well to slow release Verapamil. After two weeks of treatment, the second patient walked through 9 minutes (10 mets) without chest pain or STE. Smoking cessation and control of all risk factors were mandatory in all cases[1,9] Lowering cholesterol with statin has been favorably reported in vasospastic cases after withdrawal of the calcium antagonist.[33] Aspirin must be continued to reduce thromboxane A2 production from activated platelets.[9,34] Deficiency of magnesium[1,35] and vitamin E[36-38] had been reported in vasospasm cases and replacement of both agents were recommended in Japanese guidelines.[1] Infrequently, alcohol could induce vasospastic angina but the mechanism remained unknown.[5] It is postulated that alcohol might induce dieresis and magnesium loss, so in this particular case, alcohol restriction is mandatory.[1] In medically refractory vasospasm, coronary stent implantation[39] and coronary bypass graft surgery[40] has been performed with favorable outcomes. In aborted VF victims, the implant of a cardiovertor defibrillator had effectively prevented recurrent sudden cardiac death.[41]

Conclusion

We reported two coronary vasospasm cases with different clinical manifestations, one with VF arrest and another with unstable angina. The correlative pathology and vasospasm were discussed. Severe intense spasm was likely occur in patients who had minor disease or a normal coronary artery, like the first case. The relative young age and cigarette smoking were quite common in this group. In more advanced atheroma, less functional vascular media was left behind so it was postulated that the disease-free segment might be the site of the vasoactive spasm. This latter group, as represented by our second case, was older and had multiple risk factors. Both cases responded well to long-acting calcium antagonist. To date, it remains unclear how the different types of atheromatous plaque contribute to vasospasm. Thus, further study is mandatory.

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ISSN 2287-0237 (online)/ 2287-9674 (print)