Coronary Aneurysm Formation After Bioresorbable Vascular Scaffold Implantation Resulting in Acute Myocardial Infarction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient:	**Male, 62**
Final Diagnosis:	**Non-ST elevation myocardial infarction secondary to coronary aneurysm formation after BVS implantation**
Symptoms:	**Chest pain • diaphoresis**
Medication:	**—**
Clinical Procedure:	**Angioplasty and stenting**
Specialty:	**Cardiology**

Objective: Rare disease

Background: Development of a true coronary aneurysm after percutaneous coronary intervention is a rare event, and a coronary aneurysm resulting in acute myocardial infarction is even rarer. Coronary aneurysm formation after bioresorbable vascular scaffold (BVS) implantation, eventually leading to thrombosis, embolization, and myocardial infarction, has never been reported before in the literature.

Case Report: A 62-year-old man received an elective BVS for a proximal left anterior descending lesion. Two months later, he suffered from a non-ST-segment myocardial infarction. Coronary angiography showed a non-significant distal stent edge restenosis over the left anterior descending artery and a small aneurysm after the first diagonal branch. A XIENCE Xpedition stent was used to cover both lesions and final angiography showed shrinkage of the aneurysm and resolution of the restenosis.

Conclusions: Since a consensus or an established treatment guideline for treating coronary aneurysms is currently lacking, each case should be treated with caution and should be guided by the accompanying circumstances presented during the procedure. Although size, rapidity of growth, and the presence of high-risk features are the main determinants of whether to treat the lesion, the inherent risk of restenosis or reocclusion after use of drug-eluting stents and the coronary intervention procedure itself should also be taken into consideration. However, one must not take lightly a small coronary aneurysm when discovered, as the abnormal fluid dynamics inside may result in thrombus formation and embolization. The fundamental technical aspects of stent deployment, such as avoiding overstretching during lesion preparation, use of balloons shorter than the implanted device, and normal-to-normal or healthy "landing zone" of the device, should be followed.

MeSH Keywords: Coronary Aneurysm • Drug-Eluting Stents • Myocardial Infarction

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Background

The bioresorbable vascular scaffold (BVS) system (Absorb, Abbott Vascular, Santa Clara, CA) is a balloon-expandable device consisting of a polymer backbone of poly-L-lactide coated with a thin layer of a 1: 1 mixture of poly-D,L-lactide. The polymer controls the release of everolimus and forms an amorphous drug-eluting coating matrix that contains 100 µg of everolimus/cm^2 of scaffold [1]. This novel device provides transient vessel support without the limitations of stents with metallic platforms, as it preserves vessel geometry, has adaptive vascular remodeling, and restores physiologic vasomotion, resulting in late luminal expansion. Moreover, the neointimal growth after BVS resorption could act as a mechanical barrier that prevents potential thrombogenic plaque from reaching the bloodstream or "plaque sealing" [2]. Restoration of vascular physiology is usually achieved after 2 years, when BVS is considered fully resorbed, having been metabolized into CO_2 and H_2O via the Krebs cycle [1]. However, like drug-eluting stents (DES), BVS elutes everolimus, and complications seen after DES implantation can also be expected with BVS implantation. This is the first report of a coronary aneurysm, developing after BVS implantation, that eventually led to thrombosis, embolization, and myocardial infarction (MI).

Case Report

A 62-year-old Taiwanese man with no known systemic illness in the past was admitted to our hospital due to severe substernal chest pain and profuse diaphoresis. The pain occurred at rest and radiated to the left jaw and shoulder. He did not smoke but occasionally consumed alcoholic beverages. Two months prior to admission, the patient consulted our cardiology clinic due to intermittent effort-related chest pain that resolved after 5 min of rest. A treadmill exercise test was positive for ischemia, showing significant ST-segment depression over leads V5-6. Thus, elective coronary angiography was performed 2 weeks later and showed an 80% stenosis over the proximal left anterior descending (LAD) artery (Figure 1A, 1B). A 3.5×15 mm balloon was used to predilate the type B2 lesion at 16 atm followed by implantation of a 3.5×18 mm BVS at 14 atm (Figure 1C). This was followed by postdilation using the predilating balloon catheter at 16 atm. Final angiographic image showed excellent flow and uniform diameter of the stented and adjacent areas (Figure 1D). Intravascular ultrasound (IVUS) showed optimal stent and vessel wall apposition at the proximal area (Figure 1E), but suboptimal result over the distal area (Figure 1F). However, due to the good angiographic result, with postdilation already performed at the maximal recommended burst pressure of 16 atm, and fear of deforming the scaffolds, no further additional postdilation was carried out. The patient was discharged with dual antiplatelet therapy the next day.

On the day of admission, the patient was sitting in his office when the aforementioned symptoms recurred. He took a total of 2 tablets of nitroglycerin sublingually every 2 min, but the pain persisted. Therefore, he was taken to our hospital for further evaluation and management. At the Emergency Department (ED), an initial electrocardiogram (ECG) was normal but high-sensitivity troponin I and CK-MB levels were elevated at 1119.7 ng/mL (NR: <0.30) and 7.7 ng/mL (NR: <6.6), respectively. A non-ST-segment elevation MI (NSTEMI) was suspected, so loading doses of dual antiplatelet agents and unfractionated heparin were administered. ECG and cardiac biomarkers were checked every hour and 3 h, respectively, and the patient was observed for appearance of high-risk and very high-risk features. On the fourth hour after drug administration, the patient's ECG remained normal, troponin I and CK-MB had decreased to 914.6 ng/mL and 3.5 ng/mL, respectively, and his discomfort had subsided. After discussing his condition with him and his family, coronary angiography was performed via the right radial artery 8 h after ED arrival and 6 h after medication.

A non-significant distal edge stent restenosis was noted over the LAD, and a small aneurysm was noted immediately after the first diagonal branch (Figure 2A, 2B). No filling defect was observed. IVUS confirmed the edge restenosis and the aneurysm (Figure 2C, 2D). Therefore, a 3×8 mm balloon was used to predilate the lesion, followed by implantation of a 3.5×12 mm XIENCE Xpedition (Abbott laboratories, Abbott Park, IL) stent at 14 atm over the lesion site extending over the first diagonal branch and the aneurysm (Figure 3A). Postdilation was performed using a 3.5×9 mm balloon catheter at 24 atm. Final angiography showed decrease in the size of the aneurysm and resolution of the restenosis (Figure 3B). IVUS showed good stent and wall apposition, stent overlap, and better plaque compression (Figure 3C, 3D). Symptoms resolved and he was discharged 2 days later.

Discussion

The BVS system has been studied extensively and has shown excellent angiographic, sonographic, tomographic, and clinical outcomes in individual studies. BVS showed in-scaffold late lumen loss comparable with everolimus-eluting stents (EES) at 3 years, restoration of coronary vasomotor function at 1 year, non-obstructive neointimal proliferation at the proximal edge at 2 years, and scaffold area expansion after loss of scaffold integrity at 3 years [3]. However, a recent meta-analysis of 6 trials with 5588 patients comparing BVS with EES at 1-year follow-up showed that BVS had an increased risk of MI (4.3% *vs.* 2.3%; OR: 1.63, 95%CI: 1.18–2.25, p<0.01) and definite-or-probable scaffold thrombosis (1.3% *vs.* 0.6%; OR: 2.10, 95%CI: 1.13–3.87, p=0.02). Possible causes suggested by the authors
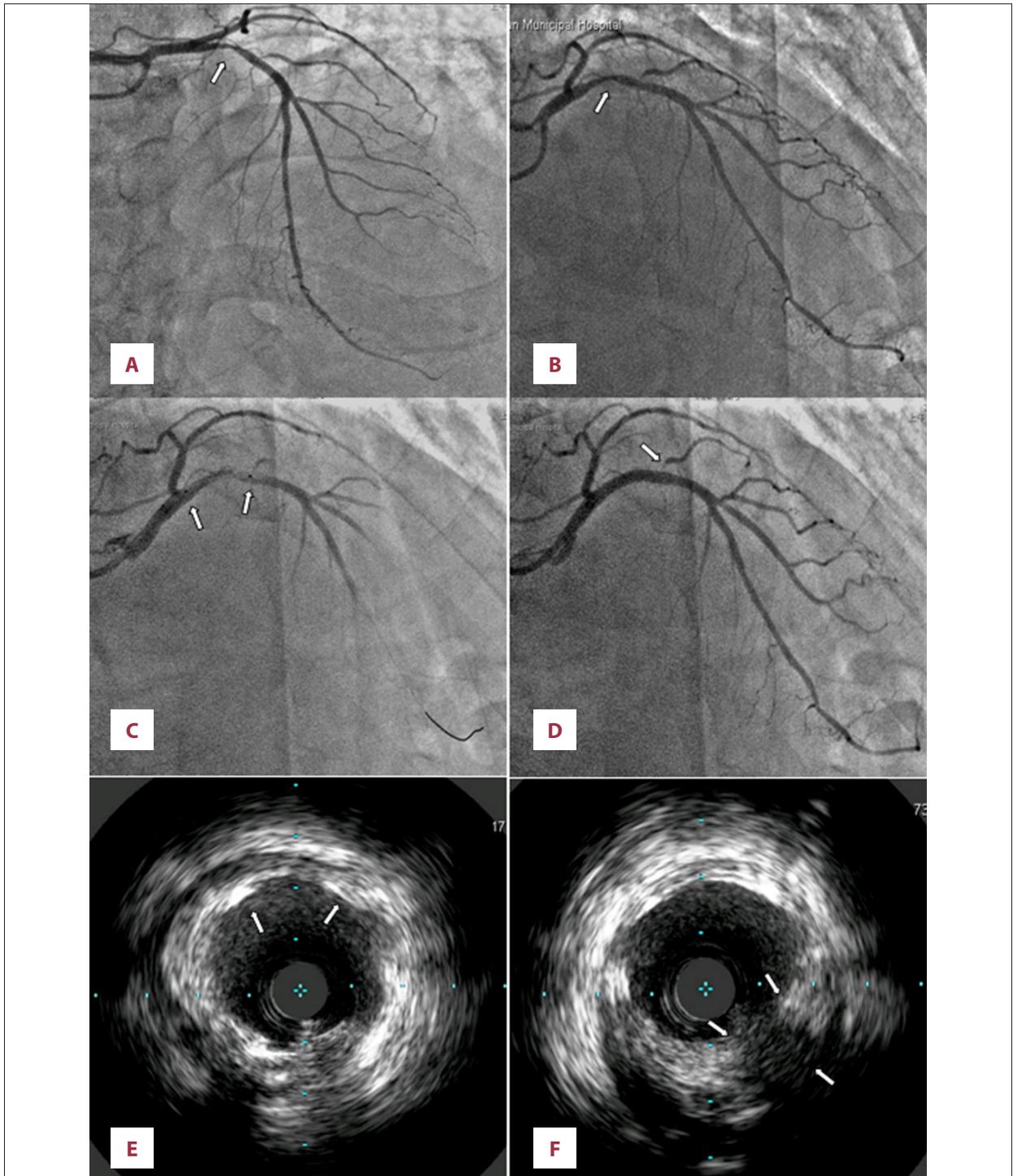
Figure 1. (**A**) Angiographic image at 5º RAO and 32º cranial view performed prior to BVS implantation showing a stenotic lesion over the proximal LAD. White arrow show the lesion. (**B**) Angiographic image at 37º RAO and 31º cranial view performed prior to BVS implantation showing a stenotic lesion over the proximal LAD. White arrow show the lesion. (**C**) Angiographic image at 43º RAO and 35º cranial view showing BVS deployment. White arrows show the faint stent edge markers. (**D**) Angiographic image at 43º RAO and 35º cranial view showing successful BVS implantation. White arrow show the patent first diagonal branch. (**E**) Intravascular ultrasound image at the proximal stent edge after BVS implantation, showing optimal stent and vessel wall apposition. White arrows show the stent struts. (**F**) Intravascular ultrasound image at the distal stent edge after BVS implantation, showing suboptimal plaque compression despite good angiographic results. White arrows show the plaque.
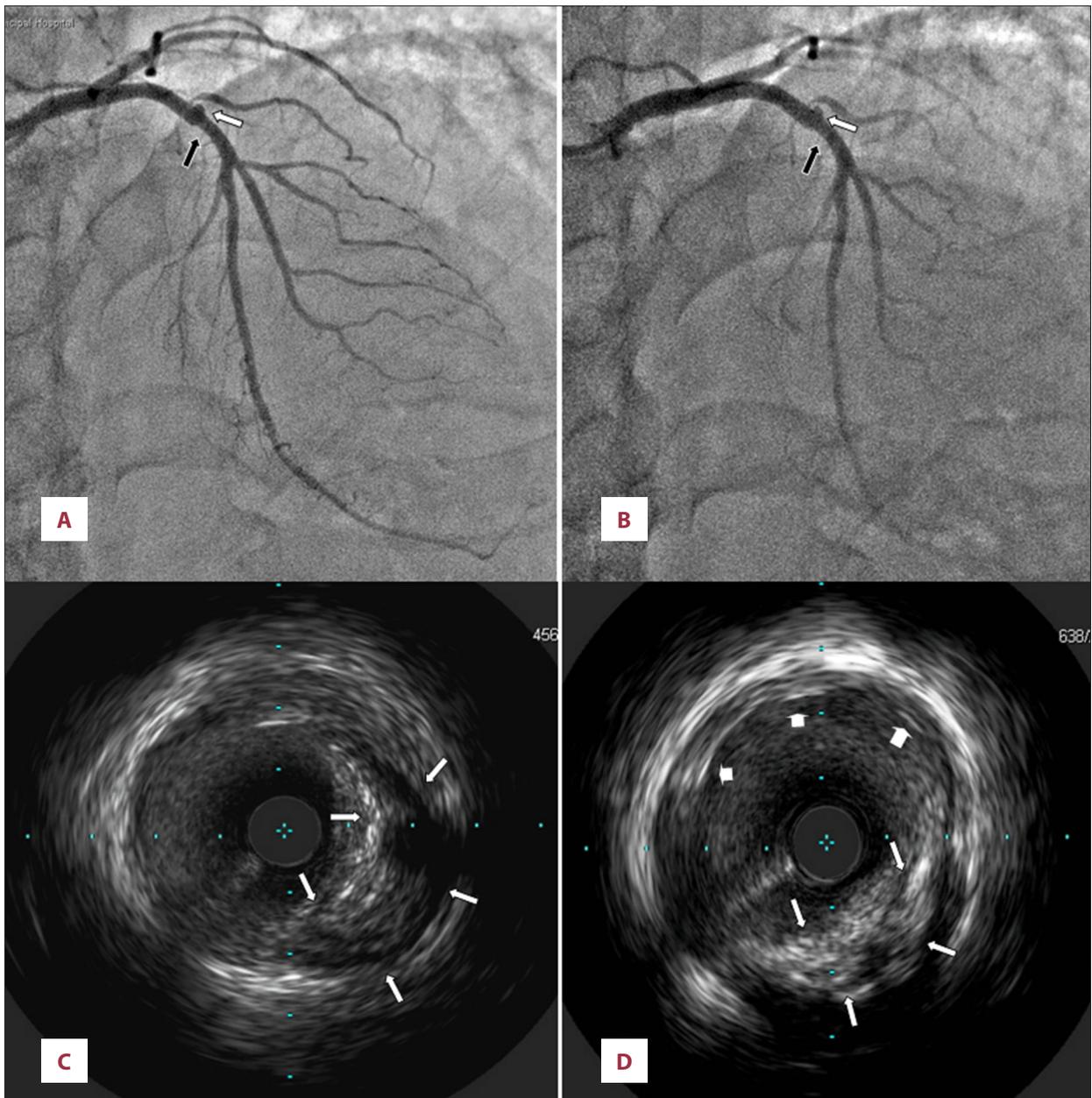
Figure 2. (**A**) Angiographic image at 8º RAO and 33º cranial view 2 months after BVS implantation showing an insignificant distal edge restenotic lesion (black arrow) over the proximal LAD. A small coronary aneurysm (white arrow) is also noted immediately after the first diagonal branch. (**B**) Enlarged angiographic image at 8º RAO and 33º cranial view showing the insignificant restenotic lesion (black arrow) and the coronary aneurysm (white arrow). (**C**) Intravascular ultrasound image at the level of the coronary aneurysm. White arrows show its dimensions. (**D**) Intravascular ultrasound image at the level of the distal stent edge. Wide arrows show stent struts and narrow arrows show restenotic lesion.

included: 1) thicker struts that may trigger platelet aggregation; 2) suboptimal implantation causing device malapposition and under-expansion affecting coronary flow pattern and activating the coagulation cascade; 3) excessive overexpansion leading to fractures of the polymer, causing thrombus formation; 4) late scaffold recoil; 5) presence of uncovered BVS struts after 12 months with discontinuation of dual antiplatelet therapy; and 6) late scaffold discontinuity causing dislocation of the strut remnants into the lumen, disturbing flow patterns, shear stress to vessel wall and subsequent recruitment of platelets, and thrombosis [4].

Vascular responses after device implantation may either be instent or edge responses over the transition zones. Edge vascular
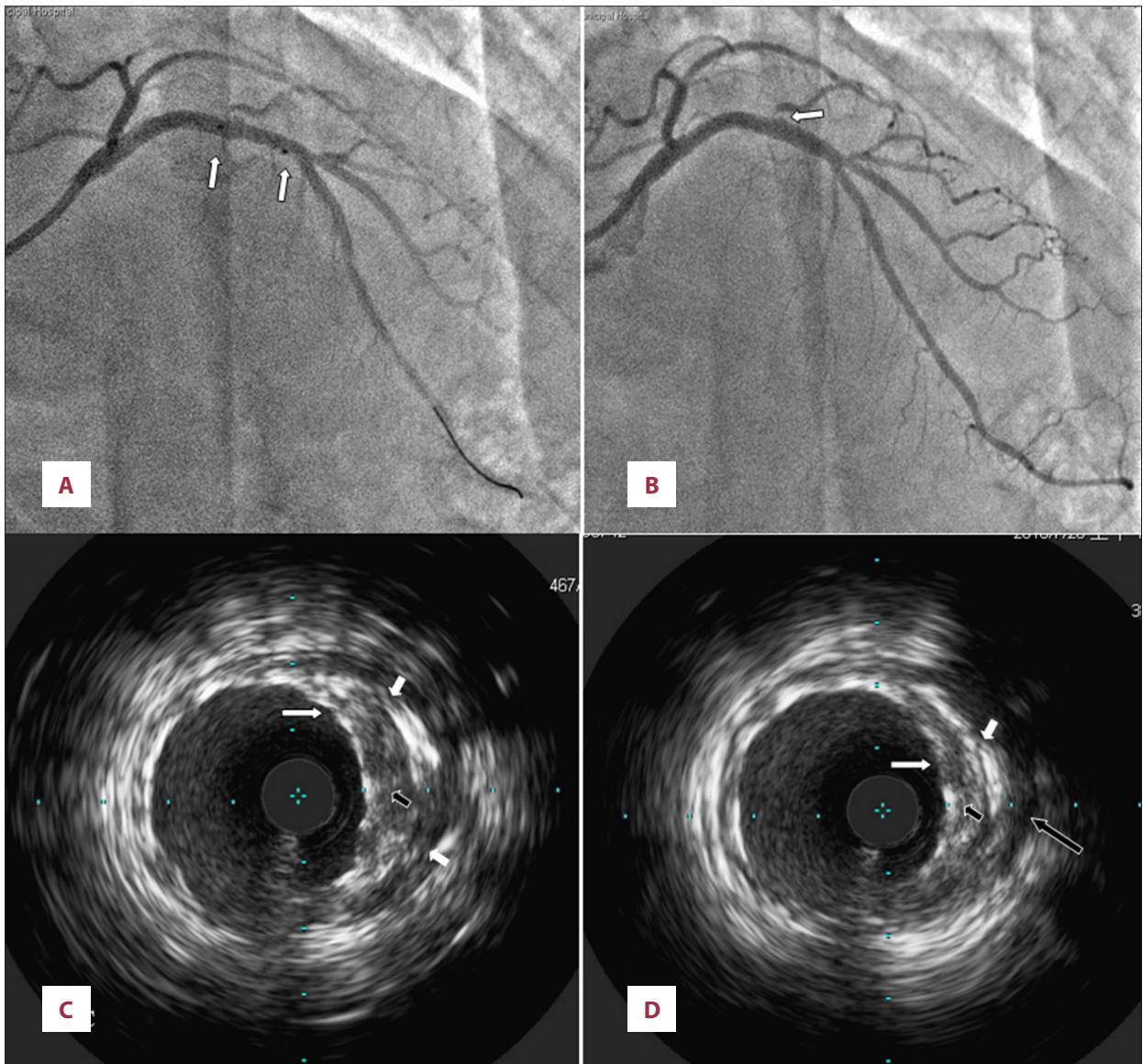
Figure 3. (**A**) Angiographic image at 43° RAO and 34° cranial view showing Everolimus-eluting stent deployment. White arrows show the stent edge markers. (**B**) Angiographic image at 43° RAO and 34° cranial view showing successful implantation of the Everolimus-eluting stent. Note that the edge restenosis has resolved and the aneurysm (white arrow) has already shrunk in size. The first diagonal branch remains patent. (**C**) Intravascular ultrasound image at the level of the proximal EES (distal BVS) showing overlapping stent struts. White arrow (EES struts), white short arrows (BVS struts), and black arrow (plaque). (**D**) Intravascular ultrasound IVUS image at the level of the distal EES showing overlapping stent struts (white arrow), artifact (white short arrow), good plaque compression (short black arrow), and aneurysm remnant (long black arrow).

response (EVR) is an observation made at the scaffold edge and is defined as a reduction in the lumen area, mainly from an increase in plaque/media and lumen area within the first 1–2 mm of the proximal and distal stent edges [3,5]. Edge restenosis, on the other hand, is a true pathologic phenomenon that results from focal exuberance of neointima, combined with constrictive remodeling and progression of the atherosclerotic process [5]. This process is multifactorial and can be caused by: 1) iatrogenic factors related to the periprocedural

axial or longitudinal geographic miss (GM); 2) device factors, like the type of implanted device (metallic or polymeric), device-induced edge dissections, type/release kinetics of the anti-proliferative drug, and drug resistance; and 3) biological factors linked to the remaining plaque burden and necrotic core tissue at the edges when the "normal-to-normal" landing of the device was not achieved [3], ultimately leading to stent thrombosis or restenosis resulting in stent failure.

A coronary aneurysm is defined as a dilation of the coronary artery that exceeds 1.5 times the reference diameter of the adjacent coronary segments that are angiographically normal [6]. It is relatively rare and was first described by Morgagni in 1761. It has an incidence of 0.5–5.3%, with the right coronary artery being most commonly affected. Causes include atherosclerosis, percutaneous coronary interventions (PCI), Kawasaki disease, dissection, mycotic, polyarteritis nodosa, Takayasu's arteritis, syphilis, systemic lupus erythematosus, Marfan's syndrome, Ehlers-Danlos syndrome, and metastatic tumors, with atherosclerosis accounting for about half of reported cases [7]. The exact mechanism of aneurysm formation is unknown. Common theories include: 1) delayed endothelialization or healing process; 2) stent malapposition or late incomplete stent apposition due to plaque regression or thrombi dissolution; 3) exaggerated positive remodeling causing vessel dilation; 4) hypersensitivity reaction to the stent material or polymers; 5) eluted drug effect via inhibition of neointimal hyperplasia and stimulation of apoptosis; 6) expansion of the weakened intima and media caused by the PCI itself; and 7) microhemorrhage, ulcers, and microdissection at the site of the atheromatous plaque during PCI. Development of a true aneurysm after PCI is rare. Its incidence after BMS and paclitaxel-eluting stent implantation is 0.2% and 1.4%, respectively [8], and tend to develop at a mean of 313±194 days after stent implantation [9]. Given the aforementioned theories and mechanistic vascular responses to coronary intervention, it is not surprising that most, if not all, of the causes for restenosis are very similar to that of coronary aneurysm formation, as the end result is a response to endothelial damage.

Due to a persistently normal ECG, patent coronary arteries, and absence of filling defects, one would challenge the diagnosis of NSTEMI. Based on the definition provided by the European Society of Cardiology (ESC) task force for the diagnosis and treatment of NSTEMI, NSTEMI includes patients with chest pain and elevated cardiac biomarkers, but without the persistent ST-segment elevation. They may have a persistent or transient ST-segment depression, T wave inversion, flat T waves, pseudonormalization of T waves, or no ECG changes at presentation. A normal or near-normal ECG does not exclude the possibility of a NSTEMI [10,11].

Cardiac troponin elevation reflects irreversible myocardial cellular necrosis, typically resulting from distal embolization of platelet-rich thrombi from the site of a ruptured plaque. They are considered surrogate markers of active thrombus formation, and in the setting of myocardial ischemia, manifested as chest pain or ST-segment changes, the ESC/American College of Cardiology (ACC)/American Heart Association (AHA) consensus document labeled and classified cardiac troponin elevations as MI [12]. The increased risk associated with elevated troponin is independent of, and additive to, other risk factors, such as

ECG changes or inflammatory marker activities [13,14]. High-sensitivity troponin I, which was used in this case, results in a 4% absolute and 20% relative increase in the detection of type I MI and a 2-fold increase in the detection of type 2 MI. It is a quantitative marker of cardiomyocyte damage, indicating greater likelihood of MI with higher levels beyond the 5-fold upper reference limit, translating to a >90% positive predictive value for acute type 1 MI [15]. Additionally, with the rise and fall of the patient's hs-troponin I levels, the ongoing damage was dynamic and correlated well with his symptoms.

One could argue that even with fulfillment of the aforementioned criteria, there were still the issue of patent coronary arteries and the absence of any filling defects, especially in the acute phase of the disease and coronary angiography. This can be explained by the timing of the cardiac catheterization procedure. Loading doses of heparin and dual antiplatelet agents were given immediately after cardiac biomarker results became available 1 h after ED arrival. However, since his hourly ECG remained normal without any appearance of very high-risk features, cardiac catheterization was performed 8 h after ED arrival. Symptom relief and decrease in troponin level afterwards suggested a possible spontaneous recanalization or thrombolysis. The platelet-rich thrombi (common for NSTEMI), may have been small initially or large but fragmented into smaller particles, and embolized downstream causing small areas of necrosis in the myocardium, leading to the release of markers of myocardial necrosis [16,17]. These small areas of necrosis may not be translated into the ECG or visible in the angiogram, and can only be detected by cardiac troponins [12]. Although this explanation seems somewhat convenient, it is the most plausible and sensible one.

About 25% of patients with proven NSTEMI actually have normal or near-normal coronary arteries on angiography [10,15]. Atherosclerosis may also be diffuse in character and leads to arterial wall remodeling in which the wall thickens and expands outwards without encroaching on the lumen [18]. It has been reported that 5 patients without any coronary stenosis developed MI and thrombosis of aneurismal vessels [19]. An optical coherence tomography (OCT) could have provided a better examination of the lesions (without the motion artifacts seen in IVUS), or even visualize the alleged thrombus, but, unfortunately, we currently do not have this modality. Other non-coronary causes of troponin elevations, including aortic dissection, trauma, pulmonary embolism, acute heart failure, hypertensive crisis, arrhythmia, hypothyroidism, renal dysfunction, stroke, intracerebral hemorrhage, vasospasm, drugs, and Takotsubo cardiomyopathy, save for a myocarditis, were ruled out using history taking, physical examination, computed tomographic scan, and intracoronary nitroglycerin. However, with the patient's history, hospital course, and normal ECG, myocarditis was deemed unlikely. With his symptoms and release

of biomarkers, this patient had a true necrosis rather than a false-positive result. Elevation of cardiac troponins that cannot be explained is very rare [10].

Secondly, one might ask if this was an iatrogenic event during PCI, or a direct effect of the BVS itself. BVS deployment in this case was carried out conventionally, as suggested in the literature [3]. We used mandatory conservative predilation with a shorter balloon (3.5×15 mm) than the BVS. Then, less forceful implantation (14 atm) at a rated burst pressure of 16 atm was performed, followed by postdilation with a balloon shorter (3.5×15 mm) than the implanted device (3.5×18 mm) at 16 atm. The final angiographic image (Fig. 1D) showed excellent results, but IVUS showed suboptimal plaque compression, as we were also trying to avoid jailing the first diagonal branch. However, this misstep probably resulted in a GM and failing to obtain a normal-to-normal landing site, resulting in edge restenosis and aneurysm formation. We were hesitant to apply further postdilation afterwards for fear of overstretching or deforming the struts, causing polymer damage and scaffold thrombosis. Overstretching may leave gaps between the strut cells, causing suboptimal drug delivery, and vessel overexpansion in animal models was shown to cause more intense neointimal proliferation [20].

The rationale for using an EES instead of a cover stent for the aneurysm was mainly to avoid jailing the first diagonal branch, and secondly because of its similar everolimus dose density to BVS. This is important since side-branch occlusion is associated with a higher incidence of in-hospital MI in patients treated with BVS (p<0.01), as BVS struts have greater vessel wall area coverage (26%) compared with EES struts (12%) [21]. Also, although cover stents have excellent immediate and short-term results, there is the issue of side-branch occlusion, and late stent occlusions have been reported. Lastly, given the financial constraints of this patient (BVS is not currently covered by our national health care and his personal insurance provider, and costs $3900–4000 USD each, excluding other expenses), only a short DES with smaller strut area coverage and similar dose density of the eluted drug could treat the "currently" non-significant edge restenosis, maintain patency of the first diagonal branch, and cover the coronary aneurysm.

Although most patients with coronary aneurysms are asymptomatic when slow-growing and discovered incidentally during angiography, they may cause restenosis, thrombosis, distal embolization, acute MI, fistula formation, rupture, and cardiac tamponade, especially in rapidly growing aneurysms. In an autopsy study, a thrombus is invariably present on the luminal surface of coronary aneurysms [22]. Treatment can be conservative, with aspirin, antiplatelets, statins, angiotensin II receptor blockers, and anticoagulants, or aggressive, like cover stents, surgical incision, or ligation. Some advocate watchful waiting since spontaneous resolution has been seen. This, however,

remains controversial, as some aneurysms may not resolve, but enlarge further. No treatment is advocated for small benign aneurysms, and aggressive intervention is reserved for symptomatic, large, or rapidly expanding aneurysms, near bifurcations, and presence of emboli resulting in ischemia.

Due to its rarity, a consensus or an established treatment guideline for treating coronary aneurysms is currently lacking. One would question whether implanting a DES is this case was justified owing to the fact that DES *per se* or the PCI itself may be more thrombogenic and causes more inflammatory reactions resulting in more harm than good to the patient in the future. We also concede that implanting a DES in this case should have been only for a "bail-out" indication, but this was not the case in our patient. However, it was a judgment call and a toss-up on whether to do nothing and just wait for another event to occur, or address the lesion immediately, as we eventually did. If the coronary aneurysm was discovered when the patient only presented with unstable angina or a positive treadmill exercise test, we may have managed this patient differently. But given the fact that the patient had indeed experienced an MI, and after a thorough discussion with the patient and his family, we decided to proceed as we did. It is impossible to know the fate of the aneurysm if we had decided not to treat it, but the risk of endothelial injury, thrombus formation, and distal embolization in the future could not be ignored. The presence of a coronary aneurysm is a significant predictor of mortality, with an overall 5-year survival rate of only 71% [23].

The fundamental technical aspects of stent deployment, like avoidance of overstretching during lesion preparation, use of balloons shorter than the implanted device during pre- or postdilation, and the importance of the normal-to-normal or healthy "landing zone" of the device during stenting, are very important. However, hard plaques, anatomical variability, equipment availability, financial constraints, and other challenges commonly encountered during the procedure may be problematic and could limit the use of the BVS system. One lesson we could learn from this case is that stent deployment and/or postdilation within the rated burst pressure is sometimes not enough to adequately compress the plaque, even when the lesion appeared "soft", as no calcification was noted. Optimal plaque compression was only achieved after postdilation of the EES at 24 atm. Implanting another BVS in an overlap fashion in this case may worsen the occlusion since a burst pressure of 16 atm is insufficient to compress the plaque, and we may end up adding another layer of thickness, especially at the overlap. This problem also occurs in complex type C lesions, but most treated lesions in the current study populations were type A [3].

Although this event has never before been reported in the BVS platform, GM, suboptimal plaque compression, vessel

trauma during PCI, lesion location, and plaque nature resulted in positive remodeling, edge restenosis, aneurysm formation, thrombosis, embolization, and MI. Although we could not provide any visual evidence (thrombus or filling defect), or prove absolutely direct causality and effect between BVS, coronary aneurysm, and MI, the non-occlusive edge restenosis and the coronary aneurysm were the only culprit present. Myocardial damage did occur in this patient, and our theory, backed up by evidence in the literature, was the most logical and plausible explanation of what transpired in this patient.

Conclusions

The fundamental technical aspects of stent deployment should be adhered to in order to prevent or decrease endothelial injury during the procedure. Further studies are needed to test this device in more complex lesions requiring more complex techniques, manipulations, and deployment. Although size, rapidity of growth, and the presence of high-risk features are the main determinants on whether to treat a coronary aneurysm, treatment should be individualized and guided by the accompanying circumstances presented during the procedure. One must not take lightly a small coronary aneurysm when discovered, as the abnormal fluid dynamics and flow pattern inside may still result in thrombus formation and embolization. As shown in this case, an MI resulted even from a very small aneurysm. It is important to remember that the behavior of each aneurysm is different and when or how it manifests is unknown.

Statement

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