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Stent-induced hypersensitivity leading to refractory in-stent restenosis: a case report

Menghuai Ma[1] and Jiong Tang[1*]

Abstract

Background Even in the era of new-generation drug-eluting stents, in-stent restenosis remains a common and challenging problem of percutaneous coronary intervention. Among the many factors that contribute to in-stent restenosis, stent-related hypersensitivity is relatively rare, but may be a significant trigger of chronic refractory in-stent restenosis. Nevertheless, it is difficult to diagnose and assess the stent-related hypersensitivity, and there is no standardized treatment strategy.

Case presentation We present the case of a 63-year-old Chinese female who experienced refractory in-stent restenosis following the successful implantation of platinum chromium everolimus-eluting stents in the left main, left anterior descending and left circumflex artery. Although the cardiovascular risk factors were well-controlled, the patient developed four episodes of acute myocardial infarction with in-stent restenosis within 1 year. Intravascular ultrasound revealed diffuse neointimal hyperplasia in the in-stent restenosis lesion, and the blood tests showed no sign of systemic inflammation or infection. Thus, we speculated that the cause of refractory in-stent restenosis was stent-mediated hypersensitivity. Initially, the in-stent restenosis was treated with paclitaxel-coated balloon angioplasty, and only mild neointimal hyperplasia was observed on intravascular ultrasound 3 months after paclitaxel-coated balloon angioplasty. However, the paclitaxel-coated balloon could not prevent in-stent restenosis recurrence, and she eventually underwent coronary artery bypass grafting. After over 2 years of follow-up, her cardiac function had significantly improved, and the bridging vessels remained patent, as confirmed by computed tomography angiography.

Conclusion When encountering refractory in-stent restenosis, physicians should consider the potential for stent-associated hypersensitivity. Since there may be difficulty in obtaining histopathological examination of restenotic vessels, intravascular imaging can be instrumental in detecting neointimal hyperplasia and diagnosing stent allergy. Coronary artery bypass grafting may be a reasonable treatment for patients with stent allergy; further clinical research is required to explore the optimal treatments.

Keywords Hypersensitivity reaction, Refractory in-stent restenosis, Acute myocardial infarction, Paclitaxel-coated balloon angioplasty, Coronary artery bypass grafting

Introduction

In-stent restenosis (ISR) is a prevailing clinical issue involving multiple underlying etiologies, among which stent-induced hypersensitivity reactions cannot be ignored. Elements of stents, including metal, antiproliferative agents, and copolymer, are known to cause contact allergies [1–3], even in the new-generation drug-eluting stents (DES) [4] or biodegradable-polymer

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stents [5]. Intravascular imaging is often used to guide ISR interventions through revealing the morphology of restenotic neointima and identifying underlying etiologies. Currently, there is no optimal treatment for stent-induced hypersensitivity. Case reports have shown that immunosuppressive drugs, paclitaxel-coated balloon (PCB), bioresorbable vascular scaffolds (BVS), or coronary artery bypass grafting (CABG) can successfully treat recurrent ISR caused by hypersensitivity reactions [1, 4, 5]. Herein, we present a patient with stent-mediated hypersensitivity who experienced four ISR episodes within 1 year and was successfully treated with CABG. Additionally, we noticed that PCB angioplasty could suppress neointimal proliferation for up to 8 months, whereas it could not prevent the recurrence of ISR. Thus, when hypersensitivity is suspected, early CABG may be an appropriate option.

Case report

A 63-year-old Chinese woman with a history of hypertension and type 2 diabetes was admitted to our hospital with acute non-ST segment elevation myocardial infarction (NSTEMI). She had no history of allergies and a family history of cardiovascular disease. Coronary angiography (CAG) showed 80%, 90%, and 60% stenosis in the left anterior descending artery (LAD) (Fig. 1a), left circumflex artery (LCX) (Fig. 2a), and right coronary artery (RCA), respectively. Intravascular ultrasound (IVUS) was performed in the left coronary artery (LCA) and revealed diffuse atherosclerosis, with a minimum lumen area of 2.0 mm^2 in proximal LCX (Fig. 4e–h), 3.4 mm^2 in the opening of LAD, and 2.0 mm^2 in the distal segment of LAD (Fig. 3a–d). We recommended that the patient consider CABG, but she refused. Finally, under guidance using IVUS, four platinum chromium everolimus-eluting stents (PtCr-EES; Promus Premier™, Boston

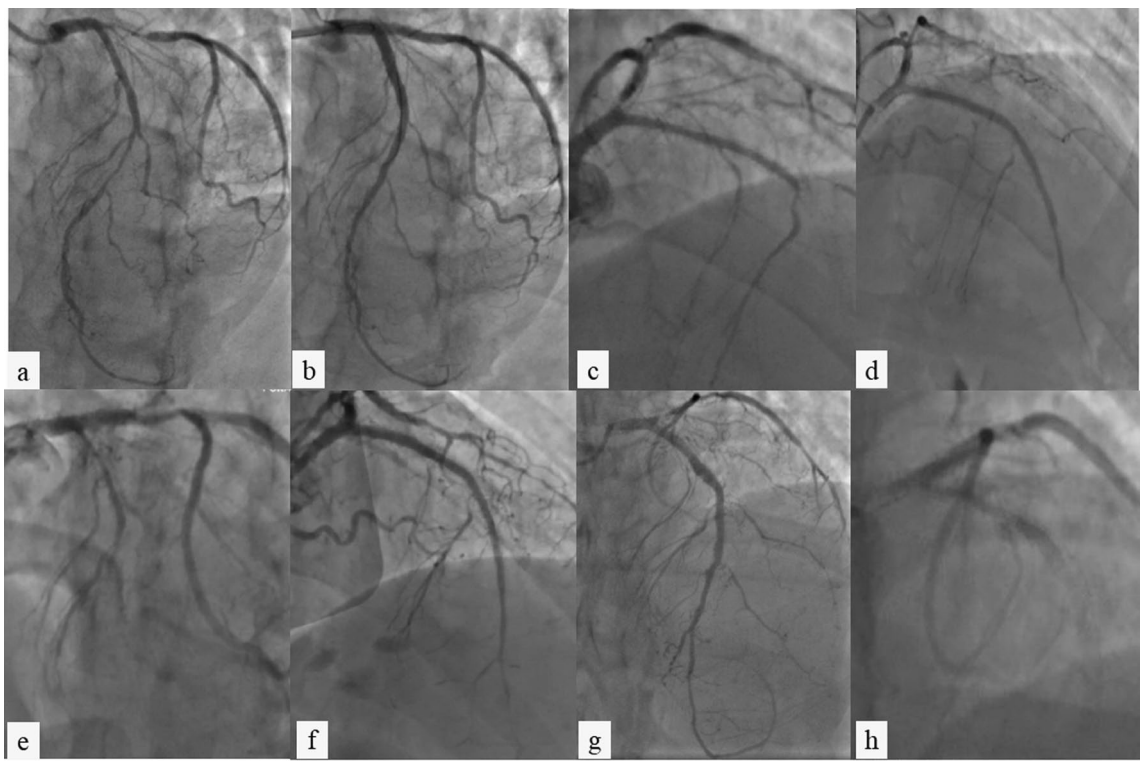

Fig. 1 A series of left anterior descending artery coronary artery angiograms. **a** Significant left anterior descending artery stenosis before the first percutaneous coronary intervention. **b** Angiogram following the first percutaneous coronary intervention with three platinum chromium everolimus-eluting stents (a 2.25 × 28 mm and a 3.0 × 28 mm were deployed at the proximal-mid left anterior descending artery, and a 3.5 × 16 mm was implanted in left main). **c** Angiogram 3 months after the first percutaneous coronary intervention showing in-stent occlusion at middle left anterior descending artery. **d** Angiogram after the second percutaneous coronary intervention with non-drug-coated balloon. **e** Angiogram 3 months after the second percutaneous coronary intervention showing severe in-stent restenosis. **f** Angiogram after the third percutaneous coronary intervention with four paclitaxel-coated balloons (the size of the paclitaxel-coated balloon arranged from the distal left anterior descending artery to left main was 2.5 × 20 mm, 2.75 × 31 mm, 3.0 × 31 mm, and 3.5 × 31 mm, respectively). **g** Angiogram 4 months after paclitaxel-coated balloon angioplasty showing mild in-stent restenosis. **h** Angiogram 8 months after paclitaxel-coated balloon angioplasty showing severe in-stent restenosis of left anterior descending artery and left main

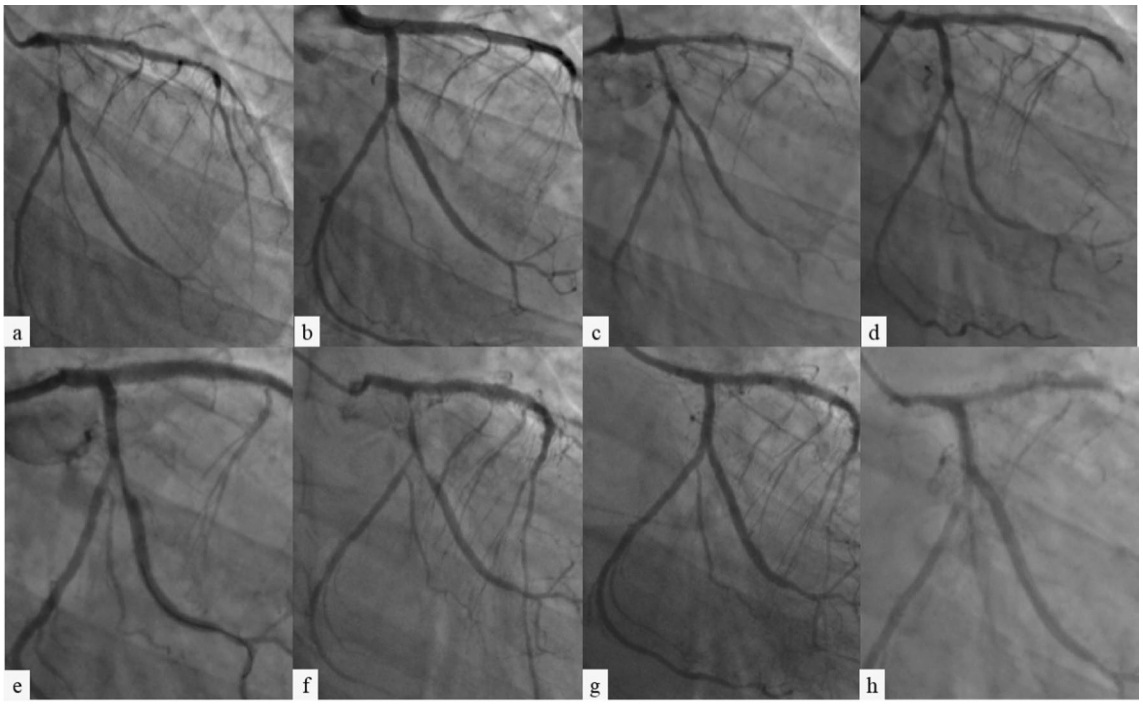

Fig. 2 A series of left circumflex artery coronary artery angiograms. **a** Significant stenosis of proximal left circumflex artery before the first percutaneous coronary intervention. **b** Angiogram after a platinum chromium everolimus-eluting stent 3.0×24 mm implantation. **c** Angiogram 3 months after the first percutaneous coronary intervention showing obvious in-stent restenosis. **d** Angiogram just after placing a 3.0×15 mm paclitaxel-coated balloon to proximal left circumflex artery. **e** Angiogram 3 months after paclitaxel-coated balloon angioplasty showing no significant in-stent restenosis. **f** Angiogram 8 months after paclitaxel-coated balloon angioplasty showing severe in-stent restenosis of proximal left circumflex artery and the progressed stenosis of the OM1 and the distal end of the stent. **g** Angiogram after angioplasty (a 2.5×31 mm paclitaxel-coated balloon was placed at proximal left circumflex artery and a 2.5×16 mm paclitaxel-coated balloon was placed at OM1). **h** Angiogram 3 months after paclitaxel-coated balloon angioplasty showing no obvious in-stent restenosis

Scientific, Marlborough, MA, USA) of different sizes were implanted into the LCA. In detail, a 2.25×28 mm stent was deployed at the middle LAD and a 2.5×12 mm balloon (NC Sprinter, Medtronic, USA) was adopted to dilate the lesion at 8–16 atmosphere (atm), a 3.0×28 mm stent was implanted into the proximal LAD, and a 3.0×12 mm balloon (NC Sprinter, Medtronic, USA) was adopted to dilate the lesion at 12–20 atm (Fig. 1b). Then, one 3.0×24 mm stent was deployed at the proximal LCX (Fig. 2b), and one 3.5×16 mm was implanted in the left main (LM); simultaneously, the double kissing crush was performed with two non-compliant balloons (3.0×12 mm and 4.0×9 mm). Finally, the proximal optimization technique was performed in LCA using a 4.0×9 mm non-compliant balloon. The images following the first percutaneous coronary intervention (PCI) are shown in Fig. 1b and Fig. 2b. IVUS re-examination demonstrated well-expanded and well-adherent struts, without any edge dissection at LAD (Fig. 3a1-d1) and LCX (Fig. 4e1-h1). Thereafter, she was discharged with optimal medical therapy, including clopidogrel (75 mg/day), aspirin (100 mg/day), and rosuvastatin (10 mg/day).

A total of 3 months later, the patient developed NSTEMI and the electrocardiogram showed significant ST-segment elevation of V1 to V5. The transthoracic echocardiography (TTE) revealed that left ventricular ejection fraction (LVEF) decreased from a preoperative 65% to 43%, and left ventricular internal diameter at end-diastole (LVIDd) increased from a preoperative 4.7 cm to 4.9 cm. Simultaneously, the low-density lipoprotein cholesterol (LDL-C) increased from thet preoperative 1.24 mmol/L to 1.99 mmol/L, and glycosylated hemoglobin decreased from the preoperative 8.7% to 7.6%. Emergent CAG showed occlusive restenosis in the middle LAD (Fig. 1c) and diffuse ISR in the proximal LCX (Fig. 2c). The ISR in the LCX was successfully treated with a PCB (SeQuent® Please NEO, B. Braun, Melsungen, Germany) and thrombolysis in myocardial infarction (TIMI) III flow was obtained. In addition, the LAD restored TIMI II flow after non-drug-coated balloon angioplasty. Postoperative treatment with evolocumab and sacubitril/valsartan was initiated; subsequently, the patient was discharged with ticagrelor to replace clopidogrel.

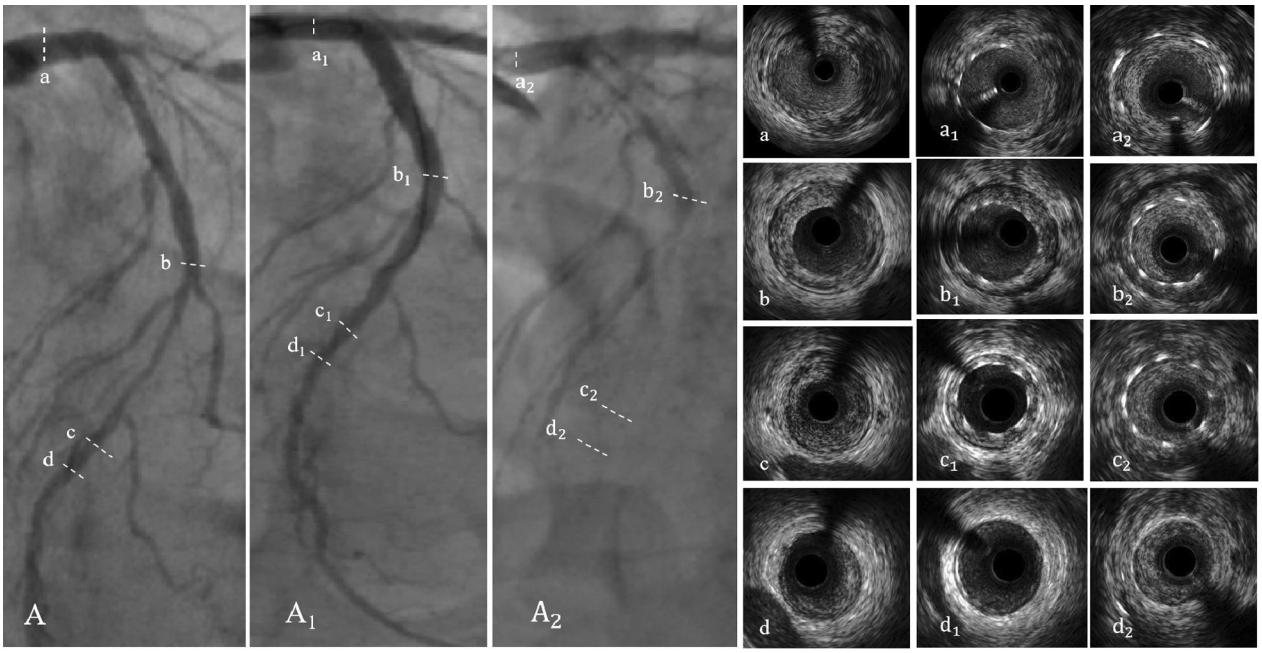

Fig. 3 Coronary angiogram and intravascular ultrasound images of the restenotic lesion of left anterior descending artery and left main. **A** Angiogram of left anterior descending artery before platinum chromium everolimus-eluting stent implantation. **a**–**d** Intravascular ultrasound images of left anterior descending artery before the first percutaneous coronary intervention. ($\mathbf{A}_1$) Angiogram of left anterior descending artery after platinum chromium everolimus-eluting stent implantation. $\mathbf{a}_1$–$\mathbf{d}_1$ Intravascular ultrasound images of left anterior descending artery after the first percutaneous coronary intervention. ($\mathbf{A}_2$) Angiogram 6 months after percutaneous coronary intervention showing obvious in-stent restenosis of left anterior descending artery. **a**2–**d**2 Intravascular ultrasound images of left anterior descending artery 6 months after first percutaneous coronary intervention showing diffuse low-echoic neointima in the in-stent restenosis lesion, especially in the overlap and opening edge of stent

Nevertheless, 3 months later, she developed NSTEMI again caused by ISR of LAD (Fig. 1e), despite her LDL-C level being even lower at 0.73 mmol/L. We considered using optical coherence tomography to evaluate the ISR lesion, however, limited by the conditions of her medical insurance, we ultimately chose IVUS as the alternative modality. IVUS revealed diffuse heterogeneous low-echoic neointima in the ISR lesion and distal end of the stent, especially at the stent edges and overlaps, with no evidence of thrombus, dissection, or stent fracture (Fig. 3a2–d2 and Fig. 4e2–h2). Interestingly, in the LCX, IVUS showed low-echoic proliferative tissue outside the stent, but not inside the stent (Fig. 4e2–h2). The patient had excellent medication adherence. A platelet aggregation test demonstrated a good response to antiplatelet drugs. Thromboelastogram test results and levels of protein C, protein S, and antithrombin were normal, effectively ruling out thrombophilia. Laboratory tests revealed low levels of C-reactive protein (2.14 mg/L), erythrocyte sedimentation rate (18 mm/h), and interleukin-6 (2.04 pg/mL). Serologic work-up showed negative results for a comprehensive panel of autoimmune antibodies, including antinuclear, anti-dsDNA, antiphospholipid, anti-neutrophil cytoplasmic, and anti-thyroid peroxidase antibodies, among others. Given the recurrent and aggressive restenosis with diffuse neointimal hyperplasia, a stent-allergy reaction was suspected. Owing to the refusal of CABG, PCB (Lepu Medical, Beijing, China) angioplasty was eventually carried out from the distal LAD to LM. Postoperatively, we suggested oral anti-inflammatory therapy with glucocorticoids, but the patient refused.

A total of 4 months later, she was readmitted and diagnosed with NSTEMI. The fourth CAG revealed severe stenosis of the first obtuse marginal (OM1) and significant ISR of proximal LCX (Fig. 2f), which were both treated with PCB (Lepu Medical, Beijing, China). Unsurprisingly, she experienced the fourth ISR 3 months later. The CAG documented 90% ISR of the proximal LM and 70–95% ISR of the proximal LAD (Fig. 1h). Finally, she underwent CABG surgery and recovered very well. The TTE revealed that LVIDd decreased from the preoperative 54 mm to 45 mm, and LVEF increased from the preoperative 52% to 55%. The patient was followed up for over 2 years. She remained asymptomatic and there was no stenosis in bridging vessels on computed tomography angiography. The timeline and characteristics of this case are summarized in Table 1.

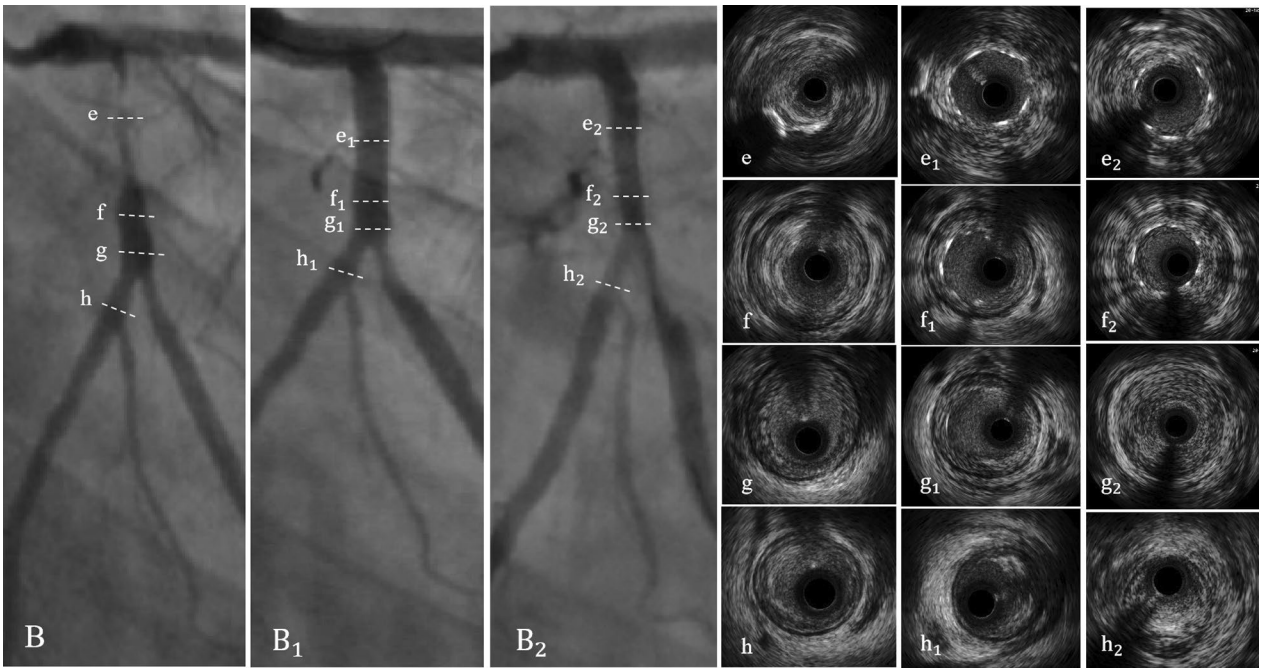

Fig. 4 Coronary angiogram and intravascular ultrasound images of the restenotic lesion of left circumflex artery. **B** Pre-stent placement coronary angiogram of left circumflex artery. **e**–**h** Intravascular ultrasound images of left circumflex artery before the first percutaneous coronary intervention. (**B**$_1$) Post-stent placement coronary angiogram of left circumflex artery. (**e**$_1$–**h**$_1$) Intravascular ultrasound images of left circumflex artery after the first percutaneous coronary intervention. (**B**$_2$) Angiogram 3 months after the in-stent restenosis was treated with paclitaxel-coated balloon showing no obvious in-stent restenosis in left circumflex artery. (e$_2$–h$_2$) A total of 3 months after the in-stent restenosis of left circumflex artery was treated with paclitaxel-coated balloon; intravascular ultrasound images showing mild intimal hyperplasia inside the stent. Whereas, on intravascular ultrasound, significant progression of the lesion was observed at the edge and distal end of the stent

Table 1 Summary of patient characteristics

Time	Diagnosis	Treated vessels	Treatment
First admission	NSTEMI	LAD, LCX, and LM	Both CAG and IVUS revealed severe stenosis of the LM, LAD and LM A total of four PtCr-EESs were implanted in these three vessels
Three months after the first admission	STEMI	LCX and LAD	CAG revealed severe ISR in both LAD and LCX stent sites PCI for the in-stent restenotic lesion of LAD was performed with non-drug-coated balloons, and only TIMI II flow was obtained. PCI for the in-stent restenotic lesion of the LCX was was performed with paclitaxel-coated balloons, and TIMI III flow was obtained
Six months after the first admission	NSTEMI	LM and LAD	Both CAG and IVUS revealed diffuse ISR in both LAD and LM stent sites PCI for the LAD and LM were performed with paclitaxel-coated balloons
Eleven months after the first admission	NSTEMI	LCX and OM1	CAG revealed diffuse ISR in LCX, and stenosis of OM1 had progressed PCI for the LCX and OM1 were performed with paclitaxel-coated balloons
Fourteen months after the first admission	NSTEMI	LAD, LCX and LM	CAG revealed diffuse ISR in LAD and LM stent sites, and the stenosis of PDA had progressed CABG was performed for three major coronary vessels

Discussion

With the application of the new-generation DES, the incidence of ISR has been reduced to 5–10% [6]. However, ISR remains a critical concern owing to its potential to cause severe complications, such as STEMI [7]. There are multiple factors may contribute to DES restenosis, including mechanical, biological, genetic, and technical factors [6]. In terms of biological factors, in addition to antiplatelet drug resistance, hypersensitivity to the stent components may promote inflammation progression and trigger ISR. In this case, refractory ISR appeared in the short term, despite well-controlled hyperlipidemia and diabetes. There were no identifiable genetic or procedural risk factors. The IVUS imaging indicated that

peri-stent tissue appeared to consist of excessive neointimal hyperplasia without thrombotic components. Therefore, we suggested that refractory ISR was due to allergic inflammation caused by the stent. However, the patient declined to undergo a patch test, and a definitive diagnosis requires histopathological examination.

Numerous reports have documented hypersensitivity reactions following stent implantation, particularly with bare metal stents and first-generation DES, which are made of 316 L stainless steel containing nickel, chromium, and molybdenum [8]. In particular, nickel is considered the most potent allergen [9] and may lead to recurrent ISR [8]. The PtCr-EES implanted in this patient is a new-generation DES that contains little nickel (9%) and uses a platinum-chromium alloy as the scaffold. The PtCr-EES also contains the antiproliferator everolimus and biocompatible fluorinated copolymer. With high biocompatibility, the fluorinated copolymer can inhibit platelet aggregation, reduce inflammation, and potentially prevent allergic reaction [10]. However, there have been reports of hypersensitivity vasculitis associated with poly *n*-butyl methacrylate, a component of the polymer [2]. As an immunosuppressive agent, everolimus can be released approximately 100% from polymer within 4 months after implantation *in vivo* and can suppress allergic reaction [11]. In this case, recurrent ISR occurred after the complete release of everolimus, suggesting that the polymer or metal components of the stent were more likely responsible for the allergic reaction and ISR.

The optimal treatment for this condition is still unclear. Although the most effective therapy of ISR is repeated DES implantation, it should be discarded in patients with stent-associated hypersensitivity reaction. To reduce the occurrence of stent allergy, some researchers have proposed using nickel-free stainless steel materials and bioresorbable metal stents. Polymer-free DES have also been evaluated in clinical studies and demonstrated no significant difference compared with permanent-polymer DES [12, 13]. Recently, a study suggested using titanium alloy as a drug reservoir layer instead of polymer coatings to create nickel- and polymer-free stents [14]. In addition, BVS have also received increasing attention. For example, absorbable magnesium alloy stents have demonstrated antithrombotic properties in short-term clinical trials; however, long-term follow-up data are required [15]. A case reported that the ISR cycle was interrupted by PCI with PCB and BVS, combined with oral low-dose steroids [4]. However, BVS have also been reported to cause an allergic reaction and ISR [5, 16], which was successfully treated with CABG [5]. Regarding PCB, IVUS imaging of this patient 3 months after PCB angioplasty revealed that PCB effectively reduced neointimal hyperplasia. Unfortunately, critical ISR recurred 8 months later, indicating that PCB alone could not terminate the ISR cycle caused by allergic inflammation. In terms of pharmacological therapy, oral immunosuppressants may inhibit the recurrence of ISR. For instance, prednisolone and tranilast have been reported to prevent ISR attributed to hypersensitivity reaction [1]. Other drugs may also have anti-inflammatory and anti-atherosclerotic functions, such as sodium cromoglycate and leukotriene receptor antagonists [8]. Finally, as reported in this case, CABG may be a reasonable treatment strategy. It is worth mentioning that the majority of surgical staples contain little amounts of nickel and may lead to aggressive coronary artery stenosis [4]. Thus, materials containing nickel should be avoided in CABG procedures.

Conclusion

When refractory ISR occurs, physicians should remain vigilant for the possibility of stent-related hypersensitivity reactions. Although PCB angioplasty can suppress neointimal proliferation, it is insufficient to prevent the recurrence of ISR. In cases where stent-related hypersensitivity is suspected, CABG may be an optimal treatment option.

Abbreviations

ISR	In-stent restenosis
DES	Drug-eluting stents
PCB	Paclitaxel-coated balloon
BVS	Bioresorbable vascular scaffold
CABG	Coronary artery bypass grafting
NSTEMI	Non-ST segment elevation myocardial infarction
CAG	Coronary angiography
LAD	Left anterior descending artery
LCX	Left circumflex artery
RCA	Right coronary artery
IVUS	Intravascular ultrasound
LCA	Left coronary artery
IVUS	Rransthoracic echocardiography
LVEF	Left ventricular ejection fraction
LVIDd	Left ventricular internal diameter at end-diastole
LDL-C	Low-density lipoprotein cholesterol
TIMI	Thrombolysis in myocardial infarction

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Author contributions

MM participated in this patient's management and follow-up, collated clinical examination results and diagrams, and wrote the manuscript. JT assessed the patient, performed the procedure, revised the manuscript, and gave final approval of the manuscript.

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Availability of data and materials
The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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