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CASE REPORT
Coronary heart disease

Repetitive restenosis in a biodegradable polymer sirolimus-eluting stent with hypersensitivity reaction: a case report

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Background Hypersensitivity reaction is a classic cause of in-stent restenosis (ISR) in coronary stents, typically reported in bare-metal stents and first-generation drug-eluting stents. Biodegradable polymer sirolimus-eluting stent (BP-SES) was developed with the concept of biocompatibility, and there has been no report of ISR of BP-SES with hypersensitivity reaction.

Case summary An 81-year-old woman presented with ST-elevation acute inferior myocardial infarction. Primary percutaneous coronary intervention was performed for the culprit lesion in the left circumflex artery with a permanent polymer everolimus-eluting stent (PP-EES), followed by BP-SES implantation in the left anterior descending artery. Eight months later, coronary angiography showed total occlusion of the PP-EES and diffuse ISR in the BP-SES, treated with a paclitaxel-eluting balloon. Fluorodeoxyglucose with positron emission tomography showed increased uptake around the BP-SES, and cardiac magnetic resonance imaging revealed a late gadolinium-enhanced area around both stents. Four months later, she developed re-ISR in the BP-SES, and optical coherence tomography demonstrated diffuse-layered neointimal hyperplasia with microvascularization and peri-strut low-intensity area. She was successfully treated with coronary artery bypass grafting.

Discussion Our case demonstrated repetitive short-term ISR of the BP-SES. Observation by both intravascular and non-invasive imaging modalities suggested the presence of hypersensitivity reaction localized in the stent. Hypersensitivity to the metal may be a possible mechanism because both stents are composed of L605 cobalt–chromium alloy. This is the first report of ISR of a BP-SES with hypersensitivity reaction. Non-invasive imaging can be useful to assess this critical condition.

Keywords Drug-eluting stent • In-stent restenosis • Biodegradable polymer sirolimus-eluting stent • Hypersensitivity reaction • Case report

Learning points

- Repetitive in-stent restenosis (ISR) with hypersensitivity reaction can occur even after implantation of a biodegradable polymer sirolimus-eluting stent.
- Non-invasive imaging modalities can be useful for assessing the aetiology of repetitive ISR of drug-eluting stents.

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Introduction

Hypersensitivity reaction is a classic cause of in-stent restenosis (ISR) in coronary stents.[1] The biodegradable polymer sirolimus-eluting stent (BP-SES, Ultimaster®, Terumo Corporation, Tokyo, Japan), a new-generation drug-eluting stent (DES), was developed with a biodegradable polymer that was believed to suppress inflammation around the stent and ameliorate this effect.[2] Here, we describe the first case of repetitive ISR after BP-SES implantation with a unique observation using multiple imaging modalities, which suggests that hypersensitivity to stent struts exacerbated in-stent stenotic progression.

Timeline

Day of admission	ST-segment elevation inferior myocardial infarction (STEMI) was diagnosed. Percutaneous coronary intervention (PCI) was performed for the left circumflex artery with a permanent polymer everolimus-eluting stent, and for the left anterior descending artery with a biodegradable polymer sirolimus-eluting stent (BP-SES).
Eight months after the first admission	Non-STEMI (NSTEMI) developed because of diffuse in-stent restenosis (ISR) in both stent sites. PCI for the in-stent restenotic lesion of the BP-SES was performed with a paclitaxel-coated balloon. PCI for the in-stent restenotic lesion of the permanent polymer everolimus-eluting stent was unsuccessful.
Eleven months after the first admission	Fluorodeoxyglucose with positron emission tomography and cardiac magnetic resonance imaging were performed to explore the cause of the ISR.
Twelve months after the first admission	NSTEMI developed because of a second episode of ISR in the BP-SES and was treated with a paclitaxel-coated balloon.
Fifteen months after the first admission	NSTEMI occurred because of a third episode of ISR in the BP-SES. Coronary artery bypass grafting was performed.

Case presentation

An 81-year-old woman presented to our hospital with ST-elevation acute myocardial infarction (STEMI) and medical history of hypertension. Her vital signs were stable, and physical examination showed no specific abnormality. The patient had no family history of cardiovascular disease. Emergent coronary angiography (CAG) showed 99% and 90% stenosis in the left circumflex artery (LCx) and left anterior descending artery (LAD), respectively (*Figure 1A*). Percutaneous coronary intervention (PCI) was performed for lesions in the LCx and LAD, and a permanent polymer everolimus-eluting stent (PP-EES, Xience Alpine, Abbott Vascular, Santa Clara, CA, USA) and BP-SES were implanted respectively, using intravascular ultrasonography (IVUS) (*Figure 1B and C*). IVUS demonstrated well-expanded (minimal stent areas: 4.5 mm^2 in the LCx and 6.1 mm^2 in the LAD) and well-apposed struts without any edge dissection. Optimal medical therapy, including antiplatelet therapy with clopidogrel (75 mg/day) and aspirin (100 mg/day), was initiated, and she was discharged without any complication.

Eight months after the procedure, the patient developed non-STEMI (NSTEMI). Emergent CAG showed total occlusion of the PP-EES in the LCx and diffuse ISR in the BP-SES in the LAD, and IVUS demonstrated a heterogeneous low-echoic area localized within the BP-SES (*Figure 2A*). We successfully treated the ISR in the BP-SES with a paclitaxel-coated balloon. Staged PCI for the ISR in the PP-EES was performed but ended in failure because of the inability to cross the lesion via several techniques. The patient was compliant with the medications, and her risk factors for coronary artery disease were well controlled. Blood test results showed no sign of systemic inflammation or infection, and the patch test for any metal allergy showed no significant finding. In order to explore the cause of the ISR, we performed fluorodeoxyglucose (FDG) with positron emission tomography (PET), and increased FDG uptake (maximum standardized uptake value = 3.3) was observed around the BP-SES (*Figure 3A*). Cardiac magnetic resonance imaging (CMR) revealed high signal intensity on T2-weighted imaging (T2WI) around the BP-SES and a late gadolinium-enhanced area around the BP-SES and PP-EES, i.e. 'peristent late gadolinium enhancement (LGE)' (*Figure 3B, C* and *D*).

Twelve months after the first admission, the patient was admitted again because of NSTEMI with re-ISR in the BP-SES (*Figure 2B*). Optical coherence tomography (OCT) demonstrated diffuse-layered neointimal hyperplasia with microvascularization, macrophage accumulation, and peri-strut low-intensity area (PLIA) (*Figure 2B*). The patient was repeatedly admitted for NSTEMI with ISR in the BP-SES and was eventually treated with coronary artery bypass grafting (CABG). Subsequently, her cardiac function was preserved, and no additional coronary events were observed after a 1-year follow-up.

Discussion

Hypersensitivity reaction after the DES implantation was reported, typically as late thrombosis with the first-generation sirolimus-eluting stent (C-SES, Cypher® Cordis J&J, Miami, FL, USA)[3] but there has been no report of hypersensitivity reaction with the BP-SES. The present patient experienced repetitive short-term ISR, although no apparent risk factor was found in both the patient and the procedure of stent implantation. Analysis by intravascular imaging showed that diffuse-layered neointima with PLIA in OCT was associated with peri-strut inflammation[4,5]; a heterogeneous 'black hole'-like low echoic area detected by IVUS was believed to be a hypocellular tissue with a proteoglycan-rich or fibrin-rich extracellular matrix, reported

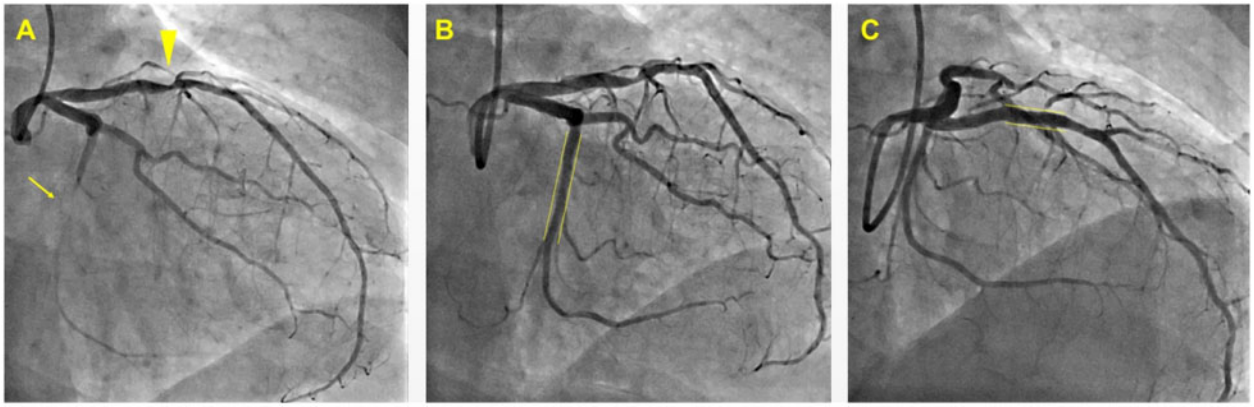

Figure 1 Coronary angiogram of ST-elevation myocardial infarction and subsequent treatment. (*A*) Angiogram of ST-elevation myocardial infarction shows total occlusion of the left circumflex artery (arrow) and 90% stenosis in the left anterior descending artery (arrowhead). (*B*) Angiogram after percutaneous coronary intervention for the left circumflex artery. (*C*) Angiogram after percutaneous coronary intervention for the left anterior descending artery.

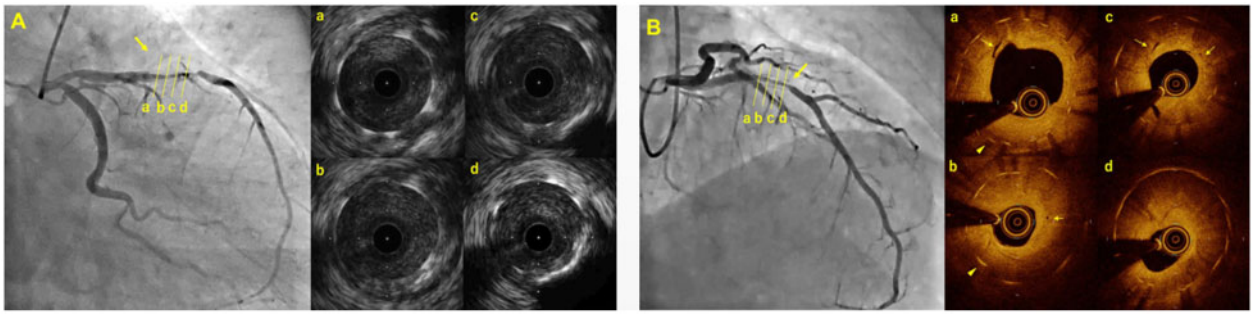

Figure 2 Coronary angiogram and intravascular imaging of the in-stent restenotic lesion. (*A*) Angiogram of the first non-ST-elevation myocardial infarction shows diffuse in-stent restenosis in the biodegradable polymer sirolimus-eluting stent (arrow) and total obstruction of the permanent polymer everolimus-eluting stent. Intravascular ultrasonogram demonstrates a heterogeneous low-echoic neointima in the in-stent restenotic lesion. The diameters of the biodegradable polymer sirolimus-eluting stent and external elastic membrane were 3.8 and 4.7 mm, respectively. (*B*) Angiogram of the second non-ST-elevation myocardial infarction demonstrates diffuse in-stent restenosis in the biodegradable polymer sirolimus-eluting stent (arrow). Optical coherence tomography reveals layered neointimal hyperplasia, microvascularization (arrow), and peri-strut low-intensity area (arrowhead).

to relate with early ISR of a C-SES.[6] Both the OCT and IVUS findings in the present case were consistent with these observations suggesting that hypersensitivity reaction to the BP-SES and PP-EES could be associated with repetitive ISR.

A non-invasive imaging modality could be useful for assessing this critical condition. We firstly reported characteristic observation by CMR as 'peri-stent LGE'. Cardiac magnetic resonance imaging leads to tissue characterization, LGE demonstrates injured cells and fibrosis, and T2WI identifies oedema from inflammation.[7] These observations were consistent with chronic inflammation localized around the BP-SES. The FDG-PET has also proven useful for quantifying inflammation within atherosclerosis.[8] We previously reported ISR and aneurysm formation with hypersensitivity reaction after the C-SES implantation, which manifested with significant uptake of FDG around the C-SES.[9] Increased accumulation of FDG around the BP-SES in the current case also indicated the role of hypersensitivity reaction in repetitive ISR. Contrarily, the PP-EES showed the LGE positive area without the FDG accumulation, suggesting slight active inflammation due to the prolonged blocked blood flow, and only fibrosis or injured cells were present around the stent. The ability of OCT or IVUS to identify tissue characteristics is controversial.[10] Observation with a combination of non-invasive imaging modalities may provide more accurate histological information and useful for assessing aetiology of ISR.

The hypersensitivity reaction, in this case, could be attributable to some components of DES: the stent platform (L605 cobalt–

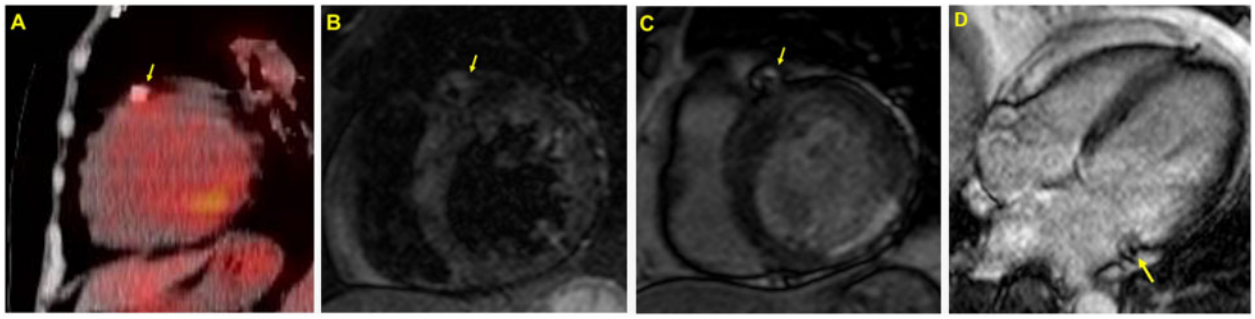

Figure 3 Non-invasive imaging assessment of in-stent restenosis. (*A*) Fluorodeoxyglucose with positron emission tomography at 10 months after the first admission shows increased fluorodeoxyglucose uptake (maximum standardized uptake value = 3.3) around the biodegradable polymer sirolimus-eluting stent (arrow). There was no increased uptake around the permanent polymer everolimus-eluting stent. (*B*) T2-weighted cardiac magnetic resonance imaging at 11 months after the first admission demonstrates the circle area with low signal intensity surrounded by increased signal intensity area in the short-axis view (arrow). The diameter of the low-intensity area is 3.6 mm, which is consistent with the biodegradable polymer sirolimus-eluting stent. The diameter of high signal intensity area is 8.2 mm, including the vessel wall and periadvential soft tissues around the stent. (*C*) Late gadolinium enhancement is seen around the stent strut, i.e. 'peri-stent late gadolinium enhancement' (arrow). (*D*) Late gadolinium enhancement is present around the permanent polymer everolimus-eluting stent (arrow).

chromium alloy for both stents), drug (everolimus for the PP-EES and sirolimus for the BP-SES), and polymer [fluorinated copolymer (poly-n-butyl methacrylate and vinylidene fluoride and hexa uoropropylene) of PP-EES and biodegradable polymer (poly dl-lactide and polyε-caprolactone) of the BP-SES].[11] In this case, hypersensitivity to L605 cobalt–chromium alloy could be a possible mechanism because both stents are composed of this alloy. In fact, the polymer or drug might not be the allergen, as ISR with hypersensitivity still occurred 8 and 12 months after the stent implantation when the biodegradable polymer and sirolimus were suspected to disappear.[11]

The patient showed no classic sign of allergy, an elevated inflammation marker, or positive patch testing. Systemic biomarkers may fail to detect localized inflammation. Additionally, the evaluation of ISR with hypersensitivity by patch testing was reported to be limited because of its low sensitivity and the difference of hypersensitivity reaction in the vessel from that on the skin.[12,13] To our knowledge, there have been only two reports on ISR of a second-generation DES due to hypersensitivity.[14,15] Further investigation is needed to reveal the mechanism and reliable evaluation method of hypersensitivity in new-generation DESs.

In addition, the optimal treatment for this condition has not been established. We successfully treated our patient with CABG, which could be a safe treatment of choice. Furthermore, a study had reported on the successful prevention of ISR with hypersensitivity by prednisolone and tranilast.[15] The utility of anti-inflammatory drugs against repetitive ISR should be further investigated.

In conclusion, we reported the first case of repetitive ISR in a BP-SES with hypersensitivity reaction. Non-invasive imaging modalities, such as CMR and FDG-PET, may be useful for assessing the aetiology of repetitive ISR. The issue of hypersensitivity remains in the newer generation DES era.

Lead author biography

Takahiro Jimba, MD, graduated from Tokyo University Faculty of Medicine in 2016. He completed post-graduate residency programme and has worked as a fellow in cardiology at NTT Medical Center Tokyo.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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