

Case Report

Metal Allergy to Everolimus-Eluting Cobalt Chromium Stents Confirmed by Positive Skin Testing as a Cause of Recurrent Multivessel In-Stent Restenosis

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A 54-year-old woman treated with cobalt-chromium everolimus eluting stents (CoCr-EES) for her left distal circumflex and diagonal branch lesions suffered from repeated in-stent restenosis in both lesions. Neointimal proliferation occurred rapidly and almost simultaneously in the two lesions. The cause was established to be metal allergy, as determined by patch tests which were strongly positive for bare metal stents and weakly positive for CoCr-EES. Following the third successive angioplasty, we initiated treatment with prednisolone (30 mg daily) and the anti-allergic and anti-proliferative drug tranilast (300 mg daily). An elective angiogram performed 3 months later showed no evidence of in-stent restenosis in any of the stented lesions. Furthermore, the patient has remained angina-free for 15 months. The unique features of this case include: (1) near-simultaneous repeated multivessel in-stent restenosis in a patient with skin test-documented metal allergy to cobalt-chromium stents; (2) adjunctive systemic medical therapy with prednisolone and tranilast appeared to terminate the malignant restenotic cycle. © 2015 Wiley Periodicals, Inc.

Key words: cobalt-chromium everolimus eluting stent; metal allergy; restenosis; prednisolone; tranilast

INTRODUCTION

In-stent restenosis (ISR) is the important problem after percutaneous coronary intervention (PCI) and coronary stent implantation [1,2]. Drug eluting stents (DES) have excellent long-term patency compared with bare metal stents (BMS), especially cobalt-chromium everolimus eluting stents (CoCr-EES) [3,4]. CoCr-EES stents also show the lowest stent thrombosis rate among all coronary stents [5]. On the other hand, metal allergy is thought to be a matter of some concern in ISR [6]. Here we report a patient with recurrent ISR after CoCr-EES implantation and demonstrable metal allergy, in whom malignant cycles of repeated restenosis were terminated by prednisolone and tranilast.

CASE REPORT

A 54-year-old woman was admitted to the emergency room complaining of chest oppression. Her coronary risk factors included dyslipidemia and smoking. Emergent coronary angiography showed several signifi-

cant stenotic lesions in the left distal circumflex and diagonal branches (Figs. 1a and 2a). Accordingly, emergent PCI was carried out and a single CoCr-EES 3.0 × 18 mm stent (XIENCE Prime, Abbott, USA) implanted in the left circumflex artery culprit lesion (Fig. 1b). Two weeks later elective coronary intervention was performed in the diagonal branch by implanting a CoCr-EES 3.0 × 15 mm stent (Fig. 2b).

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Conflict of interest: Nothing to disclose for all authors.

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Received 18 September 2014; Revision accepted 18 April 2015

DOI: 10.1002/ccd.26017

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com)

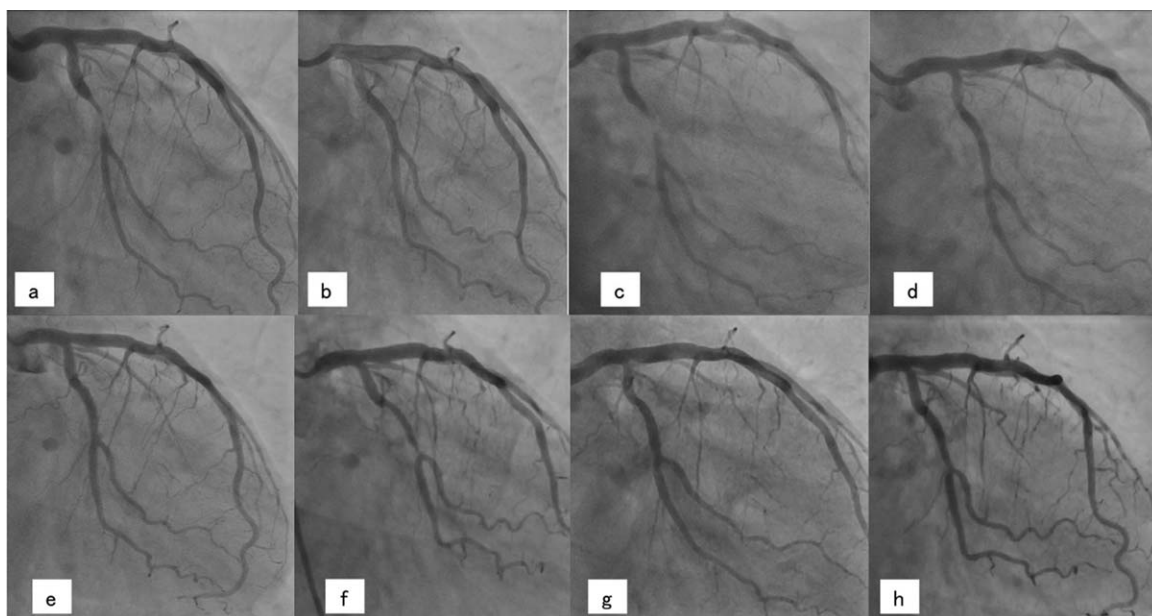


Fig. 1. A series of left circumflex coronary artery angiograms. (a) Control angiogram preceding the first PCI showing significant left circumflex stenosis; (b) angiogram following the first PCI just after CoCr-EES 3.0×18 mm implantation; (c) angiogram 6 months following the first PCI showing diffuse left circumflex ISR; (d) angiogram following the second PCI just after

dilation with a 3.0×13 mm scoring balloon; (e) angiogram 2 weeks following the second PCI showing no significant ISR; (f) angiogram 5 weeks following the third PCI showing recurrent left circumflex ISR; (g) angiogram following the fourth PCI just after dilation with a 3.0×10 mm cutting balloon; (h) angiogram 3 months following the fourth PCI showing no significant ISR

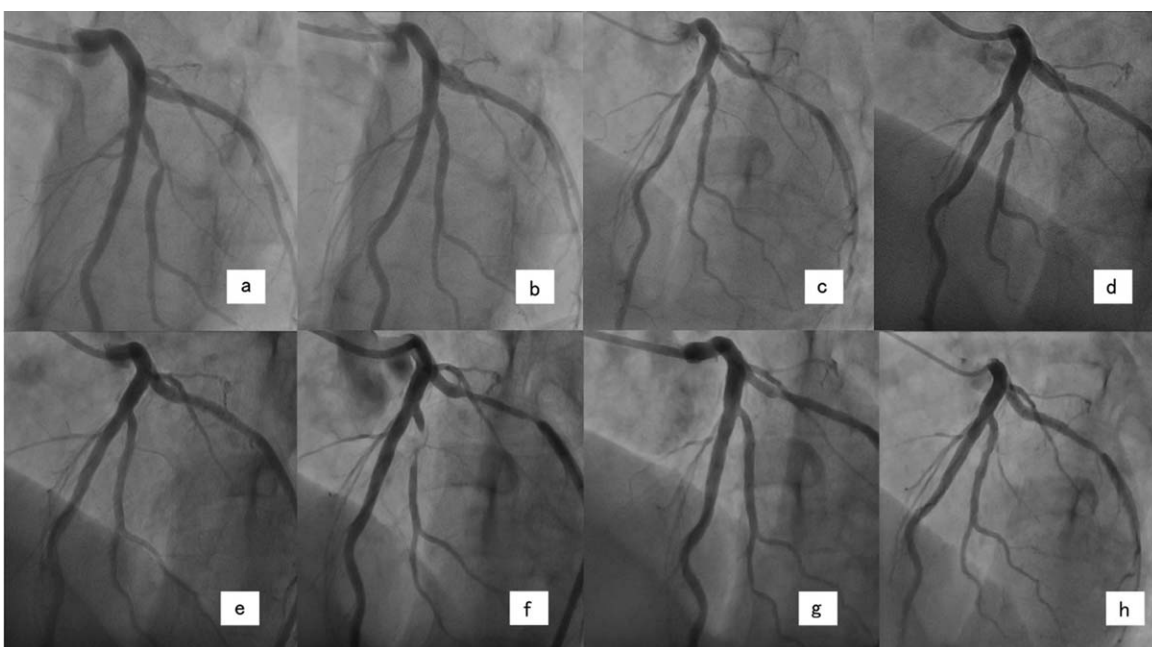


Fig. 2. A series of diagonal branch coronary artery angiograms. (a) Control angiogram preceding the first PCI showing significant diagonal branch stenosis; (b) angiogram following the first PCI just after CoCr-EES 3.0×15 mm implantation; (c) angiogram 6 months following the first PCI showing no significant ISR; (d) angiogram 2 weeks following the second PCI

showing diagonal branch ISR; (e) angiogram following the third PCI just after dilation with a 2.5×13 mm scoring balloon; (f) angiogram 5 weeks following the third PCI showing recurrent diagonal branch ISR; (g) angiogram following the fourth PCI just after dilation with a 3.0×10 mm cutting balloon; (h) angiogram 3 months following the fourth PCI showing no significant ISR

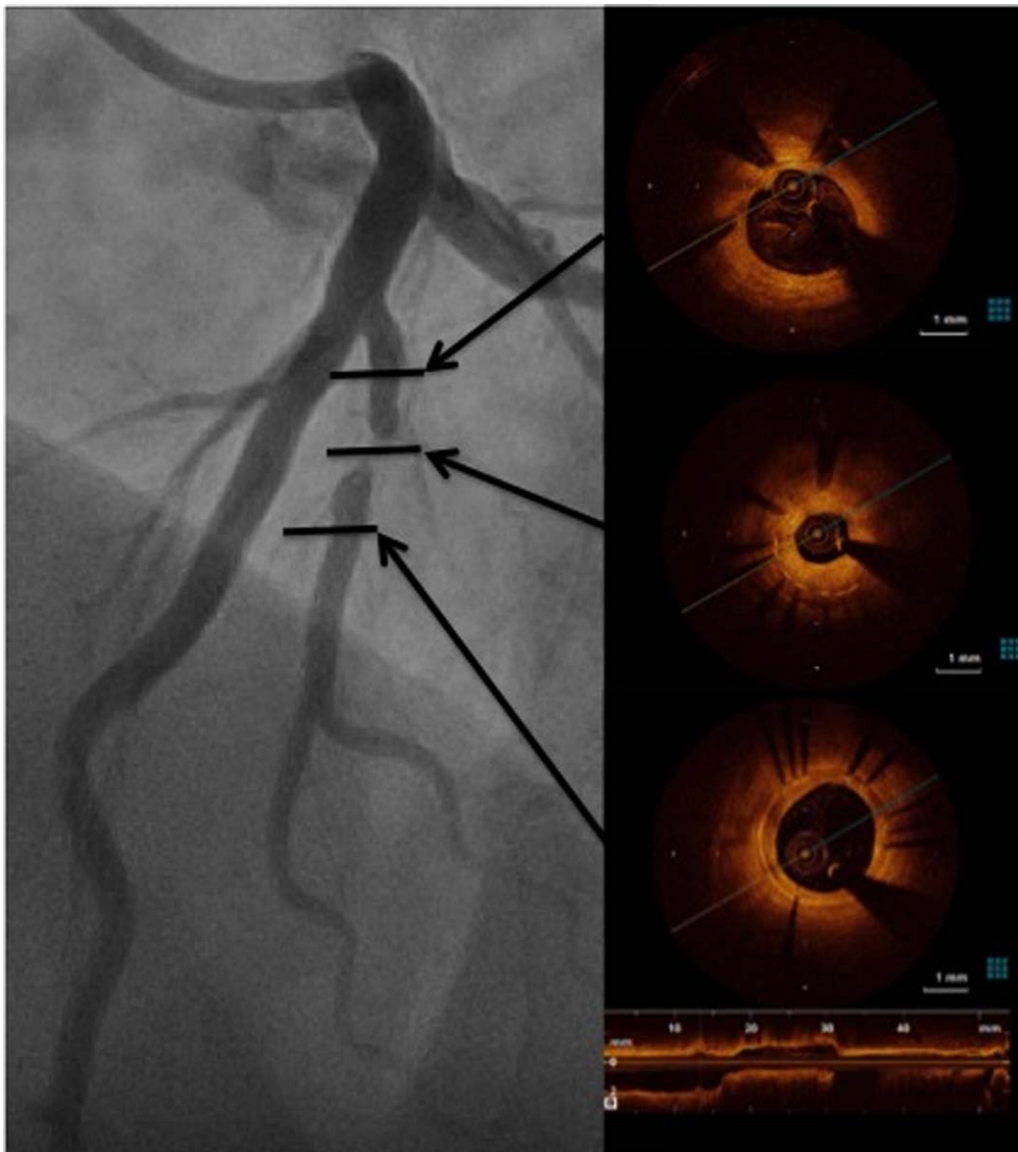


Fig. 3. OCT in the ISR site (left, arrows) revealed homogenous neointimal hyperplasia (right).

Six months after the initial PCI, the patient arrived at emergency room complaining once again of chest pain. Emergent coronary angiography was performed, and demonstrated diffuse ISR in the left distal circumflex. On this occasion, mild neointimal hyperplasia was observed within the diagonal stent segment (Figs. 1c and 2c). We performed a second PCI in the left distal circumflex (Fig. 1d) with a 3.0×13 mm scoring balloon (Lacrosse NSE alfa, Goodman, Japan). Two weeks after this second PCI the patient had another episode of chest pain. Coronary angiography revealed that rapidly progressive neointimal hyperplasia had occurred in the stented lesion in the diagonal branch within this short period of less than 2 weeks, and was

presumably the cause of the unstable angina symptoms (Figs. 1e and 2d). This led to a third PCI (2nd PCI to diagonal branch). Intravascular observation with optical coherence tomography (OCT) demonstrated (1) good stent expansion; (2) no evidence of uncovered stent struts or thrombus; (3) homogeneous neointimal hyperplasia (Fig. 3). Treatment of the stenosis was carried out (Fig. 2e) with a 2.5×13 mm scoring balloon (Lacrosse NSE alfa, Goodman, Japan).

In view of the unusual neointimal responses in all the stented segments, we inquired in detail about the patient's previous medical history. She confessed to us metal allergy except platinum after the second PCI to diagonal branch, although she did not disclose having



Fig. 4. Three days after patch test of stent materials. (1) Weakly positive test to CoCr-EES; (2) strongly positive test to CoCr-BMS; (3) negative test in control.

a history of metal allergy before the first PCI. We opted to perform skin testing. Accordingly, skin patch testing was conducted using cut “actual stents” in the Dermatology Department, and an independent dermatologist interpreted the results. The test showed (1) weak positivity in a CoCr-EES (XIENCE Prime, Abbott, USA) with appearance of red spots; (2) strong positivity in a cobalt-chromium BMS (Multi link 8, Abbott, USA) with evidence of small blisters and infiltrative erythema; and (3) control negativity (Fig. 4).

Five weeks after the third PCI, the patient arrived at the emergency room with another episode of chest pain. Emergent angiography showed recurrent ISR in both the left circumflex and diagonal branches where balloon dilatation had been performed (Figs. 1f and 2f). Since this patient had been shown to have allergic reactions to both BMS and DES by skin test, additional stenting was considered to be contraindicated. Accordingly, 3.0×10 mm cutting balloon dilatation (Flex-tome, Boston Scientific, USA) was selected as the fourth PCI device for both the recurrent ISR lesions (Figs. 1g and 2g). Additionally, we started prednisolone (30 mg daily) and the anti-allergic drug tranilast (300 mg daily) with the expectation of minimizing allergic reactions. Follow-up coronary angiography at 3 months from the fourth PCI which is at 12 months from the stents implantation revealed no ISR in either of the stented lesions (Figs. 1h and 2h). Following ischemic assessment with myocardial perfusion imaging showed negative at 10 months after the fourth PCI. The dose of prednisolone was gradually tapered over the ensuing year to a final dose of 2.5 mg/day, and the

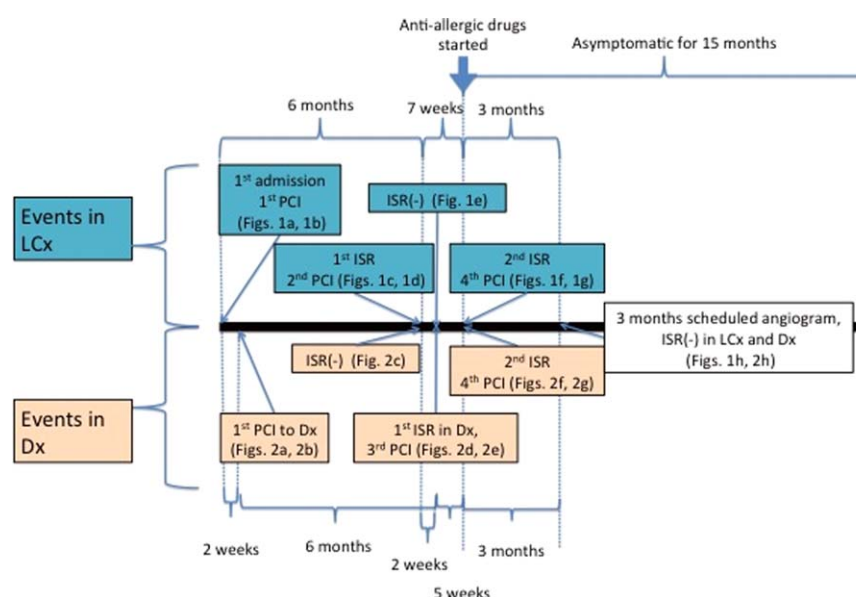


Fig. 5. Time course in this case; events in circumflex and diagonal vessels shown in the upper and lower part of the figure, respectively. Abbreviations: LCx = left circumflex; Dx = diagonal.

regimen of tranilast was continued by the same dose. Currently, the patient has experienced no chest pain for 15 months. The overall clinical course in this patient is shown in Fig. 5.

DISCUSSION

The unique features of this case are as follows: Firstly, acute progression of ISR was observed in the diagonal branch 6 months after the initial PCI. Secondly, shortly after the third PCI recurrent ISR progressed rapidly in both the left distal circumflex and diagonal branches. Thirdly, OCT images indicated that in-stent tissue appeared to consist of excessive neointimal hyperplasia rather than thrombotic components. Fourthly, skin testing using actual stents showed positivity. Finally, after initiation of therapy for metal allergy the malignant ISR cycle stopped. Combining these facts, it appears that in this case metal allergy may have caused the unusual neointimal proliferation within the stents.

Köster et al. reported that metal allergy was frequently observed in patients with BMS restenosis compared with patients without restenosis [6], and another publication has reported similar findings [7]. Nickel, cobalt, and chromium contained by Co-Cr alloy are associated with the allergic reaction, especially nickel is thought to be the strongest affect metal to allergy. Interestingly, we noted different reactions by patch test between BMS and CoCr-EES of identical metallic composition but without surface polymer in the former case. Polymer may prevent direct contact with cobalt-chromium, and might attenuate but not abolish such allergic reactions.

Interactions of several drugs should also be discussed in this case. Everolimus is well known to be an immunosuppressive agent [8], and the drug when released from polymer may suppress the contact allergic reaction. A prior study indicated that oral everolimus suppresses in-stent neointimal growth in the rabbit iliac artery [9], and it has also been shown that DES can reduce ISR in metal allergy patients by an immunosuppressive effect [10]. Considering drug kinetics, CoCr-EES releases the drug for 4 months in porcine coronary artery [11], and during this period allergic reactions could be suppressed. Tranilast may also reduce neointima formation by an anti-allergic and anti-proliferative effect [12,13]. Potentially effective agents include both steroids and tranilast, however their success in ameliorating ISR has been suboptimal [14,15]. Nonetheless they may prove to be effective in some limited clinical situations. After stent implantation everolimus may initially serve to prevent allergic reactions, but after completion of drug release allergic

reactions and ISR may occur. Prednisolone and anti-allergic drugs such as tranilast may improve prognosis in patients with metal allergy after stent implantation, but long-term follow-up may be needed to detect side effects or other coronary reactions.

In conclusion, we treated a patient with rapidly progressive recurrent ISR due to metal allergy to implanted stents. After treatment with prednisolone and tranilast recurrent ISR has not been observed for 15 months. This case and its time course may prove to be quite unique and instructive for interventional cardiologists.

ACKNOWLEDGMENT

Authors would like to thank Kazuhiro Takahashi MD (Dermatology Department), Takumi Kimura MD, Yu Ishikawa MD, Kentarou Komuro MD, Satoshi Nakajima MD, Ryohei Sakamoto MD, Tetsuya Fusazaki MD (Division of Cardiology, Department of Internal Medicine).

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