

Hypersensitivity Reaction in the US Food and Drug Administration–Approved Second-Generation Drug-Eluting Stents

Histopathological Assessment With Ex Vivo Optical Coherence Tomography

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A 55-year-old white man received 4 coronary stents, 3 Resolute zotarolimus-eluting stents (R-ZES; Medtronic, Santa Rosa, CA) and 1 XIENCE Xpedition (CoCr-EES; Abbott Vascular, Santa Clara, CA), for unstable angina pectoris 238 days antemortem. The patient was found dead and had recently been seen without any complaints. The patient had a history of hypertension, hyperlipidemia, and smoking. At the time of stent placement, coronary angiography revealed diffuse disease in the left anterior descending artery (LAD) with severe stenosis of the proximal LAD and moderate to severe stenosis of the mid LAD. Percutaneous coronary intervention was carried out, and 4 overlapping drug-eluting stents (DES) were implanted in the proximal-to-distal LAD with the following stent types and sizes used from proximal to distal: R-ZES (2.25×22 mm), CoCr-EES (2.25×28 mm), R-ZES (2.25×26 mm), and R-ZES (2.25×12 mm).

Before the histopathological assessment, postmortem coronary angiography and optical coherence tomography were performed that showed patent stented segments in the LAD (Figure 1). Histological examination of the LAD stented segments revealed the presence of persistent fibrin deposition and extensive circumferential inflammation consisting of palisading macrophages, T lymphocytes, eosinophils, and multinucleated giant cells, with focal luminal smooth muscle and the presence of focal endothelial cells in both CoCr-EES and R-ZES, consistent with hypersensitivity reaction (Figures 1 and 2).

Hypersensitivity vasculitis is a critical complication after the implantation of DES and has been reported to be associated with late and very late stent thrombosis, which has been reported almost exclusively in the first-generation sirolimus-eluting stents (SES) (Cypher, Cordis J&J, Miami, FL). Considering that hypersensitivity reaction was observed in both CoCr-EES and R-ZES in this case, the phenomenon may be attributable to any 1 of the 2 components of DES: drug (“-limus” drugs) and polymer (fluorinated copolymer [poly *n*-butyl methacrylate (PBMA) and vinylidene fluoride and hexafluoropropylene] of CoCr-EES and the BioLinx polymer

[polyethylene C primer coat combined with C10, C19, and polyvinyl pyrrolidone] of R-ZES). There is little commonality between the polymers of these stents except PBMA, which is present in both stents and has been implicated in hypersensitivity reaction in SES.¹

Peri-strut evaginations have been associated with the presence of hypersensitivity vasculitis, especially after SES implantation, and late stent thrombosis.² Our present case did not reveal peri-strut evaginations by optical coherence tomography as reported previously with SES, which clearly emphasizes the diversity in optical coherence tomography appearance of delayed type hypersensitivity reactions.

To the best of our knowledge, hypersensitivity vasculitis to R-ZES has not been reported; however, there is a case report on the occurrence of hypersensitivity pneumonitis after deployment of the Endeavor stent that resembles the reactions we observed in our patient around stent struts consisting of lymphocytes, eosinophils, macrophages, and giant cells, suggesting that zotarolimus may be the underlying mechanism.³ Although we suggested previously that the polymer in SES may be the underlying mechanism of hypersensitivity vasculitis, sirolimus drug toxicity cannot be ruled out because similar pulmonary infiltrates and hypersensitivity pneumonitis have now also been reported after sirolimus therapy in patients with kidney transplantation.⁴ As implied above in the case of the first-generation SES, we had suggested that most of the hypersensitivity vasculitis was related to PBMA; however, we believe that in the second-generation CoCr-EES and R-ZES, polymers have shown relatively less inflammation.

The inflammatory reaction in our patient was very similar in the 2 different stents, that is, R-ZES and CoCr-EES. However, there was greater severity of the inflammatory infiltrate, including eosinophils, lymphocytes, and giant cells, in the CoCr-EES than in the R-ZES, and the luminal narrowing was also greater in CoCr-EES, whereas none of the 4 stents showed significant restenosis.

DES have been implanted in millions of patients worldwide where the second-generation DES have become the

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dominant device of choice. Our findings indicate that careful long-term follow-up remains important even after placement of the second-generation DES and that we need to remain vigilant for the presence of hypersensitivity reaction.

Disclosures

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and St. Jude. Dr. Otsuka has received speaking honorarium from Abbott Vascular and Merck. The other authors report no conflicts.

References

1. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701–705. doi: 10.1161/01.CIR.0000116202.41966.D4.
2. Tada T, Kadota K, Hosogi S, Kubo S, Ozaki M, Yoshino M, Miyake K, Eguchi H, Ohashi N, Hayakawa Y, Saito N, Otsuru S, Hasegawa D, Shigemoto Y, Habara S, Imai M, Tanaka H, Fuku Y, Oka N, Kato H, Yamamoto H, Fujii S, Goto T, Mitsudo K. Optical coherence tomography findings in lesions after sirolimus-eluting stent implantation with peri-stent contrast staining. *Circ Cardiovasc Interv*. 2012;5:649–656. doi: 10.1161/CIRCINTERVENTIONS.112.968487.
3. Shin HW, Nam CW, Kim H, Hur SH, Kim YN, Kim KB, Kwon KY. Zotarolimus-eluting stent-induced hypersensitivity pneumonitis. *Korean J Intern Med*. 2013;28:108–111. doi: 10.3904/kjim.2013.28.1.108.
4. Buhaescu I, Izzedine H, Covic A. Sirolimus: challenging current perspectives. *Ther Drug Monit*. 2006;28:577–584. doi: 10.1097/01.fdt.0000245377.93401.39.

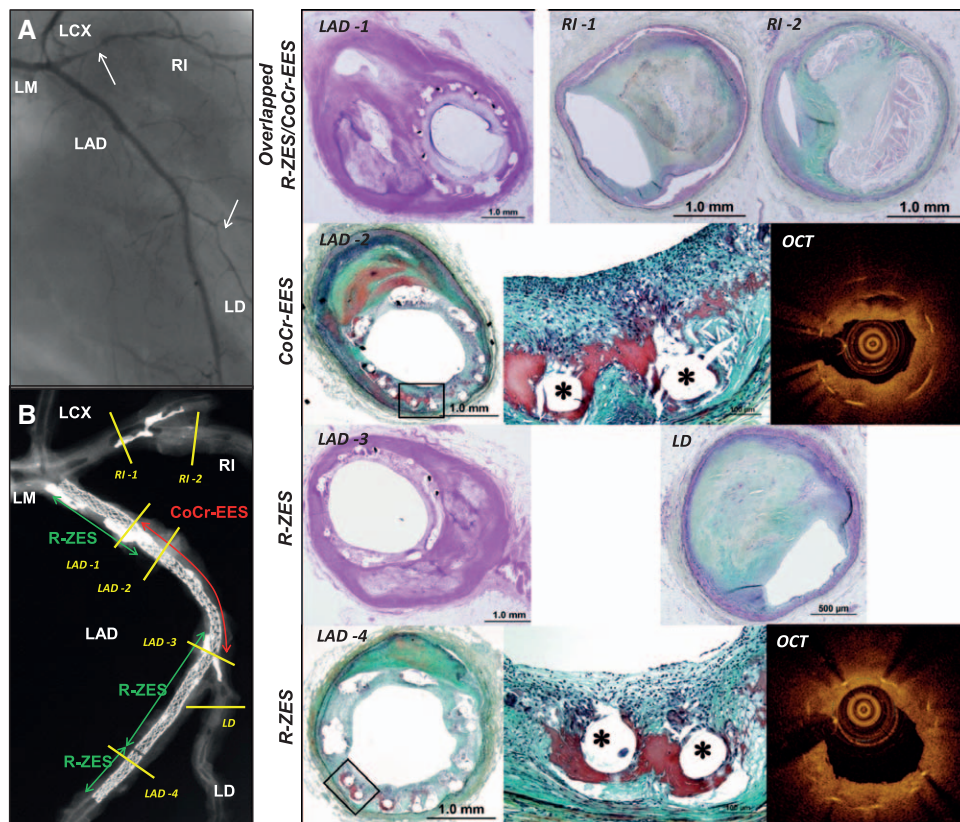


Figure 1. Hypersensitivity reaction in Resolute zotarolimus-eluting stents (R-ZES) and XIENCE Xpedition cobalt-chromium everolimus-eluting stent (CoCr-EES). **A**, Postmortem coronary angiography showing patent stented lesions in the left anterior descending artery (LAD) but severe narrowing of the ramus intermedius (RI; arrow) and left diagonal (LD; arrow) arteries. **B**, Postmortem radiograph showing 4 partially overlapped stents (from proximal to distal: R-ZES [2.25×22 mm], CoCr-EES [2.25×28 mm], R-ZES [2.25×26 mm], and R-ZES [2.25×12 mm]) in the LAD with underlying moderate calcification in the proximal LAD. Histological cross sections of the stented segments are shown on the **right** and are marked by yellow lines in the radiograph on the **left** in positions LAD-1 (overlapped R-ZES and CoCr-EES), LAD-2 (CoCr-EES), and LAD-3 and -4 (R-ZES) showing extensive inflammation and mild neointimal thickening. **Right**, High-power images from the boxed areas in LAD-2 and -4. The region of struts (asterisk) is surrounded by fibrin (red) and severe chronic inflammatory reaction on the luminal surfaces. **Far right**, Corresponding ex vivo optical coherence tomography (OCT) images are depicted, corresponding to LAD-2 and -4 and showing mild to moderate neointimal growth with focal signal poor region around stent struts. LCX indicates left circumflex; and LM, left main.

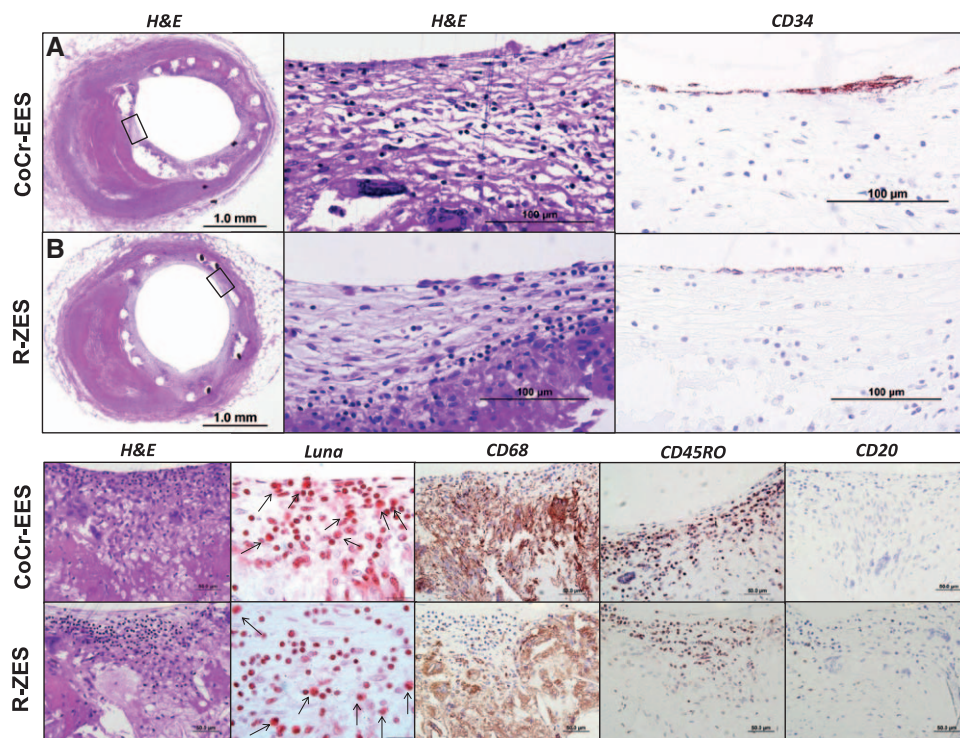


Figure 2. Chronic inflammatory reaction consisting of eosinophils (Luna stain), macrophages (CD68), T lymphocytes (CD45RO), and B lymphocytes (CD20) surrounding the cobalt-chromium everolimus-eluting stent (CoCr-EES) and Resolute zotarolimus-eluting stents (R-ZES) with focal presence of luminal endothelial (CD34) cells. **A** and **B**, Low-power images of CoCr-EES (**A**) and R-ZES (**B**) with corresponding high-power images of boxed areas in **A** and **B** illustrating focal presence of endothelial cells (hematoxylin and eosin [H&E]). **Far right**, The corresponding immunohistochemistry images stained with antibodies against CD34 showing focal presence of endothelial cells (brown staining). **Bottom**, High-power H&E-stained images of histological sections showing persistent fibrin deposition and extensive chronic inflammation with prominent palisading macrophages and giant cells. Other high-power images show the presence of eosinophils (Luna stain, black arrows), macrophages and giant cells (CD68 staining, brown areas), and T lymphocytes (CD45RO, brown areas) and the absence of B-lymphocytes (CD20).