Journal of Cardiology Cases 12 (2015) 150–151

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Editorial

Editorial: Remaining issue after drug-eluting stent implantation: Histopathological mechanisms of early-phase in-stent restenosis

Keywords:
In-stent restenosis
Histopathology
Angioscopy
Optical coherence tomography

Stent implantation has been used to treat coronary artery stenosis for about three decades. Treatment with bare metal stent (BMS) successfully restores the acute vessel lumen, but the long-term outcomes are often compromised by in-stent restenosis (ISR). Use of drug-eluting stents (DES) has significantly reduced ISR compared with BMS over mid-term follow-up [1]. However, recent studies have shown that DES are associated with delayed and progressive neointimal proliferation during long-term follow-up, termed the "late catch-up" phenomenon [2]. One of the established mechanisms underlying late or very late ISR in DES is neoatherosclerosis developing within neointima. Neoatherosclerosis is pathohistologically recognized as clusters of lipid pools within the neointima, representing the entire spectrum from lipid-rich plaque to plaque rupture.

In contrast to late or very late ISR, histopathological evaluation of early-phase (within 12 months after stent implantation) ISR lesions in DES has not been systematically conducted due to insufficient availability of autopsy samples. The availability of optical coherence tomography (OCT) has enabled us to identify the morphological characteristics of neointimal tissue (homogeneous, layered, or heterogeneous patterns) *in vivo* [3]. Early-phase ISR lesions in DES are more often hypocellular heterogeneous tissue comprising scanty smooth muscle cells and abundant extracellular matrix such as proteoglycan and fibrin [4]. A comparison of OCT findings and histopathological findings of retrieved restenotic tissue demonstrated that layered or heterogeneous intima without attenuation on OCT images may represent extracellular matrix or fibrin accumulation [5]. The neointimal healing process was materialized by the substitution of smooth muscle cells for fibrin deposition after stent implantation [6]. DES delays this neointimal healing process, and neointima with fibrin accumulation (so-called fibrin thrombus) shows a heterogeneous OCT pattern in early-phase ISR lesions in DES [7]. In addition, serial OCT examinations 9–18 months after DES implantation have shown that heterogeneous tissue composition detected at 9 months might be associated with late neointimal tissue growth at 18 months [8].

Excessive in-stent neointimal hyperplasia is the main factor contributing to early-phase ISR, particularly with BMS [9]. On the other hand, the main cause of early-phase ISR in DES remains unclear. In this issue of the *Journal of Cardiology Cases*, Ito et al. report a case of coronary angioscopic imaging of early-phase ISR after biolimus-eluting coronary stent implantation [10]. Coronary angioscopy is an endoscopic technology allowing direct visualization of the surface color and superficial morphology of ISR lesions. Based on the heterogeneous pattern of OCT images, and the white paste-like appearance on coronary angioscopy, the authors speculated that fibrin thrombus formation based on delayed vascular healing process after DES implantation represented the pathological cause in this case. DES strongly inhibits neointimal growth by pharmacologically suppressing smooth muscle cell proliferation and extracellular matrix production. Thus, DES delays endothelial cell coverage of stent struts. Even after re-endothelialization, endothelial function could be impaired after DES implantation [11]. Endothelial dysfunction after DES implantation may be related to excessive fibrin thrombi causing coronary flow disturbance and the development of early-phase ISR. In addition, this case has a history of type 2 diabetes mellitus (DM) [12]. In general, DM is a well-known independent risk factor for ISR [12]. Patients with DM have more complex coronary lesion morphology, and higher plaque volume that may cause incomplete and asymmetric stent expansion. Furthermore, patients with DM often have systemic prothrombotic conditions related to the activation of the platelet aggregation and coagulation systems [13]. Resistance to both aspirin and clopidogrel occurs more commonly in patients with DM compared to patients without DM [14]. Considering the above-mentioned factors, not only local factors but systemic factors also may contribute to the development of early-phase ISR of DES with thrombus formation.

Despite ISR being markedly reduced by DES, a 5–7% incidence of early-phase ISR lesions has been reported with DES in trials and registries of percutaneous coronary intervention [15]. The findings from this case report need to be further confirmed, but this report provides invaluable observations of early-phase ISR lesions in DES. A clinical approach with multimodal coronary imaging, such as intravascular ultrasound, OCT, and coronary angioscopy, could

DOI of original article: http://dx.doi.org/10.1016/j.jccase.2015.06.004

http://dx.doi.org/10.1016/j.jccase.2015.07.007

reveal the underlying mechanisms of early-phase ISR in DES and overcome the remaining problems after DES implantation.

References

[1] Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME, TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.

[2] Nakazawa G, Finn AV, Vorpahl M, Ladich ER, Kolodgie FD, Virmani R. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. J Am Coll Cardiol 2011;57:390–8.

[3] Gonzalo N, Serruys PW, Okamura T, van Beusekom HM, Garcia-Garcia HM, van Soest G, van der Giessen W, Regar E. Optical coherence tomography patterns of stent restenosis. Am Heart J 2009;158:284–93.

[4] Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57:1314–22.

[5] Nagai H, Ishibashi-Ueda H, Fujii K. Histology of highly echolucent regions in optical coherence tomography images from two patients with sirolimus-eluting stent restenosis. Catheter Cardiovasc Interv 2010;75:961–3.

[6] Farb A, Sangiorgi G, Carter AJ, Walley VM, Edwards WD, Schwartz RS, Virmani R. Pathology of acute and chronic coronary stenting in humans. Circulation 1999;99:44–52.

[7] Nakano M, Vorpahl M, Otsuka F, Taniwaki M, Yazdani SK, Finn AV, Ladich ER, Kolodgie FD, Virmani R. Ex vivo assessment of vascular response to coronary stents by optical frequency domain imaging. JACC Cardiovasc Imaging 2012;5:71–82.

[8] Fukuhara K, Okura H, Kume T, Yamada R, Neishi Y. In-stent neointimal characteristics and late neointimal response after drug-eluting stent implantation: a preliminary observation. J Cardiol 2015. in press.

[9] Grewe PH, Deneke T, Machraoui A, Barmeyer J, Muller KM. Acute and chronic tissue response to coronary stent implantation: Pathologic findings in human specimen. J Am Coll Cardiol 2000;35:157–63.

[10] Ito S, Saeki T. Coronary angioscopic imaging of in-stent restenosis after biolimus-eluting coronary stent implantation. J Cardiol Cases 2015;12:145–9.

[11] van den Heuvel M, Sorop O, van Beusekom HM, van der Giessen WJ. Endothelial dysfunction after drug eluting stent implantation. Minerva Cardioangiol 2009;57:629–43.

[12] Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: Data from a large two-institutional cohort study. Lancet 2007;369:667–78.

[13] Yonetsu T, Kato K, Kim SJ, Xing L, Jia H, McNulty I, Lee H, Zhang S, Uemura S, Jang Y, Kang SJ, Park SJ, Lee S, Yu B, Kakuta T, et al. Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry. Circ Cardiovasc Imaging 2012;5:660–6.

[14] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Costa MA, Bass TA, Macaya C. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. Diabetes 2005;54:2430–5.

[15] Puricel S, Arroyo D, Corpataux N, Baeriswyl G, Lehmann S, Kallinikou Z, Muller O, Allard L, Stauffer JC, Togni M, Goy JJ, Cook S. Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds. J Am Coll Cardiol 2015;65:791–801.

Teruyoshi Kume (MD, FJCC)*
Shiro Uemura (MD, FJCC)
Department of Cardiology, Kawasaki Medical School, Kurashiki, Japan

*Corresponding author at: Department of Cardiology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan. Tel.: +81 86 462 1111; fax: +81 86 462 1199
E-mail address: tteru@med.kawasaki-m.ac.jp (T. Kume).

13 July 2015