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A Case of In-Stent Neoatherosclerosis 10 Years after Carotid Artery Stent Implantation: Observation with Optical Coherence Tomography and Plaque Histological Findings

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Abstract

We report a patient's case of slow progressive in-stent restenosis 10 years after bare-metal stent implantation to his carotid artery. We treated the patient with an additional stent placement under a distal filter protection device. Optical coherence tomographic assessment and plaque histology during the carotid artery stenting (CAS) revealed atheromatous change at in-stent neointima, which contained lipid-rich plaque and calcification deposits. These findings suggest that in-stent neoatherosclerosis may play an important role in the pathogenesis of very late stent restenosis after CAS.

Key words: in-stent restenosis, atherosclerosis, carotid artery stenting, optical coherence tomography

Introduction

According to previous studies, the incidence of restenosis seems to be highest in the first year after carotid artery stenting (CAS), and neointimal hyperplasia is the major pathophysiologic process leading to early restenosis after CAS.[1–4] Neointimal hyperplasia has been considered a benign and stable vascular wall response after bare-metal stent (BMS) implantation. Although the short-term restenosis rates after CAS are acceptable, there is little information about long-term follow-up restenosis after CAS. We report a case of slow progressive in-stent restenosis (ISR) 10 years after BMS implantation to the carotid artery. We confirmed the atherosclerotic change of in-stent neointima with optical coherence tomography (OCT) imaging and plaque histology. Recently, several coronary intervention studies have reported on the problem of very late in-stent thrombosis after coronary drug-eluting stent (DES) or BMS implantation.[5–9] Neointimal atheromatous change, which is a new concept linked to neoatherosclerosis, has been thought to play an important role in late stent thrombosis. A similar process might be observed after CAS.

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Case Report

A 73-year-old man was admitted to our institution to undergo an examination for progressive ISR after right CAS. He underwent CAS 10 years ago, under the distal balloon protection technique because of right internal carotid artery stenosis with amaurosis fugax of the right eye (Fig. 1A, B). He had a history of diabetes and he was also treated for angina pectoris with coronary intervention 9 years ago. He had received dual antiplatelet therapy with aspirin and clopidogrel since the previous CAS. There was slight evidence of ISR upon follow-up carotid angiography (CAG) 9 months after the previous CAS (Fig. 1C). Thereafter, a follow-up carotid ultrasonography and the CAG showed gradually progressive ISR of the right carotid artery (Fig. 1D). Ten years after the previous CAS, the patient complained of a clumsy left hand. Magnetic resonance imaging on this admission demonstrated newly ischemic lesions on the right cerebral hemisphere (Fig. 2A). Carotid ultrasonography also demonstrated significant intimal thickness with a hypoechoic signal (Fig. 2B). The CAG revealed evidence of progressive diffuse in-stent stenosis and previous stent enlargement (Fig. 2C). We made a plan to treat the progressive restenotic lesion with in-stent balloon angioplasty and additional stent placement.

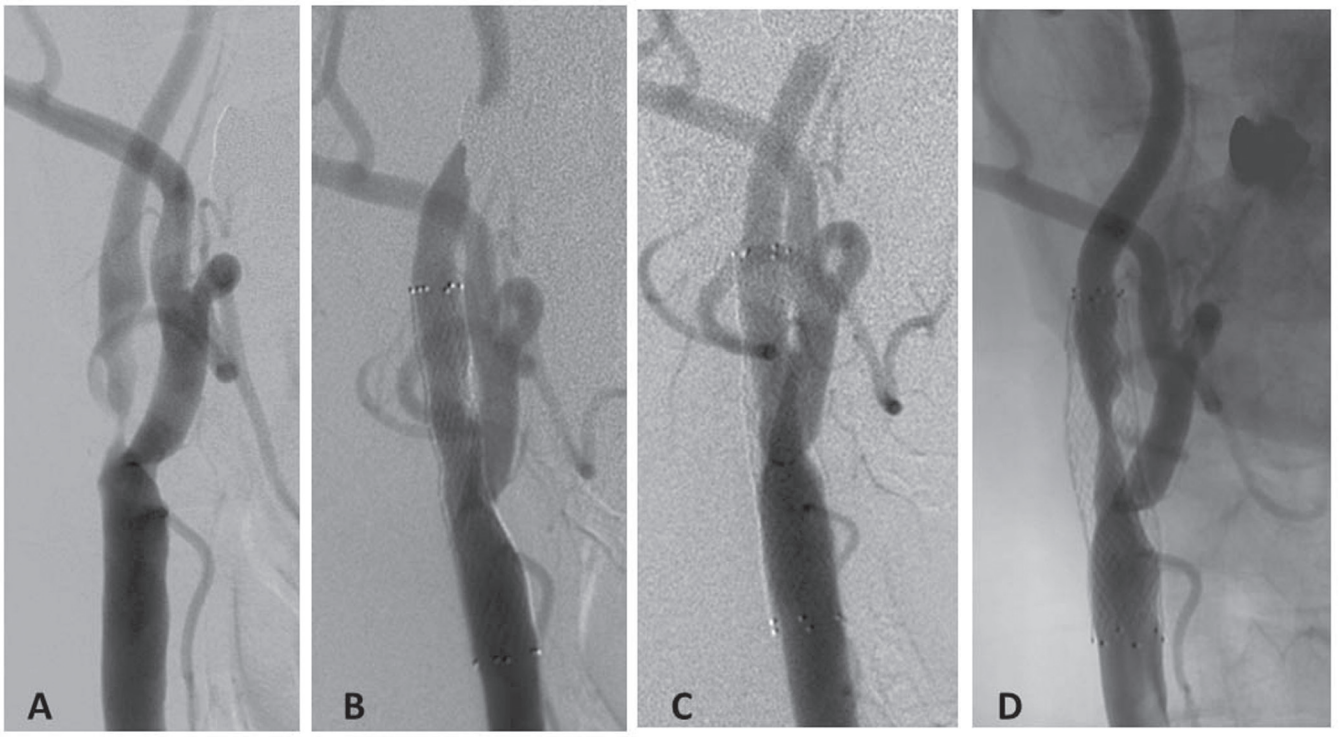

Fig.1 Right common carotid angiography of anteroposterior (A-P) view. A: Initial angiography before treatment showing the right internal carotid artery severe stenosis. B: Angiography immediately after previous carotid artery stenting (CAS) revealing a well-expanded stenotic lesion. C: Follow-up angiography 9 months after the CAS, showing slight in-stent restenosis. D: Follow-up angiography 6 years after the CAS, demonstrating diffuse in-stent restenosis and the expanded previous stent.

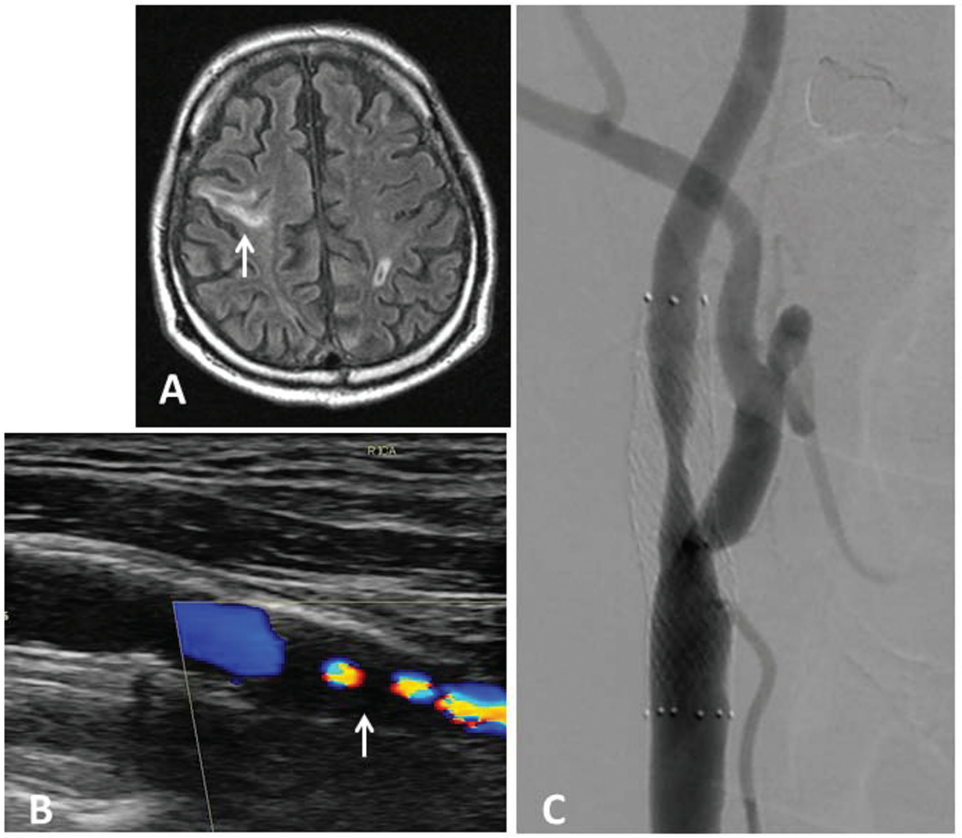

Fig. 2 A: Magnetic resonance imaging demonstrating ischemic lesion (*arrow*) on the right cerebral hemisphere. B: Cervical ultrasound image showing intimal thickness with low-echoic signal (*arrow*). C: Angiography on admission revealing more progressive in-stent restenosis and previous stent enlargement.

Treatment

Additional CAS was performed using a distal filter protection method with the "Filter Wire EZ™ Embolic Protection System" (Boston Scientific, Galway, Ireland). A 6-French ultra-long sheath guiding catheter was advanced to the right common carotid artery. CAG just before the procedure revealed more than 70% diffuse stenosis within the previous stent (Fig. 2C). The EZ filter device was manipulated to cross the stenotic lesion and positioned in the proximal petorus portion of the internal carotid artery. The stenotic site was scanned by intravascular ultrasound (IVUS) (Eagle Eye Gold; Volcano Corp., San Diego, California, USA). The IVUS imaging demonstrated a previously deployed carotid stent and remarkable neointimal proliferation causing luminal narrowing (Fig. 3A). To observe the morphologic characteristics of the in-stent intimal thickness in detail, the stenotic site was imaged with OCT (Dragonfly, St. Jude Medical Inc., St. Paul, Minnesota, USA) from the distal section at 20 mm/s using an automatic pull-back device. We used a new-generation OCT imaging system which had high-speed resolution, without the balloon-occlusion technique. The OCT imaging clearly demonstrated the in-stent neointimal thickness, which included lipid-rich tissue, thin fibrous cap atheroma with a lipid core, and a ruptured plaque-like appearance (Fig. 3B, C). These findings indicated atheromatous plaque.

A "Precise" stent (10 × 40 mm; Cordis Corp., Miami, Florida, USA) was successfully deployed to cover the in-stent stenotic lesion, and poststenting angioplasty was performed with a balloon catheter. No-flow phenomenon was seen after the poststenting angioplasty. The EZ filter was captured and rapidly removed. A postprocedural angiography revealed a well-expanded in-stent stenotic lesion (Fig. 4A). Plaque component was seen in the captured filter device (Fig. 4B). Finally, postprocedural IVUS and OCT imaging were performed. These findings

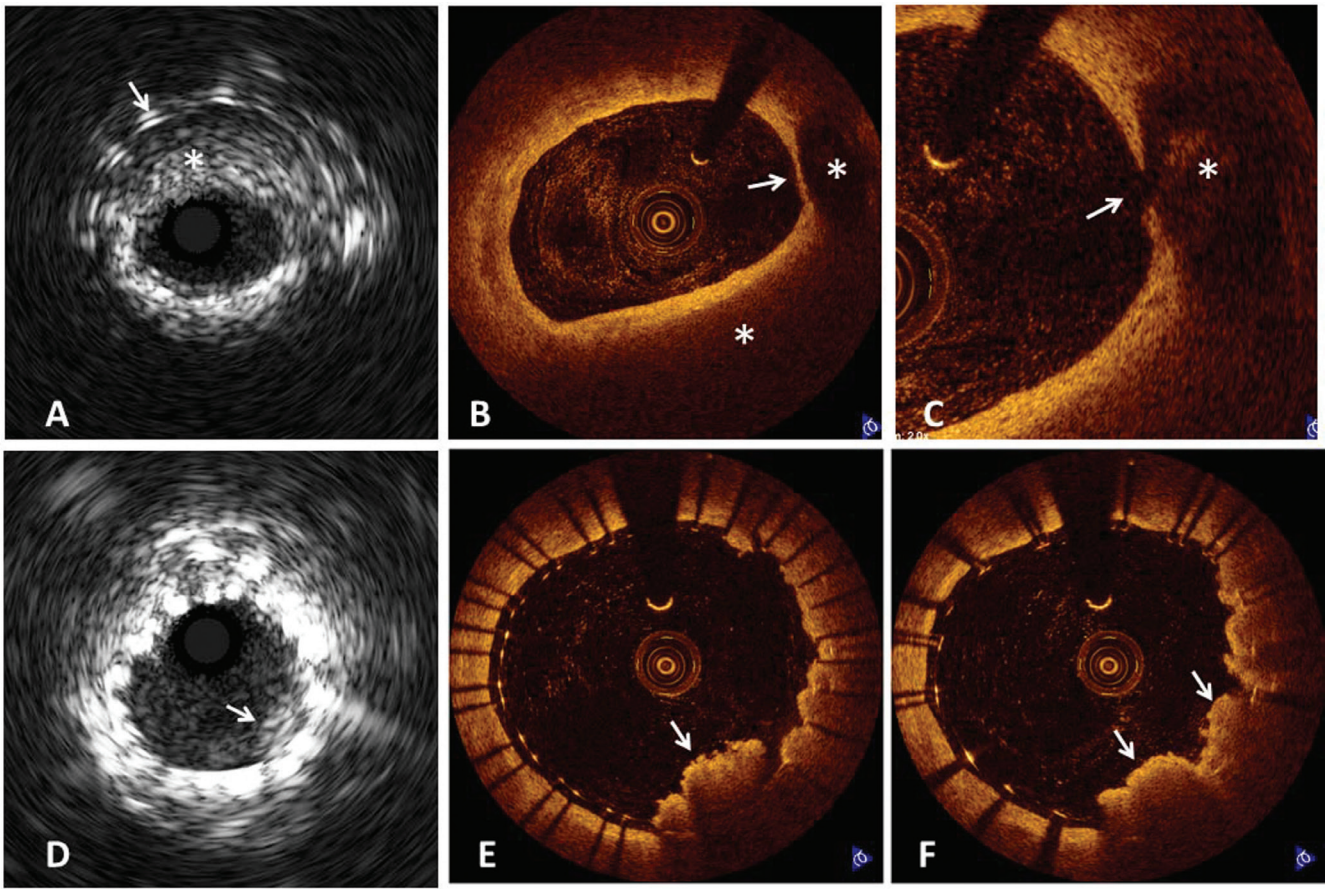

Fig. 3 Findings of neointima inside the previous bare-metal stent. A: Gray-scale intravascular ultrasound (IVUS) imaging showing neointimal thickness (*asterisk*) inside the previous stent (*arrow*). B: Optical coherence tomography (OCT) imaging demonstrating heterogeneous intima and thin fibrous cap (*arrow*) with lipid-rich component (*asterisk*). C: Another section of OCT imaging revealing fibrous cap disruption (*arrow*) with lipid component (*asterisk*). Findings of inside the additional stent. D: Gray-scale IVUS imaging showing suspicious tissue protrusion (*arrow*) inside the additional stent. E, F: OCT imaging clearly demonstrating tissue protrusion (*arrow*) from the spaces between stent struts.

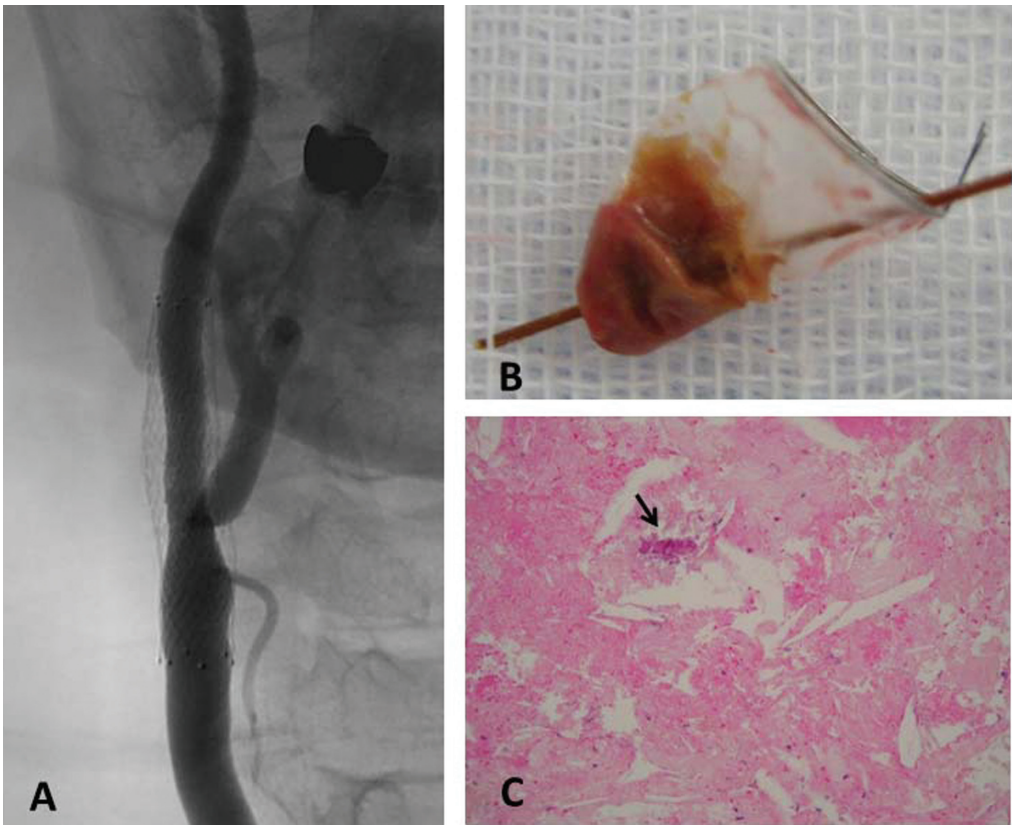

Fig. 4 A: Angiography immediately after additional stenting revealing a well-expanded in-stent previous restenotic lesion. B: Filter device used for distal protection during carotid artery stenting captures soft plaque. C: Histological finding of the captured plaque demonstrating cholesterol crystals, calcification deposits (*arrow*), and fibrinoid material (hematoxylin and eosin stain 10 × 20).

after additional stenting revealed tissue protrusion from the space between stent struts (Fig. 3D–F).

The plaque specimen obtained during CAS histologically demonstrated cholesterol crystals, calcification deposits, and fibrinoid material, which indicates atheromatous plaque (Fig. 4C). The patient was supplemented with cilostazol and discharged without postoperative ischemic events. There was no ISR on follow-up angiography 6 months after the treatment.

Discussion

To our knowledge, this is the first case report of very late ISR with neointimal atheromatous change demonstrated by plaque imaging and histology after CAS. ISR after CAS is generally considered to be a stable process with neointimal hyperplasia inside the stent struts.[1,10,11] Neointimal hyperplasia is the major pathophysiologic process leading to early restenosis after CAS. Several ultrasound studies reported that neointimal proliferation was mostly observed during the first 12 months after CAS, and the ISR rate after CAS appears to be acceptable and restenosis is mainly asymptomatic.[1,2,10–12] Postmortem pathological study in coronary intervention demonstrated that neointimal hyperplasia consisted of transformed vascular smooth muscle cells and fibrotic maturation of the matrix substances and led to the formation of more stable neointimal tissue inside the stent wall.[13] An experimental study reported that the inflammatory responses to chronic vascular wall injuries from metallic prosthetic devices were causally related to intimal proliferation.[14] Other studies and a review of the literature indicated that appropriate predictors of ISR after CAS are advanced age, female gender, hyperglycemia, implantation of multiple stents, prior revascularization treatment, suboptimal result with residual stenosis, elevated postprocedural serum levels of acute-phase reactants, and the use of balloon expandable stents.[1–4,12]

Recently, very late stent thrombosis (VLST) after coronary stenting has received significant attention in the field of coronary intervention.[5–9,15] The main causes of VLST are thought to be neointimal atherosclerotic changes inside the stent and plaque ruptures of the neointima.[16,17] These findings of neointimal response, called "neoatherosclerosis," have been assessed in coronary interventions by various imaging techniques and by the pathological features. Nakazawa et al. reported that atherosclerotic change of the neointima was observed significantly earlier and more frequently in cases where DES were used compared to BMS.[8,18] Cook et al. observed extensive inflammatory response and eosinophilic infiltration in aspirated thrombi in patients with VLST after DES implantation.[19] Lee et al.

used IVUS to examine VLST after both DES and BMS and they demonstrated that neointimal atherosclerotic changes were also the cause of BMS-related VLST.[7] Yamaji et al. described that disruption of neoatherosclerosis inside the stents could be an important underlying mechanism of VLST beyond 3 years post-BMS implantation.[9]

Most recently, several OCT studies demonstrated that neointima within BMS or DES may transform into unstable atherosclerotic plaque.[5,15,17,20,21] OCT has been used for human coronary imaging.[22,23] OCT has a 10-fold higher image resolution than conventional IVUS and is able to provide superior intraluminal image quality.

Takano et al. reported that lipid-laden neointima, neointimal disruption, and thrombus as detected by OCT were more frequently seen in the late phase compared to the early phase after BMS implantation.[15] Kang et al. demonstrated the OCT findings of in-stent neoatherosclerosis such as thin-cap fibroatheroma, neointimal microvessels, neointimal rupture, and thrombi in DES-treated lesions presenting with ISR.[20]

These studies indicate that in some patients there is degenerative evolution of neointima into an unstable atherosclerotic lesion and that ISR should not always be regarded as a benign entity.

There appears to be no literature on neoatherosclerosis of VLST after CAS. To our knowledge, the present report is the first to describe neoatherosclerosis of very late (10 years) ISR after CAS. With OCT imaging, we observed the patient's atherosclerotic change of in-stent neointimal tissue proliferation. We also detected the small fibrous cap disruption in the atheromatous neointima, which could not be detected by IVUS. These findings raise the possibility that the new right cerebral ischemic lesion demonstrated by MRI was caused by a distal embolism due to an atheromatous plaque rupture of the neointima. The plaque, which was captured by the filter device during the additional CAS procedure, histologically revealed fragments of atherosclerotic plaque composed of cholesterol crystals, calcification deposits, and fibrous material. These components of neoatherosclerosis matched the OCT findings. OCT can be a valuable tool for evaluating intravascular plaque that cannot be detected by CAG and IVUS. Yoshimura et al. first reported the utility of OCT for examinations of the carotid artery.[24–26] They visualized structures of symptomatic and asymptomatic plaque of carotid artery wall. This imaging modality may be useful in the near future for assessments of carotid plaque before and after CAS.

The optimal treatment strategy for ISR after CAS is not established, because restenosis after CAS is relatively uncommon. Zhou et al. reported seven patients with 80% or greater ISR confirmed by follow-up angiography.[27] All patients were successfully treated with endovascular techniques, including balloon angioplasty alone, a cutting balloon, and additional stent placement. We propose that a distal protection method is necessary for CAS with very late ISR, to prevent the occurrence of a distal embolism during the procedure.

Although many neurologists are under the impression that neointimal growth after CAS has benign consequences, our findings suggest that some cases after CAS show atherosclerotic change in neointima and that neoatherosclerosis inside the stent may present a risk for plaque rupture leading to very late in-stent thrombosis or a distal embolism after CAS. The problem of restenosis after CAS should not be underestimated, and an active and long-term follow-up of all stented arteries is merited.

Conclusion

We reported the first case of very late ISR with neointimal atherosclerosis demonstrated by OCT and plaque histology. Our findings indicate that neoatherosclerosis may play an important role in the mechanism of very late ISR after CAS. It is important to conduct a long-term follow-up after CAS and to manage the general risk factors for atherosclerosis.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

References

1) Clark DJ, Lessio S, O'Donoghue M, Tsalamandris C, Schainfeld R, Rosenfield K: Mechanisms and predictors of carotid artery stent restenosis: a serial intravascular ultrasound study. *J Am Coll Cardiol* 47: 2390–2396, 2006
2) Gröschel K, Riecker A, Schulz JB, Ernemann U, Kastrup A: Systematic review of early recurrent stenosis after carotid angioplasty and stenting. *Stroke* 36: 367–373, 2005
3) Skelly CL, Gallagher K, Fairman RM, Carpenter JP, Velazquez OC, Parmer SS, Woo EY: Risk factors for restenosis after carotid artery angioplasty and stenting. *J Vasc Surg* 44: 1010–1015, 2006
4) Van Laanen J, Hendriks JM, Van Sambeek MR: Factors influencing restenosis after carotid artery stenting. *J Cardiovasc Surg (Torino)* 49: 743–747, 2008
5) Habara M, Terashima M, Nasu K, Kaneda H, Inoue K, Ito T, Kamikawa S, Kurita T, Tanaka N, Kimura M, Kinoshita Y, Tsuchikane E, Matsuo H, Ueno K, Katoh O, Suzuki T: Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study. *Circ Cardiovasc Interv* 4: 232–238, 2011
6) Kang SJ, Mintz GS, Park DW, Lee SW, Kim YH, Lee CW,

Han KH, Kim JJ, Park SW, Park SJ: Tissue characterization of in-stent neointima using intravascular ultrasound radiofrequency data analysis. *Am J Cardiol* 106: 1561–1565, 2010
7) Lee CW, Kang SJ, Park DW, Lee SH, Kim YH, Kim JJ, Park SW, Mintz GS, Park SJ: Intravascular ultrasound findings in patients with very late stent thrombosis after either drug-eluting or bare-metal stent implantation. *J Am Coll Cardiol* 55: 1936–1942, 2010
8) 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* 57: 1314–1322, 2011
9) Yamaji K, Inoue K, Nakahashi T, Noguchi M, Domei T, Hyodo M, Soga Y, Shirai S, Ando K, Kondo K, Sakai K, Iwabuchi M, Yokoi H, Nosaka H, Nobuyoshi M, Kimura T: Bare metal stent thrombosis and in-stent neoatherosclerosis. *Circ Cardiovasc Interv* 5: 47–54, 2012
10) Chakhtoura EY, Hobson RW, Goldstein J, Simonian GT, Lal BK, Haser PB, Silva MB, Padberg FT, Pappas PJ, Jamil Z: In-stent restenosis after carotid angioplasty-stenting: incidence and management. *J Vasc Surg* 33: 220–225; discussion 225–226, 2001
11) Lal BK, Kaperonis EA, Cuadra S, Kapadia I, Hobson RW: Patterns of in-stent restenosis after carotid artery stenting: classification and implications for long-term outcome. *J Vasc Surg* 46: 833–840, 2007
12) Khan MA, Liu MW, Chio FL, Roubin GS, Iyer SS, Vitek JJ: Predictors of restenosis after successful carotid artery stenting. *Am J Cardiol* 92: 895–897, 2003
13) Grewe PH, Deneke T, Machraoui A, Barmeyer J, Müller KM: Acute and chronic tissue response to coronary stent implantation: pathologic findings in human specimen. *J Am Coll Cardiol* 35: 157–163, 2000
14) Mnjoyan ZH, Doan D, Brandon JL, Felix K, Sitter CL, Rege AA, Brock TA, Fujise K: The critical role of the intrinsic VSMC proliferation and death programs in injury-induced neointimal hyperplasia. *Am J Physiol Heart Cric Physiol* 294: H2276–2284, 2008
15) Takano M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y, Mizuno K: Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. *J Am Coll Cardiol* 55: 26–32, 2009
16) Buja LM: Vascular responses to percutaneous coronary intervention with bare-metal stents and drug-eluting stents: a perspective based on insights from pathological and clinical studies. *J Am Coll Cardiol* 57: 1323–1326, 2011
17) Yoon HJ, Hur SH, Kim SK, Kim H, Park HS, Cho YK, Nam CW, Kim YN, Kim KB: A case of in-stent neointimal plaque rupture 10 years after bare metal stent implantation: intravascular ultrasound and optical coherence tomographic findings. *Korean Circ J* 41: 671–673, 2011
18) Nakazawa G: Stent thrombosis of drug eluting stent: pathological perspective. *J Cardiol* 58: 84–91, 2011
19) Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, Togni M, Wenaweser P, Billinger M, Seiler C, Gay S, Meier B, Pichler WJ, Jüni P, Virmani R, Windecker S: Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation* 120: 391–399, 2009
20) Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, Lee SW, Kim YH, Whan Lee C, Park SW, Park SJ: Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation* 123: 2954–2963, 2011
21) Otake H, Shite J, Shinke T: Ruptured-plaque-like appearance of restenotic tissue following sirolimus-eluting stent implantation: an optical coherence tomography case study. *J Invasive Cardiol* 23: E49–E50, 2011
22) Ben-Dor I, Mahmoudi M, Pichard AD, Satler LF, Waksman R: Optical coherence tomography: a new imaging modality for plaque characterization and stent implantation. *J Interven Cardiol* 24: 184–192, 2011
23) 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* 158: 284–293, 2009
24) Yoshimura S, Kawasaki M, Hattori A, Nishigaki K, Minatoguchi S, Iwama T: Demonstration on intraluminal thrombus in the carotid artery by optical coherence tomography: technical case report. *Neurosurgery* 67(3 Suppl Operative): ons E305; discussion ons E305, 2010
25) Yoshimura S, Kawasaki M, Yamada K, Enomoto Y, Egashira Y, Hattori A, Nishigaki K, Minatoguchi S, Iwama T: Visualization of internal carotid artery atherosclerotic plaques in symptomatic and asymptomatic patients: a comparison of optical coherence tomography and intravascular ultrasound. *AJNR Am J Neuroradiol* 33: 308–313, 2012
26) Yoshimura S, Kawasaki M, Yamada K, Hattori A, Nishigaki K, Minatoguchi S, Iwama T: OCT of human carotid arterial plaques. *JACC Cardiovasc Imaging* 4: 432–436, 2011
27) Zhou W, Lin PH, Bush RL, Peden EK, Guerrero MA, Kougias P, Lumsden AB: Management of in-stent restenosis after carotid artery stenting in high-risk patients. *J Vasc Surg* 43: 305–312, 2006

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