Late Angiographic Stent Thrombosis in a Drug-Eluting Stent That Occurred 20 Months After Premature Discontinuation of Clopidogrel Administration

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SUMMARY

Late angiographic stent thrombosis (LAST) in a drug-eluting stent has been reported in several studies. Most LAST occur just after discontinuation of antiplatelet therapy. We report the first case of LAST that occurred 21 months after implantation of a Cypher stent and 20 months after discontinuation of clopidogrel, results that suggest a mechanism other than the discontinuation of antiplatelet therapy might be responsible for LAST. (Int Heart J 2006; 47: 707-713)

Key words: Drug-eluting stent, Sirolimus, Thrombus, Antiplatelet, Clopidogrel, Coronary angioplasty

STENT implantation is used extensively in percutaneous coronary intervention and improves the clinical outcome significantly in coronary heart disease, but it is limited by in-stent restenosis which can not be corrected by drug therapy such as angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker administration.¹⁾ Drug-eluting stents have significantly reduced the risk of in-stent restenosis and the need for repeated revascularization.^{2,3)} Although the safety of drug-eluting stents is similar to that of bare-metal stents in the short- to medium-term, concern about the safety of drug-eluting stents in the long-term has arisen due to potential late angiographic stent thrombosis (LAST), which is thought to be related to the delayed endothelialization of stent struts. LAST is defined as an intrastent thrombosis more than 30 days after stenting and has been reported in several recent studies using bare-metal and drug-eluting stents.⁴⁻⁸⁾ However, neither the cause nor the incidence of LAST has been determined. The US Food and Drug Administration recently issued a warning indicating that a sirolimus-eluting stent (Cypher) may cause subacute thrombosis and hypersensitivity reactions to the stent polymer.⁹⁾ The discontinuation of antiplatelet therapy

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and hypersensitivity reactions to the stent strut may be responsible for the LAST. Here we report a case of LAST occurring 21 months after Cypher (Cordis, Miami, FL) stenting and 20 months after premature discontinuation of clopidogrel in our center in order to draw attention to the possibility of LAST in this drug-eluting stent.

CASE REPORT

The 43-year-old male patient was a heavy smoker with a 5-year history of hypertension. He did not have diabetes or hyperlipidemia. The patient was admitted to hospital on June 15, 2004 because of unstable angina manifested as chest

Figure 1. Ninety-five percent diameter stenosis extending from the proximal to mid left anterior descending artery and 99% diameter stenosis in the proximal segment of the first diagonal artery.

Figure 2. One sirolimus-eluting Cypher stent (3.5×18 mm) was implanted in the left anterior descending artery which had TIMI grade 3 flow.

pain during exercise for the previous 2 years. The angina had worsened beginning 1 week prior to hospitalization. An electrocardiogram was normal and an exercise stress test was positive. A coronary angiogram performed on June 17 showed a 95% diameter stenosis extending from the proximal to mid left anterior descending artery, and a 99% diameter stenosis in the proximal portion of the first diagonal artery (Figure 1). The left anterior descending artery lesion was predilated with a balloon and a sirolimus-eluting stent (Cypher 3.5 × 18 mm, Cordis, Miami, FL) was implanted on June 25 (Figure 2). Ticlopidine and aspirin administration was started on June 15. However, the patient developed a skin rash on his trunk and wrist that was accompanied by itching, which was thought to be an allergic response to ticlopidine. Therefore, ticlopidine was replaced with clopidogrel (75 mg/day) on June 27. The rash subsequently resolved within a few days. The patient was discharged without in-hospital complications on clopidogrel (75 mg/day), aspirin (100 mg/day), atorvastatin (20 mg/day), and metoprolol (25 mg/day). The patient had discontinued clopidogrel himself 2 weeks after discharge from the hospital because of intolerance so it was replaced with dipyridamole (150 mg/day). He continued to take aspirin (100 mg/day), atorvastatin (20 mg/day), and metoprolol (25 mg/day) and to smoke heavily and drink. In addition, he climbed a hill about 500 meters high daily and played basketball almost everyday. He discontinued dipyridamole himself a year after discharge from the hospital. He was followed-up once every other week because of his premature discontinuation of clopidogrel. Laboratory blood tests, including platelet, serum glucose, triglyceride, total cholesterol, low density lipoprotein, and high density lipoprotein values at about 20-months clinical follow-up were all normal. The patient remained asymptomatic both at rest and during exercise until February 26, 2006 when the chest pain reappeared while he was climbing the hill. However, the

Figure 3. Q wave and ST changes in leads V₁-V₃ compatible with anterior myocardial infarction.

Figure 4. Occlusion at the entrance of the proximal Cypher stent by fresh thrombosis with TIMI grade 0 flow.

Figure 5. Fresh thrombosis could be observed while predilated by balloon with TIMI grade 3 flow.

symptom subsided after he rested a while. He experienced severe and persistent chest pain again the next day while playing basketball and was soon thereafter admitted to hospital. A 12-lead electrocardiogram showed changes in leads V_1 - V_5 compatible with an anterior myocardial infarction (Figure 3). Blood pressure was 80/50 mmHg and arterial oxygen saturation was 92%. An intra-aortic balloon pump was first implanted before a coronary angiogram because of cardiogenic shock. Emergency coronary angiography showed total occlusion (TIMI grade 0 flow) at the site of the Cypher stent by fresh thrombosis (Figure 4). Intravascular ultrasound was not performed due to severe hypotension. The lesion was predilated with an undersized balloon and 2 sirolimus drug-eluting stents (FIRE BIRD 3.0×18 mm and 3.5×18 mm, MicroPort, Shanghai, China) were implanted in the CYPHER stent with TIMI grade 3 flow (Figures 5 and 6). The intra-aortic

Figure 6. Two FIRE BIRD stents were implanted at the site of a previous stent that had TIMI grade 3 flow.

balloon pump was used for one week in the Cardiac Care Unit. The patient was discharged without any complications on March 6, 2006 and was recovering well during a 2-month follow up.

DISCUSSION

Stent thrombosis in a drug-eluting stent is a serious complication associated with high mortality, and presents clinically as acute myocardial infarction, cardiogenic shock, and sudden death. It can occur acutely, subacutely, or late. Stent thrombosis that occurs within 24 hours, 7 days, and more than 30 days after stenting is termed acute stent thrombosis, subacute stent thrombosis, and LAST, respectively. Theoretically, LAST maybe higher in drug-eluting stents than that in bare-metal stents due to delayed endothelialization of the stent strut. An animal study has showed that a drug-eluting stent is prone to LAST.¹⁰⁾ However, recent studies have showed that the incidence of stent thrombosis in drug-eluting stents is similar to that in bare-metal stents, and that drug-eluting stents are beneficial in reducing clinical events at 300 days after percutaneous coronary intervention.¹¹⁻¹³⁾ The use of drug-eluting stents in clinical practice however has expanded beyond the indications applied in trials, which inevitably increases the potential of a higher incidence of stent thrombosis. The exact cause of stent thrombosis has not been elucidated. Possible causes include delayed endothelialization, hypotension, and damage to the stent. Kuchulakanti and Iakovou^{14,15)} observed stent thrombosis in the “real world” and concluded that the independent predictors for stent thrombosis included premature dual-antiplatelet discontinuation, renal failure, diabetes, bifurcation lesions, and lower ventricular ejection. Premature dual-antiplatelet discontinuation is thought to be the most likely cause of LAST. Most

LASTs occur just after discontinuation of clopidogrel and/or aspirin, consequently thorough and long-term antiplatelet treatment consisting of clopidogrel (75 mg/day) + aspirin (100 mg/day) for more than 1 year followed by aspirin at 100 mg/day for the remainder of the patient's life is recommended after drug-eluting stent implantation.¹⁶⁾ A recent study reported 2 cases of LAST that occurred after discontinuation of clopidogrel which had been administered for about 2 years, raising the question at what time is it suitable to discontinue the dual-antiplatelet therapy?⁶⁾

Most LASTs occurred just a few days or weeks after discontinuation of dual-antiplatelet therapy. LAST that occurred 20 months after discontinuation of clopidogrel in a drug-eluting stent has not yet been reported. The reasons for this kind of very late LAST observed in this patient include 1) premature clopidogrel discontinuation, and 2) continued heavy smoking, drinking, and rigorous exercise. Smoking promotes platelet aggregation and impairs endothelial function, which are involved in thrombosis.^{17,18)} In this patient, the majority of the LAST occurred just after discontinuation of clopidogrel. Why did it happen 20 months after premature discontinuation of clopidogrel? This suggested that other mechanisms in addition to antiplatelet therapy might be responsible for the LAST. One possible mechanism could be hypersensitivity to the stent polymer. Virmaniet, *et al*⁴⁾ reported a case of LAST that occurred 18 months after CYPHER implantation. Autopsy revealed delayed endothelialization, aneurysmal dilatation, and hypersensitivity reaction to the stent strut and polymer. The report of a CYPHER related death to the US FDA mentioned there was hypersensitivity to the CYPHER stent.⁹⁾ A drug-eluting stent without polymers may be beneficial in preventing LAST.

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