Case Report

Very very late stent thrombosis: 9.5 years after DES implantation

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ABSTRACT
Very late stent thrombosis (VLST) has been recognized as a class effect of 1st generation drug eluting stents (DES) implantation. Although rare, VLST has been reported between 1 and 4 years after DES implantation. Very very late stent thrombosis (VVLST) occurring more than 5 years after DES implantation is extremely rare. We report the first case of a VVLST from India occurring 3465 days (9.5 years) after DES implantation with a brief discussion on its pathogenesis and prevention.

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1. Introduction

Percutaneous coronary intervention (PCI) is the standard of care for patient with ST elevation myocardial infarction (STEMI). Drug eluting stents (DES) are preferred over bare metal stents (BMS) since DES could significantly reduce in-stent restenosis (ISR) by inhibiting neo-intimal proliferation. However, stent thrombosis (ST) remains a rare but life threatening complication of all stent deployment. ST usually presents as sudden death or STEMI with hypotension, arrhythmias, or acute heart failure. According to Academic Research Consortium criteria and classification, ST can occur either acutely (within 24 h), subacutely (within 1–30 days), late (1–12 months) or very late (beyond one year) after stent implantation.1 Very late stent thrombosis (VLST) occurred more frequently with 1st generation DES than BMS and majority of VLST occurred within 1–4 years of stent implantation.2 VLST is extremely rare after five years of stent implantation. The first case was reported in 2009.3 A new term “very (or extreme) very late stent thrombosis (VVLST)” was suggested when ST occurred after five years of stent implantation. The second case of VVLST occurring after five years of implantation was reported in 2011.4 In 2014, Kaliyadan5 published a case series of 7 patients with VVLST over a period from 2008 to 2013, where the interval between stent implantation and VVLST varied from 5.6 to 7.1 years.

We report the first case of VVLST presenting as STEMI from India occurring 3465 days (9.5 years) after implantation of 1st generation DES.

2. Case report

A 55-year-old man first reported in December 2005 with acute substernal chest pain of 36 h duration. He presented with shock and cardiac arrest. He was revived with active cardiopulmonary resuscitation. Electrocadiogram revealed acute inferior wall STEMI with complete heart block. He was a chronic smoker for over 20 years. There was neither history of diabetes, hypertension, angina nor any family history of ischemic heart disease or stroke. He was mildly overweight...
with BMI 27 kg/m². Investigations revealed normal hematological data, blood sugar (R) 98 mg/dl, serum creatinine 1.0 mg/dl, normal lipid profile and positive trop T. 2D-ECHO showed inferior wall hypokinesia with EF 40% and no mitral regurgitation (MR). He received aspirin (325 mg), clopidogrel (600 mg), and atorvastatin (80 mg) in the intensive coronary care unit. He underwent emergency temporary pacing (TPI) and coronary angiography which showed normal left main (LM) and left circumflex artery (LCx). The mid left anterior descending artery (LAD) showed 95% stenosis. The right coronary artery (RCA) was proximally occluded (100%) with thrombus. He underwent PCI to the RCA with implantation of two 1st generation serolimus eluting stents (SES) (3 × 33 mm × 16 atm and 2.75 × 38 mm × 18 atm) and one SES to LAD (2.75 × 28 mm × 16 atm). He received GpIIb/IIIa blocker (Eptifibatide) in the catheterization laboratory in view of large thrombus burden. His recovery was uneventful and TPI was removed after 24 h. He was discharged on 4th day on daily aspirin (150 mg), clopidogrel (75 mg), metoprolol (25 mg) and atorvastatin (80 mg). He has been on regular follow-up every 3–6 months. The clopidogrel was stopped after 12 months, and he was advised to continue aspirin (150 mg), metoprolol (50 mg), and atorvastatin (20 mg) daily indefinitely.

The patient remained asymptomatic on the above medication and was on regular medical follow-up. There was no discontinuation of medical therapy at any time. On May 15, 2015 he presented to the cardiac emergency with chest heaviness and giddiness for the last 30 min. His pulse rate was 40/min irregularly irregular and blood pressure 90/60 mmHg with few basal crepts. His ECG showed acute inferior wall STEMI with slow atrial fibrillation (AF, 40 bpm). Troponin T was positive. 2D-ECHO showed LVH with hypokinesia of inferior wall and no MR. Random blood sugar was 110 mg/dl, HbA1c 6.0, INR 1.4, creatinine 1.2 mg/dl, SGOT 86 U/L, total cholesterol 128 mg/dl, HDL 42 mg/dl, LDL 69 mg/dl and TG 87 mg/dl. Patient underwent emergency temporary pacing (via right femoral vein) and coronary angiography (via right radial approach). His angiography showed occluded proximal RCA1 (100% VVLST), new disease in proximal LCx (90%), and no ISR on LAD. He was given 60 mg prasugrel in the catheterization laboratory before PCI. He underwent primary PCI to RCA with implantation of two 2nd generation everolimus eluting stent (EES) and one 2nd generation zotarolimus eluting stent (ZES) to the LCx. TIMI 3 flow was achieved after complete revascularization of culprit vessels (Fig. 1) without any need for thrombosuction or glycoprotein IIb/IIIa inhibitors. Patient returned to sinus rhythm on catheterization table. Temporary pacing was removed after 24 h and patient discharged on third post-operative day on aspirin (150 mg), prasugrel (10 mg), atorvastatin (80 mg), and carvedilol (20 mg). The current plan
for dual antiplatelet therapy (DAPT) is to give aspirin and prasugrel for one year and thereafter to shift to combination of aspirin with clopidogrel indefinitely in the absence of any contraindication.

3. Discussion

Today DES is preferred over BMS due to their property of reducing ISR. However DES implantation is associated with delayed arterial healing resulting in delayed endothelialization, uncovered stent struts, and stent mal-apposition. The pathological process of neo-atherosclerosis sets in within the neo-intima. These changes have been identified as the basic pathology of VLST in 62 coronary lesions from 46 human autopsies resulting in VLST due to plaque rupture. Neoatherosclerosis in the neointima of stent is the final pathway of VLST and stent failure.

In-stent neoatherosclerosis has emerged as the most significant contributing factor toward the genesis of VLST occurring after the implantation of DES and may account for up to 30% of VLST at autopsy. Histologically neoatherosclerosis is characterized by an accumulation of lipid laden foamy macrophages with (or without) necrotic core formation and calcification within the neo-intima of the stent. Neoatherosclerosis may be associated with atherosclerotic process in the other native arterial vessels. Neoatherosclerosis in the stent causing VLST may thus present with accompanying significant blockage in other native vessels. However neoatherosclerosis develops gradually over months or years after DES implantation, while atherosclerosis in native vessels develops more slowly over decades. The mechanism underlying developments of neoatherosclerosis is little understood at present. The risk factors for neoatherosclerosis and the effective preventive strategies are still to be established. Some of the risk factors could be functional immaturity of the intimal endothelium, uncovered struts, overlapping stents, malapposition of stents, plaque rupture, hypersensitivity reactions, and neointimal erosion. Modern methods to study and evaluate neoatherosclerosis during life include serial angioscopy, virtual histology intravascular imaging and ultrasound (IVUS), optical coherence tomography (OCT), quantitative angiography, near infra-red spectroscopy and other methods of molecular imaging. Due to non-availability of OCT and IVUS at our center, we could not perform these latest imaging procedures, which would have provided additional information regarding delayed vascular re-endothelialization, stent malapposition, stent fracture, and neo-atherosclerosis.

The patient was diagnosed to have VLST and not ISR on following grounds:

(a) The patient was asymptomatic prior to his presentation with STEMI.
(b) ISR usually presents within the first few years after stent implantation. The patients usually have progressive angina and need uptitration of medical therapy. Our non-diabetic patient was asymptomatic and stable on medical therapy since 2005.
(c) Clinical profile of present illness with STEMI, hypotension, and arrhythmia favors an acute event rather than restenosis.
(d) Stress thallium done earlier was not suggestive of any reversible ischemia thereby lowering the possibility of restenosis.

Propensity of ST is maximal up to 3-4 years after implantation. However, it remains unknown, whether the risk of ST eventually abates or persists indefinitely. VLST is an extremely rare event. We report the first case of VLST from India. Chronic smoking and mild raised BMI were the two obvious risk factors. The patient was neither diabetic nor hypertensive. The patient had received DAPT for one year after the index procedure and was on aspirin 150 mg daily at the time of developing ST. The clinical profile has been compared with other published reports in Table 1.

Following DES implantation, DAPT is normally recommended for a minimum period of one year followed by aspirin alone indefinitely. ST is, however, a complex multi-factorial process depending upon many factors including procedural factors, patient characteristics, and pharmacological interventions. Procedural factors include stent generation type, stent length, and extent of stent apposition. The lesion factors include ostial lesions, bifurcation lesions and small vessels. The patient risk factors are hypercholesterolemia, diabetes, hypertension, obesity, malignancy and old age. Pharmacological factors are the duration of DAPT, the increased rebound clotting tendencies on cessation of DAPT and slow metabolizers of antiplatelet pro-drugs. Exact duration of recommended DAPT remains a subject of debate. One standard DAPT regime may not seem to benefit all patients equally. Every patient has a unique risk of either bleeding or ST. These factors play an important role in deciding the duration of DAPT therapy for the prevention of VLST and VVLST. A personalized DAPT regime based on the individual bleeding hazards and the ischemic risks may be a more logical way in the future.

Continuation of DAPT is the preferred method to prevent the risk of ST in DES implantation. In the recent DAPT trial, more than 9000 patients with DES implantation were randomized to receive either 12 months or 30 months of DAPT. The primary end point of cardiac death, myocardial infarction or stroke was significantly decreased with 30 months in comparison with 12 months DAPT (4.3 vs 5.9%, p < 0.001). However the incidence of bleeding also increased with prolonged DAPT. There may be an increase in the CV events within 3 months of DAPT withdrawal. Whether DAPT cessation unmasks the patients with incomplete stent endothelialization or vulnerable plaque or represents true platelet aggregability remains to be determined. There may be a small subgroup of patients, who may benefit from a prolonged or indefinite DAPT but the recognition of such patients is difficult. Coronary angioscopy, IVUS, and OCT may be informative.

There is a growing literature suggesting that newer DES (2 or 3 generations) are much safer in terms of ST. Spanish ESTROFA-A registry has shown similar results with zotarolimus eluting stents (ZES) and ZES-RESOLUTE SPIRIT studies have shown that the incidence of VLST with EES is less than
half compared with 1st generation DES. A recent meta-analysis of 8 studies of biodegradable polymer III generation stents has shown a still lower incidence of VLST. We hopefully expect that newer stents will reduce or eliminate the problem of ST.

In India, cost and reimbursement policies still permit patients to receive 1st generation DES. This and earlier case reports clearly highlight the risk of VVLST with the 1st patients to receive 1st generation DES. It may be advisable that these, small but significant, number of patients be monitored for ST and in absence of any contraindication, be continued indefinitely on DAPT.

Bioresorbable vascular scaffold may be the final answer to avoid VLST or VVLST. However its use is limited at this time, because the device is bulky and expensive, not available in all sizes and needs aggressive preparation of vascular bed before implantation.

### Conflicts of interest

The author has none to declare.

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| Table 1 – Comparison of clinical profile of VVLST case reports. | Present case | Layland (Ref. no. 3) | Jennifer (Ref. no. 4) | Kaliyadan (Ref. no. 5) |
|---|---|---|---|---|
| Number of patients | 1 | 1 | 1 | 7 |
| Sex | Male | Male | Male | Male 6, female 1 |
| Age (years) | 65 | 64 | 69 | 30–70 (m = 54) |
| Time interval between stent deployment and stent thrombosis | 3465 days (9.5 years) | 2037 days | 2506 days | 2010–2610 days (m = 2220 days) |
| Type of DES | SES | SES | SES | SES = 4, PES = 3 |
| Clinical presentation | STEMI | STEMI | STEMI | NSTEMI 1 |
| Risk factors | Overweight | – | Hypertension | Hypertension (n = 4) |
| | Chronic smoker | | Hypercholesterolemia | Diabetes (n = 1) |
| | | | Chronic smoker | Hypercholesterolemia (n = 7) |
| | | | Stoppage of clopidogrel | Chronic smoking (n = 6) |
| | | | 10 days prior to onset of ST | Obesity (n = 6) |
| | | | | Stoppage of DAPT 7–14 days prior to ST (n = 3) |
| Type of stent deployed to treat ST | 2nd generation DES EES | – | BMS | BMS |

VVLST – very very late stent thrombosis; m – mean; DES – drug eluting stent; SES – serolimus eluting stent; PES – paclitaxel eluting stent; STEMI – ST elevation myocardial infarction; NSTEMI – nonST elevation myocardial infarction; ST – stent thrombosis; DAPT – dual antiplatelet therapy; BMS – bare metal stent; EES – everolimus eluting stent; n = number of patients
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