Drug-Eluting Stent Treatment of a Radiation-Induced Left Internal Mammary Arterial Graft Stenosis

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A 62-year-old man underwent radiotherapy to the left upper chest for treatment of Pancoast syndrome on a background of previous coronary artery bypass grafting 12 years earlier. Within 1 year, he developed significant stenoses of both the left internal mammary artery (LIMA) graft and ostial left vertebral artery, presumably related to therapeutic radiation exposure. Initially diagnosed using computed tomography coronary angiography, the patient underwent percutaneous coronary intervention and insertion of a drug-eluting stent (DES) to the ostium of the LIMA graft via a left radial approach. He remains clinically well at 6-month follow-up. This is the first reported case in the literature of DES treatment of a radiation-induced vascular stenosis; however, the incidence of cardiovascular disease is elevated in such cases. In patients with a prior history of mantle radiation, consideration should be given to the routine assessment of internal mammary conduits prior to coronary artery bypass surgery. (Circ J 2008; 72: 1904–1906)

Key Words: Drug-eluting stent; Left internal mammary artery (LIMA) graft; Mantle radiation; Stenosis

Exposure of the heart to ionizing radiation is now considered to be associated with an increased risk of developing clinical coronary artery disease (CAD). Coronary artery bypass grafting (CABG) has been the traditional revascularization therapy for those affected with radiation-induced CAD, but not without increased morbidity. Although case reports have highlighted the successful use of coronary angioplasty and bare metal stents (BMS) for the treatment of radiation-induced CAD, a recent study reporting 6-month BMS restenosis rates in excess of 80% in such patients has cast doubt over the efficacy of a percutaneous approach! At present, there are no reports of the use of drug-eluting stents (DES) for the treatment of such lesions. The present case presented highlights the usefulness of computed tomography coronary angiography (CTCA) in the diagnosis of concomitant coronary graft and multiple arch vessel stenoses in a patient treated with external beam radiation for a left-sided Pancoast syndrome following CABG 12-years earlier. We also describe the first reported use of a DES for the successful treatment of a radiation-induced stenosis involving the ostium of a left internal mammary artery (LIMA) graft.

Case Report

A 62-year-old man underwent CABG in 1995 for stable angina, receiving a LIMA graft and 2 saphenous vein grafts (SVG). In December 2005, he experienced atypical left anterior chest pain radiating to the scapula and left arm. Exercise stress testing at that time was negative and the pain was deemed to be non-cardiac in origin. The pain persisted despite physiotherapy and simple analgesics, and was associated with subsequent development of impaired sensation along the medial aspect of the left arm, hand and little finger in a dermatomal distribution. Neurology consultation additionally confirmed a mild left-sided Horner’s syndrome. Magnetic resonance imaging of the left brachial plexus revealed a tissue mass measuring 54×47×34 mm located at the left lung apex, abutting the left subclavian artery and left first rib. The lower cervical and upper thoracic nerve roots were also compressed. Fine-needle aspiration biopsy revealed a large cell malignancy consistent with a bronchogenic carcinoma. In July 2006, the patient began a 6-week course of radical radiation therapy with curative intent, receiving a total of 60 Gy directed exclusively to the apex of his left lung. He made a satisfactory recovery and CT scanning at 5 months post-radiotherapy showed complete resolution of the previous mass and only localized residual scarring and fibrotic change within the left lung apex.

In April 2007 the patient developed recurrent anginal chest pain, confirmed with exercise stress testing that revealed typical angina and ischemic electrocardiographic changes after only 5 min of the Bruce protocol (expected duration, 7.5 min). CTCA was performed to further clarify the extent of disease, revealing a focal 80% narrowing of the ostium of the left vertebral artery (Fig 1A) and a critical ostial stenosis at the origin of the LIMA graft (Figs 1A,B), adjacent to the apical fibrotic changes within the left lung. The CTCA also revealed the very close approximation of the origin of the LIMA and left vertebral artery, being only 8 mm apart. Significant native coronary disease was also noted, with a moderate—severe stenosis within the right coronary SVG also seen, but otherwise the grafts were patent. Invasive coronary angiography confirmed the CTCA
findings, showing severe focal ostial narrowing involving the LIMA (Fig 2A) and left vertebral artery (Fig 2A), which failed to improve despite generous administration of intracoronary glyceryl trinitrate (GTN). There was also severe native 3-vessel CAD, in addition to a 70% lesion in the SVG supplying the posterior descending artery (PDA). On balance of procedural risks, it was decided that the patient undergo percutaneous coronary intervention (PCI) to the ostial stenosis of his LIMA graft, followed by staged PCI to the lesion in the SVG if LIMA PCI was successful.

A 6F sheath was placed in the left radial artery. The ostium of the LIMA graft was engaged with an IMA guiding catheter and following 200 µg of intracoronary GTN and 6,000 units of intravenous heparin, a 0.014-inch balance guidewire was passed into the distal vessel. The lesion was eventually successfully pre-dilated with sequential 2.5×15 mm and then 3.0×15 mm Maverick balloons inflated to 20 atmospheres (Fig 2B), following initial resistance of the fibrotic lesion to pre-dilatation with a 2.5-mm balloon at lower pressures. A 3.0×20 mm Taxus stent was deployed and aggressively post-dilated with a 3.5×15 mm Quantum non-compliant balloon to 28 atm to achieve a successful final angiographic result (Fig 2C).

The PDA SVG was sufficiently distant from the previous radiation field to confidently dismiss radiation as an etiological link. Additionally, the large vessel size (>5.0 mm) favored BMS insertion, performed successfully 1 week later. The patient completed a normal exercise stress test (8 min of the Bruce protocol) at 6-month clinical follow-up, and remains asymptomatic on dual antiplatelet therapy.

**Discussion**

Prior to 1960, the heart was believed to be resistant to the effects of ionizing radiation; but since then there have been numerous published reports highlighting an increased prevalence of premature CAD in patients at varying time intervals (range, 1–32 years) after the delivery of mediastinal external beam radiation therapy. Most striking in many of those reports is not only the young age of the affected patients, but also their lack of traditional cardiovascular risk factors. More recent analyses of cancer survivors in large cancer and radiotherapy trials have revealed vascular injury as a major cause of late radiation morbidity. A recent meta-analysis has found that the reduction in cancer-related death from radiotherapy for breast cancer was offset by a corresponding increase in late vascular disease mortality. Trials examining the effects of radiotherapy for the treatment of Hodgkin’s disease have demonstrated 6-fold higher rates of cardiovascular disease, with patients irradiated prior to the age of 21 years having a 13-fold higher rate of cardiovascular disease. A recent large, retrospective single-center study of 415 consecutive patients treated with mantle radiation therapy for Hodgkin’s disease between 1962 and 1998 found an actuarial incidence of CAD to be 3% at 5 years, 6% at 10 years, and 10% at 20 years.

There have been numerous pathological studies implicating ionizing radiation as a stimulus for atherogenesis in vivo. Autopsy studies of human coronary arteries known to have been exposed to ionizing radiation have shown markedly similar characteristics to those lesions seen in typical atherosclerotic CAD in the absence of radiation therapy exposure. Radiation injury, however, is associated with marked adventitial fibrosis and thickening, medial thinning and destruction and a greater calcium and lipid content within intimal plaques in the radiation-induced lesions. Similar detrimental vascular effects of radiation have been well documented in animal models, with studies suggesting...
a more unstable plaque phenotype consisting of greater amounts of intraplaque hemorrhage and macrophage-rich infiltrate.

Ionizing radiation appears to exert a dose-dependent effect upon vascular tissue, with clinical CAD markedly increased in patients exposed to doses exceeding 3,000 rad (30 Gy) regardless of the use of cardiac shields. The ostia of the left and right coronary arteries are particularly vulnerable to fibrosis and vascular damage. Of particular relevance are reports of the susceptibility of the internal mammary arteries (IMAs) to the detrimental effects of ionizing radiation, which have resulted in such conduits being grossly inadequate for harvesting during CABG. Some surgeons have advocated a formal assessment of the IMAs in those with a history of mediastinal irradiation prior to anticipated CABG. Although invasive angiography is considered the ‘gold standard’, a non-invasive approach using CTCA would appear to be an acceptable alternative, as demonstrated here.

The frequent involvement of the coronary ostia has resulted in CABG being the traditional choice of revascularization following cardiac irradiation. However, mediastinal fibrosis, sternal dehiscence and unsuccessful harvesting of the IMAs have resulted in greater surgical morbidity. PCI has been successfully used to treat radiation-induced coronary stenoses; however, most experience with PCI is based on published case reports. Rapid progression of CAD at sites of previous angioplasty or stenting has been previously described and systematic large-scale analyses of the clinical utility of PCI for the treatment of radiation-induced coronary stenoses is still lacking. Recently, Schomig et al undertook a retrospective review of patients with Hodgkin’s lymphoma, thoracic external beam radiotherapy, and coronary stenting. Although the study is not without limitations, it was the first investigation of the incidence of coronary restenosis treatment using BMS in patients with lymphoma previously treated with mantle radiation. That study included 12,626 consecutive patients with CAD and BMS over a 10-year period. Within the cohort, 3 subgroups of patients were assessed: patients with lymphoma and prior mantle radiation (15 patients), patients with lymphoma without radiotherapy (7 patients), and patients without lymphoma or prior thoracic radiotherapy (12,604 patients), which formed the control group. Coronary angiography performed at 6 months demonstrated a statistically significant and unprecedented 86% angiographic restenosis rate in the irradiated group, compared with 17% in the lymphoma only group, and 26% within the control group. Target vessel revascularization rates were 66% in the irradiated group, a statistically significant difference compared with the 14% in the lymphoma only group, and 18% in the control group, with PCI performed in these patients occurring at a mean of 8 years after radiation therapy. Statistical analysis suggested that mantle radiation was a strong independent predictor of angiographic restenosis (odds ratio 21.7, 95% confidence interval 4.7–100.9, p=0.01). Hence, that study revealed external ionizing radiation may exert a profound effect upon vascular tissue, with the inflammatory and fibro-hyperplastic response contributing significantly to high BMS restenosis rates many years after the original exposure.

At present, there are no published case reports of the use of DES for the treatment of such lesions. It is therefore unknown whether DES will reduce restenosis rates to an acceptable level, in the setting of a strongly pro-inflammatory and hyperproliferative state within the vascular endothelium after radiation exposure and subsequent procedural disruption.

In conclusion, we report for the first time the use of a DES for the treatment of radiation-induced vascular stenosis, with an unprecedented 6-month clinical follow-up. The location of the lesion (ostium of a LIMA graft) is most unusual and has also been rarely reported as a target for PCI. Moreover, the effect of ionizing radiation on the surrounding vascular structures was accurately highlighted by CTCA, assisting procedural planning prior to PCI. We therefore advocate the use of routine pre-operative screening assessment of the IMAs in patients with previous mantle radiation exposure in whom CABG is being planned. Furthermore, CTCA is an accurate and useful alternative for this purpose. The finding of IMA stenoses may favor a percutaneous, rather than operative approach to revascularization, given the poorer long-term results with SVGs. The off-label use of DES for the treatment of radiation-induced coronary artery stenoses appears feasible and may prove to be a significant advance in the management of such lesions, given the usually high rates of angiographic and clinical restenosis reported with BMS. The use of antiplatelet agents for primary prophylaxis of vascular events in patients exposed to radiation may warrant further investigation.

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References