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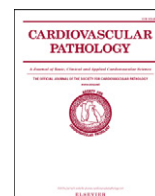
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## Cardiovascular Pathology



## Case Report

Radiation coronary arteritis refractory to surgical and percutaneous revascularization culminating in orthotopic heart transplantation<sup>☆</sup>Richard K. Cheng<sup>a</sup>, Michael S. Lee<sup>a</sup>, Atsuko Seki<sup>b</sup>, Richard J. Shemin<sup>c</sup>, Daniel Cruz<sup>a</sup>, Gentian Lluri<sup>a</sup>, George D. Mitchell<sup>d</sup>, Eric H. Yang<sup>a,\*</sup><sup>a</sup> Department of Medicine, Division of Cardiology, University of California, Los Angeles, Los Angeles, CA 90095, USA<sup>b</sup> Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA 90095, USA<sup>c</sup> Department of Surgery, Division of Cardiothoracic Surgery, University of California, Los Angeles, Los Angeles, CA 90095, USA<sup>d</sup> Cardiology Associates Medical Group, Ventura, CA 93003, USA

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## ABSTRACT

**Background:** Hodgkin's lymphoma (HL) comprises of 4% of malignancies diagnosed in children from birth to 14 years of age. While overall survival rates have increased, HL survivors can be at risk of late cardiovascular complications from radiotherapy. HL survivors with a history of mediastinal RT have been found to have an increased incidence of myocardial infarction, angina, congestive heart failure, and valvular disorders compared to the general population.

**Methods:** A 33 year old female with a history of HL status post chemotherapy and mediastinal radiation 11 years ago became symptomatic with multivessel coronary artery disease with aggressive progression of her disease despite coronary bypass graft surgery, patch angioplasty of the left main coronary artery (LMCA) with an extracellular bioscaffold, and repeated percutaneous coronary intervention of the LMCA. She eventually underwent orthotopic heart transplant and did well postoperatively.

**Results:** Histopathological analysis of the explanted heart revealed a variety of sequelae of radiation arteritis, including thrombosis of both native vessels and arterial grafts, intimal hyperplasia and involvement of the bioscaffold in the left main coronary vasculature. The bioscaffold did not contribute significantly to the stenosis within the LMCA.

**Conclusion:** Our case demonstrates an unusual indication for OHT due to severe refractory radiation induced CAD, as well the wide spectrum of the histopathologic manifestations of radiation induced arteritis.

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## 1. Clinical course

A 33 year old woman with a history of Hodgkin's Lymphoma (HL), previously treated with combined chemoradiation therapy 11 years prior, presented at an outside hospital with exertional chest discomfort radiating to the jaw and dyspnea suggestive of typical angina. Her prior HL therapy included an ABVD regimen (adriamycin, bleomycin, vinblastine, and dacarbazine) with a adriamycin dose of 300 mg/m<sup>2</sup> followed by mantle field radiation therapy with a total administered dose of 3930 cGy, resulting in full remission of her disease.

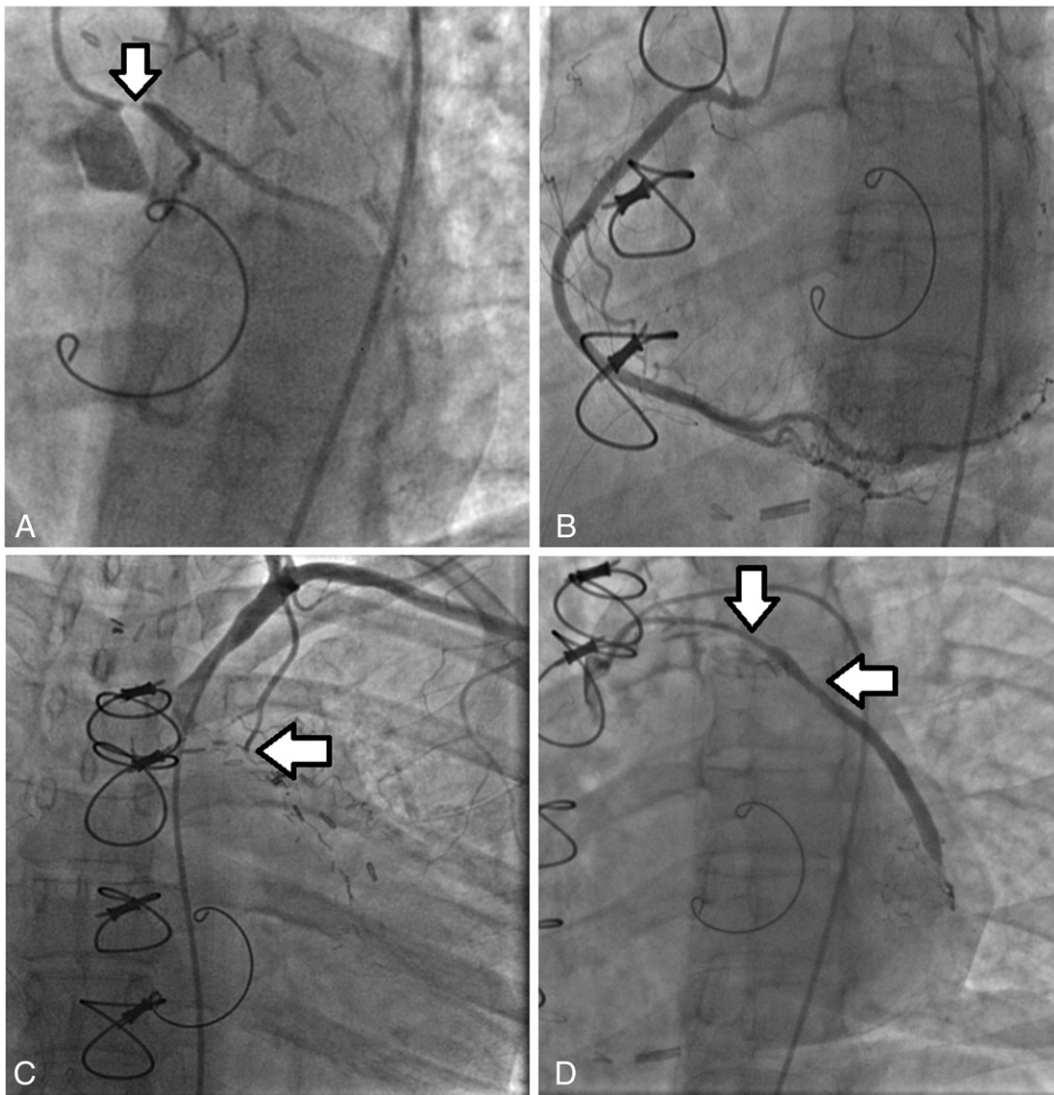
Stress testing was positive and subsequent angiography demonstrated severe disease involving the ostial left main coronary artery (LMCA) with 80% stenosis, and moderate disease of the left anterior descending artery (LAD) and the left circumflex artery. Due to ostial left main involvement, the patient underwent coronary artery bypass graft surgery (CABG). The left internal mammary artery (LIMA) graft was used to bypass the LAD and was attached to a diagonal branch, and a radial artery graft was attached to an obtuse marginal branch (OM). The patient was discharged home uneventfully.

However, 2 months later she again developed exertional angina and presented with a non-ST segment myocardial infarction (NSTEMI) with a peak troponin level of 2.9 ng/mL. On coronary angiography, her radial artery-OM graft was completely occluded with a heavily diseased and stenotic LIMA-diagonal graft. The decision was made to undergo repeat CABG. The LAD could not be successfully bypassed, and the patient underwent reconstruction of the left main ostium with surgical patch angioplasty, utilizing a Extracellular Matrix (ECM) Technology biomaterial (CorMatrix, Alpharetta, GA). A saphenous venous graft (SVG) was placed to the obtuse marginal.

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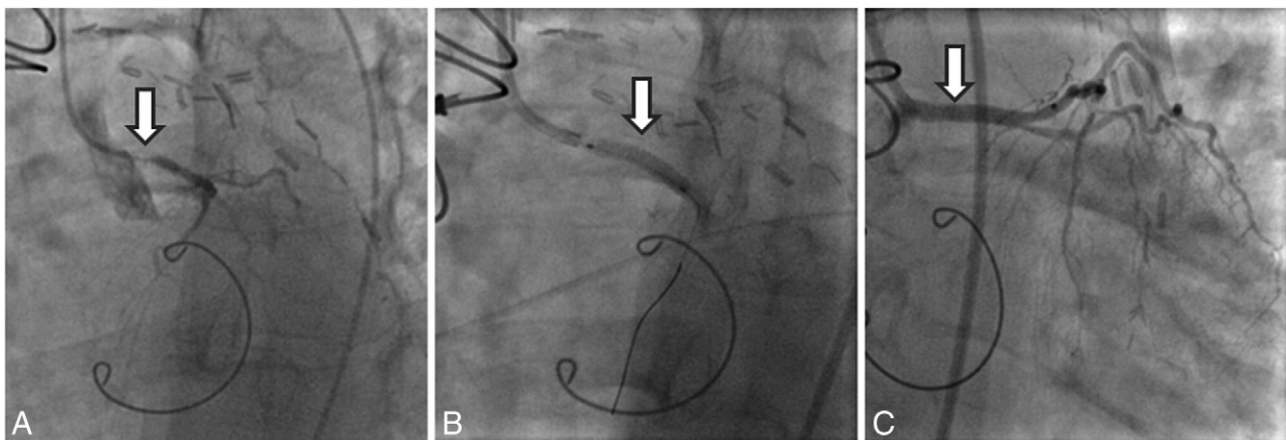
E-mail address: [Datsunian@gmail.com](mailto:Datsunian@gmail.com) (E.H. Yang).



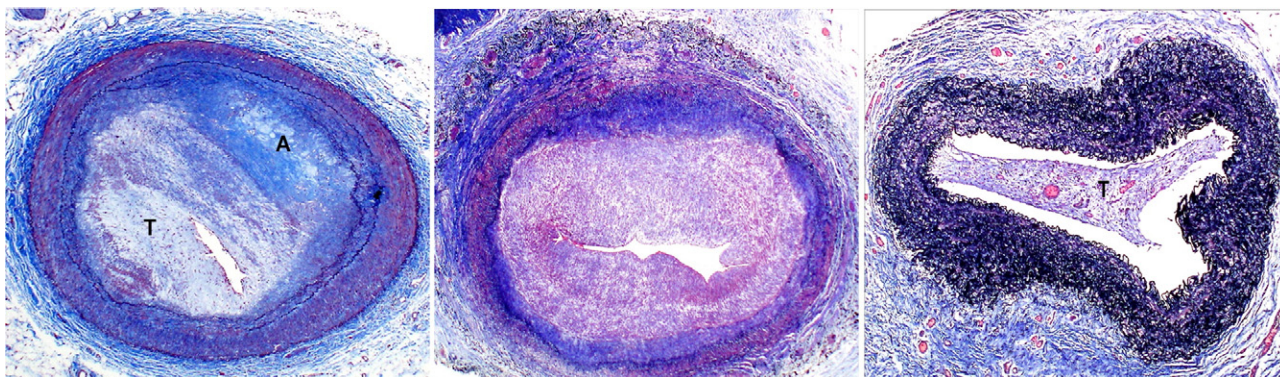
**Fig. 1.** Coronary angiography after failure of second surgical revascularization. (A) Subtotal occlusion involving a large region of the left main coronary artery (LMCA) (arrow). (B) Minimally diseased right coronary territory. (C) Occluded LIMA (arrow at area of occlusion) to LAD graft. (D) Diffusely diseased saphenous venous graft (vertical arrow) to obtuse marginal branch (horizontal arrow).

Moderate mitral regurgitation was also seen and repaired with a 30 mm CG Future annuloplasty ring (Medtronic, Minneapolis, MN). She tolerated the surgery well and was discharged.

After another 2 months, she again developed angina. Repeat stress testing was performed, with nuclear stress imaging demonstrating a reversible defect and hypokinesis in the apical septal and apical



**Fig. 2.** Surveillance coronary angiography of the Left main coronary artery status post initial stent placement. (A) Coronary angiography at 7 months when patient presented with recurrent angina, showing in-stent restenosis of the LMCA (arrow). (B) Re-do PCI of the LMCA (arrow). (C) Final angiographic result of the LMCA (arrow) after repeat intervention.



**Fig. 3.** Histopathology of coronary vessels in native explanted heart. Trichrome elatin stain 40x. (Left) Atherosclerosis (A) and organized thrombus (T) in the proximal diagonal branch of the LAD. (Middle) Severely narrowed saphenous venous graft to obtuse marginal. (Right) Complete occlusion of the arterial graft by organized thrombus.

anterior walls. These findings were concerning for recurrent ischemia involving the LAD territory. Repeat angiography (Fig. 1) revealed subtotal occlusion of the entire length of the recently reconstructed left main with moderate ostial LAD disease. The LIMA-LAD graft was totally occluded just proximal to the anastomosis and the SVG-OM graft was patent but diffusely diseased.

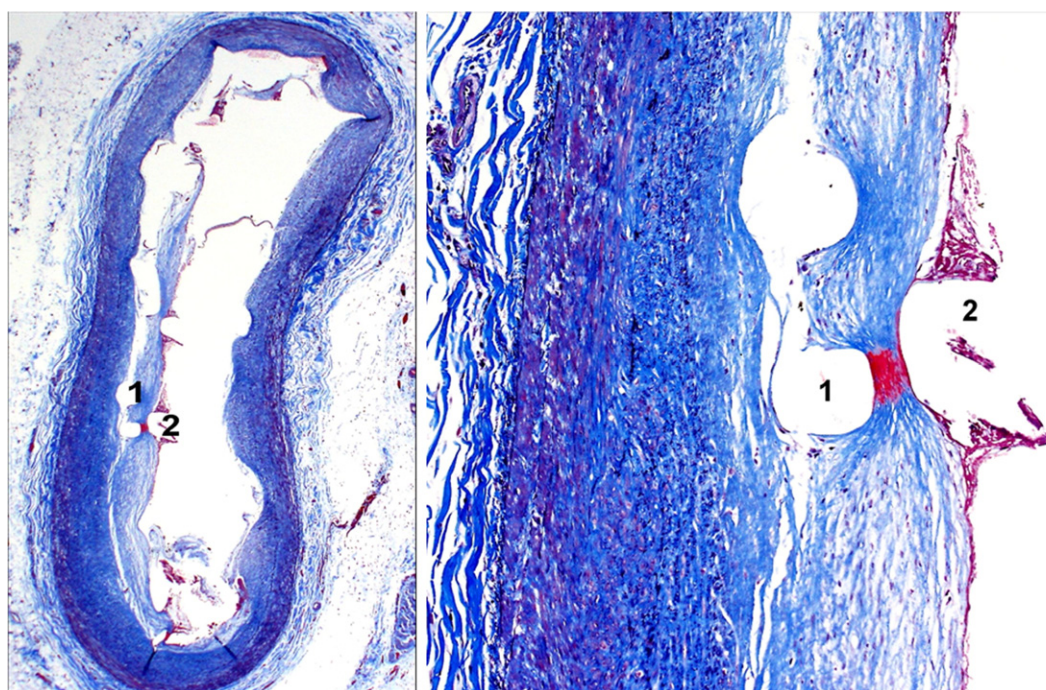
Multidisciplinary discussions were held over her proposed treatment plan as neither repeat CABG nor percutaneous coronary intervention (PCI) were ideal. From a CABG perspective, the lack of optimal targets and perioperative risks of a third sternotomy did not make a surgical approach an ideal strategy. From a PCI standpoint, there was a concern for a high rate of restenosis given the nature of the patient's presumed radiation arteritis, the unknown contribution and concern for the CorMatrix patch's ability to withstand the stress of the stent inflation with the possibility of rupture.

Because of these concerns, the decision was initially made to pursue orthotopic heart transplant (OHT) evaluation rather than attempted revascularization. She was deemed an acceptable candidate for OHT

and was listed status 1AE due to her aggressive CAD with left main involvement and risk of death. While waiting for a suitable donor, she developed resting angina on hospital day (HD) 8. Electrocardiography (ECG) showed new ST segment elevations in lead aVR.

Due to her unstable symptoms, the patient underwent urgent PCI. A 2.5 X 15 mm everolimus eluting stent (Xience, Abbott Vascular, Abbott Park, IL) was deployed from the left main into the LAD, along with balloon angioplasty of the left circumflex artery. Extensive fibrous/fatty plaque were seen throughout the vessel on intravascular ultrasound (IVUS). She tolerated the procedure well with resolution of her symptoms. Her OHT status was put on hold, and the patient did well post-PCI and was discharged on HD# 15.

Surveillance angiography was performed at 3 months (Fig. 2), which demonstrated a patent left main stent. The patient was then scheduled for repeat angiography in another 6 months. However, the patient developed progressive exertional angina at 7 months post-PCI. Repeat angiography (Fig. 3D) demonstrated severe 80-90% in-stent restenosis of the left main stent. She then underwent



**Fig. 4.** Trichrome elatin stain. (Left) Magnification 40x. Site of overlapping stents in the left main (1=first stent, 2=second stent). (Right) Magnification 200x. There is intimal hyperplasia seen between the two stents with fibrin adherent to the second stent.

PCI of the in-stent restenosis with a paclitaxel eluting 3.0 x 12 mm stent (Ion, Boston Scientific, Natick, MA) DES within the restenosed segment.

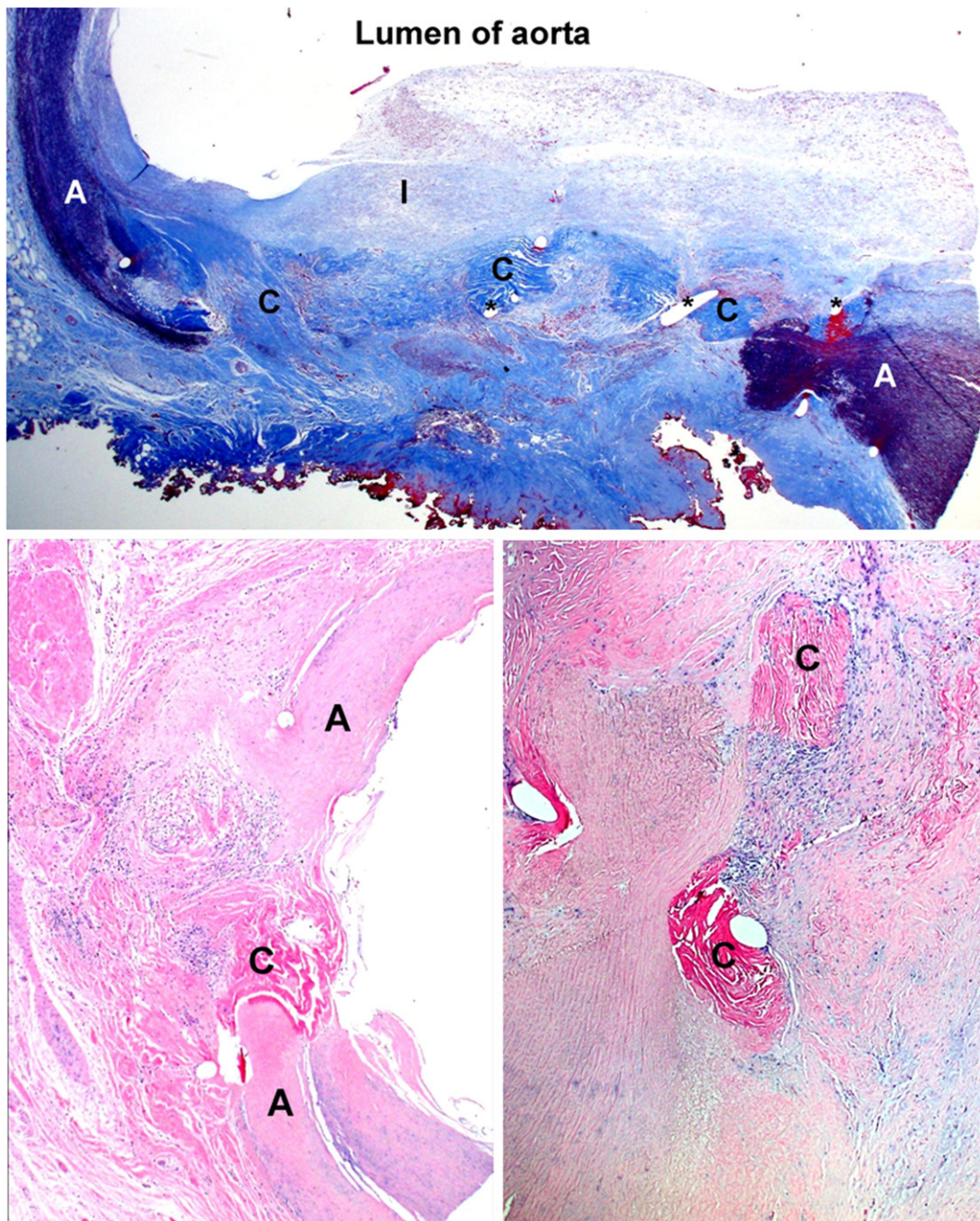
Due to concern of instability of her coronary artery disease, she was re-listed for transplant as status 1AE. Her hospital course remained uneventful until she underwent OHT on HD# 17, tolerating the surgery well.

The patient's post-transplant course remained relatively uncomplicated except for a hemodynamically stable pericardial effusion that was monitored conservatively. She was discharged to home on HD# 31. She is continuing to do well, with routine surveillance left heart catheterization at 1 month of the transplanted heart showing no evidence of significant transplant CAD by angiography. Further,

intravascular ultrasound showed minimal intimal thickening of the proximal LAD.

## 2. Pathological findings

Extensive pathological evaluation was performed of the explanted heart, revealing severe coronary vasculopathy due to prior irradiation, including 90% occlusion of the left circumflex with fibromuscular intimal hyperplasia, 50% occlusion of the LAD, significant occlusion of the venous grafts to obtuse marginal and diagonal, and complete occlusion of the radial artery graft by organized thrombus (Fig. 3).



**Fig. 5.** Underlying tissue at the left main ostium. (Upper) Trichrome elastin stain 20x. Cormatrix reconstruction of left main with evidence of intimal hyperplasia, A=aortic wall, C=ECM Technology, I=intimal hyperplasia, \*=suture sites. (Bottom Left) Hematoxylin eosin stain 20x. Region of ECM Technology reconstructed coronary (C) adjacent to native artery wall (A). (Bottom Right) Hematoxylin eosin stain 100x. Areas of inflammation are seen surrounding the ECM Technology (C).

After dissolving the metallic stents in the LMCA by electrolysis, histopathologic analysis of the LMCA revealed intimal hyperplasia between the two overlapping stents with fibrin adherent to the second stent (Fig. 4). There was no evidence of thrombus inside the stent or extension of the ECM Technology into the stent. Mild inflammation was also seen at the site of ECM Technology (Fig. 5).

### 3. Discussion

Approximately 8,830 new cases of Hodgkin's lymphoma (HL) were diagnosed in the United States as well as 1,300 deaths in 2011. [1] Late cardiovascular complications from radiotherapy (RT) is a concern in this population [2]. Cardiovascular events have been found in increased frequency in HL survivors with a history of mediastinal RT, with a 2- to 7-fold increase in myocardial infarction (MI), angina, congestive heart failure (CHF), and valvular disorders compared to the general population [3]. A British cohort study, where 7033 HL survivors were followed for an average of 11.1 years per patient, revealed that 2.4% patients died during follow-up due to MI, with a relative risk of death from MI significantly increased more than twofold compared with the general population [4].

The spectrum of cardiovascular disease caused by radiotherapy is broad, potentially affecting the valves, pericardium, myocardium, and conduction system [5]. Risk factors for radiation CAD include anterior exposure without shielding, total radiation dose of greater than 35 Gy, young age at time of exposure, and preexisting heart disease [5,6]. Because of the radiation fields involved, ostial coronary artery stenoses are seen of all of the three major coronary arteries, but left main coronary artery stenosis has been commonly seen in angiographic studies of small groups of studied patients [7–10] and has been associated with more extensive radiation therapy in disease states such as HL, thymoma, and testicular cancer [11].

Postmortem histopathologic studies of epicardial coronary arteries of patients have revealed a wide spectrum of morphologic findings. There is more significant proximal than distal narrowing of the coronary arteries, with predominantly fibrous tissue, which replace the media and adventitia [12]. Further, coronary medial thinning and adventitial fibrosis occur [13,14]. These lesions often exhibit common features of atherosclerosis, including lipid accumulation, inflammation and thrombosis. After radiation exposure, there is acute upregulation of pro-inflammatory cytokines and adhesion molecules that recruits inflammatory cells. Long-term effects are believed to be due to oxidative stress that results in chronic inflammation by upregulation of NF- $\kappa$ B, with eventual vasculopathy [15]. Interestingly, studies with direct intracoronary endoluminal irradiation at higher doses has been shown to decrease the rate of restenosis after balloon angioplasty [16] and after stenting, but may increase the risk of thrombosis [17].

Options for treatment of radiation-induced coronary artery stenoses include CABG as well as PCI. CABG has been considered the gold standard of treatment. However, with advancements in stent technology and operator experience, PCI of the left main coronary artery (LMCA) has been viewed as an alternative, less invasive treatment modality [18]. PCI of the unprotected LMCA now holds a Class IIa indication as an alternative to CABG as long as the anatomy of the lesion and the procedure is associated with a low risk of complications and a high likelihood of good long-term outcome [19]. Orthotopic heart transplantation (OHT) has been performed in a small number of patients with end stage heart failure from the effects of radiation therapy with varying results [19,20]. However, there has not been a documented case of OHT due to significant recurrent radiation induced CAD in the English literature.

ECM Technology (CorMatrix, Alpharetta, GA) is an extracellular matrix (ECM) that provides a temporary bioscaffold for tissue repair that is eventually repopulated by a patient's own cells [21]. Currently,

it is FDA approved for reconstruction and repair of the pericardium, cardiac tissue repair, and for patch repair of the carotid artery. It is harvested from porcine small intestinal submucosa and provides a scaffold for remodeling at the site of implantation. The ECM is comprised of structural proteins, adhesion glycoproteins, glycosaminoglycans and proteoglycans, and matricellular proteins. The patient's cells migrate and integrate into the ECM to remodel the biomaterial with tissue-specific differentiation [22,23]. Although there has been experience with repair of larger vascular structures, its use in smaller vessels and predisposition to atherosclerotic processes is still being investigated.

In summary, we present a patient with a history of HL status post chemoradiation therapy who developed severe multivessel radiation arteritis. Despite extensive surgical revascularization, including CABG and patch angioplasty, she continued to have recurrent disease resulting in multiple PCIs of the left main coronary artery. Our patient had an unusual indication for OHT as she had recurrent angina and cardiac ischemia due to repeated episodes of restenosis of her LMCA. This also appears to be the first reported case of ECM used for patch angioplasty to our knowledge, with histopathological visualization of its short term effects in coronary vasculature prior to transplantation. In addition, we present a wide spectrum of radiation induced CAD with varying mechanisms of graft and native vessel compromise. Future studies regarding the use of ECM for coronary patch reconstruction are needed.

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