Case reports

Radiation-induced ostial stenosis of the coronary artery as a cause of acute coronary syndromes: a novel mechanism of thrombus formation?

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Mediastinal irradiation can induce coronary artery disease characterized by fibrous lesions developing in the absence of lipid/foam cell accumulation. We document several consecutive cases of acute coronary artery occlusion developing over radiation-induced lesions in patients who were relatively young, without evidence of classical risk factors for atherosclerosis, and in whom the coronary vasculature was otherwise apparently free of disease. The finding of acute coronary artery occlusion at the site of a fibrous lesion lends further support to the hypothesis that acute coronary syndromes may not necessarily be identifiable with ulceration/disruption of the atherosclerotic plaque as the underlying mechanism of acute thrombus formation.

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Mediastinal irradiation is a cause of coronary artery disease even in the absence of the classical risk factors for atherosclerosis. Coronary artery disease has been reported in 5.5-6.3% of patients subjected to mediastinal irradiation[1,2], although its incidence is likely to be underestimated, being influenced by several factors (radiation dose, volume of heart irradiated, time elapsed since exposure). Post-radiation coronary artery disease is characterized by the peculiar localization of lesions at the ostia or at the proximal segment of the arteries, with the rest of the cardiac vasculature being typically free of atherosclerotic disease[1,3-5]. Whereas the occurrence of chronic coronary artery disease in patients who have been irradiated is now established[1,2,5,6], little is known about the role of radiation-induced lesions as a possible cause of acute coronary syndromes. In fact, it is often assumed that thrombus formation is unlikely to develop at the site of such lesions, as they do not present the classical features of vulnerable plaques, the typical appearance being instead that of a fibrous lesion with little or no cholesterol deposition[3,4,7]. However, this widely held contention may prove incorrect.

We here report several cases of acute coronary syndromes developing over isolated, radiation-induced lesions, which have come to our attention over the last year. Of note, these patients were relatively young and largely free of major risk factors for coronary artery disease according to the American Heart Association/American College of Cardiology criteria[8], as summarized in table I.

Description of cases

Case 1. A 50-year-old man was admitted to our coronary care unit (CCU) for acute myocardial infarction. On arrival, the patient was in cardiogenic shock; blood pressure was 90/60 mmHg and heart rate 36 b/min. ECG revealed ST-segment elevation in leads II, III, aVF and in the right precordial leads. Complete atrioventricular block was present. Transvenous pacing was instituted and the patient was transferred to the cath lab. Coronary angiography revealed total occlusion of the ostium of the right coronary artery and ostial stenosis (60%) of the left main coronary artery. The angiographic appearance of the coronary vasculature was otherwise normal. Percutaneous transluminal coronary angioplasty (PTCA) with stenting of the right artery ostial occlusion was performed with a final TIMI grade 3 flow. The patient returned to the CCU with

Table I. Patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	M	M	F	F
Age (years)	50	38	68	53
Total cholesterol (mg/dl)	168	190	132	212
HDL cholesterol (mg/dl)	41	32	57	27
LDL cholesterol (mg/dl)	118	130	62	130
Triglycerides (mg/dl)	72	140	82	274
Fasting glucose (mg/dl)	93	91	104	93
Uric acid (mg/dl)	6.4	6.4	4.4	6.6
History of hypertension	Absent	Absent	Absent	Absent
History of smoking	Absent	Absent	Absent	Absent
Family history of coronary artery disease	Absent	Absent	Absent	Absent

Cholesterol blood samples were taken within 12 hours after admission.

arterial blood pressure of 140/75 mmHg, heart rate 83 b/min (sinus rhythm), and pulmonary artery pressure 31/15 mmHg. The peak serum levels of creatine kinase (CK) and of the MB fraction were 2035 and 177 IU/l respectively. Blood chemistry was otherwise within limits. The patient's medical history was unremarkable, except for mediastinal irradiation at age 40 because of Hodgkin's disease. B-mode echocardiography and Doppler spectrum analysis revealed that the carotid arteries and internal mammary arteries were free of disease. Two months after discharge, coronary artery bypass surgery off-pump was performed with a left internal mammary artery graft to the left anterior descending coronary artery (LAD) and a saphenous vein graft to the circumflex coronary artery. At 12- month follow-up the patient is still asymptomatic.

Case 2. A 38-year-old man was admitted to our CCU for acute myocardial infarction. The patient was in cardiogenic shock, with blood pressure 95/60 mmHg and heart rate 106 b/min. ECG revealed ST-segment elevation in leads II, III, aVF and in the right precordial leads. An intra-aortic balloon was positioned, and transvenous pacing begun because of the subsequent development of a third degree atrioventricular block. Coronary angiography revealed an acute thrombotic occlusion of the right coronary artery at the ostium (Fig. 1) and a 75% stenosis of the proximal segment of the LAD, with the rest of the coronary branches being free of disease. He was submitted to a primary PTCA with stenting of the right coronary artery lesion, with a final TIMI grade 3 flow. The peak concentrations of CK and of the MB fraction reached 1173 and 74 IU/l respectively. Blood chemistry was otherwise normal. His medical history included mediastinal irradiation for Hodgkin's disease when he was 15 years old. Coronary angiography at 6-month follow-up showed restenosis of the right coronary ostium and no progression of the proximal LAD lesion. PTCA with direct stenting was performed on the right coronary artery lesion for in-stent restenosis; PTCA with cutting balloon and elective stenting was performed on the LAD lesion with a satisfactory outcome.

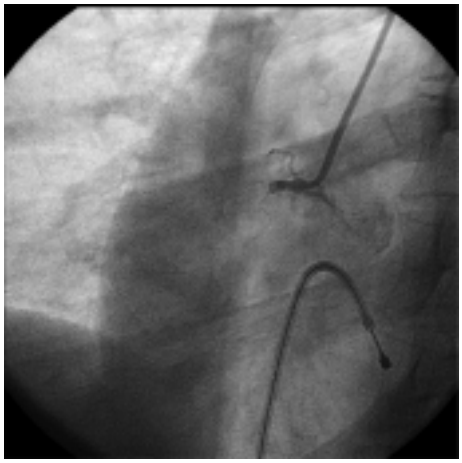

Figure 1. *Coronary angiogram of patient no. 2 showing ostial occlusion of the right coronary artery.*

Case 3. A 68-year-old woman was admitted to our CCU for evolving anterior myocardial infarction. She had experienced intense chest pain for which she initially did not seek treatment 15 hours earlier. On admission she was asymptomatic. Blood pressure was 120/80 mmHg and heart rate 110 b/min. ECG revealed ST-segment elevation in leads V_1-V_6 with concomitant T wave inversion. Revascularization therapy was not attempted because of the delayed presentation and also because of allergy to contrast agents. She was treated with heparin, aspirin and beta-blockers. The peak serum levels of CK and of the MB fraction were 2238 and 212 IU/l respectively. Her medical history was unremarkable except for mediastinal irradiation at 55 years of age because of a thymoma. Pre-discharge coronary angiography revealed LAD occlusion at the ostium with otherwise angiographically normal coronary arteries. She was successfully treated with PTCA and stenting. After 8 months she is still asymptomatic.

Case 4. A 53-year-old woman was transferred to the CCU from a community hospital because of an episode of chest pain at rest with transient ST-segment elevation

treated with i.v. nitroglycerin. While in hospital, in spite of ongoing i.v. nitrates, she experienced a new episode of chest pain at rest. During this episode, blood pressure was 130/80 mmHg and heart rate 60 b/min. ECG revealed ST-segment elevation in leads II, III, aVF and in the right precordial leads. Pain and ECG changes resolved within 15 min of administration of aspirin and heparin. At the echocardiogram, akinesia of the inferior wall was observed during chest pain, with a return to a normal global and regional function after resolution of ischemia; echocardiography also revealed thickening of the mitral valve and of the pericardium without pericardial effusion. Physical examination was normal. Her medical history was unremarkable, except that she had undergone mediastinal irradiation when she was 21 years old because of a mediastinal lymphoma. Emergency coronary angiography revealed ostial stenosis of the left main coronary artery (70%) and of the right coronary artery (70%) with no other visible lesions (Fig. 2). Total CK, MB fraction and troponin I concentrations were normal. Angiography showed a normal appearance of the aorta and of the left and right internal mammary arteries. B-mode echo imaging with Doppler spectrum analysis of both internal mammary arteries confirmed adequate flow. B-mode echo imaging with Doppler spectrum analysis of the carotid arteries did not reveal any lesion. Coronary artery bypass grafting was performed off-pump, 10 days after admission, with a left internal mammary artery graft to the LAD and saphenous vein grafts to the right coronary and circumflex coronary arteries. At 12-month follow-up the patient is still asymptomatic.

Discussion

It is not clear why radiation causes coronary artery disease. Available human pathology specimens consistently show fibrous thickening and smooth muscle cell proliferation in a proteoglycan-rich matrix, with foam-cell or lipid deposition conspicuously absent[3,4,7,9]. In experimental studies, exposure to a radiation source injures the coronary arteries causing intimal hyperplasia and fibrosis without lipid/foam-cell deposition[7,9]. Thus, both clinical and experimental data indicate that radiation may cause coronary artery lesions which differ from the "classical" atherosclerotic disease. An ostial localization of stenosis is also typical of radiation-induced coronary artery disease[10-12]. This peculiar localization is commonly ascribed to the different energy exposure of the different areas of the heart during mediastinal irradiation. The observation that the distal coronary vasculature is free of disease and that radiation-induced coronary artery disease is often seen in relatively young patients who lack evidence of risk factors for atherosclerosis lends further credence to the hypothesis that the mechanisms of lesion formation/proliferation must differ from those responsible for typical atherosclerotic disease.

In addition to confirming important differences in the process of lesion formation following mediastinal irradiation, our data provide a potentially important description of a seemingly novel mechanism of acute coronary artery occlusion. We report 4 consecutive cases of acute coronary syndrome with ST-segment elevation and ostial stenosis as the culprit lesion. The patients were relatively young, without a family history of premature coronary artery disease and no known risk factors for atherosclerosis, except for serum levels of HDL cholesterol < 40 mg/dl in 2 patients (Table I). In 3 out of 4 patients, coronary angiograms were performed while transmural ischemia was ongoing, and in all cases they showed complete occlusion by thrombus, thus ruling out spasm as a possible mechanism of ischemia. We have no immediate explanation as to why the thrombus developed acutely over those lesions. Even though there may be other causes of coronary atherosclerosis, such as the disease seen in the transplanted

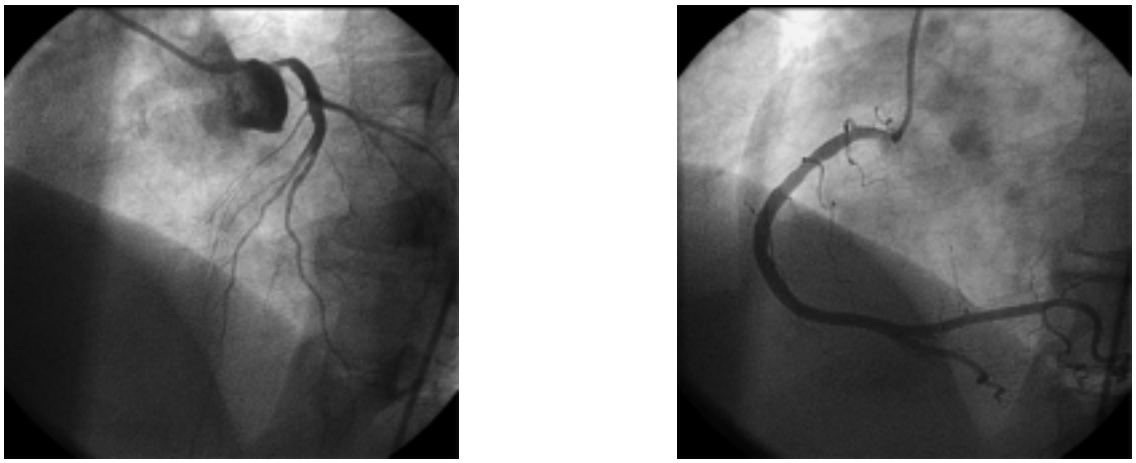

Figure 2. Left panel: *coronary angiogram of the left coronary artery of patient no. 4, showing a 70% ostial stenosis of the left main tract.* Right panel: *coronary angiogram of the right coronary artery of patient no. 4, showing a 70% ostial stenosis.*

heart[13], ulceration of lipid-laden, necrotic plaques has long been considered as the tenet of acute intravascular thrombosis[14]. In this respect, the histology of radiation-induced disease would apparently not favor plaque ulceration[3,4,7,9]. We could not perform any direct imaging study (e.g., intracoronary echography, angioscopy) because the patients were brought to the cath lab for emergency procedures. However, data which suggest that acute coronary thrombosis may also develop over eroded plaques in the absence of plaque disruption are accumulating[15,16]. Interestingly, eroded plaques are characterized by abundant smooth muscle cells and proteoglycans and a small or absent lipid core[17]. With regard to this, it is possible that the thrombus developed over an area of endothelial erosion by virtue of an increased shear stress at the site of stenosis[18]. It is also interesting to speculate about an apparent similarity between radiation-induced coronary lesions and pathological alterations seen at the site of brachytherapy. In fact, it is becoming evident that intracoronary radiation may be associated with a relatively high incidence of late coronary thrombosis[19,20]. Although it should be noted that this complication has been so far described within months following the procedure, a time frame considerably shorter than what observed in our patients, and that mechanical trauma at the site of the procedure might have also played a role, it is noteworthy that the histological alterations induced by the intravascular delivery of radiation are remarkably similar to those observed following external radiation[7,9].

In conclusion, mediastinal irradiation is a rare cause of coronary artery disease[21-23] that could present either as stable angina pectoris or as an acute coronary syndrome episode. The development of a thrombotic occlusion over a fibrous lesion in young patients without risk factors for atherosclerosis supports the view that acute coronary syndromes may not be unequivocally associated with atherosclerotic plaque disruption.

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