

Predicting heart attack in a patient post-radiation therapy using plaque CCTA analysis and serum biomarker test. Case report

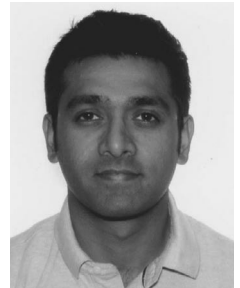
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ABSTRACT

Accelerated coronary artery disease (CAD) is a long term manifestation of chest irradiation that may progress to acute myocardial infarction (MI). We report the use of an algorithm-based biomarker test and coronary computed tomography angiography (CCTA) to identify accelerated CAD in a patient treated with chest irradiation and combination chemotherapy for non-Hodgkin's lymphoma (NHL). Using a seven protein biomarker test with four incorporated clinical factors, we identified the patient had a 6 fold higher risk for future MI than expected for individuals at his age. Using CCTA, we characterized his plaques based on the following parameters: percent diameter stenosis (ranging from 30–70), percent area stenosis, percent necrotic core (NC), percent fibrotic core (FC), percent calcium core (CC), FC thickness, percent vessel wall to lumen, and NC to FC ratio. We identified a plaque in his left circumflex (LCX) with moderate percent diameter stenosis, high percent NC, low percent FC, absent FC thickness, high percent vessel wall to lumen ratio, and high NC to FC ratio as the most vulnerable to rupture and cause MI. The patient was educated about his risk of a future MI and started on maximum medical therapy. Nevertheless, he experienced a ST elevation MI (STEMI) in 185 days with occlusion at the vulnerable plaque site of his LCX. The recognition of a vulnerable plaque in a vulnerable patient may necessitate prophylactic stenting in vessels without severe obstruction. The serum biomarker test and CCTA plaque analysis may detect these patients in need of aggressive therapy.

KEY WORDS: coronary computed tomography angiography, myocardial infarction risk assessment, coronary artery disease, chest irradiation, cardiac biomarkers, plaque characterization

INTRODUCTION

Cardiovascular (CV) disease and cancer are the leading causes of death. As efforts to combat these diseases continue to evolve, the prognosis of patients with CV disease and cancer has improved. Unfortunately, many anticancer treatments pose significant threat to the heart and the success in treating cancer might be followed by defeat from life-threatening cardiotoxicity [1, 2]. Furthermore, CV disease and cancer coexist in many patients due to the increased life span of the population. This has led to the advent of cardioncology: an interdisciplinary specialty aimed at understanding how anticancer treatments stress and damage the CV system, what CV complications result from anticancer treatments, how to promptly identify oncologic patients at highest risk for cardiotoxicity and tailor their anticancer treatment, and how to manage patients with both CV disease and cancer.

All patients being considered for potentially cardiotoxic chemotherapy should undergo a detailed CV evaluation prior to, during and for years after exposure [1, 2]. Several tests have been used, each with their own benefits and disadvantages. These include a baseline electrocardiogram for assessing conduction abnormalities and arrhythmias, and a two-dimensional echocardiogram for assessing cardiac function in terms of valvular characteristics, myocardial contractility, and left ventricular ejection fraction (LVEF). The gold standard for assessing myocardial function and LVEF in cancer patients is the use of cardiac magnetic resonance (CMR) imaging but three-dimensional echocardiography is emerging to be a feasible and reproducible method of comparable significance [3]. Cardiac computed tomography (CT) allows for the non-invasive evaluation of coronary circulation but radiation exposure in cardiac CT has been a concerning issue in the past. New protocols have now been developed with dramatically reduced radiation exposure and have made cardiac CT a promising assessment tool. Cardiac markers troponin I and brain natriuretic peptide (BNP) have been positively correlated with cardiotoxicity. The use of these markers for detecting early stages of cardiotoxicity is well established [4, 5]. Standard guidelines intended to reduce CV disease risk in patients undergoing anticancer treatments recommend blood pressure monitoring and control, lipid level reduction, smoking cessation, and lifestyle modifications. Best practice model has been developed by the International Cardioncology Society and is under review for publication [6].

Coronary ischemia is a long term complication of mediastinal or left chest irradiation [1, 2, 7]. In terms of incidence, severity, mortality risk, and the chances of prevention, early diagnosis and effective therapy, accelerated CAD has been recognised as a dangerous cardiac complication of radiation treatments and is wort-

hy of significant focus in patient follow-up [7]. This case report investigates the potential of accelerated CAD in a patient with history of chronic lymphocytic leukemia (CLL) and NHL. Here, we demonstrate the utility of CCTA and inflammatory protein markers for the evaluation of accelerated CAD and risk prediction of acute coronary events in a patient exposed to radiation therapy.

CASE PRESENTATION

This case is of a 67-year-old Caucasian male real estate developer with a past medical history of tonsillectomy, two herniorrhaphies, kidney stones, gastroesophageal reflux disease (GERD) related to fatty food intolerance, diverticulosis, surgical removal of tumors in the lumbar spine, and a family history significant for hypertension and CAD. He was diagnosed with NHL in 1989 and treated on a National Institute of Health (NIH) trial with radiation to the chest and a chemotherapy regimen consisting of methotrexate, adriamycin/doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine (Oncovin), procarbazine and prednisone (ProMACE-MOPP). He has not had any relapses since that time. Five years ago, he was diagnosed with CLL and has since been treated at NIH. In August, 2013, the patient experienced an episode of left arm and left chest discomfort that awakened him from sleep and prompted a visit to the local hospital. The pain was described as sharp and pinpointed in the chest with no relation to exertion, food, excitement or emotion, and no alleviation by rest. Patient reported a preceding busy day at work with a single, large meal consisting of fried and fatty foods. At the hospital, the patient was administered nitroglycerin that did not alleviate his chest pain. He had a complete cardiac workup, which consisted of an electrocardiogram (EKG) that showed normal sinus rhythm and left axis deviation, a chest X-ray (CXR) with a linear scar or atelectasis at the right lung base and elevation of right hemidiaphragm, a transthoracic echocardiogram (TTE) that showed left ventricular hypertrophy (LVH) with a normal cavity size and moderate aortic regurgitation, and an exercise myocardial perfusion single photon emission computed tomography (SPECT) with no MI or ischemia. Lab results consisted of a troponin I of 0.031, creatine phosphokinase (CPK) of 118, blood urea nitrogen (BUN) of 24, creatinine of 1.0, potassium of 4.4, 26000 white blood cells (WBCs) and 106000 platelets. The patient was diagnosed as having a bad episode of GERD. The pain subsided spontaneously the morning after and the patient was discharged with instructions to follow-up with a cardiologist.

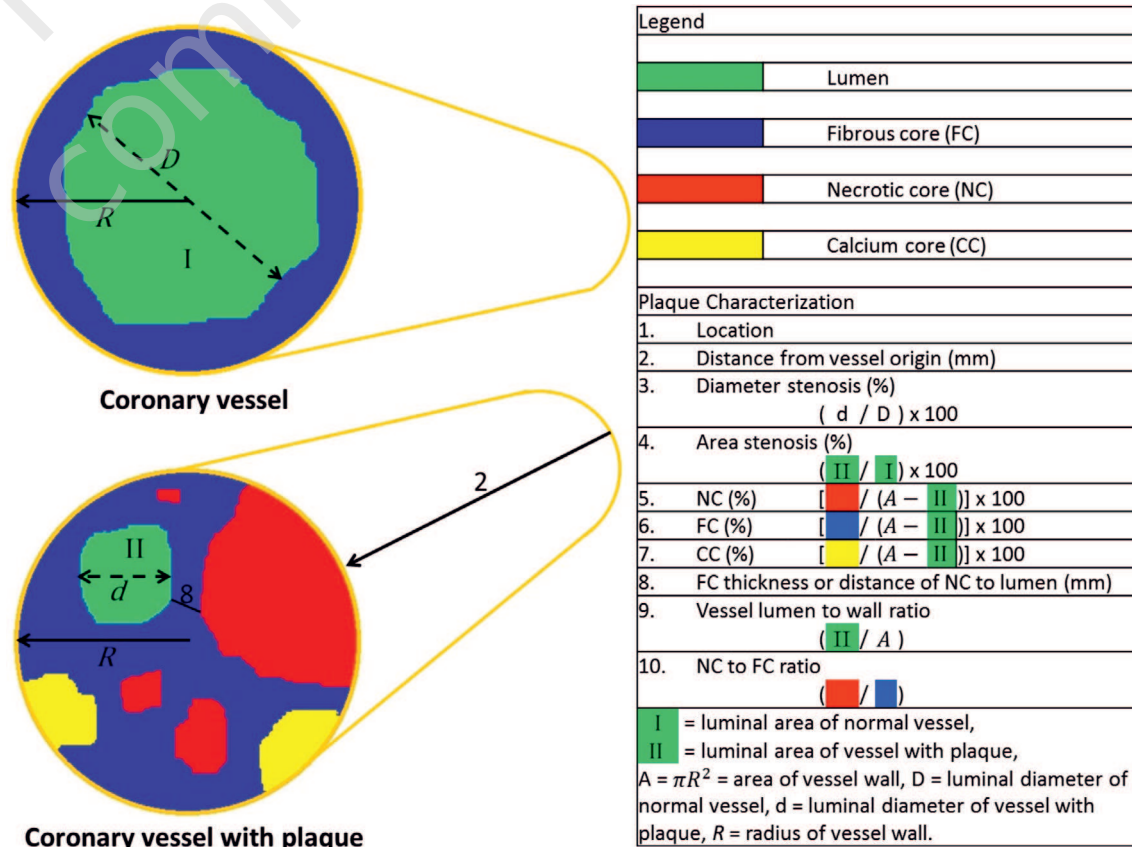
The patient presented to CV clinic in September 2013, with no complaints for a second opinion about his episode of chest pain and evaluation of his CV disease risk. His medications were 600

mg chlorthalidopoxide (Librax) as needed, 81 mg acetyl-salicylic acid (ASA) taken twice daily, probiotic, multivitamin, coenzyme Q10, fish oil, olive leaf, and red marine algae. He reported being a nonsmoker and drinking alcohol five times a week. Physical examination at that time revealed a 6 feet 1 inch, 206 pound (185 cm, 93.4 kg), body mass index (BMI) of 26 kg/m², well-nourished male in no acute distress. He was found to be afebrile with a blood pressure of 140/74 mmHg, a pulse of 79 beats/min, and oxygen saturation of 97%. Overall exam findings were unremarkable. Lab results included a total cholesterol of 252 mg/dL, high-density lipoprotein of 57 mg/dL, low-density lipoprotein of 121 mg/dL, and triglycerides of 79 mg/dL. To assess the risk of CV disease and follow-up on previous echocardiogram findings, a repeat TTE, carotid intima-media thickness (CIMT) test, and CCTA were performed. The images were processed with the Vital Images Vitrea SurePlaque software for coronary plaque analysis. The repeat TTE showed a bicuspid aortic valve with moderate regurgitation, mild mitral regurgitation, minimal tricuspid regurgitation, LVEF of 55%, right ventricular systolic pressure (RVSP) of 37 mmHg, normal chamber sizes, no evidence of LVH, and diastolic dysfunction. The CIMT test revealed normal hemodynamics

with bilateral non-calcified carotid plaques. Also, an algorithm driven test that looks at seven clinically relevant atherosclerotic, serum proteins and certain clinical factors for five-year CAD risk prediction was conducted. The seven protein biomarker test revealed that he was a vulnerable patient at high risk for an acute coronary event, with a 6.4 fold higher risk than expected for a 67-year-old male.

The CCTA was intended to evaluate the coronary anatomy in a non-invasive manner as accurately as possible. Specifically, the interest was to rule out left main coronary artery (LMCA) and proximal left anterior descending (LAD) artery diseases over other possible but less dangerous lesions. This is because we suspected coronary vessels traversing the anterior portion of the heart to have had the biggest impact from anterior chest irradiation. We chose to identify the plaque burden of coronary circulation and to characterize it in terms of severity or vulnerability to rupture and cause MI. Several plaque parameters were taken into consideration: location, distance from vessel origin, percent diameter stenosis, percent area stenosis, percent NC, percent FC, percent CC, FC thickness (minimum distance of NC to vessel lumen), percent vessel wall to lumen ratio, and NC to FC ratio (Figure 1).

FIGURE 1.
Plaque parameters used for characterization via coronary computed tomography angiography.

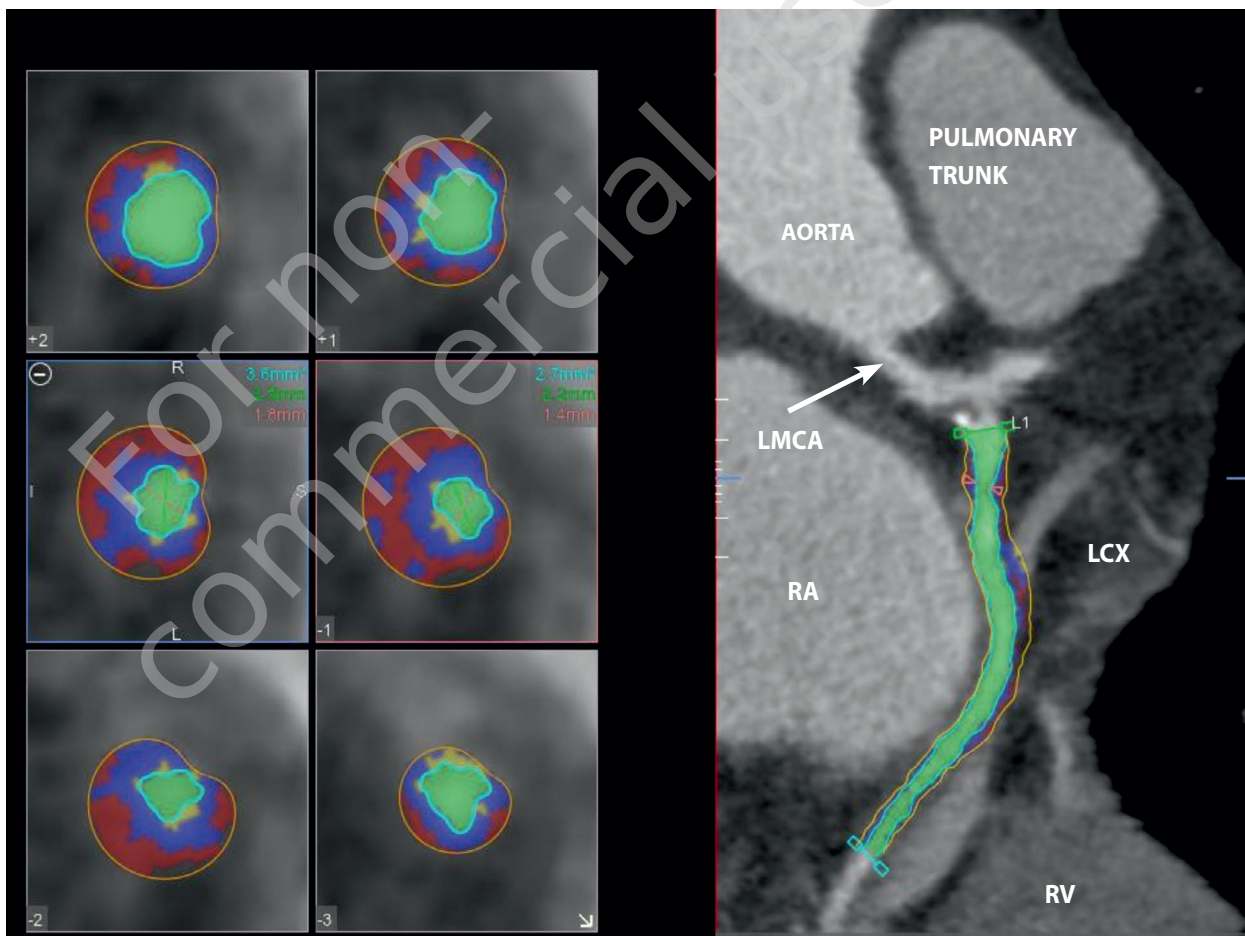


The vulnerability of plaques was suspected to increase with increasing diameter stenosis, increasing area stenosis, increasing NC, decreasing FC, decreasing FC thickness, increasing percent vessel wall to lumen ratio, and increasing NC to FC ratio. Using this CCTA protocol, we identified a 50–60% stenosis in the proximal LCX with a lipid-rich plaque that appeared to be high risk and vulnerable (Figure 2).

tor) daily was started. Also, the patient was recommended to avoid fatty foods, cut down on alcohol intake, and exercise regularly. On follow-up, the atorvastatin calcium (Lipitor) was switched to 5 mg pravastatin daily due to a statin myopathy. The CCTA overread for extracardiac anatomy demonstrated possible bronchiectasis at the medial right lung base and prominent lymph nodes in the left axillary region. A subsequent chest CT

FIGURE 2.

Vulnerable left circumflex (LCX) coronary artery plaque identified using coronary computed tomography angiography. Longitudinal view displaying the luminal narrowing at the vulnerable plaque site in LCX (right). Cross-sectional view of the vulnerable plaque site in LCX (left). Green: lumen, Red: necrotic core, Blue: fibrotic core, Yellow: calcium core, LMCA: left main coronary artery, LCX: left circumflex coronary artery.



No evidence of calcification was seen in this lesion. There were also moderate partially-calcified plaques seen in the proximal and distal LMCA, and proximal LCX. The right coronary artery (RCA) was found to have mild to moderate partially-calcified plaques with some evidence of positive remodeling. The coronary findings and the increased risk of an acute cardiac event involving the proximal LCX were discussed with the patient and maximum medical therapy with ASA and 40 mg atorvastatin calcium (Lipi-

tor) daily was started. Also, the patient was recommended to avoid fatty foods, cut down on alcohol intake, and exercise regularly. On follow-up, the atorvastatin calcium (Lipitor) was switched to 5 mg pravastatin daily due to a statin myopathy. The CCTA overread for extracardiac anatomy demonstrated possible bronchiectasis at the medial right lung base and prominent lymph nodes in the left axillary region. A subsequent chest CT

revealed bilateral axillary lymphadenopathy, mild splenomegaly, volume loss and scarring in the right lower lobe, and bronchiectasis in the right middle lobe. The patient was advised to follow-up with a pulmonologist to assess his respiratory system and an oncologist for his CLL status. Despite maximum medical management, the patient had an acute cardiac event in April, 2014. He presented to the emergency department in cardiogenic shock with 4 hours of substernal chest

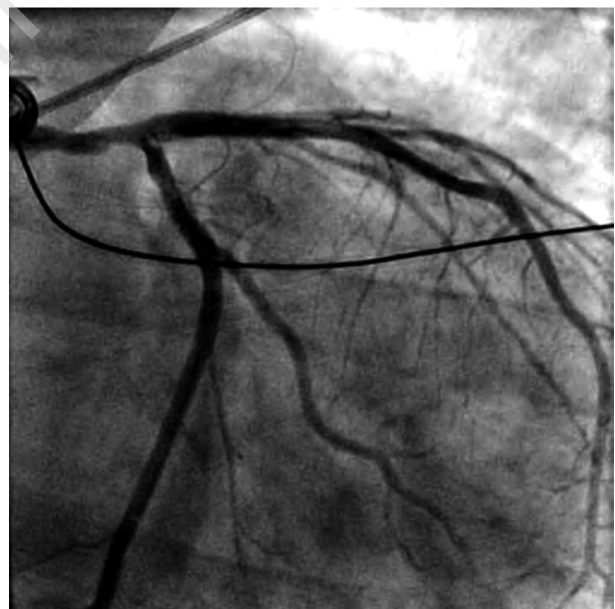
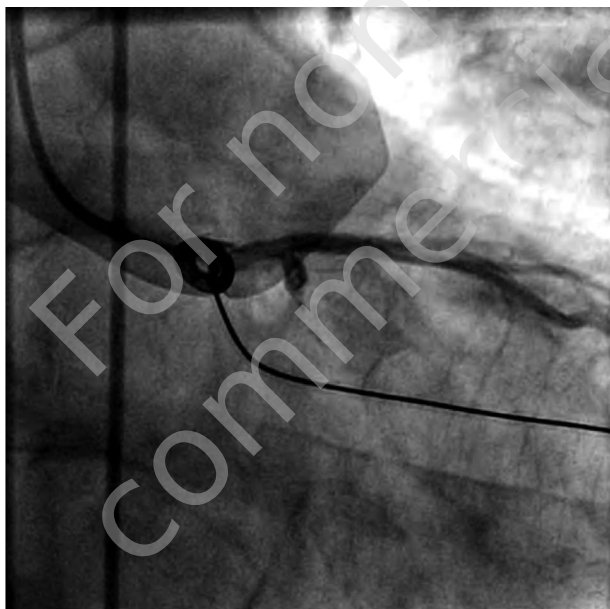
pressure, shortness of breath, and diaphoresis. His EKG revealed an inferior ST elevation with reciprocal lateral changes. A bolus of clopidogrel bisulfate (Plavix) was given and emergency cardiac catheterization was planned. He was heparinized but not given beta-blockers and nitrates because of a low blood pressure and complete heart block. His cardiac catheterization revealed a 100% occlusion of the dominant LCX 185 days after the plaque was characterized as vulnerable to rupture (Figure 3).

The patient had a near occlusion of the LMCA likely due to vasospasm. Also, he was found to have a 70% proximal RCA lesion, a 50% ostial LMCA lesion, and a 50% lesion in the first diagonal

and maintained on vasopressors. He had a TTE that revealed a 35% LVEF with lateral akinesis. The patient was started on piperacillin and tazobactam (Zosyn) and vancomycin for possible aspiration pneumonia that were later discontinued. He had a few episodes of hemoptysis that were attributed to possible pulmonary edema in addition to his anticoagulation. The patient was diuresed with furosemide (Lasix) and slowly resolved to the point of no pulmonary edema or infiltrate as per a follow-up CXR. Vasopressors and intra-aortic balloon pump were discontinued. He was eventually discharged on formoterol and mometasone (Dulera) twice daily, 90 mcg albuterol as needed, 40 mg omeprazole daily, pravastatin, 75 mg clopidogrel bisulfate (Plavix), ASA,

FIGURE 3.

Cardiac catheterization showing 100% occlusion of left circumflex coronary artery at the same vulnerable site predicted using coronary computed tomography angiography (left). Successful revascularization of the vulnerable LCX lesion (right).



branch off LAD. In the catheterization lab, the patient started having bradycardia and received epinephrine. He had aspiration thrombectomy performed and an intravascular ultrasound (IVUS)-guided Xience stent placed that reduced his LCX lesion to 0% (Figure 3). The patient then started having more bradycardia that progressed to pulseless electrical activity. Cardiopulmonary resuscitation was initiated, and then the patient went into ventricular fibrillation that was cardioverted to sinus tachycardia. The patient was intubated and an intra-aortic balloon pump was placed through the left groin. There was a remaining 30% ostial LCX lesion and a 40 to 50% LMCA lesion that were evaluated by IVUS. The patient was transferred to the intensive care unit

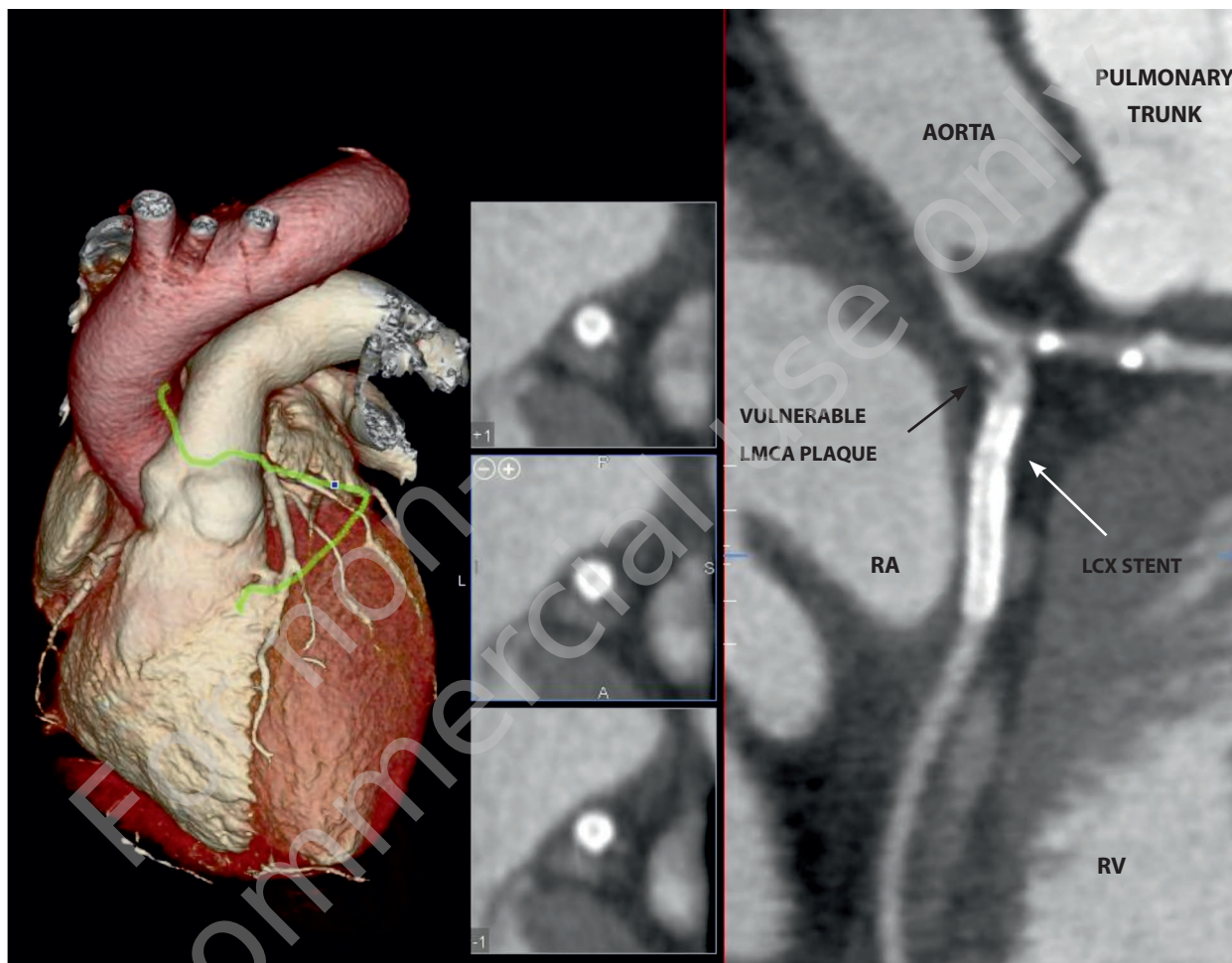
0.4 mg sublingual nitroglycerin as needed, 20 mg furosemide (Lasix) daily, 2.5 mg ramipril twice daily, 6.25 mg carvedilol twice daily, 25 mg spironolactone daily, and a defibrillator vest.

The patient reported to the CV clinic for follow-up and underwent a repeat CCTA to determine his residual plaque burden and assess his risk of another cardiac event. A significant non-calcified plaque of moderate range in the LMCA was identified that extended into the origin of the LCX and was followed by a stent (Figure 4).

Furthermore, there appeared to be an area in the LMCA that had an ulcerated lipid-rich plaque (Figure 4). Besides the LMCA, there were calcified plaques with positive remodeling in the proximal

FIGURE 4.

Residual coronary artery disease in the case patient as seen by coronary computed tomography angiography. Vulnerable plaque located in the distal left main coronary artery extending into LCX and a visible stent within the revascularized left circumflex coronary artery (LCX).



LAD and proximal RCA. The patient was educated about his risk of a future cardiac event involving the LMCA and maintained with aggressive medical therapy. On subsequent follow-up, a CMR was ordered to monitor myocardial function and assess the need for prophylactic management of cardiac remodeling.

DISCUSSION

This case demonstrated that CCTA and seven protein biomarker test in conjunction hold great prognostic value for an acute coronary event. We used the seven protein biomarker test to identify that the case patient was a vulnerable patient with an elevated risk for future MI. This test was developed and validated in two population cohorts and has been shown to identify significantly more individuals who experienced a MI as being at high risk for such an event versus the National Institutes of

Health 10-year CV disease risk assessment tool, which is the current standard of measuring CV risk [8]. This improved accuracy in CV risk assessment is expected to lead to improved preventive care and fewer MI-related deaths [8]. Nevertheless, it has been realized that the sole use of population-based prediction models has limited utility for risk prediction of individual patients and it has been proposed that individual parameters of subclinical disease be incorporated into models [9]. Non-invasive imaging-based screening of subclinical atherosclerosis for the characterization of vulnerable plaques promises great potential in CV risk prediction [9].

We report here the use of CCTA for the identification of accelerated CAD in a patient with prior chest irradiation and exposure to chemotherapeutic drugs for NHL. We characterized his plaque burden in terms of severity and identified a vulnerable lipid-rich lesion at high risk in his proximal LCX. Based on the

imaging results, the patient was diagnosed with CAD and started on maximum medical therapy. Unfortunately, the patient had an acute cardiac event in 185 days, with occlusion of his LCX at the same vulnerable site predicted using our plaque characterization scheme. The patient course prompted us to revisit his CCTA findings, specifically the suspected LCX plaque that was deemed vulnerable. We established that our method of characterization may be appropriate to identify high-risk lesions that may lead to acute coronary events in vulnerable patients. CCTA remains the only modality that allows for reliable non-invasive visualization of coronary arteries and this makes it very useful for the evaluation of patient risk. This is especially important when compared with more invasive modalities like IVUS that not only has been associated with serious adverse events, including coronary dissections and perforations, but also has been inadequate at predicting acute coronary events based on lesion characteristics i.e. small luminal area, large plaque burden, and the presence of thin-cap fibroatheromas [10]. Several publications in the last few years have evaluated the utility of CCTA to delineate individual plaque components. The active Plaque Registration and Evaluation Detected In Computed Tomography (PREDICT) registry was developed to relate plaque characteristics on CCTA with clinical findings, mortality and morbidity [11]. Although pending, its results are anticipated to confirm at least some of the plaque features in this case report that proved to be useful predictors of acute coronary events. Taken together, using CCTA and the seven protein biomarker test, this case identified a high-risk patient with a high-risk co-

ronary lesion that led to a subsequent MI. Also, it demonstrated that maximum medical therapy was insufficient at preventing an MI in this patient with accelerated CAD secondary to prior chest irradiation and exposure to chemotherapeutic drugs. Understandably, the feasibility of CCTA in combination with the seven protein biomarker test for the risk prediction of acute coronary events needs to be evaluated in a large cohort of patients (PROTECT registry). Moreover, this strategy of CV risk assessment needs to be evaluated against conventional prediction models including the Framingham Risk Score to determine its accuracy or clinical value. Vulnerable plaques in vulnerable patients may require aggressive stenting to prevent MIs.

CONCLUSION

We identified accelerated CAD in a patient with prior chest irradiation and exposure to chemotherapeutic drugs for NHL. Using a seven protein biomarker test and CCTA, we identified the patient to be at a vulnerable patient with a vulnerable plaque at high-risk for rupture. We also determined that maximum medical therapy was insufficient at preventing MI in this patient. The combination of CCTA and seven protein biomarker test may hold great prognostic value for the risk prediction of acute coronary events. Further research with the PROTECT registry will continue to document the results of this approach.

ABBREVIATIONS

Acetyl-salicylic acid	ASA	Creatine phosphokinase	CPK
Blood urea nitrogen	BUN	Electrocardiogram	EKG
Body mass index	BMI	Fibrotic core	FC
Brain-type natriuretic peptide	BNP	Gastroesophageal reflux disease	GERD
Calcium core	CC	Intravascular ultrasound	IVUS
Cardiac magnetic resonance	CMR	Left anterior descending	LAD
Cardiovascular	CV	Left circumflex	LCX
Carotid intima-media thickness	CIMT	Left main coronary artery	LMCA
Chest X-ray	CXR	Left ventricular ejection fraction	LVEF
Chronic lymphocytic leukemia	CLL	Left ventricular hypertrophy	LVH
Computed tomography	CT	Methotrexate, adriamycin/doxorubicin,	
Congestive heart failure	CHF	cyclophosphamide, etoposide,	
Coronary artery disease	CAD	mechlorethamine, oncovin/vincristine,	
Coronary computed tomography angiography	CCTA	procarbazine and prednisone	ProMACE-MOPP

Myocardial infarction	MI	Right ventricular systolic pressure	RVSP
National Institute of Health	NIH	Single photon emission computed tomography	SPECT
Necrotic core	NC	Transthoracic echocardiogram	TTE
Non-Hodgkin Lymphoma	NHL	White blood cell	WBC
Right coronary artery	RCA		

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