Case Report

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Myocardial Infarction Type 4b in Human Immunodeficiency Virus-Infected Patient

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We report a case of a 52-year-old human immunodeficiency virus (HIV)-infected male patient receiving combined antiretroviral therapy (cART), who presented with acute ST-elevation myocardial infarction (STEMI). He was properly treated (e.g., prescribed anti-coagulation drugs: aspirin, clopidogrel, enoxaparin) and discharged. After 1.5 months, another STEMI related with in-stent thrombosis took place. The cART scheme was altered, resulting in no further cardiac events in the follow-up period, with undetectable levels of HIV ribonucleic acid. This case highlights the association between HIV infection and the specific drugs of cART, and the risk of cardiovascular disease development. **(Korean Circ J 2014;44:42-44)**

KEY WORDS: Human immunodeficiency virus; Myocardial infarction; Antiretroviral therapy.

Introduction

Human immunodeficiency virus (HIV) infection is a problem affecting many patients reporting to health care professionals of many specialties, including cardiologists. Taking care of these patients can be challenging due to number of HIV-related comorbidities, as well as possible drug-to-drug interactions which can be detected between antiretroviral medications and drugs commonly used in other conditions.

Case

A 52-year-old male with HIV infection, asthma and varicose veins presented to the hospital with first-ever chest pain. The patient had no history of diabetes mellitus, kidney disease or smoking. Initial 12-lead electrocardiography (ECG) revealed ST-segment elevation in V 2-5 leads, and ST-segment depression in II, III and aVF. The patient was immediately transferred to a catheterization laboratory, where coronary angiography was performed, which showed a dominant right coronary artery with no significant stenosis, acute occlusion of the left anterior descending artery and chronic occlusion of the intermediate branch. Primary percutaneous coronary intervention (PCI) with implantation of an Integrity bare metallic stent (Medtronic Cardiovascular, Santa Rosa, CA, USA) 3.0×1.2 mm into the left anterior descending artery was performed, resulting in complete reperfusion {Thrombolysis in Myocardial Infarction (TIMI) 3 flow}. Intravascular ultrasound was not performed during the procedure. Initial echocardiography revealed a 1.65×1.55 cm blood clot, fixed in an area near the apical part of the left ventricle (LV). His total cholesterol was 4.29 mmol/L, low density lipoprotein-cholesterol (LDL-C) 2.7 mmol/L and triglycerides 1.37 mmol/L and estimated glomerular filtration rate was >60 mL/min/ 1.73. The patient was prescribed aspirin 75 mg, clopidogrel 75 mg, enoxaparin 60 mg, ramipril 2.5 mg, nebivolol 2.5 mg and atorvastatin 40 mg. Because of the retroviral infection, he had been receiving combined antiretroviral therapy (cART) for 6 years. The cART regiment consistied of 2 nucleoside reverse transcriptase inhibitors (emtricitabine and tenofovir), and protease inhibitor lopinavir boosted with ritonavir (lopinavir/r). His plasma HIV ribonucleic acid (RNA) levels, measured by real-time polymerase chain reaction were undetectable. The counts of T lymphocytes CD4 and CD8 were 625 cells/μL (norm, 410-1590 cells/μL) and 818 cells/μL (norm, 190-1140 cells/μL), respectively. The CD4/CD8 ratio was 0.76. After 5 days of hospitalization, he was discharged and instructed to continue the prescribed

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Table 1. Types of myocardial infarction by the Third Universal Definition of Myocardial Infarction[1)]

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis.
Type 2: Myocardial infarction secondary to an ischaemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new left bundle branch block, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5×99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either 1) symptoms suggestive of myocardial ischaemia, or 2) new ischaemic ECG changes or new LBBB, or 3) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or 4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10×99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either 1) new pathological Q waves or new LBBB, or 2) angiographic documented new graft or new native coronary artery occlusion, or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

CAD: coronary artery disease, LVH: left ventricular hypertrophy, ECG: electrocardiography, URL: upper reference limit, LBBB: left bundle branch block

medications.

Two weeks after discharge, the patient was readmitted to the hospital because of general fatigue and malaise. Full examination did not reveal any abnormalities other than the previously described blood clot in LV. The patient was discharged and referred for ambulatory surveillance by a cardiologist when his coagulation parameters including the activated partial thromboplastin time (aPTT) were in the normal range. After 10 days (37 days from the first hospitalization), the patient again presented to the hospital with acute chest pain. His troponin I level was 4.74 ng/mL, and in the ECG, a QS complex was seen in leads V 1-3, with new ST-segment elevation. With an initial diagnosis of type 4b myocardial infarction (MI) (Table 1), the patient again underwent coronary angiography, which showed acute occlusion of the left anterior descending artery because of in-stent thrombosis. After a bolus of eptifibatide, the thrombus was aspirated with good hemodynamic results (TIMI 3 flow). Follow up echocardiography showed a change in the diameter of the clot in the LV (from 1.65×1.55 cm to 2.2×1.2 cm), and akinesis of the apex, a part of the intraventricular septum, and the anterior wall, with an ejection fraction of 33%. Due to the thrombosis, platelet function tests were performed. The aspirin reaction unit was 394, and the P2Y12 reaction unit was 155. At this time, his total cholesterol was 2.8 mmol/L, LDL-C 1.4 mmol/L and triglycerides 1.7 mmol/L. The patient was prescribed aspirin 75 mg, prasugrel 10 mg, carvedilol 25 mg, torasemide 5 mg, ramipril 2.5 mg, spironolactone 12.5 mg, atorvastatin 40 mg and warfarin (to keep the INR at 2.5). A modification of the cART regimen was introduced. The patient still received the combination of emtricitabine and tenofovir, but the protease inhibitor was changed from lopinavir/r to darunavir/r. After 6 months of follow-up, the patient is in good general condition, with undetectable HIV RNA levels and no drop of T helper lymphocytes CD4.

Discussion

In taking care of patients after an MI, we have to take into consideration the patient's co-morbidities and modify the treatment accordingly. In our patient's case, during the first MI, he received the proper treatment including double antiplatelet therapy that consisted of aspirin and a P2Y12 inhibitor, clopidogrel, along with enoxaparin, a low molecular weight heparin. Nevertheless, only after 1.5 months, the patient suffered another major adverse cardiac event due to in-stent thrombosis. Referring to the newest universal definition of MI developed in 2012 by the European Society of Cardiology, we diagnosed the patient with MI type 4b, which covers MI related to stent thrombosis, which was detected in our case by coronary angiography.[1)] After the second event, the patient was prescribed

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prasugrel instead of clopidogrel. Comparison of those two drugs in the TRITON-TIMI study showed that the newer drug (prasugrel) is more effective in patients with ST-elevation myocardial infarction who have undergone PCI, in the prevention of ischemic events, without being associated with an excessive risk of bleeding.[2] The alteration in the antiplatelet therapy was important because of the increased risk of cardiovascular disease and hypercoagulation, which our patient was exposed to through his co-morbidities.

For not yet fully disclosed reasons, patients with HIV infection suffer from a large number of non-AIDS conditions. cART prolongs life but does not fully restore health. Both, HIV and antiretroviral treatment increase the risk of development of conditions such as kidney and liver dysfunction, cancer, osteoporosis, neurological diseases and other end-organ diseases. HIV-positive patients are also known to not only have a shorter life-expectancy, but also to face accelerated aging.[3] One of the biggest concerns in this group of patients is diseases of the cardiovascular system. cART therapy is known to cause endothelial dysfunction and alterations in the lipid profile (including elevated triglyceride levels, a high proportion of small and dense LDL particles, and low high density lipoprotein-cholesterol levels), leading to an increased risk of MI.[4] Specific antiretroviral drugs have different influences on cardiovascular disease risks. It was established that exposure to most of the protease inhibitors is associated with an increased risk of MI. This risk is especially strong when patients receive ritonavir-boosted lopinavir (odds ratio 1.33; 95% confidence interval 1.09-1.61 per year).[5] Darunavir/r, which the patient received after the treatment modification, is at least as equally effective as lopinavir/r and is related to fewer adverse effects.[6] Up to this day, there is no convincing evidence for ritonavir increasing the cardiovascular disease risk.

So should we consider delaying the onset of cART when HIV RNA is undetectable? Patients with untreated HIV infection also have increased cardiovascular risks because of HIV-related proatherogenic mechanisms, like ongoing immune activation, inflammation, increased coagulation, and changes in blood lipids.[7][8] This along with other commonly underdiagnosed conditions can contribute to in-stent thrombosis.[9] Probably the total harm on the cardiovascular system done by the untreated HIV is greater than the one from cART. With all this in mind, for HIV-infected patients at high cardiovascular risk, we have to remember certain things. The cART scheme should be chosen from the least harmful drugs, and all patients should be treated individually, taking into account modifications in the cardiovascular risk factors and changes in the aggressive pharmacological treatment made as necessary. Drugs prescribed by a cardiologist should be checked for possible interactions with cART drugs. For example, simvastatin and lovastatin should not be used in patients who are taking protease inhibitors because of potential interactions via cytochrome P-450 enzyme CYP3A4. On the other hand, atorvastatin and rosuvastatin are safe to use in this case.[10]

Today a cardiologist rarely deals with a patient afflicted only with an isolated disease of the heart or vessels. Due to prolonged life expectancy, our patients are more and more often burdened with many comorbidities. Now we have to deal with not only diseases related to the fields of cardionephrology, cardiodiabetology, cardiosexology, cardiooncology, but also diseases in other fields like the combination of cardiology with infectious diseases. It is important to remember to look at the whole patient instead of only the heart. There is a need for close cooperation between a cardiologist and doctors of other fields, with an expansion of the Heart Team concept to everyday practice. Cardiologists rarely deal with HIV-infected patients and often do not have much knowledge of cART interactions, so that every time a new drug is added to a patient's regimen, it can be helpful to consult with an infectious diseases specialist.

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