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CASE REPORT

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Rapid progression of atherosclerotic coronary artery disease in patients with human immunodeficiency virus infection

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Abstract We describe the case of a 39-year-old human immunodeficiency virus (HIV)-infected man with angiographically documented rapid progression of coronary artery disease. Over a time course of only 2 months, he developed high-grade stenosis of the left anterior descending coronary artery. The risk of myocardial infarction is increased in patients with HIV infection receiving antiretroviral therapy. However, the absolute risk is small and the marked overall benefits of antiretroviral therapy are evident. Patients receiving HIV protease inhibitors should be screened for hyperlipidemia, hyperglycemia, and hypertension. They may be candidates for lipid-lowering therapies depending on their long-term prognosis and individual risk of cardiovascular disease. Care is need because of possible drug interactions between lipid-lowering drugs and antiretroviral therapy. Invasive treatment of acute myocardial infarction does not differ from that in patients not infected with HIV. The rate of progression of coronary artery disease and the restenosis rate, however, are often unexpectedly high in these patients.

Key words Human immunodeficiency virus · Atherosclerosis · Coronary artery disease · Antiretroviral therapy

Case report

A 39-year-old man was admitted for elective coronary angiography because of postinfarctious exercise-induced atypical chest pain 2 weeks after an acute posterolateral myocardial infarction (maximum creatine kinase 937 U/l). The myocardial infarction had not been heralded by symptoms.

The patient was known to have had human immunodeficiency virus (HIV) infection for 14 years, and he received highly active antiretroviral drug therapy (HAART) consisting of the protease inhibitor nelfinavir, the non-nucleoside reverse transcriptase inhibitor nevirapine, and the nucleoside reverse transcriptase inhibitor stavudine for 5 years. Moderate arterial hypertension was successfully controlled with a β-blocker for 1 year. Laboratory analyses showed untreated dyslipidemia (total cholesterol 6.4 mmol/l, high-density lipoprotein cholesterol 0.92 mmol/l; triglycerides 7.1 mmol/l). Blood sugar was normal, he was a non-smoker, and there was no family history of cardiovascular disease.

The coronary angiography showed high-grade stenosis of the circumflex branch of the left coronary artery (Fig. 1A, arrow). In addition, an intermediary branch was severely stenosed. The left anterior descending coronary artery (LAD) was free of stenosis, as was the right coronary artery (RCA). The circumflex was successfully stented with a sirolimus-eluting stent (Fig. 1B). The patient was dismissed with a prescription including aspirin, clopidogrel, carvedilol, lisinopril, and pravastatin. The antiviral triple-drug regime was not changed.

Two months later, the patient was readmitted because of worsening exercise-induced chest pain. Coronary angiography showed a filiform *de novo* lesion of the LAD (Fig. 1C, arrow). The previously implanted stent in the circumflex artery was open. In addition, the RCA showed several low-grade lesions, and high-grade stenosis of a posterolateral branch of the RCA receiving collaterals from the LAD. Based on the clinical presentation and the angiographic appearance of the lesion, plaque rupture seemed unlikely. Instead, the lesion appeared to have rapidly progressed from a minor plaque. Traditional predictors of rapid plaque progression such as bifurcation location, plaque irregularity, or presence of a thrombus had not been present initially.[1,2] Whereas it is not uncommon for minor plaques to progress over subsequent years, the present rapid progression to a subtotal lesion was unusual.[3,4] The LAD was stented using a sirolimus-eluting stent (Fig. 1D). Lipid-lowering therapy was optimized by adding ezetimibe to the statin. The patient remained asymptomatic over the following 6 months.

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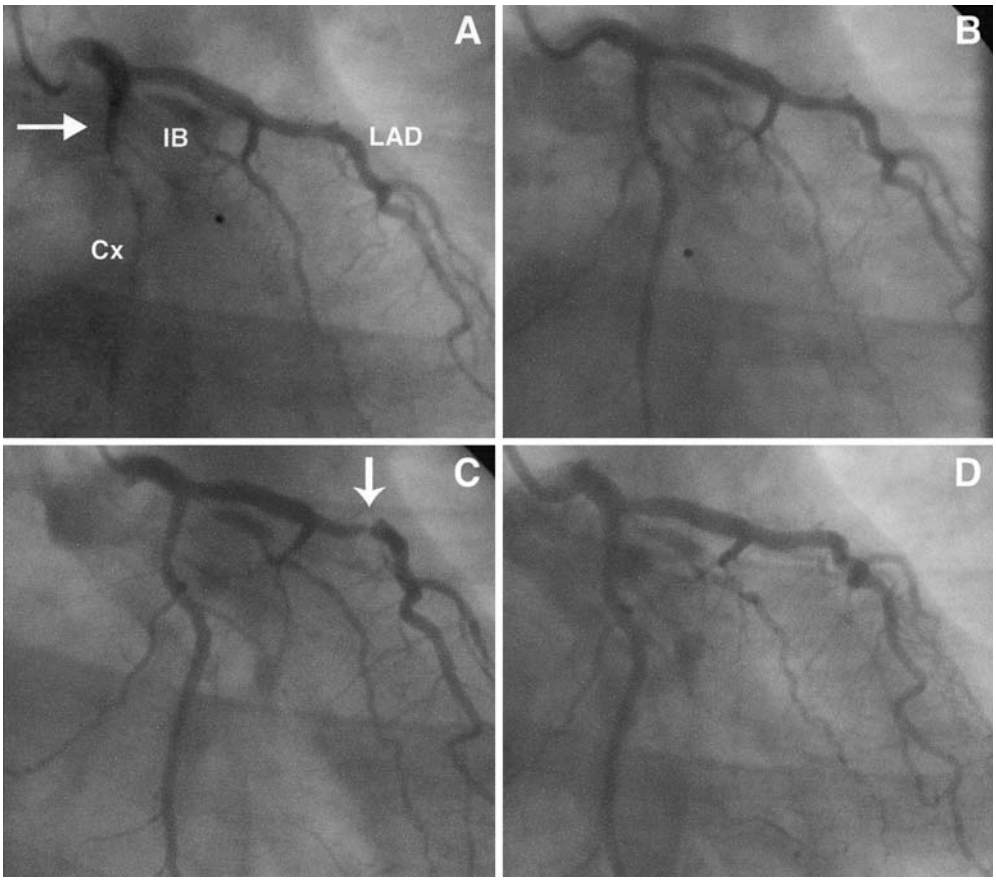

Fig. 1A–D. Coronary angiography. **A** High-grade stenosis of the circumflex branch (*Cx*) of the left coronary artery (*arrow*). In addition, an intermediary branch (*IB*) is severely stenosed. The left anterior descending coronary artery (*LAD*) is free of stenosis. **B** The circumflex coronary artery was successfully stented with a sirolimus-eluting stent. **C** Two months later, coronary angiography shows a filiform *de novo* lesion of the LAD (*arrow*). The previously implanted stent in the circumflex artery is open. **D** The LAD stented with a sirolimus-eluting stent

In conclusion, we are reporting an unusually rapid progression of atherosclerosis in the coronary artery of an HIV-infected patient who developed a severe LAD stenosis within 2 months. This case highlights the importance of aggressive lipid-lowering strategies in patients with HIV infection treated with HAART. However, care is needed because of possible drug interactions between lipid-lowering drugs and antiretroviral therapy.

Discussion

Metabolic changes associated with HIV infection and antiretroviral therapy

Human immunodeficiency virus infection itself is associated with dyslipidemia. Following HIV infection, an early decrease in high-density lipoprotein (HDL) cholesterol and elevations in triglycerides are observed while low-density lipoprotein (LDL) cholesterol decreases later in the course of the disease.

HIV patients are at higher risk of developing hypertension at a younger age than the general population. Predisposing factors for developing hypertension include vasculitis,[5,6] which may also be associated with aneurysms of the large vessels, such as the carotid and femoral arteries and the abdominal aorta.[7] Acquired glucocorticoid resistance in patients with HIV hypercortisolism promotes the development of hypertension.[8]

Besides reverse transcriptase inhibitors, HIV protease inhibitors are key components of antiviral therapy. However, they can cause hyperlipidemia, hyperglycemia, and central obesity.[9,10] Cardiovascular risk is increased by this metabolic derangement and premature atherosclerotic vascular disease may be the consequence. Indeed, insulin resistance occurs in as many as 25%–60% of patients treated with protease inhibitors.[11–13] Protease inhibitors lead to typical alterations in lipid metabolism commonly associated with insulin resistance, i.e., decreased HDL, increased LDL cholesterol and triglycerides, and hyperinsulinemia. As a consequence, there is reduced uptake of serum lipids by fat cells, increased lipolysis in the subcutaneous adipose tissue, and increased production of lipids by hepatocytes. Increased tumor necrosis factor α (TNFα) induces elevation of free fatty acids and insulin resistance. Decreased perosixome-proliferator activated receptor (PPARγ) function causes increased subcutaneous adipocyte and macrophage apoptosis, as well as reduced promotion of cholesterol efflux via ATP-binding cassette transporter (ABCA1). Therefore, hyperinsulinemia is not necessarily a feature of this derangement; dyslipidemia also occurs without insulin resistance.

In addition, protease inhibitors such as ritonavir, indinavir, and amprenavir upregulate CD36, a scavenger receptor that mediates cholesterol uptake in macrophages.[14]

Highly active antiretroviral drug therapy thus directly promotes atherosclerosis independently from the metabolic changes described above.

Mitochondrial dysfunction due to nucleoside-analogue reverse transcriptase inhibitors such as stavudine may also contribute to metabolic changes. This class of antiretroviral drugs, often prescribed in combination with protease inhibitors, may cause dyslipidemia itself.

Premature coronary artery disease in patients with HIV infection

Premature coronary artery disease in HIV-infected patients treated with HAART has been postulated in retrospective analyses of large-cohort studies.[15–20] In a French cohort of 700 HIV-infected patients treated with HAART, 9 patients (1.3%) suffered acute coronary events after an average treatment duration of 18 months.[19] Patients with an event were young men (average age, 40 years) infected with the virus for an average of 7 years. In the HIV outpatient study (HOPS) that included 5672 patients with HIV-1 infection, patients taking protease inhibitors were at significantly increased risk for myocardial infarction (1.4 vs 0.5 cases per 1000 person-years; hazard ratio 6.5, 95% confidence interval [CI] 0.9–47.8, adjusted for cardiovascular risk factors).[16] Although occurring infrequently, these events are of clinical and epidemiological significance considering the young age of these patients. In the large DAD (Data collection on Adverse events of anti-HIV Drugs) study comprising 23468 HIV-infected patients, 27% of protease inhibitor-treated patients had hypercholesterolemia (total cholesterol $\geq$6.2 mmol/l), and 27% showed low HDL cholesterol ($\leq$0.9 mmol/l).[21] Over 36199 person-years, 126 patients developed a myocardial infarction. The incidence of myocardial infarction increased with longer exposure to combination antiretroviral therapy with an adjusted relative risk per year of exposure of 1.3 (95% CI 1.1–1.4; $P < 0.001$). combination antiretroviral therapy was independently associated with a 26% relative increase in the rate of myocardial infarction per year of exposure over the first 4–6 years of use.[20]

In summary, the risk of myocardial infarction is increased in patients with HIV infection receiving HAART. However, the absolute risk is small and the marked overall benefits of antiretroviral therapy are evident. Thus, individual cardiovascular risk factors should be assessed and treated.

Treatment strategies

Although the risk for atherosclerotic vascular disease is increased, the benefits of antiretroviral therapy outweight the risk.[22] Patients receiving HIV protease inhibitors should be screened for hyperlipidemia, hyperglycemia, and hypertension. They may be candidates for lipid-lowering therapies depending on their long-term prognosis and individual risk of cardiovascular disease. Invasive treatment of acute myocardial infarction does not differ from that in patients not infected with HIV.[23] The restenosis rate, however, is unexpectedly high in these patients.[24]

When initiating lipid-lowering therapy, interaction between statins and HIV protease inhibitors affecting cytochrome P450 (CYP) function must be considered. Simvastatin, atorvastatin, and lovastatin – but not pravastatin and fluvastatin – are metabolized by CYP3A4 and thus should be avoided in persons taking protease inhibitors such as ritonavir and saquinavir. Pravastatin does not alter nelfinavir pharmacokinetics, and thus appears to be safe for concomitant use. In general, starting statin therapy using a low initial dose is recommended. In patients with protease inhibitor-associated hypertriglyceridemia, the use of a fibrate such as gemfibrozil does not normalize triglyceride levels.[25] Ezetimibe may be combined with a statin to minimize its dose and potential drug interactions. However, there are no studies investigating the safety and efficacy of this combination in patients with HIV infection.

In patients with lipodystrophy, switching protease inhibitors to reverse transcriptase inhibitors may be considered. However, in a randomized trial in patients with peripheral lipoatrophy, switching from HIV protease inhibitor therapy to abacavir, nevirapine, adefovir, or hydroxyurea led to improved lipids and less intra-abdominal fat, but also to less peripheral fat, and had a minimal effect on insulin resistance. Virological control in these patients was unaffected, despite frequent-switch drug cessations.[26] Another study reports on a trend towards worse virological control after switching from protease inhibitors to nevirapine, efavirenz, or abacavir.[27] Abacavir may cause a hypersensitivity reaction in about 10% of patients, with the need to stop the drug indefinitely. Switching nucleoside analogues to a less toxic reverse transcriptase inhibitor such as abacavir only causes a modest increase in limb fat.[28]

In conclusion, the risk of myocardial infarction is increased in patients with HIV infection receiving HAART. However, the absolute risk is small and the marked overall benefits of antiretroviral therapy are evident. Patients receiving HIV protease inhibitors should be screened for hyperlipidemia, hyperglycemia, and hypertension. They may be candidates for lipid-lowering therapies depending on their long-term prognosis and individual risk of cardiovascular disease. Invasive treatment of acute myocardial infarction does not differ from that in patients not infected with HIV. The rate of progression of coronary artery disease and the restenosis rate, however, are often unexpectedly high in these patients.

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