OPIS PRZYPADKU CASE REPORT

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Alcohol induced severe hypertriglyceridemia in HIV/HCV coinfected patient – case report

Hipertrigliceryderemia indukowana nadużywaniem alkoholu u chorego z koinfekcją HIV/HCV – opis przypadku

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Key words
HIV, HCV, dyslipidemia

Słowa kluczowe
HIV, HCV, dyslipidemia

Summary

Alcohol use is one of the most prominent causes of dyslipidemia. The effects of alcohol on lipid metabolism are diverse: it induces synthesis of triglycerides, formation of very low density cholesterol and stimulates lipolysis in fatty tissue. HIV infection also predisposes to lipid disturbances resulting from direct influence of the virus as well as from the action of antiretroviral drugs, however coinfection with HCV is considered to be protective against significant dyslipidemia in some cases. Hypertriglyceridemia is a risk factor of cardiovascular disease and severe form is considered to be at increased risk for acute pancreatitis. 36-years old HIV/HCV coinfected patient was diagnosed with severe hypertriglyceridemia exciding 8000 mg/dL. Periodic alcohol abuse was stated. Fenofibrate initiation and antiretroviral therapy switch did not influence the lipid levels significantly. Increase in lipids levels occurred simultaneously with periods of alcohol abuse. In conclusion, HIV/HCV coinfection does not seem to influence severe dyslipidemia induced by alcohol use.

Streszczenie

Zaburzenia lipidowe mogą mieć charakter pierwotny lub wtórny, a nadużywanie alkoholu jest jedną z głównych przyczyn wtórnej dyslipidemii. Wpływ alkoholu na metabolizm lipidów polega między innymi na pobudzeniu syntezy trójglicerydów i lipoprotein o bardzo małej gęstości, jak również stymulacji lipolizy w tkance tłuszczowej. Zakażenie HIV również predysponuje do zaburzeń gospodarki lipidowej na skutek bezpośredniego działania wirusa czy też działania leków antyretrowirusowych. Inhibitory protezy wiążą się z największym ryzykiem hipertriglicerydemii i hipercholesterolemii, spośród wszystkich leków antyretrowirusowych. Natomiast koinfekcja z HCV rozważana jest jako czynnik chroniący przed znaczną dyslipidemią. Hypertriglicerydemia jest czynnikiem ryzyka chorób sercowo-naczyniowych, a jej ciężka postać ze stężeniem trójglicerydów przekraczającym 1000 mg/dL, wiąże się z ryzykiem ostrego zapalenia trzustki. U 36-letniego chorego z koinfekcją HIV/HCV rozpoznano ciężką hipertriglicerydemię przekraczającą 8000 mg/dL. Ustalono, że pacjent okresowo nadużywa alkohol, rozpoczęcie leczenia fenofibratami i zmiana leków antyretrowirusowych nie spowodowały istotnego obniżenia stężenia lipidów. Najwyższe stężenia cholesterolu i trójglicerydów obserwowano w okresach nadużywania alkoholu, co wiązało się z jednoczesnym narastaniem aktywności GGT. Reasumując, nie wydaje się, aby koinfekcja HIV/HCV miała wpływ na przebieg ciężkiej hipertriglicerydemii indukowanej spożywaniem alkoholu.

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INTRODUCTION

Lipid disorders seen in human immunodeficiency virus (HIV) infected patients include: elevated concentration of triglycerides (TGs) and total cholesterol (TC), decreased high-density lipoprotein (HDL) and variable changes in low-density lipoprotein (LDL). The mechanism of lipid disturbances accompanying HIV infection is unexplained and probably multifactorial (1). While lipid profile abnormalities have been described before the HAART (Highly Active Antiretroviral Therapy) era, hyperlipidemia associated with antiretroviral (ARV) drugs use is now more common and more severe. Protease inhibitors (PIs) create the greatest risk of hypertriglyceridemia and hypercholesterolemia among the all classes of ARV drugs (2, 3).

In general, lipid disorders can be divided into primary and secondary defects of lipid metabolism. One of the most prominent secondary causes of hypertriglyceridemia is excessive alcohol use. The effects of alcohol on lipid metabolism are diverse and includes

stimulation of TG synthesis, very low-density lipoprotein (VLDL) formation, and lipolysis in fatty tissue (4, 5).

Although hypertriglyceridemia is often asymptomatic, it is a risk factor for cardiovascular disease. Patients presenting with severe hypertriglyceridemia are at increased risk for acute pancreatitis (6, 7).

Here we present a case report of severe hypertriglyceridemia in HIV/HCV (hepatitis C virus) co-infected patient with a history of chronic alcohol abuse. Informed consent has been obtained from the patient.

CASE REPORT

A 36-years old Caucasian male identified 6 years earlier with HIV and HCV without any other health complaints and who declared good adherence to ARV treatment (saquinavir, ritonavir and abacavir/lamivudine) for the past 2 years, came to the clinic for a routine blood test. He was subsequently diagnosed to have dyslipidemia with severe hypertriglyceridemia (2417 mg/dL) based on current American Association of Clinical Endocrinologists' (AACE) guidelines (8). The concentrations of TC, HDL and LDL were 537, 44 and 493 mg/dL, respectively. Laboratory tests also revealed elevated activities of alanine (ALT) and aspartate (AST) aminotransferases (80 U/L and 62 U/L respectively), gamma glutamyl transferase (GGT – 416 U/L) and increased mean corpuscular volume (MCV – 101fl). The most recent lymphocyte counts revealed: CD3+ – 1266 cells/μl, CD4+ – 563 cells/μl and CD8+ – 728 cells/μl. HIV-RNA was undetectable. Blood pressure was normal and patient body mass index was 24. It was further revealed that he had been smoking about 20 cigarettes a day and drinking a moderate amount of alcohol over the past weeks. Physical examination was unremarkable. The patient refused admission to the hospital. Fenofibrate was prescribed and he was advised to introduce low-fat diet as well as eliminate alcohol and cigarettes. In the subsequent months the patient remained asymptomatic, yet despite the hypolipidemic treatment, his serum was lipemic with lipid concentrations as follows: TG – 6011 and 8396 mg/dL, TC – 896 and 990 mg/dL. ARV treatment was modified and atazanavir was introduced instead of saquinavir. Four months later, the patient was admitted to the hospital. TG concentration at a day of admission was 7199 mg/dL and total cholesterol – 1018 mg/dL, GGT activity – 795 U/L, amylase activity and CRP concentration were in norm. Abdominal ultrasonography revealed hepatosteatosis, although no changes in the pancreas, gallbladder, bile ducts and other organs were found. Gastroscopy showed slight mucosal inflammation of the antrum. Fenofibrate treatment was maintained and during the subsequent weeks, TG concentration decreased to 475 mg/dL, TC to 320 mg/dL, GGT activity to 338 U/L. After leaving the hospital, the patient made monthly visits to the HIV outpatient center. During the past several months lipid levels and GGT activity were again found to increase. The patient admitted that he periodically consumed excessive amounts of alcohol during this time. He refused both hospital readmission and treatment for alcohol dependence. Successive laboratory test results showed simultaneous increases in the concentrations of TG and TC concentrations as well as GGT activity, a marker of toxic liver damage (fig. 1).

DISCUSSION

In Bessembinders et al. study (4), the strong association between severe hypertriglyceridemia and excessive alcohol use was demonstrated. The highest TG levels were found in patients with coexistence of metabolic syndrome and excessive alcohol intake. However, in contrast to alcohol, there were no relationship between hypertriglyceridemia and the presence of obesity and/or diabetes mellitus. The highest values of TGs were noted in the combination of all three conditions, however not all patients with metabolic syndrome and with a history of alcohol abuse, developed severe hypertriglyceridemia. The above result suggested possible genetic links behind the lipid metabolism defects. While cessation of alcohol consumption resulted in a quick drop in TG levels, continuous alcohol consumption led to poor response to lipid lowering treatment, which is in line with clinical observation of our patient.

Acute alcohol consumption leads to catecholamine secretion, which induces lipolysis in adipose tissue and increases the supply of free fatty acids to the liver (9). Acute alcohol intake is known to inhibit lipoprotein lipase, the enzyme that breaks down TG within TG-rich particles: VLDL and chylomicrons (10). Impaired lipolysis also leads to marked increase in plasma TG. Alcohol is also known to induce the synthesis of TG-rich lipoproteins in the liver (11). In the case of our patient, increases in lipids levels was clearly associated with periods of high alcohol consumption. Furthermore, the relationship between alcohol and hypertriglyceridemia was confirmed by a rapid decrease in lipid levels during four weeks hospitalization.

Dietary TGs are hydrolyzed by pancreatic lipase, absorbed by intestinal mucosal cells and secreted into mesenteric lymphatics as chylomicrons. The combination of alcohol and fat shows synergism in increasing plasma TG concentration, because ethanol suppresses the clearance of intestine-derived chylomicrons. The degree of hypertriglyceridemia is related to the stage of alcoholic liver injury as in the decreased lipemic response in patients with cirrhosis (11). The function of our patient's liver was impaired due to alcohol abuse as well as HCV infection, however there were no signs of liver cirrhosis.

Regarding the HIV infection, increased TG levels have been detected in HIV infected patients since the late 1980s, before the HAART era. The increased TG

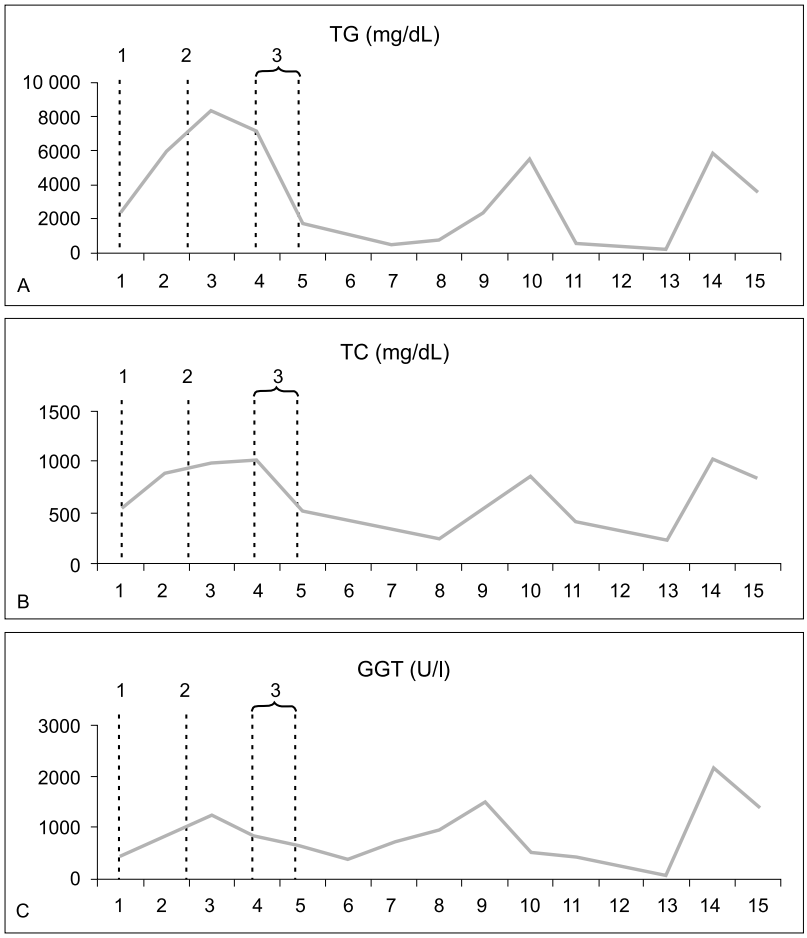

Fig. 1. A. Triglyceride (TG), B. total cholesterol (TC) concentrations and C. gamma glutamyl transpeptidase (GGT) activity during 16 months observation. 1. Initiation of fenofibrate treatment; 2. switch of antiretroviral therapy; 3. hospitalization.

levels were often accompanied by low serum levels of HDL, LDL, and TC, which interestingly also demonstrated at the time of HIV seroconversion in previously uninfected men (12, 13). Treatment-naïve, HIV infected patients had lower levels of total cholesterol and HDL and greater TGs, as compared to matched HIV seronegative controls (14). The changes in lipids with the initiation of ARV therapy were not accompanied by changes in diet, dietary intake, weight, or body composition. It was also shown that HIV infected treatment naive patients had higher HIV RNA level independently associated with lower LDL, higher VLDL and TG levels, while a history of AIDS-defining disease was associated with higher total cholesterol, VLDL cholesterol and TG levels (15). The influence of HIV replication was confirmed in a study by Rasheed et al. (16), which revealed that HIV replication alone without ARV drugs induced production of free fatty acids, lipoproteins and many proteins associated with lipid synthesis, transport and metabolism. However, our patient's HIV-RNA became undetectable shortly after introduction of ARV therapy and remains so to the present time. While records of lipid laboratory results prior to HIV infection are lacking, lipid profiles have been continuously borderline since initial HIV infection diagnosis, and during ARV treatment start, until the first bout of alcohol overuse.

Introduction of protease inhibitors into HAART significantly decreased the mortality rate of HIV infected patients and changed the clinical course of HIV infection from subacute lethal disease to a chronic ambulatory condition (17). However, more than 50% of patients receiving HAART develop lipid abnormalities including increased serum concentrations of TC, LDL cholesterol and TG. Protease inhibitor based treatment is associated with development of metabolic syndrome characterized by dyslipidemia, insulin resistance and lipodystrophy (18). It was shown that PIs lead to endoplasmic reticulum stress and subsequent activation of the unfolded protein response what represent an important cell signaling mechanism of PI-induced metabolic syndrome. Zhou et al. (19) also demonstrated that the PI ritonavir increases the accumulation of free cholesterol, depletes the endoplasmic reticulum calcium stores, activates the unfolded protein response, induces apoptosis and promotes foam cell formation in macrophages. More to the point, the PIs ritonavir and lopinavir are most strongly associated with dyslipidemias (20). The use of new PIs, such as atazanavir, has not been associated with adverse alterations in lipid profiles (21), prompted the switch from saquinavir to atazanavir in our patient. While, a better option might have been the use of Non Nucleoside Reverse

Transcriptase Inhibitors, these were rejected due to the adherence concerns. Moreover, the borderline lipid disturbances were observed even before HAART was started.

The patient described by us was infected by both HIV and HCV. Unexpectedly, according to the recent study, metabolic complications were more common in patients with HIV monoinfection and mitigation of antiretroviral induced hyperlipidemia by HCV coinfection was observed (22). It also might argue for non drug related origin of dyslipidemia in our patient. Also in the Visnegarwala et al. (23) study the mean total cholesterol level was significantly lower in the HIV/HCV coinfected, treatment-naïve group, when compared to the non co-infected treatment-naïve group, despite the higher age and waist to hip ratio in co-infected patients.

Moderate hypertriglyceridemia is an independent risk factor for cardiovascular disease. Meta analysis of thousands of patients followed up for more than 10 years showed that TG elevation of 1 mmol/L increases risk of cardiovascular disease by 32% in men and 76% in women, independently of HDL cholesterol levels (24). TG-rich lipoproteins and their remnants may directly lead to the formation of arterial-wall foam cells (25).

The most serious complication of severe hypertriglyceridemia is acute pancreatitis usually with concomitant TG level exceeding 1000 mg/dL. TG-induced pancreatitis may be explained by insufficient capacity of the pancreas to produce an exocrine lipase and may be preceded by episodic nausea and epigastric pain, during which serum amylase may not exceed common diagnostic level (25). So, far this complication was not observed in our patient and his pancreatic enzymes are within the normal range.

Due to the treatment recommendations for dyslipidemia in HIV infected patient, lifestyle changes, dietary modification and exercise should be addressed firstly. Weight reduction, avoidance of alcohol and drugs with adverse effect on lipid profile, smoking cessation and proper hypertension and diabetes mellitus control are all modifiable cardiovascular risk factors in management of dyslipidemia (26). If reduction of lipids concentrations is not achieved, use of lipid-lowering therapy should be considered. HMG-CoA reducates inhibitors (statins) are recommended for patients with elevated LDL cholesterol concentration or when TG level is 200-500 mg/dL. Statins of choice are parvastatin and atorvastatin. Some data suggest that rosuvastatin is more effective than parvastatin in patients treated with ritonavir-boosted PIs. In HIV infected patients with TG level exceeding 500 mg/dL fibrate therapy (fenofibrate or gemfibrozil) is appropriate (27, 28). In our case fenofibrate was prescribed, however according to the patient's wife, the patient did not take the medicine regularly. Cessation of alcohol consumption and cigarettes smoking, low fat diet and regular physical activity were continuously recommended but probably with rather poor compliance.

CONCLUSIONS

Concluding, HIV/HCV coinfection does not seem to influence severe dyslipidemia induced by excessive alcohol use; however, according to available literature it may play a protective role against ARV drug induced dyslipidemia.

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received/otrzymano: 05.03.2014
accepted/zaakceptowano: 12.05.2014