ACTA ABP BIOCHIMICA POLONICA

Vol. 62, No 3/2015
621–623
http://dx.doi.org/10.18388/abp.2015_971

Case report

Rapid normalization of severe hypercholesterolemia mediated by lipoprotein X after liver transplantation in a patient with cholestasis — a case report

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Hypercholesterolemia is a common disorder in adult population, but total cholesterol concentrations beyond 1000 mg/dl occur rarely, and are found in patients with homozygous familial hypercholesterolemia and familial lecithin-cholesterol acyltransferase deficiency, in chronic graft-*versus*-host disease of the liver, after intravenous infusion of fat emulsion (intralipid), in newborn infants with immature liver function, and in obstructive biliary cholestasis. Cholestasis induces a dramatic increase in plasma cholesterol and the appearance of an abnormal lipoprotein, lipoprotein X (LpX), in the plasma. We report a case of severe hypercholesterolemia mediated by LpX in a patient transplanted for primary biliary cirrhosis (PBC), who was qualified for liver re-transplantation (re-LTx) due to chronic cholestasis. Four months after re-LTx, the cholesterol concentration was normal. The problems in diagnosis and treatment are discussed.

Key words: hypercholesterolemia, lipoprotein X, PBC

Received: 10 January, 2015; revised: 24 May, 2015; accepted: 31 July, 2015; available on-line: 28 August, 2015

BACKGROUND

Total plasma cholesterol concentrations beyond 1000 mg/dl occur rarely. Such severe hypercholesterolemia can result in several complications such as hyperviscosity syndrome, pulmonary cholesteroloma, multiple xanthelasmas, and lipemia retinalis (Rosenson *et al.*, 1990; Toren & Nagler, 1996).

This paper reports a case of severe hypercholesterolemia mediated by lipoprotein-X (LpX) in a patient after liver transplantation (LTx) for primary biliary cirrhosis (PBC) and recurrence of biliary strictures and cholestasis, with severe jaundice and pruritus, qualified for liver re-transplantation (re-LTx). A rapid decrease in cholesterol concentration was observed after re-LTx.

CASE REPORT

A 53-year-old woman was admitted for cardiological evaluation before elective re-LTx. Eight years earlier she has undergone LTx for liver failure in the course of PBC. In the first month after LTx, immunosuppressive therapy (cyclosporine and prednisone) was intensified (mycophenolate mofetil) for acute rejection, and continued until current admission. Five years later, multiple biliary dilatation and stenting (last time 2 months before the current hospitalization in a cardiology ward) were performed because of cholangitis and biliary stricture, but without complete improvement. Owing to the recurrent bouts of cholestasis with severe pruritus, recurrence of PBC was considered; however, liver biopsy was not performed due to severe clotting disturbance. Patient was qualified for re-LTx.

On admission to the cardiology ward, the patient was in good condition, without any cardiovascular complaints, with severe jaundice and pruritus (9 points on visual analogue 10-point scale), and without ascites or encephalopathy (23 points on the MELD scale). During clinical work up we found significant abnormalities in plasma lipids (Table 1).

There were no data on the complete lipid profile prior to the liver transplantation, except for a normal result of cholesterol concentration about 5 years before LTx. After LTx, the lipid profile was determined only once (see Table 1: I hospitalization). Considering the confusing results of current lipid test, plasma lipids were reassayed by carrying out ultracentrifugation in a Beckman Optima-TLX preparative ultracentrifuge. Each lipoprotein fraction was recovered by tube-slicing using a Beckman CentriTube Slicer.

Cardiac assessment including coronary artery catheterization was normal in the patient. She was scheduled for re-LTx. Four months after re-LTx, the cholesterol concentration was normal (Table 1). The donor records did not indicate treatment for hyperlipidemia.

Discussion. Severe hypercholesterolemia occurs in patients with homozygous familial hypercholesterolemia and familial lecithin-cholesterol acyltransferase (LCAT) deficiency. It has also been reported in chronic graft-versus-host disease of the liver in patients with an allogenic bone marrow transplant, following intravenous infusion of fat emulsion (intralipid) and in newborn infants with immature liver function (Glomset *et al.*, 1973; Tashiro *et al.*, 1992; Turchin *et al.*, 2005; Witt & Ober, 1976; Zidan *et al.*, 2008).

Hypercholesterolemia is one of the known complications of cholestatic liver disease. The pathogenesis of hypercholesterolemia in cholestasis is unknown. Results of animal studies show that LpX fails to the activity of hydroxymethylglutaryl coenzyme A reductase, suggesting

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Abbreviations: LpX, lipoprotein X; LTx, liver transplantation; PBC, primary biliary cirrhosis

Table 1. Results of laboratory tests

Parameter	Time of determination					
	I	II	III	IV (Ultracentrifugation)	V	VI
Total cholesterol [mg/dL]	235	612	577	1227	211	183
LDL-C[1] [mg/dL]	107	510	1625	576	127	
HDL-C[2] [mg/dL]	100	60	9	33	78	
Triglyceride [mg/dL]	98		248	247	80	
VLDL[3] [mg/dL]				50		
LpX[4] [mg/dL]				568		
Bilirubin total [mg/dL]	0. 8	5.3	18.4		0.6	0.5
INR	1	1.7	1.6		1.0	1.0
ALP[5] [U/L]	224	722	1821		93	135
GGTP[6] [U/L]	420	460	1114		26	133
ALT[7] [U/L]	118	311	158		20	65
Albumin[8] [g/dL]			2.3		4.1	3.6
Creatinine[9] [mg/dL]	0.6		0.5		0.9	0.8

[1]LDL-C, LDL cholesterol; [2]HDL-C, HDL cholesterol; [3]VLDL, very-low-density lipoprotein; [4]LpX, lipoprotein-X; [5]ALP, alkaline phosphatase; N: 40–150 U/L; [6]GGTP, gammaglutamyltranspeptidase; N: 0–55 U/L, [7]ALT, alanine transaminase, N: 1–45 U/L; [8]Albumin, N: 3.4–5 g/dL; [9]Creatinine, N: 0.6–1.3 mg/dL. Time of determination: I — 6 years after LTx, outpatient department, II — 7 years after LTx, regional hospital, III-IV — hospitalization in cardiological ward, V — 2 months after re-LTx, VI — 4 months after re-LTx.

its possible contribution to hypercholesterolemia in liver disease (Edwards *et al*., 1993; Ritland, 1975).

LpX is composed mainly of phospholipids and unesterified cholesterol. One hypothesis of LpX formation involves the reflux of bile into the plasma. The present patient`s normal cholesterol concentration reported before liver failure, together with a negative history of familial hypercholesterolemia, allowed excluding with high probability congenital disorders of lipid metabolism or LCAT deficiency. Hypothyroidism, well documented to cause hyperlipidemia, was also excluded. Therefore, cholestasis was a potential cause of the hyperlipidemia.

In our patient assay bias has been found for serum LDL-cholesterol in the presence of LpX, which is important for estimating correctly the LDL-cholesterol level in severely cholestatic patient. Nonstandard laboratory methods should be used in such a situation. Various assays are available for measuring serum LpX: ultracentrifugation, agarose gel electrophoresis, nuclear magnetic resonance spectroscopy, and immunological techniques (Herzum *et al*., 2007; Crook, 2013). In this case, ultracentrifugation, precipitation, and electrophoresis were used.

Lipoprotein analysis in our patient gave substantially lower LDL-C and higher HDL-C concentration results than those obtained from the automated system. We suppose that LpX present in the lower fraction was not fully precipitated along with LDL and thus was assayed as HDL-C. The LDL-C, HDL-C, and total cholesterol concentrations determined using the ultracentrifugation method were higher than the levels detected with the automated system. Because LDL-C was determined by subtracting HDL-C from total cholesterol in the bottom fraction, the LDL-C concentration obtained by ultracentrifugation method was lower than that calculated from the automated method. Inaccurate LDL-C levels were obtained by the both methods when LpX was present at high concentrations. This is because most of LDL-C measured is derived from the LpX particles.

It is suggested that the severe hypercholesterolemia observed in presented patient was caused by high LDL concentration and also by LpX. On the other hand, cyclosporine and prednisone have been shown to cause dyslipidemias (Kuster *et al*., 1994; Sholter & Armstrong, 2000). Although it is impossible to exclude the potential role of the aforementioned drugs, it is important to point out the substantial presence of LpX.

Hypercholesterolemia increases the incidence of atherosclerosis in the general population but not in patients with PBC. Although hypercholesterolemic LDL contains oxidized subfractions with atherogenic properties, atherosclerosis incidence is low in patients with PBC. Ritland suggested that LpX reduces LDL atherogenicity by preventing LDL oxidation (Ritland, 1975; Jahn *et al*., 1985; Kuster *et al*., 1994; Kaplan, 1996; NCEP Expert Panel, 2002; Chang *et al*., 2004). In accord, we found no evidence of atherosclerosis, including coronary artery disease, in the patient.

Few papers describing the possibility of hypercholesterolemia after liver transplantation due to transmission of low density lipoprotein receptor mutation from the donor have been published (Nikkilä *et al*., 2014). Unfortunately, we have no data about the donor lipid levels before the first LTx except that her total cholesterol concentration was normal.

Yeh and coworkers (2011) reported severe hypercholesterolemia as a complication of biliary stricture after liver transplantation but in that case LpX concentration was not as high as in the present case or in PBC cases.

Zidan and coworkers (2008) emphasized that in the case of cholestasis the elevated serum cholesterol concentration associated with LpX and is not due to cholesterol overproduction by hepatocytes, but rather to regurgitation of cholesterol and bile salts into the circulation. The use of statins would therefore not be effective. Moreover, due to significant hepatic dysfunction, statin therapy was impossible in the patient described (Catapano *et al*., 2011). A potential intervention in that case was the use of ezetimib, but an increase of transaminases' activity and thrombocytopenia in the course of such a treatment was possible. In described patient, cyclosporine was replaced with tacrolimus, having a more favorable lipid profile. It should be emphesized that the

treatment of the underlying liver disease by transplantation remains the mainstay of therapy in such case. The patient was scheduled for re-LTx; we observed a rapid decrease of cholesterol concentration after re-LTx and its normalization after 4 months.

Conclusion. LpX may be found in serum samples of patients with cholestasis, which in some cases results in extremely high total cholesterol concentration. An assay bias for serum LDL-cholesterol in the presence of LpX may occur requiring the use of nonstandard laboratory methods. A rapid decrease of cholesterol concentration after LTx and even its normalization may be observed.

Declarations

Competing interests: none

Approval of the final version: All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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