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CASE REPORT

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When LDL Cholesterol Is Not LDL Cholesterol

LpX, A Clinical Lesson

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ABSTRACT

LpX is a lipoprotein formed in cholestatic conditions and often erroneously reported as LDL-C. A low ApoB level can support the diagnosis of LpX. Treatment should not automatically focus on lowering serum lipid levels, but primarily on resolving the cause of cholestasis. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:690–693)
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Secondary hypercholesterolemia is defined as hypercholesterolemia not explained by a known genetic disease but caused by conditions such as hypothyroidism, nephrotic syndrome, or liver diseases.[1] More specifically in the case of liver disease, cholestasis may lead to the formation of lipoprotein X (LpX).[2] In routine laboratory tests LpX can be suspected by an increased level of low-density lipoprotein cholesterol (LDL-C),[3] leading to the suspicion of a genetic disorder or treatment incompliance. It is therefore important to recognize and distinguish LpX from LDL-C because complications and therefore treatment choices can differ markedly.[4] Here we emphasize and review the link between cholestatic liver disease and hypercholesterolemia, using the cases of patients we have seen in 2 Dutch hospitals.

LEARNING OBJECTIVES

- To recognize LpX as a cause of secondary hypercholesterolemia in patients with cholestasis and elevated LDL-C levels.
- To differentiate LpX from LDL-C by determining ApoB and including its results in treatment choices.

CASE 1

An 82-year-old woman with a diagnosis of non-small-cell lung carcinoma stage 4 started treatment with pembrolizumab. Her medical history included Morbus Waldenström macroglobulinemia without treatment, peripheral arterial disease. and an aneurysm of the abdominal aorta. Her LDL-C level before treatment was elevated (3.8 mmol/L) (**Table 1**); however, she did not use any lipid-lowering drugs. Three months later, she was seen with because of jaundice. Laboratory investigation showed severely disturbed liver parameters and elevated LDL-C (10.5 mmol/L) (**Table 1**). Autoimmune hepatitis and viral hepatitis were excluded. and ultrasonography of the abdomen did not reveal any bile duct abnormalities. She

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received a diagnosis of pembrolizumab-induced hepatitis. In the diagnostic workup of hypercholesterolemia, secondary causes such as hypothyroidism and nephrotic syndrome were excluded. We assumed that cholestasis had led to an increased formation of LpX, erroneously reported by the laboratory as elevated LDL-C. A disproportionally low apolipoprotein B (ApoB) (1.8 g/L) supported the existence of LpX, but still exceeded the normal range, corresponding with a coexisting elevated amount of LDL-C. Treatment focused on resolving the hepatitis with corticosteroids. No lipid-lowering drugs were given. After 4 months, her liver parameters and LDL-C level (3.9 mmol/L) had decreased to previous levels, confirming our diagnosis of LpX secondary to pembrolizumab-induced hepatitis.

CASE 2

A 79-year-old man was admitted with drug-induced liver injury with cholestasis due to amoxicillin/clavulanic acid as treatment for a respiratory tract infection and erysipelas. His medical history included HIV infection, with an undetectable viral load under treatment with Trizivir (abacavir/lamivudine/zidovudine). Increased levels of LDL-C (13.1 mmol/L) were measured during the follow-up investigation of the abnormal liver parameters (Table 1). Secondary causes of hypercholesterolemia were excluded, and LpX was assumed to be present. This was supported by a disproportionally low serum ApoB (2.21 g/L). We started treatment with a combination of colesevalam and pravastatin. After 5 months, liver enzymes and LDL-C (2.9 mmol/L) had substantially reduced, confirming the diagnosis of LpX.

DISCUSSION

We present 2 patients with cholestatic liver disease with corresponding development of hypercholesterolemia, diagnosed as the presence of LpX.

Under physiological circumstances, cholesterol is excreted from the body in the bile.[2] In the setting of cholestasis, high bile levels can have toxic effects on surrounding structures. Binding of bile to hepatocyte farnesoid X receptors inhibits bile acid synthesis and stimulates bile secretion to prevent toxicity.[2] Reduced bile production leads to the inability to excrete cholesterol into bile, and free cholesterol will migrate into the blood. Together with phospholipids, albumin, a small number of triglycerides, esterified cholesterol, Apo-C and E, ultimately this will form LpX.[5] LpX is a lipoprotein characterized by the same density as LDL and the same size as very-low-density lipoprotein (VLDL), but without ApoB (Figure 1).[4,5] LpX is also described in patients with graft-versus-host disease of the liver after a stem cell transplantation[6] and in patients with lecithin-cholesterol-acyltransferase deficiency. Missing the lecithin-cholesterol-acyltransferase enzyme leads to the inability to convert free cholesterol into esterified cholesterol for transportation in HDL-C, resulting in an

ABBREVIATIONS AND ACRONYMS

ApoB = apolipoprotein B
HDL = high-density lipoprotein
HDL-C = high-density lipoprotein cholesterol
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
LpX = lipoprotein X
TC = total cholesterol
VLDL = very-low-density lipoprotein

TABLE 1 Laboratory Results Before and After Diagnosis and Treatment

	Case 1			Case 2			Reference Values
	Prior	Lab 1	Lab 2	Prior	Lab 1	Lab 2	
Bilirubin total (μmol/L)		252	4		196	7	0-17
Bilirubin direct (μmol/L)		178			102		0-5
ASAT (IU/L)		369	25		72	32	0-35
ALAT (IU/L)		405	25		101	29	0-45
Alkaline phosphatase (IU/L)		112	67		661	148	0-115
Gamma GT (IU/L)		864	56		371	81	0-55
Natrium (mmol/L)		144	145		136	131	135-145
Cholesterol total (mmol/L)	5.7	10.5	5.9	5.3	16.9	4.9	
Triglycerides (mmol/L)	1.7	2.6	1.9	3.8	6.6	1.6	0.8-2.0
HDL-C (mmol/L)	1.3	0.3	1.0	1.07	0.8	1.3	>1.0
LDL-C (mmol/L) calculated[a]	3.6	9.0	4.0	2.5	13.1	2.9	
LDL-C (mmol/L) directly measured[b]	3.8	10.5	3.9		10.5		
Non-HDL-C[c] (mmol/L)		10.2	4.9	4.3	16.1	3.6	
ApoB (g/L)		1.8			2.2		0.6-1.3

Case 1: Lab 1: admission laboratory studies. Lab 2: after stopping pembrolizumab and completing treatment with corticosteroids. Case 2: Lab 1: admission laboratory studies. Lab 2: after 4 months with colesevalam and pravastatin. [a]Total cholesterol: HDL-C – estimated amount of VLDL (triglycerides/2.2). [b]Using ultracentrifugation and precipitating other cholesterol containing particles with detergents. [c]Total cholesterol – HDL-C.

ApoB = apolipoprotein B; ALAT = alanine transaminase; ASAT = aspartate transaminase; Gamma GT = gamma glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Non-HDL-C = non-high-density lipoprotein cholesterol.

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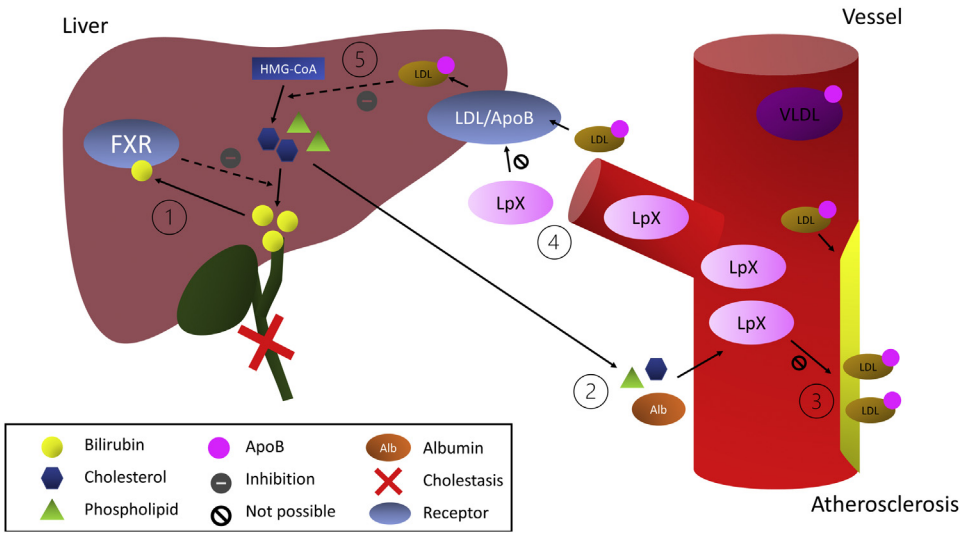
FIGURE 1 Lipoprotein X Explained



(1) Binding of bile to the FXR inhibits bile production and stimulates excretion. Reduced bile production leads to the inability to excrete cholesterol. **(2)** Cholesterol and phospholipids migrate to the blood, where together with other particles they bind to albumin and form lipoprotein X (LpX). **(3)** LpX cannot enter the vessel wall because of its size, similar to VLDL-C, and will remain circulating in the blood. **(4)** LpX cannot enter the liver via the LDL/ApoB receptor and accumulates in the blood, causing hypercholesterolemia. **(5)** LDL-C in the liver inhibits the formation of cholesterol. Because LpX cannot enter the liver, the formation process continues. ApoB = apolipoprotein B; FXR = farnesoid X receptor; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

accumulation of cholesterol and eventually leading to LpX formation.[4]

Distinguishing LpX from LDL-C is important because they differ in corresponding risks and treatment.[4] LDL-C can be calculated by using the Friedewald formula (total cholesterol [TC] − HDL-C and the estimated amount of VLDL [triglycerides / 2.2]) or by measuring it directly. In our cases, using both tests led to different results of LDL-C levels in the same person. Both methods can include some VLDL-C and intermediate-density cholesterol, leading to different amounts of LDL-C.[7] In our second case the level of triglycerides (6.6 mmol/L) exceeded the range of the formula (4.5 mmol/L), which can give an inaccurate LDL-C level. Having the same density as LDL-C, LpX will be measured as an elevated amount of LDL-C, making these tests invalid to distinguish between the lipoproteins.[3] Measuring the amount of ApoB can be a good method to distinguish them; a laboratory report showing high LDL-C levels with normal levels of ApoB is suggestive of the presence of LpX because this does not contain ApoB.[3] If an increased LDL-C exists next to LpX, ApoB can be elevated, but it will still be disproportionally low. Determining the TC:ApoB ratio can be helpful in these cases. If there are non-ApoBcontaining lipoproteins, the ratio is elevated. The reference ranges described are 3.8 to 6.3 mmol/g for men and 4.0 to 7.7 mmol/g for women.[3] Another ratio used is the (HDL-C + LDL-C): TC ratio. A decreased ratio <0.695 was seen in patients with LpX.[8] At the end, directly determining LpX is the ideal method, but available methods are lacking. Agarose electrophoresis is used to identify a characteristic LpX band but seems not always accurate because it is not present in every patient with LpX.[3] Unfortunately, we did not measure LpX directly, nor do we have follow-up values of ApoB in our patients.

ApoB-containing lipoproteins, such as LDL, constitute an important risk factor for cardiovascular events.[9] LpX has a similar size as VLDL and is too large to enter the vascular wall. Some studies even report that LpX has antiatherogenic properties that reduce LDL-C oxidation.[4] One article mentions that monocytes in patients with LpX have an increased uptake capacity for oxidated LDL-C.[10] Although the cardiovascular risk is not increased, treatment for LpX is sometimes required because lipid levels can quickly increase. Lipid accumulation in circulating monocytes changes the monocyte phenotype and its

surface markers, causes foamy cell formation, and may contribute to tissue inflammation leading to xanthoma formation.[10]

Complications such as xanthomas, neuropathic pain, and plasma hyperviscosity refractory to medication, are anecdotally reported in the literature to be treated with plasma filtration.[11] Typically, the abovementioned signs are the direct reason to start plasma filtration in most reports, not a specific level of TC, which varies from 11.3 mmol/L[11] to 53 mmol/L.[10] In the case of xanthomas, plasma filtration can reduce lipid accumulation and normalizes the expression of monocyte surface markers, leading to regression.[10]

Treatment of high lipid levels due to LpX is primarily based on resolving the cause of cholestasis. With a restored bile excretion, no more lipid particles migrate into the blood, and the formation of LpX is stopped.[5] Depending on the amount of "normal" LDL-C left, there is a role for lipid-lowering drugs, but this is not different from the general population. Our second patient received pravastatin and colesevalam because of a coexisting elevated ApoB. It can be debated whether this contributed to the improvement of elevated LDL levels caused by LpX and whether both should have been given in this situation. Because LpX does not contain ApoB, it cannot be absorbed via the LDL/ApoB receptor and remains circulating in the blood when standard LDL-lowering therapy is used.[2] Drug-induced liver injury is a condition that improves itself after withdrawal of the causative medicine, and it would have been justified to wait with lipid-lowering drugs, especially because statins should be used with caution in patients with cholestasis. Normally statins are metabolized via cytochrome P enzymes in the liver and excreted via bile.[4] Cholestasis may lead to accumulation and cause toxic effects.[2] Using a statin that is also metabolized renally, such as pravastatin, may reduce side effects, but to the best of our knowledge, there are no published reports on this topic. One article recommended dose reduction of statins.[2] Ezetimibe is not advisable because in cholestasis intestinal cholesterol absorption does not contribute to high serum lipid levels because of insufficient micellar formation.[4]

CONCLUSIONS

LpX is a lipoprotein formed in cholestatic conditions and is often erroneously reported as increased level of LDL-C. A lower-than-expected level of ApoB can be a key finding to distinguish LpX, and should be determined if LpX is suspected. Treatment should not automatically focus on lowering serum lipid levels but primarily on resolving the cause of cholestasis. Statins can be helpful but should be used with caution, given that statin monotherapy can have adverse effects. Therefore, in patients with hypercholesterolemia and cholestasis, it is important to consider LpX as a possible cause of hypercholesterolemia.

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