Case Report

A Case of Obstructive Jaundice with Severe Hypercholesterolemia Probably Due to Lipoprotein-Y

Takeyoshi Murano, Tomokazu Oyama, Yoh Miyashita, and Kohji Shirai

Department of Research and Development, Toho University Sakura Medical Center, Chiba, Japan.

Aim: We analyzed the lipoproteins of a patient with pancreatic cancer causing obstructive jaundice, with marked hypercholesterolemia.

Methods: The patient was a 49-year-old female. Serum total cholesterol, triglyceride, LDL-cholesterol and HDL-cholesterol levels were 1,170 mg/dL, 282 mg/dL, 1,070 mg/dL, and 53 mg/dL, respectively. Cholesterol ester and lecithin:cholesterol acyltransferase decreased, and so-called remnant like particle-cholesterol increased remarkably.

Results: Fractionation of the patient's serum by polyacrylamide gel disc electrophoresis showed an abundant VLDL fraction, whereas agarose gel electrophoresis demonstrated a high level of beta-lipoprotein. Sepharose 6B gel filtration of the serum revealed that the levels of free cholesterol and apolipoprotein B were high in the VLDL- corresponding fraction.

Conclusion: The results suggested that the high cholesterol level was due to the presence of abnormally large particles rich in free cholesterol and apoB, and this abnormal fraction may correspond to lipoprotein-Y that was increased in obstructive jaundice.

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Key words; Hypercholesterolemia, Obstructive jaundice, Lipoproteins, Large particles, Lipoprotein-Y

Introduction

Although hypercholesterolemia is commonly observed in the clinical setting, severe hypercholesterolemia with total cholesterol levels above 1,000 mg/dL (25.9 mmol/L) is very rare. The well known causes of hypercholesterolemia of this magnitude are homozygous LDL-receptor deficiency (familial hypercholesterolemia), apolipoprotein E deficiency, hepatic lipase deficiency, and obstructive biliary cholestasis. Hypercholesterolemia associated with hepatic disease differs in lipoprotein profile from that of other causes. The lipoproteins frequently have an abnormal composition and electrophoretic mobility. Lipoprotein X (LpX), which is fractionated in the LDL range, is an abnormal lamella particle rich in free cholesterol and phospholipids, and is found in patients with cholestasis. It contains little core lipid (triglyceride or cholesterol ester) and approximately 6% protein made up mainly of apolipoprotein C and albumin. Another abnormal lipoprotein observed in cases of cholestasis is lipoprotein-Y (Lp-Y), which is a large triglyceride-rich LDL.

Materials and Methods

Case Presentation

A 49-year-old female patient had hyperalphalipoproteinemia rather than hyperbetalipoproteinemia until the onset of obstructive jaundice. Hyperbilirubinemia was observed a few weeks in advance. Obstructive jaundice due to pancreatic cancer was diagnosed. The laboratory findings are shown in Table 1. Severe hypercholesterolemia was observed. Serum total cholesterol, triglyceride, LDL-cholesterol and HDL-cholesterol levels were 1,170 mg/dL, 282 mg/dL, 1,070 mg/dL, and 53 mg/dL, respectively. Cholesterol ester and lecithin:cholesterol acyltransferase decreased, and so-called remnant like particle-cholesterol increased remarkably.
mg/dL, and 53 mg/dL, respectively. Percutaneous transhepatic cholangio-drainage was performed immediately, and the obstructive jaundice improved gradually. The serum total cholesterol level decreased as the obstructive jaundice improved. After the pancreatic cancer was removed by surgical treatment, the patient was discharged.

**Lipid Analysis**

The serum of the patient was subjected to lipoprotein fractionation and analyses of the cholesterol ester ratio, phospholipids, and apolipoproteins. Lipoprotein fractionation was performed by polyacrylamide gel electrophoresis and agarose gel electrophoresis. Lecithin: cholesterol acyltransferase (LCAT) activity was measured by the method of Nagasaki et al. using dipalmitoyl lecithin as a substrate. The remnant like particle-cholesterol (RLP-C) level was measured with a commercial kit (JIMRO Co. Ltd.) using anti-apoB antibody and apoA-\( \beta \)-antibody-conjugated column. The LDL-cholesterol concentration was measured by homogeneous methods.

**Table 2. Patient's serum lipids data**

|                         | Hyper bilirubinemia term | Improve ment term | Hyper bilirubinemia term | Improve ment term |
|-------------------------|--------------------------|-------------------|--------------------------|-------------------|
|                         | 12 days                  | 26 days           | 12 days                  | 26 days           |
| T-CHO                   | 150-220                  | 802 ††            | 175                      |                   |
| TG                      | 30-150                   | 309               | 140                      |                   |
| PL                      | 150-280                  | 781 ††            | 191                      |                   |
| F-CHO                   | 30-60                    | 450 †             | 56                       |                   |
| E-CHO                   | 80-200                   | 241               | 114                      |                   |
| CHO/PL                  | 1                       | 1.027             | 0.916                    |                   |
| ester ratio             | 65-80                    | 30.05 ††          | 65.143                   |                   |
| apoAI                   | 119-165                  | 73 †              | 112                      |                   |
| apoAII                  | 24.6-35.7                | 8.3 †             | 13.4                     |                   |
| apoB                    | 66-110                   | 198 †             | 88                       |                   |
| apoCII                  | 1.5-4.6                  | 30 †              | 4.6                      |                   |
| apoCIII                 | 5.4-10                   | 22.9 ††           | 6.2                      |                   |
| apoE                    | 2.7-4.6                  | 23.5 ††           | 6.3                      |                   |
| LCAT                    | Not detected             |                   |                           |                   |
| RLP-C                   | 792 †                    |                   |                           |                   |

**Results**

**Serum Lipid Profile of the Patient**

Results of analyses of the patient’s serum are shown in Table 2. Serum levels of phospholipid (PL) and free cholesterol (F-CHO), the ratio of free cholesterol to esterified cholesterol, and the RLP-C level were 781 mg/dL, 450 mg/dL, 30.05% and 792 mg/
Electrophoresis of Serum Lipoproteins

The patterns of fractionation of the patient’s serum on electrophoresis are shown in Fig. 1. Agarose gel electrophoresis showed a large beta migratory fraction. This fraction was rich in cholesterol and also contained triglycerides. However, the pre-beta fraction was scanty. Polyacrylamide gel electrophoresis showed a large VLDL-corresponding fraction. From these analyses, the main component of this patient’s serum lipoprotein was cholesterol-rich VLDL.

Fractionation of Patient’s Serum by Gel Filtration

The patient’s serum was subjected to gel filtration. The elution profile is shown in Fig. 2. Usually, serum lipoproteins are fractionated depending on particle size by gel filtration, and VLDL, LDL and HDL are eluted in that order. In our case, most of the triglycerides were found at the position of VLDL. Cholesterol was found at the position of not only LDL and HDL, but also VLDL. Cholesterol content was highest in VLDL. These results indicated that the hypercholesterolemia in our patient was due to choles-
The lipid compositions of each fraction were analyzed (Fig. 2B). In the VLDL fraction, the amount of free cholesterol was increased and the cholesterol ester ratio was decreased. In this fraction, triglyceride, apoB, and E levels were high compared with the normal LDL level.

**Discussion**

We encountered a case of severe hypercholesterolemia with obstructive jaundice. The patient had no remarkable family history and had hyperbilirubinemia caused by pancreatic cancer. In whole serum, the concentration of LDL-cholesterol measured by homogeneous methods was remarkably increased. In addition, phospholipid (PL) and free cholesterol levels were increased, and the cholesterol ester level was decreased. LCAT activity was too weak to be detected.

Polyacrylamide gel (PAG) disc electrophoresis showed that the fraction corresponding to VLDL was dominant. In agarose gel electrophoresis, however, beta migratory lipoprotein was dominant. It seems that the VLDL-corresponding fraction of this patient on PAG disc electrophoresis was not native VLDL.

Next, the patient's serum was isolated by Sepharose 6B gel filtration. LDL-cholesterol was found in the VLDL-corresponding fraction as well as in the native LDL-corresponding fraction. These results suggest the increased lipoprotein component to be due to the so-called LDL. The level of free cholesterol was high and the ester ratio decreased in the VLDL-corresponding fraction. Moreover, this fraction was rich in triglycerides, apoB and apoE compared with the native LDL. The composition of this unusual lipoprotein was different from that of native VLDL or native LDL.

**Table 3. Abnormal lipoprotein in liver disease**

| Characteristics          | Electrophoresis                  | Serum lipids | Disease                  |
|--------------------------|----------------------------------|--------------|--------------------------|
| Lp (X)                   | Increased PL and F-CHO           | LDL fraction by ultra-centrifugation | T-CHO †, F-CHO †, CE ‡, LCAT ‡ | Cholestasis (Obstructive Jaundice etc) |
|                          | TG- and CE-poor                  | Slow β position in agarose | Migration to cathode side on agar gel electrophoresis | |
|                          | Contains apoC and Alb            |               |                          | |
| Lp (Y)                   | Large particle                    | LDL fraction by ultra-centrifugation | HTGL ‡, LCAT ‡ | Cholestasis (Obstructive Jaundice etc) |
|                          | Triglyceride-rich                | Broad β position in agarose |               | |
|                          | Contains apoB and E              |               |                          | |
| Abnormal LDL             | Conatins apoB and E              | VLDL fraction by ultra-centrifugation | HTGL ‡, LCAT ‡ | Severe liver dysfunction |
|                          | Triglyceride-rich                | β position in agarose |               | |
| slow α-HDL               | Contains PL and apoE             | β ~ α position in agarose gel |               | PBC, Cholestasis (mild case) |
|                          | Large particle HDL               |               |                          | |

The characteristics of this abnormal lipoprotein appear to be similar to those of beta-VLDL except that the free cholesterol content was high and the electrophoretic pattern did not correspond to that of beta-VLDL.

Several abnormal lipoproteins are known to appear in patients with liver diseases (Table 3). In the present case, the patient had severe obstructive jaundice, and decreases in LCAT activity and unesterified cholesterol were observed. The abnormal lipoprotein fraction isolated from the serum of this patient had higher triglyceride and free cholesterol levels and unusually high concentrations of apoB and apoE. With a clinical background like this, lipoprotein-X (Lp-X) or lipoprotein-Y (Lp-Y) may be considered a candidate for the abnormal lipoprotein. Lp-Y is a large particle characterized by unusually high levels of triglycerides in addition to apoC, the presence of apoB, and beta migratory pattern on agarose gel electrophoresis. The abnormal lipoprotein in the present case resembles Lp-Y in many aspects. These results suggest the abnormal lipoprotein to be LP-Y. Several mechanisms have been proposed for the synthesis of Lp-Y. Muller et al. suggest that Lp-Y is formed as result of a deficiency of hepatic lipase\(^\text{19}\). Moreover, Agorastos et al. found Lp-Y in cases of cholestasis only when LCAT activity was weak, although they did not measure concomitant HL activity. These results suggested that the synthesis of Lp-Y was associated with a deficiency of HL or LCAT. In our study, the level of LCAT activity was low, although we did not measure HL activity. These results indicated a LCAT deficiency to be associated with the synthesis of Lp-Y. But the association of HL activity is still unclear. Further study will be required.
The concentration of RLP-C increased remarkably, and was almost the same as that of LDL-cholesterol, however, little intermediate-density-lipoprotein (IDL; midband-lipoprotein) was observed on PAG disc electrophoresis. These results also indicate that the patient’s serum contained an abnormal lipoprotein, which has a beta charge like LDL and is larger than normal LDL. They suggest that the lipoprotein has an abnormal apoB epitope, since detection of RLP-C depends on such an epitope.

The precise cause of hypercholesterolemia in cholestasis remains unknown, but several factors may be involved. The clinical significance of the presence of an abnormal lipoprotein as in this case is unclear. Ooi et al.\textsuperscript{12} reported that abnormal lipoproteins were often observed in patients with a poor outcome. The presence of abnormal lipoprotein may serve as a prognostic factor in cases of liver dysfunction. Further studies are required to clarify this point.

The results of our analyses suggest that triglyceride-rich LDL was an important factor causing severe hypercholesterolemia in the present case, and that Lp-Y may be the abnormal lipoprotein associated with obstructive jaundice.

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