JACC: CASE REPORTS VOL. 2, NO. 1, 2020
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CASE REPORT

INTERMEDIATE

CLINICAL CASE

A Woman With Hypertriglyceridemia Who Acquired Antibody Against GPIHBP1

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ABSTRACT

We report a case of a woman with primary hypertriglyceridemia caused by acquired glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1) autoantibody. This case highlights the necessity of detecting GPIHBP1 autoantibody in patients with acquired hypertriglyceridemia. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:15–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A regular medical check-up in a 35-year-old woman showed a triglyceride level of 2,715 mg/dl, which was much higher than the level 1 year previously (121 mg/dl).

PAST MEDICAL HISTORY

The patient had given birth to 4 children. She experienced chronic thyroiditis and hypothyroidism (antithyroglobulin antibody: 407 IU/ml; microsome test result: 1,600 times; thyroid-stimulating hormone receptor antibody: 2.0 IU/l) after her second childbirth and had been taking 75 μg/day levothyroxine sodium. The patient had not previously been shown to have congenital primary hypertriglyceridemia or pancreatitis.

LEARNING OBJECTIVES

- To recognize the possibility of autoimmune disease in a patient with hypertriglyceridemia.
- To evaluate LPL and GPIHBP1 after excluding secondary hypertriglyceridemia.
- To evaluate autoantibody against GPIHBP1 in patients with low GPIHBP1 mass.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses included other primary hypertriglyceridemia and secondary hypertriglyceridemia.

INVESTIGATIONS

Her body mass index was 20.1 kg/m^2, and she did not have xanthoma or hepatosplenomegaly. There was no family history of familial hypercholesterolemia. Laboratory testing was performed (Table 1). Total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol levels after an overnight fast were 297 mg/dl, 2,517 mg/dl, 17 mg/dl, and 76 mg/dl, respectively (Table 2). A cream layer of chylomicron appeared on the top of serum after standing overnight at 4°C (Figure 1).

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Informed consent was obtained for this case.

Manuscript received November 1, 2019; revised manuscript received November 23, 2019, accepted November 25, 2019.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.11.052

ABBREVIATIONS AND ACRONYMS

GPIHBP1 = glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1

HDL = high-density lipoprotein

LDL = low-density lipoprotein

LPL = lipoprotein lipase

VLDL = very low-density lipoprotein

Secondary hypertriglyceridemia, such as that associated with excessive alcohol consumption, anorexia nervosa, nephrotic syndrome, diabetes mellitus, acromegaly, Cushing syndrome, systemic lupus erythematosus, multiple myeloma, or drug use (such as diuretic, steroid, estrogen, or beta-blockers) was not detected. Hypertriglyceridemia may have been due to hypothyroidism.

Genetic examinations did not show mutations in the genes for lipoprotein lipase (LPL), apolipoprotein C-II, lipase maturation factor 1, or apolipoprotein A-V. However, the gene for glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1) had a non-synonymous substitution with a heterozygous mutation in which cysteine was changed to phenylalanine at amino acid 16. This mutation was not diagnosed as congenital hyperglyceridemia because the triglyceride level had been normal 1 year previously, and the frequency of this mutation has been reported to be 34.7% in Japan and 15.1% worldwide.

The autoantibody against GPIHBP1 was detected by Immuno-Biological Laboratories Co., Ltd. (Gunma, Japan). The standard value is <58.4 U/ml. The autoantibody against GPIHBP1 was positive and was 3,387 U/ml. The mass of GPIHBP1 was 79.8 pg/ml. The LPL mass and activity were 22 ng/ml and 59 U/l, respectively (Table 2).

Major classes, including chylomicron, very-low-density lipoprotein (VLDL), LDL, and HDL, and 20 component peaks of lipoprotein in triglycerides were investigated by LipoSEARCH 1 (Table 3). In 1,098.62 mg/dl of total triglycerides, the combined value of the chylomicron-containing first and second component peaks was 426.33 mg/dl; the individual first and second component peaks were 334.85 mg/dl and 91.48 mg/dl, respectively. The large VLDL-containing third, fourth, and fifth component peaks; medium VLDL-containing sixth component peak; and small VLDL-containing seventh component peak were 411.62 mg/dl (the third, fourth, and fifth component peaks were 117.98 mg/dl, 146.14 mg/dl, and 147.50 mg/dl, respectively), 67.85 mg/dl, and 19.54 mg/dl, respectively. (The results of major classes and component peaks of lipoprotein in cholesterol are not shown.)

MANAGEMENT

Fenofibrate was administered from 80 mg/day against hypertriglyceridemia, and dosing up was abandoned because of liver dysfunction. We talked to the patient about the need for a low-fat diet and added 4 g/day omega-3 fatty acid ethyl esters. The triglyceride level finally decreased to 778 mg/dl.

TABLE 1 Laboratory Test Results

White blood cells	8,300/μl
Red blood cells	448 × 10^4/μl
Platelet	374 × 10^3/μl
Total protein	7.7 g/dl
Albumin	4.6 g/dl
Blood urea nitrogen	8 mg/dl
Creatinine	0.61 mg/dl
Sodium	137 mmol/l
Potassium	4.2 mmol/l
Chloride	102 mmol/l
Aspartate aminotransferase	52 IU/l
Alanine aminotransferase	62 IU/l
Lactic acid dehydrogenase	205 IU/l
Alkaline phosphatase	148 IU/l
γ-glutamyl transpeptidase	24 IU/l
Amylase	114 IU/l
Blood sugar	91 mg/dl
Hemoglobin $A1_c$	5.4%
Thyroid-stimulating hormone	3.090 IU/ml
Free thyroxine	1.39 ng/dl

DISCUSSION

Hypertriglyceridemia is classified as primary or secondary (1). Primary hypertriglyceridemia causes

TABLE 2 Laboratory Tests for Lipid Metabolism

Total cholesterol	297 mg/dl
Triglyceride	2,517 mg/dl
HDL cholesterol	17 mg/dl
LDL cholesterol	76 mg/dl
RLP cholesterol	102.6 mg/dl
Apolipoprotein A-I	91 mg/dl
Apolipoprotein A-II	23.5 mg/dl
Apolipoprotein B	81 mg/dl
Apolipoprotein C-II	18.7 mg/dl
Apolipoprotein C-III	26.2 mg/dl
Apolipoprotein E	16.1 mg/dl
HDL2 cholesterol	7.8 mg/dl
HDL3 cholesterol	5.4 mg/dl
Lipoprotein lipase	22 ng/ml
Lipoprotein lipase activity	59 U/l
HTGL activity	243 U/l
GPIHBP1	79.8 pg/ml
Autoantibody against GPIHBP1	3,387 U/ml

GPIHBP1 = glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; HDL = high-density lipoprotein; HTGL = hepatic triglyceride lipase; LDL = low-density lipoprotein; RLP = remnant-like particles.

congenital defects or acquired autoantibodies in triglyceride synthesis and metabolism, including GPIHBP1, LPL, apolipoprotein C-II, lipase maturation factor 1, and apolipoprotein A-V (2). GPIHBP1 is a protein in lymphocyte antigen 6 (3). GPIHBP1 binds and carries LPL, which is produced by myocytes and adipocytes, from the interstitial space to the capillary lumen. LPL in the capillary lumen can hydrolyzes triglycerides in triglyceride-rich lipoproteins. In the presence of antibody against GPIHPB1, there is low GPIHBP1 mass and LPL mass and activity in the plasma. Under these conditions, triglyceride-rich lipoproteins such as chylomicron and VLDL, are not hydrolyzed in the plasma and cause hypertriglyceridemia. In the present case, the masses of GPIHBP1 and LPL were low, and the activity of LPL was low.

We analyzed 4 major classes including 20 component peaks of lipoprotein in triglycerides (4). There were larger triglyceride-rich lipoproteins such as chylomicron and VLDL, especially in the first component peak. LPL would not be able to hydrolyze the first component peak lipoprotein in plasma, because GPIHBP1 could not carry LPL from the interstitial space to the capillary lumen due to the antibodies against GPIHBP1.

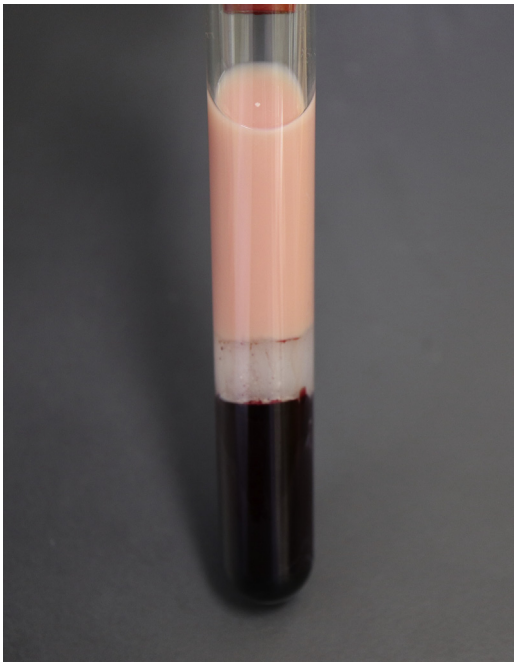
Beigneux et al. (5) reported the existence of autoantibodies against GPIHBP1. In their article, 5 of the 6 patients with GPIHBP1 autoantibodies were female. Female patients are generally more frequently affected by autoimmune disease than male patients (6), and female patients would more frequently acquire autoantibodies against GPIHBP1 than male patients. Although little is known about the association between chronic thyroiditis and GPIHBP1 autoantibodies, both are autoimmune diseases and cause hypertriglyceridemia. The transient appearance of GPIHBP1 autoantibodies during interferon β1a therapy has also been reported (7). Further studies on GPIHBP1 autoantibodies are necessary.

Little is known about the association between a nonsynonymous substitution with a heterozygous mutation in which cysteine is changed to phenylalanine at amino acid 16 and the production of GPIHBP1 autoantibodies. We have to follow up with such patients because acquired hypertriglyceridemia might cause atherosclerosis.

FOLLOW-UP

The triglyceride level was controlled at approximately 800 mg/dl with a low-fat diet, 80 mg/day fenofibrate, and 4 g/day omega-3 fatty acid ethyl

FIGURE 1 A Cream Layer of Chylomicron



The top of the serum was a cream layer of chylomicron after standing overnight at 4°C.

TABLE 3 Major Classes and Subclasses of Lipoproteins in Triglycerides

Major Class	Subclass	Particle Diameter, nm	Component Peak No.	Value, mg/dl
CM		>90	1	334.85
		75	2	91.48
VLDL	Large	64	3	117.98
		53.6	4	146.14
		44.5	5	147.50
	Medium	36.8	6	67.85
	Small	31.3	7	19.54
LDL	Large	28.6	8	26.65
	Medium	25.5	9	33.51
	Small	23.0	10	28.85
	Very small	20.7	11	11.73
		18.6	12	7.32
		16.7	13	4.97
HDL	Very large	15.0	14	4.45
		13.5	15	5.18
	Large	12.1	16	10.79
	Medium	10.9	17	12.73
	Small	9.8	18	13.58
	Very small	8.8	19	5.94
		7.6	20	7.46

CM = chylomicron; VLDL = very-low-density lipoprotein; other abbreviations as in Table 2.

JACC: CASE REPORTS, VOL. 2, NO. 1, 2020
JANUARY 2020:15–8

esters. Pancreatitis has not occurred. We will continue to dose up fenofibrates and omega-3 fatty acid ethyl esters.

CONCLUSIONS

This is a rare case of autoantibodies against GPIHBP1. Acquired hypertriglyceridemia, especially in female patients, indicates that LPL mass, LPL activity, and GPIHBP1 mass should be checked in addition to possible causes of secondary hypertriglyceridemia.

ACKNOWLEDGMENTS The authors thank Koji Kuriyama (Skylight Biotech, Inc., Akita, Japan) for detecting GPIHBP1 autoantibodies and Dr. Akira Matsunaga from Department of Laboratory Medicine, Fukuoka University School of Medicine, Fukuoka, Japan, for genetic examination.

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KEY WORDS autoantibody, GPIHBP1, hypertriglyceridemia