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A case of hyperchylomicronemia associated with GPIHBP1 autoantibodies and fluctuating thyroid autoimmune disease

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Recent studies have reported that patients with autoimmune hyperchylomicronemia caused by glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1) autoantibodies are associated with rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, Basedow's disease, and immune thrombocytopenia. We report a rare case of hyperchylomicronemia due to GPIHBP1 autoantibodies and fluctuating thyroid autoimmune disease.

A 28-year-old woman, diagnosed with Hashimoto's thyroiditis at 26 years of age, started taking 50 μg/day of levothyroxine sodium. She had an episode of acute pancreatitis at 27 years of age; her serum triglyceride (TG) level was 1291 mg/dL at that time. The patient was referred to our hospital because her hyperchylomicronemia (hypertriglyceridemia) did not improve on treatment with pemafibrate and eicosapentaenoic acid (EPA). Serum total cholesterol and TG levels were 237 mg/dL and 2535 mg/dL, respectively, while plasma pre-heparin lipoprotein lipase (LPL) mass was 15 ng/mL (26.5-105.5 ng/mL). We diagnosed her as Basedow's disease based on autoimmune antibodies and ultrasound examination. Targeted exome sequencing revealed no pathogenic variants in the LPL or GPIHBP1 genes. The serum GPIHBP1 autoantibody level was 686.0 U/mL (<58.4 U/mL) and GPIHBP1 mass was 301.9 pg/mL (570.6-1625.6 pg/mL). The patient showed hyperchylomicronemia during periods of hypothyroidism and hyperthyroidism, whereas GPIHBP1 autoantibodies were positive during episode of hyperchylomicronemia but negative during periods of normal TG levels. Based on these findings, the patient was diagnosed with hyperchylomicronemia due to GPIHBP1 autoantibodies and treated with rituximab. GPIHBP1 autoantibodies remained undetectable and TG levels were controlled at approximately 200 mg/dL.

Introduction

Primary hyperchylomicronemia is a rare and intractable disease characterized by marked accumulation of chy-

Abbreviations: GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1.

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lomicrons in the plasma, and elevated triglyceride (TG) levels exceeding 1,000 mg/dL. It is caused by defects in the lipoprotein lipase (LPL) pathway due to genetic mutations, autoantibodies, or other unidentified causes. The monogenic type is typically caused by dysfunctional mutations in LPL, apolipoprotein C2, apolipoprotein A5, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1), and lipase maturation factor 1 (LMF1).[1] Secondary and environmental factors (diabetes, alcohol intake, pregnancy, diet, exercise, medications etc.) often exacerbate hypertriglyceridemia.[1]

In addition to genetic dysfunction, antibodies against LPL induce autoimmune hyperchylomicronemia.[1] Some cases of hyperchylomicronemia are caused by autoantibodies against GPIHBP1, an endothelial cell protein that binds and carries LPL to the capillary lumen, resulting in impaired processing of TG-rich lipoproteins. Hyperchylomicronemia resulting from GPIHBP1 autoantibodies is known as the "GPIHBP1 autoantibody syndrome".[2]

Autoimmune hyperchylomicronemia caused by GPIHBP1 autoantibodies is associated with rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, Basedow's disease, and immune thrombocytopenia.[2-8] We report a rare case of hyperchylomicronemia due to GPIHBP1 autoantibodies and fluctuating thyroid autoimmune disease.

Case Report

A 28-year-old woman, who was diagnosed with Hashimoto's thyroiditis at 26 years of age (August 2019), started taking 50 μg/day of levothyroxine sodium from November 2019. She had an episode of acute pancreatitis at 27 years of age (July 2020), with serum TG level of 1291 mg/dL at that time. Levothyroxine sodium was discontinued in February 2021 because the thyroid stimulating hormone (TSH) levels were extremely low (below measurable level). She was treated with pemafibrate (0.2 mg – 0.4 mg/day) and eicosapentaenoic acid (EPA) (1800 mg/day), but the hyperchylomicronemia did not improve (Fig. 1); she was referred to our hospital in May 2021. Her height, body weight, and body mass index were 162 cm, 75.4 kg, and 28.7 kg/m^2, respectively. She had no xanthoma or hepatosplenomegaly. She had no dietary factors such as excessive alcohol intake, high-fat diet, high-carbohydrate diet rich in fructose and other simple sugars. In addition, she had no pregnancy and no medications except for lipid-lowering therapy. There was no family history of autoimmune diseases or dyslipidemia. Serum total cholesterol and TG levels were 237 mg/dL and 2535 mg/dL, respectively. Plasma pre-heparin LPL mass was 15 ng/mL (26.5-105.5 ng/mL) (Table 1). Antinuclear antibody (speckled type), anti-thyroid peroxidase antibody (TPOAb), and anti-thyroglobulin antibody (TgAb) were all positive. Furthermore, TSH receptor antibody (TRAB) and thyroid stimulating antibody (TSAb) were also positive, although these antibodies were negative at 26 years of age

Table 1 Laboratory results of lipid metabolism.

		Reference range
Total cholesterol (mg/dL)	237	130-220
Triglycerides (mg/dL)	2535	50-150
HDL cholesterol (mg/dL)	16	40-99
LDL cholesterol (mg/dL)	31	<140
Apolipoprotein A1 (mg/dL)	99	126-65
Apolipoprotein A2 (mg/dL)	23.4	24.6-33.3
Apolipoprotein B (mg/dL)	52	66-101
Apolipoprotein C2 (mg/dL)	15.9	1.5-3.8
Apolipoprotein C3 (mg/dL)	30.5	5.4-9.0
Apolipoprotein E (mg/dL)	17.1	2.8-4.6
Lipoprotein lipase (ng/mL)	15	26.5-105.5
RLP cholesterol (mg/dL)	64.7	<7.5
Lipoprotein(a) (mg/dL)	<1	<40
GPIHBP1 mass (pg/mL)	301.9	570.6-1625.6
GPIHBP1 antibody (U/mL)	686.0	<58.4
Recovery rate (%)	22.2	90<

HDL, high-density lipoprotein; LDL, low-density lipoprotein; RLP, remnant-like particles, GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1.

(Table 2). Serum levels of TSH, free triiodothyronine (FT3), and free thyroxine (FT4) were <0.004 μIU/mL, 3.59 pg/mL, and 1.39 ng/dL, respectively. Ultrasound examination revealed that the thyroid gland was hypervascular associated with enlargement. Based on these findings, we diagnosed her as Basedow's disease and thiamazole was initiated at 10 mg/day in September 2021. Targeted exome sequencing of the patient's genomic DNA[9] revealed no pathogenic variants in 21 lipid-related genes (ABCA1, ABCG5, ABCG8, ANGPTL3, APOA1, APOB, APOC2, APOC3, APOA5, APOE, CETP, GPIHBP1, LCAT, LDLR, LDLRAP1, LIPG, LMF1, LPL, MTTP, PCSK9, and SAR1B). To look for an autoimmune cause for the hyperchylomicronemia, a serum sample was tested for autoantibodies against GPIHBP1. GPIHBP1 autoantibodies were examined with two ELISAs as a previous report.[2] To assess the recovery rate, different concentrations of recombinant human GPIHBP1 were added to samples, and the amount of GPIHBP1 in each sample was measured by ELISA. The recovery rate was determined as the difference between the measured concentration and the theoretical concentration.[10] GPIHBP1 mass levels were measured with a solid-phase monoclonal antibody-based sandwich ELISA (Immuno-Biological Laboratories, Fujioka, Japan).[10] Serum GPIHBP1 antibody level was 686.0 U/mL (<58.4 U/mL), GPIHBP1 mass was 301.9 pg/mL (570.6-1625.6 pg/mL), and the recovery rate was reduced to 22.2% (90%<). Based on these findings, the patient was diagnosed with hyperchylomicronemia due to GPIHBP1 autoantibodies. After written informed consent was obtained, we planned to initiate treatment with rituximab (375 mg/m^2) at 1-to-2 week intervals for up to four doses. After the first rituximab dose, we found that the pre-treatment GPIHBP1 autoantibodies were not detectable. We continued the complete schedule of rituximab therapy for four doses on time. GPIHBP1 autoantibodies remained undetectable

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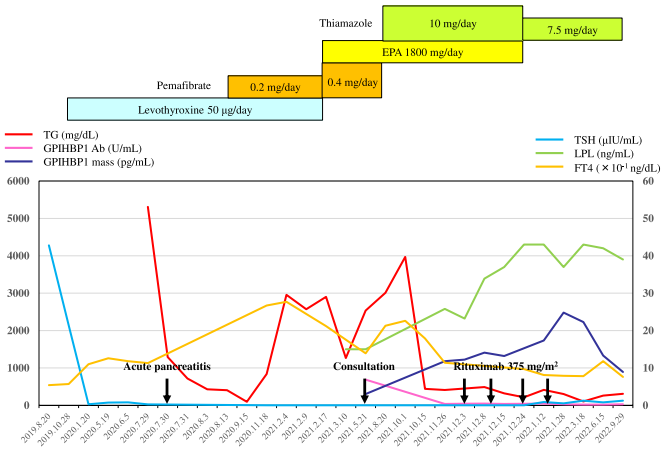

Fig. 1 Clinical time-course. The patient, who was diagnosed with Hashimoto's thyroiditis at 26 years of age (August 2019), started taking 50 μg/day of levothyroxine sodium from November 2019. She had a history of acute pancreatitis at 27 years of age (July 2020). Levothyroxine sodium was discontinued in February 2021 because of extremely low TSH levels. Hyperchylomicronemia (hypertriglyceridemia) did not improve despite treatment with pemafibrate and eicosapentaenoic acid (EPA). She was referred to our hospital in May 2021. We diagnosed her as Basedow's disease and thiamazole was initiated at 10 mg/day in September 2021. We performed initiate treatment with rituximab at 1-to-2 week intervals for up to four doses. GPIHBP1 autoantibodies could not be detected immediately before initiation of rituximab therapy. GPIHBP1 autoantibodies remained undetectable and TG levels were controlled at approximately 200 mg/dL. GPIHBP1 mass and LPL levels were also controlled within reference range.

Table 2 Laboratory results.

		Reference range			Reference range
WBC (/μL)	6300	4000-8000	FT3 (pg/mL)	3.59	1.68-3.67
RBC ($\times 10^4$/μL)	433	380-480	FT4 (ng/dL)	1.39	0.7-1.48
Platelets ($\times 10^4$/μL)	31.4	15.0-35.0	TSH (μIU/mL)	<0.004	0.49-4.67
BUN (mg/dL)	8.2	7.1-20.4	IgG (mg/dL)	2527	1155-1723
Cr (mg/dL)	0.43	0.44-0.79	IgA (mg/dL)	427	167-331
AST (U/L)	55	10-27	IgM (mg/dL)	221	136-256
ALT (U/L)	69	5-33	IgG4 (mg/dL)	37.3	4.8-105
LDH (U/L)	221	124-222	ANA	80	<40
ALP (U/L)	145	38-113	TPOAb (IU/mL)	1490	<3.30
γ-GTP (U/L)	14	10-55	TgAb (IU/mL)	548.0	<28.0
CRP (mg/dL)	<0.10	<0.4	TRAb (IU/L)	9.3	<2
PG (mg/dL)	92	<200	TSAb (%)	459	<120
HbA1c (%)	5.6	<6.5	Proteinuria	(-)	

WBC, white blood cells; RBC, red blood cells; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyltranspeptidase; CRP, C-reactive protein; PG, plasma glucose;, HA1c, hemoglobin A1c; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; ANA, antinuclear antibody; TPOAb, anti-thyroid peroxidase antibody, TgAb, anti-thyroglobulin antibody; TRAb, TSH receptor antibody, TSAb, thyroid stimulating antibody.

and TG levels were controlled at approximately 200 mg/dL. GPIHBP1 mass and LPL levels were also controlled within reference range.

Discussion

Our patient had a history of acute pancreatitis, complicated by thyroid autoimmune disease (Hashimoto's thyroiditis and Basedow's disease). At first, the patient was diagnosed with Hashimoto's thyroiditis, thereafter she was diagnosed with Basedow's disease. Thus, transformation of Hashimoto's thyroiditis to Basedow's disease was observed and thyroid function was fluctuated. Serum TG levels were markedly elevated (hyperchylomicronemia), and plasma pre-heparin LPL and GPIHBP1 masses were low. We could not identify any LPL and GPIHBP1 mutations, but serum GPIHBP1 autoantibodies were positive. The patient showed hyperchylomicronemia during periods of hypothyroidism and hyperthyroidism, whereas GPIHBP1 autoantibodies were positive during episode of hyperchylomicronemia but negative during periods of normal TG levels. Based on these findings, we diagnosed GPIHBP1 autoantibody syndrome.

Autoimmune hyperchylomicronemia caused by GPIHBP1 autoantibodies is associated with rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, Basedow's disease, and immune thrombocytopenia.[2-8] Hashimoto's thyroiditis and Basedow's disease are usually diagnosed with elevation of serum autoimmune antibodies. TPOAb and/or TgAb are usually

used for diagnosis of Hashimoto's thyroiditis and TRAb and/or TSAb are for diagnosis of Basedow's disease. It is sometimes difficult to diagnose these two diseases, because TPOAb and TgAb are elevated in both diseases.[11] Furthermore, Basedow's disease and Hashimoto's thyroiditis are closely related to each other from the point of pathophysiological process. The onset of Basedow's disease or Hashimoto's thyroiditis are influenced by balance of Th1/Th2 cytokines and it seems that increase of the Th1/Th2 cell ratio induces Hashimoto's disease rather than Basedow's disease.[12] Indeed, there are a few reports showing the transformation of Hashimoto's thyroiditis to Basedow's disease.[13, 14] Thus, to the best of our knowledge, this is the first case report of hyperchylomicronemia due to GPIHBP1 autoantibodies and fluctuating thyroid autoimmune disease.

Treatment of this syndrome is not well-established. Pemafibrate combined with EPA was ineffective in our case. Thus, pemafibrate may not be fully effective against autoimmune primary hyperchylomicronemia.[3] A few cases of GPIHBP1 autoantibody syndrome have been successfully treated with prednisolone;[3,4] however, Lutz et al.[5] and Ashraf et al.[15] reported that GPIHBP1 autoantibodies were still detectable after treatment with prednisolone, whereas these were undetectable after treatment with rituximab, a CD20-specific monoclonal antibody used to treat autoimmune diseases. Thus, despite their limited use in the treatment of GPIHBP1 autoantibody syndrome, immunosuppressive drugs are a viable treatment option in these cases.[16]

Another important finding of this case was that GPIHBP1 autoantibodies could not be detected immediately before initiation of rituximab therapy, which became apparent to us after the first rituximab dose was administered. Ashraf et al. have reported that GPIHBP1 autoantibodies are not always persistent, but intermittent.[15] Hu et al. reported a case of hyperchylomicronemia caused by GPIHBP1 autoantibodies that resolved without any immunosuppressive drugs.[6] Transient appearance of GPIHBP1 autoantibodies during interferon β1a therapy has also been reported.[7] Thus, GPIHBP1 autoantibody syndrome can resolve spontaneously in some cases, but the mechanism is unknown. We could not determine whether the disappearance of GPIHBP1 autoantibodies after the first rituximab dose in our case was intermittent or persistent. Therefore, we continued treatment with rituximab as planned.

GPIHBP1 is a member of the lymphocyte antigen 6/urokinase-type plasminogen activator receptor (LU) protein superfamily. Mature GPIHBP1 has two functional domains; an N-terminal disordered acidic domain (containing a sulfated tyrosine and multiple aspartates and glutamates) and a three-fingered LU domain containing 10 cysteines.[17] The epitopes for GPIHBP1 autoantibodies require the proper conformation of the cysteine-rich LU domain. The LU domain is primarily responsible for the stability of the GPIHBP1-LPL complex.[2] It is intriguing that other autoantibodies associated with autoimmune disease bind to cysteine-rich domains in proteins. For example, autoantibodies against the cysteine-rich region of ADAMTS13 cause thrombotic thrombocytopenic purpura.[18] In addition, autoantibodies against a cysteine-rich domain of the thyrotropin receptor have been identified in Basedow's disease.[19,20] It is unlikely that an ELISA for quantifying GPIHBP1 autoantibodies would be capable of detecting GPIHBP1-GPIHBP1 autoantibodies immune complexes in the plasma. In the future, it would be desirable to develop an ELISA for measuring levels of GPIHBP1-GPIHBP1 autoantibodies immune complexes.

GPIHBP1 autoantibodies are the only manifestation of autoimmune disease in many cases.[2,16] GPIHBP1 autoantibody syndrome is sometimes overlook in the differential diagnosis of hyperchylomicronemia, even in clinical lipidology.[8] Therefore, GPIHBP1 autoantibody syndrome should be considered in any patient with newly acquired and unexplained hyperchylomicronemia.

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Authors' contributions

Tsuyoshi Nozue collected data, wrote and contributed to review/editing the manuscript. Hayato Tada contributed to perform targeted exome sequencing. Masami Murakami and Ichiro Michishita contributed to collect data. All authors have read and approved the final manuscript.

Conflict of interest

None.

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