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Case Report

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Anti-GPIHBP1 Antibody-Positive Autoimmune Hyperchylomicronemia and Immune Thrombocytopenia

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Primary hyperchylomicronemia is characterized by marked hypertriglyceridemia exceeding 1,000 mg/dL. It is caused by dysfunctional mutations in specific genes, namely those for lipoprotein lipase (LPL), glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1), apolipoprotein C2 (ApoC-II), lipase maturation factor 1 (LMF1), or apolipoprotein A5 (ApoA-V). Importantly, antibodies against LPL or GPIHBP1 have also been reported to induce autoimmune hyperchylomicronemia.

The patient was a 46-year-old man diagnosed with immune thrombocytopenia (ITP) at 41 years. At the time, he was administered prednisolone (PSL) and eltrombopag, a thrombopoietin receptor agonist. At 44 years, he suffered from acute myocardial infarction, and PSL was discontinued to avoid enhancing atherogenic risks. He was maintained on eltrombopag monotherapy. After discontinuing PSL, marked hypertriglyceridemia (>3,000 mg/dL) was observed, which did not improve even after a few years of pemafibrate therapy. Upon referral to our clinic, the triglyceride (TG) level was 2,251 mg/dL, ApoC-II was 19.8 mg/dL, LPL was 11.1 ng/mL (0.02–1.5 ng/mL), GPIHBP1 was 47.7 pg/mL (740.0–1,014.0 pg/mL), and anti-GPIHBP1 antibody was detected. The patient was diagnosed to have anti-GPIHBP1 antibody-positive autoimmune hyperchylomicronemia. He was administered PSL 15 mg/day, and TG levels were controlled at approximately 200 mg/dL.

Recent studies have reported that patients with anti-GPIHBP1 antibody-induced autoimmune hyperchylomicronemia had concomitant rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's disease, and Graves' disease. We report a rare case of anti-GPIHBP1 antibody-positive autoimmune hyperchylomicronemia with concomitant ITP, which became apparent when PSL was discontinued due to the onset of steroid-induced acute myocardial infarction.

Key words: **GPIHBP1, Autoimmune hyperchylomicronemia, Anti-GPIHBP1 antibody, Immune thrombocytopenia, Pemafibrate**

Introduction

Primary hyperchylomicronemia (PCM) is characterized by marked elevation of triglyceride (TG) levels exceeding 1,000 mg/dL and accumulation of chylomicron. It is caused by dysfunctional mutations in the genes encoding lipoprotein lipase (LPL), apolipoprotein C2 (ApoC-II), apolipoprotein A5 (ApoA-V), glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1), and lipase maturation factor 1 (LMF1), which are involved in a complex with LPL[1, 2]. In addition to genetic dysfunction, antibodies against LPL induce autoimmune hyperchylomicronemia,

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Table 1. Concentration of LPL, antibody against LPL, GPIHBP1 and antibody against GPIHBP1

	Before PSL treatment (X)*	After PSL treatment (X + 3 month)**	Unit	Standard range
LPL	11.1	13.3	ng/mL	0.02-1.5
Antibody against LPL	Not detected			
GPIHBP1	47.7	697.4	pg/mL	740～1014
Antibody against GPIHBP1	670.1	158.4	U/mL	9～57

* and ** were indicated in Figure 2.

which was first reported by Kihara *et al.* in 1989 [3]. Recently, a monoclonal antibody against human GPIHBP1 in plasma was developed by Miyashita *et al.*[4], and autoimmune hyperchylomicronemia with anti-GPIHBP1 antibodies was reported by Beigneux AP *et al.* in 2017 [5]. GPIHBP1 is a glycolipid-modified anchor protein that resides on capillary endothelial cell membranes and plays a role in transporting LPL from outside the capillaries into the lumen of blood vessels. In patients with GPIHBP1 deficiency, LPL is mislocalized in the interstitial spaces and never reaches the capillary lumen. The absence of intraluminal LPL prevents the lipolytic processing of TG-rich lipoproteins, resulting in severe hyperchylomicronemia[6, 7].

A few cases have been reported regarding anti-GPIHBP1 antibodies[5, 8-13]. These reports show that autoimmune hyperchylomicronemia from anti-GPIHBP1 antibodies is associated with rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's disease, and Graves' disease. However, to our knowledge, no case has been associated with immune thrombocytopenia (ITP).

We report a case of anti-GPIHBP1 antibody-positive autoimmune hyperchylomicronemia with concomitant ITP, which was diagnosed when the steroid was discontinued due to the onset of steroid-induced acute myocardial infarction.

Case Presentation

The patient was a 46-year-old man. At 41 years old, a low platelet count ($2\times10^4/\mu L$) was noted for the first time. On further workup, he was diagnosed with ITP, and oral prednisolone (PSL) treatment was initiated. Oral administration of eltrombopag, a thrombopoietin receptor agonist, was initiated in addition to PSL, and the platelet count improved to about $10\times10^4/\mu L$.

At 44 years, he developed acute left anterior descending myocardial infarction. He did not have any atherosclerotic risk factors such as dyslipidemia, hypertension, diabetes mellitus, and smoking. Because of this, PSL was discontinued to avoid worsening of the cardiovascular risk factors induced by steroids. Immediately after discontinuing PSL, he developed markedly elevated TG levels (>3,000 mg/dL). Although a low-fat diet was recommended and pemafibrate was administered, it did not improve for a few years. He does not have any xanthoma, and he had never been suffered from acute pancreatitis.

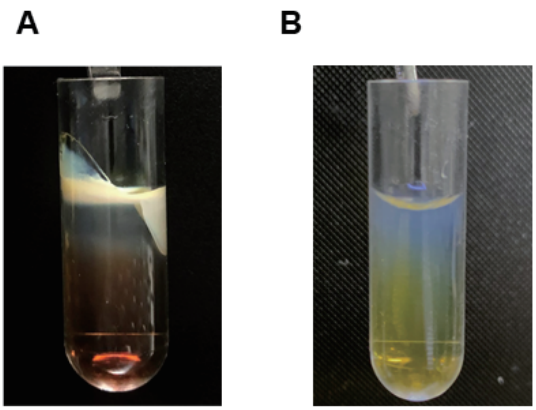

Fig. 1. Ultracentrifugation (specific density liquid:1.006, 26,000g, 4℃, 30min)

A. Chylomicron was detected in the upper layer when triglyceride was over 3,000 mg/dL.
B. Chylomicron was not detectable after PSL treatment.

Upon referral to our clinic, TG level was 2,251 mg/dL, ApoC-II was 19.8 mg/dL,¬chylomicron was detected at the top of the serum after ultracentrifugation **(Fig. 1A)**. Based on his medical history, we suspected autoimmune hyperchylomicronemia and examined the LPL mass, GPIHBP1 mass, anti-LPL antibody and anti-GPIHBP1 antibody as previously described by Beigneux AP. *et al.*[5]. As shown in **Table 1**, LPL was 11.1 ng/mL (0.02-1.5 ng/mL), GPIHBP1 was 47.7 pg/mL (740.0-1014.0 pg/mL) and we detected anti-GPIHBP1 antibody in serum.

After obtaining the informed consent, targeted exon sequencing was performed to investigate 36 lipid-related genes (LDLR, PCSK9, ApoB, LDLRAP1, ABCG5, ABCG8, LCAT, ABCA1, LPL, ApoC-II, ApoC-III, ApoA-V, GPIHBP1, LMF1,

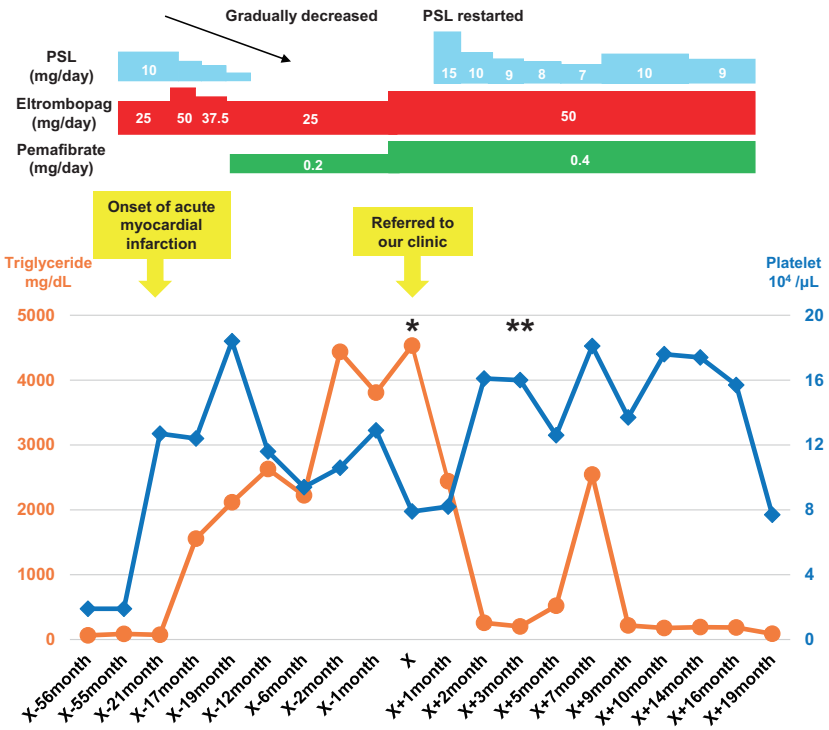

Fig. 2. After onset of ITP, clinical time-course

After discontinuation of PSL, marked hypertriglyceridemia was observed. Although pemafibrate was administrated, it was not effective. After PSL was re-administered, triglyceride levels were decreased and platelets counts were increased. When PSL was reduced to 7 mg/day, hyperchylomicronemia recurred again. Then, PSL was increased to 10 mg/day, and TG levels have been controlled. LPL mass, GPIHBP1 mass, anti-LPL antibody and anti-GPIHBP1 antibody were measured at this point (*) and LPL mass, GPIHBP1 mass and anti-GPIHBP1 antibody were measured at this point (**) (Table 1).

CYP27A1, MTTP, ApoA-I, CETP, ApoE, CD36, ABCC6, ANGPTL3, ANGPTL8, ApoBEC1, IDOL, LIPA, LIPC, LIPG, MLXIPL, NPC1L1, PNPLA2, SAR1B, SCARB1, SORT1, STAP1, USF1). Among variants with a minor allele frequency of <5% in 1000 Genomes Project of East-Asian population, we have defined pathogenic variants if they fulfilled i) protein truncating variants, ii) damaging missense variants, and iii) ClinVar-registered pathogenic or likely pathogenic variants. However, we have never detected any mutations of ApoC-II, ApoA-V, LMF, LPL, and GPIHBP1. The patient was diagnosed with autoimmune hyperchylomicronemia induced by anti-GPIHBP1 antibodies. He was administered PSL 15 mg/day, and the chylomicron disappeared after PSL treatment **(Fig. 1B)**. Serum TG levels were significantly improved to around 200 mg/dL, and platelet counts were approximately 10×10^4 /μL **(Fig. 2)**. PSL was gradually reduced to avoid worsening of the cardiovascular risk factors induced by steroids. While taking PSL 9 mg/day, LPL mass was 13.1 ng/mL, GPIHBP1 mass was 697.4 pg/mL and anti-GPIHBP1 antibodies were 158.4 U/mL. LPL mass was unchanged, but GPIHBP1 and anti-GPIHBP1 antibodies showed improvement.

When decreased to 7 mg/day, the TG levels again rose to over 2,500 mg/dL. Therefore, PSL was increased to 10 mg/day. Currently, PSL is maintained at 9 mg/day in combination with pemafibrate 0.4 mg/day, and the TG levels have been consistently under 150 mg/dL.

Discussion

We report the first case with autoantibodies against GPIHBP1 with concomitant ITP **(Table 2)**. Our patient was initially treated for ITP with PSL, but when PSL was discontinued to avoid the enhancement of atherogenic risk factors, hyperchylomicronemia became apparent.

The efficacy and safety of pemafibrate have been reported for patients with dyslipidemia[14]. Recently, pemafibrate has also been reported to be effective against patients with primary hyperchylomicronemia[15]. However, in our patient, pemafibrate was not effective without PSL administration. This suggests that pemafibrate might not be fully effective against autoimmune primary hyperchylomicronemia without

Table 2. Summary of Cases

No.	Autoimmune disease diagnose	Immunosupressive treatment (Initial Treatment)	Ref.
1	Rheumatoid arthritis Sjogren syndrome Hashimoto disease SLE	Prednisolone (10 mg/day) Salazosulfapyridine (1000 mg/day)	(5)
2	None	Mycophenolate mofetil	(5)
3	Sjogren syndrome	Mycophenolate mofetil (1250 mg/day)	(5)
4	SLE	Prednisolone (5 mg/day)	(5)
5	Neonatal lupus	None	(5)
6	None	None	(8)
7	None	None (*only during the IFNβ1a treatment)	(9)
8	SLE	Prednisolone	(10)
9	Grave's disease	Prednisolone (60 mg/day)	(11)
10	None	Mycophenolate mofetil (2000 mg/day) Prednisolone (60 mg/day)	(12)
11	Hashimoto disease	None	(13)
our case	ITP	Prednisolone (15 mg/day)	

PSL. The patient was referred to a lipid specialist when the TG levels were not reduced by pemafibrate.

It was interesting to determine whether anti-platelet and anti-GPIHBP1 antibodies share the same antigen. Therefore, we tested for anti-platelet antibodies in the patient's blood and combined them with recombinant GPIHBP1, but these antibodies did not recognize the recombinant GPIHBP1. This lack of reactivity might be because eltrombopag and steroids had already been administered to treat ITP and autoimmune hyperchylomicronemia, and hence the antibody reaction was suppressed.

When PSL was reduced to 7 mg/day, hyperchylomicronemia recurred. PSL was increased to 10 mg/day, and since then, the TG level has been maintained under 150 mg/dL. Because he had previously suffered from myocardial infarction, we will need to evaluate for the presence of atherogenic TG-rich lipoprotein remnants continuously. We might also have to consider the challenge with other immunosuppressive treatments based on previous reports.

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Conflict of Interest

M.K. received research grant from Kowa company, Ltd. M.K., S.Y. , and Y.S. received a lecture fee from Kowa company, Ltd. The others do not have any conflicts of interest.

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