Anti-GPIHBP1 Antibody-Positive Autoimmune Hyperchylomicronemia and Immune Thrombocytopenia

Katsunao Tanaka1, Masahiro Koseki1, Hisashi Kato2, Kazuya Miyashita3, Takeshi Okada1, Kotaro Kanno1, Ayami Saga1, Jiuyang Chang1, Takashi Omatsu1, Hiroyasu Inui1, Tohru Ohama1, Makoto Nishida4, Shizuya Yamashita5 and Yasushi Sakata1

1 Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan.
2 Department of Hematology and Oncology, Osaka University Graduate School of Medicine, Osaka, Japan.
3 Immuno-Biological Laboratories (IBL) Co., Ltd., Fujioka, Gunma, Japan
4 Health Care Division, Health and Counseling Center, Osaka University, Osaka, Japan.
5 Rinku General Medical Center, Osaka, Japan.

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 LPL1. 2). In addition to genetic dysfunction, antibodies against LPL induce autoimmune hyperchylomicronemia,
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 (2×10\(^4\)/µL) 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 10×10\(^4\)/µL.

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.

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, 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\(^6,7\).

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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.

**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.

**Fig. 1.** Ultracentrifugation (specific density liquid:1.006, 26,000g, 4°C, 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.

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,
BOBLBFUBM 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. Recently, pemafibrate has also been reported to be effective against patients with primary hyperchylomicronemia. 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          | Immunosuppressive 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 IFNβ1α treatment)                                 | (9) |
| 8   | SLE                                  | Prednisolone (60 mg/day)                                                | (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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