Triglyceride Turmoil: Unraveling a Complex Case

Tharsini Sarvanandan,[a,*] Jeyakantha Ratnasingam,[a] Pavai Sthaneswar,[b] Masami Murakami,[c] and Soo Kun Lim[d]

[a]Endocrine Unit, Department of Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia; [b]Department of Pathology, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia; [c]Department of Clinical Laboratory Medicine, Gunma University Graduate School of Medicine, Gunma, Japan; [d]Division of Nephrology, Department of Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia.

*Address correspondence to this author at: Endocrine Unit, Department of Medicine, Faculty of Medicine, University Malaya, Lembah Pantai, Kuala Lumpur 50603, Malaysia. E-mail s.tharsini@ummc.edu.my.

CASE DESCRIPTION

A 46-year-old woman was referred to our clinic for a markedly increased serum fasting triglyceride (TG) concentration discovered during a routine clinic visit; total cholesterol: 452.4 mg/dL [reference interval (RI) <201.1] [11.7 mmol/L (<5.2)], fasting plasma TG: 2014.7 mg/dL (RI < 65.7) [52.1 mmol/L (<1.7)], high-density lipoprotein: 30.9 mg/dL (RI > 42.5) [0.8 mmol/L (>1.10)], and a low-density lipoprotein level that could not be calculated due to the high TG concentration.

Her past medical history included a total thyroidectomy at the age of 21 for Graves' disease, for which she had been on levothyroxine replacement therapy at a dose of 100 µg daily. At age 32, she was diagnosed with chronic immune thrombocytopenic purpura and after that point was maintained on prednisolone 5 mg daily. She was not using any hormonal contraception and had a negative urine pregnancy test. Her first-degree relatives had hyperlipidemia, and a brother had suffered from a myocardial infarction in his forties. She did not consume alcohol or smoke.

Physical examination revealed a lean woman with a body mass index of 22.6 kg/m$_2$ and a waist circumference of 79 cm. Other clinical examination was unremarkable, with no hepatosplenomegaly, eruptive xanthomas, or lipemia retinalis. Investigations for hypertriglyceridemia including liver, kidney and thyroid function tests, and screening for diabetes were done. Her thyroid function was within reference interval with a free T4 of 1.7 ng/dL (RI 0.9–1.8) [22.2 pmol/L (11.5–22.7)] and TSH of 2.1 µIU/L (RI 0.5–4.6), but with an increased antithyroid peroxidase antibody concentration of 200 IU/mL (RI < 35) and a thyroid-stimulating immunoglobulin concentration of 3.82 IU/L (RI < 0.55). No signs of nephrotic syndrome were present, as evidenced by a normal urinalysis and renal profile. The liver function tests were normal.

Since the routine investigations were normal in this case of hypertriglyceridemia, further investigations including genetic testing and autoimmune disease screen were performed. Although less likely, she was screened for genetic causes of hypercholesterolemia, including apolipoprotein CII (*ApoC2*), lipoprotein lipase (*LPL*), and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*) genes. Genetic and autoimmune disease screen were negative.

She was prescribed rosuvastatin 20 mg daily, fenofibrate 160 mg daily, and ezetimibe 10 mg daily with a low-fat, low-carbohydrate diet and daily calorie intake of 1400 kilocalories. All conventional treatment approaches for hypertriglyceridemia failed to normalize TG, and her fasting TG levels ranged between 591.6 and 2096 mg/dL (15.3 to 54.2 mmol/L) over the next 3 months. She was subsequently admitted for a trial of intravenous insulin infusion given at 0.05 unit/kg/h to decrease the plasma TG concentration due to concern for complications including atherosclerotic cardiovascular disease and pancreatitis, but this was also futile. Unfortunately, she suffered acute pancreatitis, which was managed supportively. This was managed at a different center: as such, the details of the admission are unavailable.

https://doi.org/10.1093/clinchem/hvaf103

Considering the age of onset of the hypertriglyceridemia, rapid progression, lack of response to conventional treatment and her background of autoimmunity, an autoimmune cause was suspected after common secondary and genetic causes were excluded (1). Autoimmune causes of severe hypertriglyceridemia are uncommon, with glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) and lipoprotein lipase (LPL) autoantibodies being the 2 most well-established ones (2). Of these, GPIHBP1 autoantibody testing is more accessible, while LPL autoantibody syndrome has a lower prevalence. Because of this, GPIHBP1 antibody screening was done. The serum concentration of the GPIHBP1 autoantibody was markedly increased at 4279.9 U/mL (RI<58.4), with a corresponding decreased GPIHBP1 mass 1.0 pg/mL (RI 570.6–1625.6) and decreased LPL mass of 3.7 ng/mL (RI 26.5–105.5), leading to a diagnosis GPIHBP1 autoantibody syndrome. GPIHBP1 is an endothelial protein needed for lipid metabolism. Immune complexes are formed when autoantibodies bind to GPIHBP1, rendering it nonfunctional and decrease detectable GPIHBP1 concentrations. This also prevents the transport of LPL into the capillary lumen for effective TG hydrolysis (2).

After discussing immunotherapy options with the patient, low dose intravenous rituximab infusions at 200 mg were initiated. Following 4 doses of rituximab given over 3 months, her plasma TG level decreased significantly and normalized over the subsequent 3 months. No changes were made to her regular medications at that time. The GPIHBP1 autoantibody concentration decreased from 4279.7 to 21.0 U/mL with a corresponding increase in the GPIHBP1 mass (Fig. 1). Antibody concentrations can fluctuate spontaneously, leading to reductions in GPIHBP1 autoantibody levels and serum TG concentrations even before initiation of rituximab therapy (2). In fact, ezetimibe and fenofibrate have since been discontinued. Five months post-rituximab, her serum TG remain normal at 1.1 mmol/L.

QUESTIONS TO CONSIDER	
1.	What are the primary and secondary causes of hypertriglyceridemia?
2.	How should hypertriglyceridemia be evaluated in an adult?
3.	What is the role of GPIHBP1 in lipolysis?
4.	What is the underlying mechanism of hypertriglyceridemia in an individual with autoimmune diseases such as immune thrombocytopenic purpura and Graves' disease?

Continued on the next page….

https://doi.org/10.1093/clinchem/hvaf103

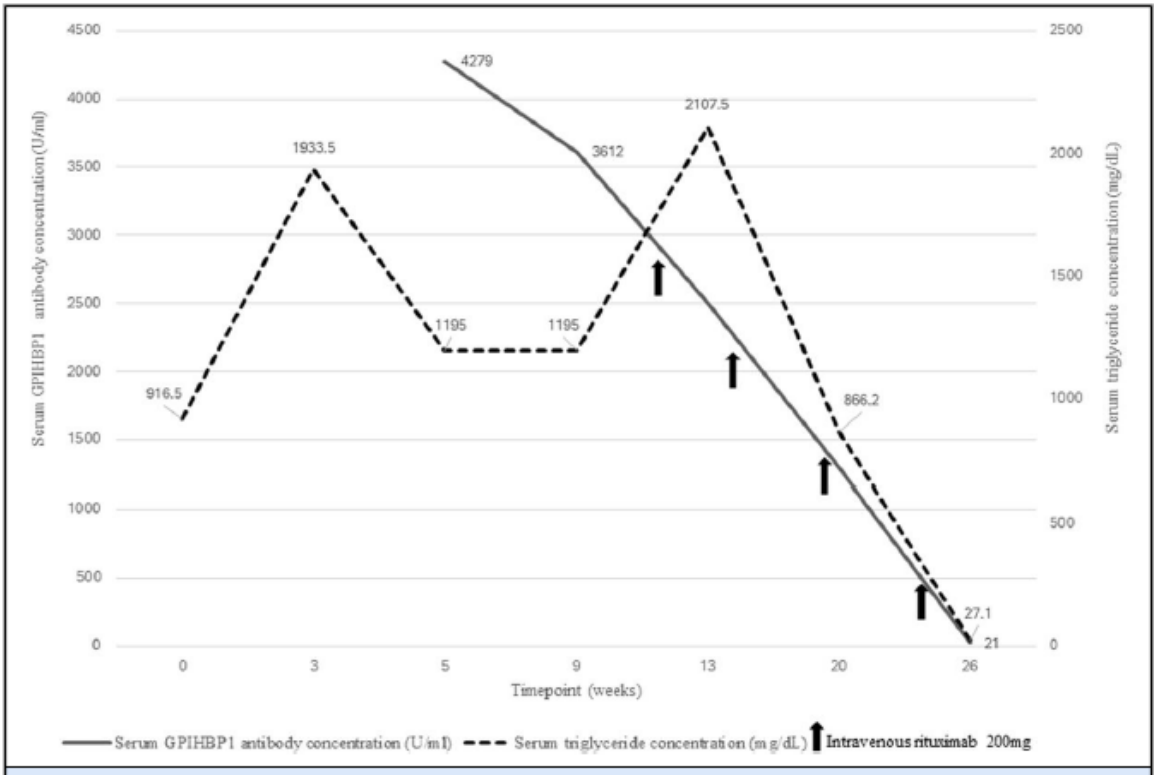

Fig. 1. Plasma TG in relation to plasma GPIHBP1 antibody levels.

REFERENCES

1. Miyashita K, Fukumachi I, Machida T, Nakajima K, Young S, Murakami M, et al. An ELISA for quantifying GPIHBP1 autoantibodies and making a diagnosis of the GPIHBP1 autoantibody syndrome. Clin Chim Acta 2018;487:174–8.
2. Beigneux AP, Miyashita K, Ploug M, Blom DJ, Ai M, Linton MF, et al. Autoantibodies against GPIHBP1 as a cause of hypertriglyceridemia. N Engl J Med 2017;376:1647–58.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the February 2026 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/72/2 and follow the link to the Clinical Case Study and Commentaries.

Educational Centers

If you are associated with an educational center and would like to receive the cases and questions 1 month in advance of publication, please email clinchemed@myadlm.org.

All previous Clinical Case Studies can be accessed and downloaded online at https://www.myadlm.org/science-and-research/clinical-chemistry/clinical-case-studies.

https://doi.org/10.1093/clinchem/hvaf103

ADLM is a leading professional society dedicated to improving healthcare through laboratory medicine. Its nearly 10,000 members are clinical laboratory professionals, physicians, research scientists, and others involved in developing tests and directing laboratory operations. ADLM brings this community together with programs that advance knowledge, expertise, and innovation. ADLM is best known for the respected scientific journal *Clinical Chemistry* and the world's largest conference on laboratory medicine and technology. Through these and other programs, ADLM advances laboratory medicine and the quality of patient care.

https://doi.org/10.1093/clinchem/hvaf103