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Case Report

Highly efficacious, long-term, triglyceride lowering with rituximab therapy in a patient with autoimmune hypertriglyceridemia

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Abstract: We report the first case of an autoimmune hypertriglyceridemia successfully treated with rituximab, an anti-CD20-targeted monoclonal antibody. A 45-year-old man, with prior autoimmune conditions, developed severe, acquired hypertriglyceridemia resistant to traditional triglyceride lowering therapies. After the elimination of secondary or genetic causes, we detected the presence of anti-LPL-IgG by immunoblot. After 3 infusions of rituximab, we observed a marked improvement of his hypertriglyceridemia, concomitant with a reduction in plasma anti-LPL antibody titer and B-lymphocytes counts. The patient has been receiving rituximab maintenance therapy for 5 years without any serious adverse events and with excellent control of his previous, marked hypertriglyceridemia.

Introduction

Hyperchylomicronemia is a subset of severe hypertriglyceridemia (>10 mmol/L) that is characterized by the abnormal persistence of chylomicrons in fasting plasma.[1] The relatively rare familial chylomicronemia syndrome (FCS) is an autosomal recessive condition that can be diagnosed either in childhood or adulthood. FCS is due to genetic deficiency of genes implicated in chylomicrons and very-low-density lipoprotein (VLDL) lipolysis and clearance from the circulation: lipoprotein lipase (LPL) or related proteins such as apoC-II, apoA-V, lipase maturation factor 1 (LMF1), or glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1).[1,2] More commonly, hypertriglyceridemia is caused by high burden of multiple risk alleles, each making a small contribution to the hypertriglyceridemic condition (ie, polygenic basis of hypertriglyceridemia), interacting with acquired or environmental factors, usually presenting later in life and frequently characterized by accumulation of both intestinally derived chylomicrons and hepatically derived VLDLs.[3,4] Complex interactions between environmental factors such as poor diet, obesity, alcohol intake, certain medications, pregnancy, and uncontrolled diabetes on a genetically predisposed background may lead to hypertriglyceridemia.[5]

Rare cases of autoimmune severe hypertriglyceridemia due to autoantibodies against LPL[6,7], apoC-II,[8] and GPIHBP1[9] have been described leading to severe

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hypertriglyceridemia. Immunosuppressive therapies have been used to treat this autoimmune disorder to restore LPL activity and decrease triglyceride levels.[6,10,11] Here, we report the first case of a patient with autoimmune hypertriglyceridemia due to anti-LPL antibodies who was successfully treated with rituximab, an anti-CD20-targeted biotherapy commonly used in various autoimmune diseases.[12]

Case report

A 45-year-old man was referred to our nutrition department with severe hypertriglyceridemia (fasting plasma triglycerides 76 mmol/L, upper limit of normal approximately 1.5 mmol/L). He had no symptoms or prior history of acute pancreatitis and was not noted to have eruptive xanthomas, which may be seen in cases of marked hypertriglyceridemia. He was overweight, with a body mass index of 29 kg/m^2. His past medical history was significant for genetically determined and treated, heterozygous familial hypercholesterolemia (heterozygous mutation in the exon 6 [c.829 G>A] of the low-density lipoprotein receptor [LDLR] gene), ischemic stroke at the age of 44 years, Grave's disease treated by neomercazole and in remission since 6 years, known positive antinuclear antibodies (nucleolar: 1/160). We ruled out secondary causes of hypertriglyceridemia: alcohol consumption, hypothyroidism, uncontrolled diabetes, renal disease, or drugs. His severe hypertriglyceridemia was discovered during one of his low-density lipoprotein (LDL) apheresis treatment sessions (see below) when his plasma was noted, for the first time, to be lactescent. Indeed, the patient had been treated for 7 years by LDL apheresis every 3 weeks associated with rosuvastatin 20 mg/d and ezetimibe 10 mg/d for severe, heterozygous familial hypercholesterolemia with uncontrolled LDL-cholesterol >2 g/L in secondary prevention. His plasma triglyceride concentration had been regularly monitored since the beginning of the LDL apheresis treatment, revealing moderated hypertriglyceridemia between 4.5 and 9.1 mmol/L (until this occasion, never >10 mmol/L).

For this severe hypertriglyceridemia, the patient was first treated with 48-hour fasting followed by a hypocaloric, low-fat, sugar-free diet. This nutritional therapy was associated with 5 plasma exchanges every 5 days leading to a substantial decrease of plasma triglyceride concentration immediately following the plasma exchanges, with a nadir triglyceride concentration of 3.88 mmol/L. However, triglyceride concentration increased before each plasma exchange therapy (reaching 33 mmol/L immediately before the sixth plasma exchange). Next, we tried insulin/glucose intravenous infusion, but triglyceride levels remained elevated at 19.4 mmol/L. Then, monthly plasma exchanges were performed for 6 months leading to triglyceride levels between 14.8 mmol/L and 52.4 mmol/L.

To further investigate the etiology of his severe hypertriglyceridemia, we performed a series of laboratory investigations. The fasting lipogram showed a high quantity of chylomicrons and excess of VLDLs. The genetic analysis showed his apolipoprotein E genotype as *E3/E4*, and no genetic mutations (nor any polymorphisms) were found in genes coding for proteins known to be involved in triglyceride metabolism: *LPL*, *APOC2*, *APOA5*, *GPIHBP1*, and *LMF1*. Considering the autoimmune background of the patient, we looked for the presence of LPL antibodies and found anti-LPL IgG antibodies by immunoblot using human LPL as ligand (Fig. 1).

When the potential autoimmune basis of his marked hypertriglyceridemia was confirmed and due to the lack of efficacy of conventional therapies, we elected, after obtaining informed consent from the patient, to treat him with a chimeric monoclonal antibody binding to CD20 and depleting B cells, commonly used in several autoimmune diseases: rituximab (375 mg/m^2/wk for 3 weeks). We ensured that the patient received pretreatment vaccinations against B hepatitis and pneumococcus. Plasma triglyceride concentration declined dramatically from 27 mmol/L pretreatment to 1.9 mmol/L after three infusions, in parallel with a decrease of CD19$^+$ B lymphocytes (108 to 2/mm^3) (Fig. 1). Anti-LPL antibodies also decreased after the first infusion of rituximab and were barely detectable after the third infusion (Fig. 1). Six months after the first cycle of rituximab infusions, triglyceride levels gradually increased again up to 44.8 mmol/L. At the same time, anti-LPL antibodies were again strongly detectable and CD19$^+$ B lymphocytes increased up to 22/mm^3 (Fig. 1A and B). A single new infusion of rituximab was successfully performed, inducing a marked reduction of plasma triglyceride concentration to 2 mmol/L. The patient is currently treated with rituximab maintenance infusions when triglyceride levels exceed 10 mmol/L. Rituximab infusions are performed for an average of once a year. The patient has received a total of 7 rituximab infusions during the past 5 years.

Patient and laboratory methods

The patient was evaluated at the Conception hospital in Marseille, France. A written informed consent was obtained for genetic testing. After the genomic DNA extraction, the coding regions and the adjacent splice sites of *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, and *LMF1* were polymerase chain reaction-amplified using gene-specific primers. The purified polymerase chain reaction products were sequenced to determine the nucleotide alternations. Serum triglycerides and lipoproteins were measured enzymatically in commercial laboratories. Detection of circulating autoantibodies directed against LPL was performed using previously described.[13] Briefly, bovine LPL was subjected to 4–12% polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate and then transferred onto a nitrocellulose membrane. After saturation of the nonspecific binding capacity, the blots were incubated for 1 hour 15 minutes with total plasma from a previous