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Case Report

Severe Hypertriglyceridemia in a Patient Treated With Sirolimus for Graft-vs-Host Disease Prophylaxis

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Abstract

Hypertriglyceridemia is an important and well documented adverse effect caused by the immunosuppressive agent sirolimus. Patients treated with sirolimus require frequent monitoring of blood lipid panels and prompt treatment with appropriate triglyceride-lowering therapies. We report the case of an asymptomatic 65-year-old female stem cell transplant recipient who developed extreme hypertriglyceridemia with levels > 19,000 mg/dL (214 mmol/L) (reference range, < 150 mg/dL [< 1.7 mmol/L]), secondary to sirolimus for prophylaxis of graft-vs-host disease. Acute treatment included admission to the intensive care unit for initiation of an intravenous insulin infusion, low-fat diet, and discontinuation of sirolimus. These measures, in addition to initiation of oral triglyceride-lowering agents and improved glycemic control, led to substantial improvement in triglyceride levels.

Key Words: hypertriglyceridemia, sirolimus, graft-vs-host-disease

Abbreviations: CKD, chronic kidney disease; FDA, US Food and Drug Administration; GvHD, graft-vs-host disease; LPL, lipoprotein lipase; mTORC1, modified mTOR complex 1.

Introduction

Sirolimus is an mTOR inhibitor immunosuppressant medication. It is most often used for prophylaxis of rejection after solid organ transplants. It is also used as a second line agent for both treatment and prophylaxis of graft-vs-host disease (GvHD). Hypercholesterolemia and hypertriglyceridemia are well-known metabolic effects associated with sirolimus [1]. The Federal Drug Administration (FDA) recommends regular monitoring for hyperlipidemia in patients taking sirolimus. If lipid abnormalities are identified, lipid-lowering therapies should be initiated promptly. While hypertriglyceridemia related to sirolimus is more commonly modest [2], there have been case reports of severe hypertriglyceridemia [3]. We report a case of severe hypertriglyceridemia in a 65-year-old woman treated with sirolimus for prophylaxis of GvHD after stem cell transplant for treatment of diffuse large B-cell lymphoma.

Case Presentation

An asymptomatic 65-year-old woman with past medical history of stage IV diffuse large B-cell lymphoma (diagnosed 7 years ago) and type 2 diabetes mellitus presented to the outpatient oncology clinic for routine laboratory monitoring. She had received multiple courses of chemotherapy since diagnosis. Six months prior, she had received an allogenic stem cell transplant and was initiated on oral sirolimus for GvHD prophylaxis at 2 months post-transplant. Sirolimus had since been titrated to a dosage of 2 mg by mouth daily on Mondays, Wednesdays, and Fridays. Two weeks before this office visit, a lipid panel was completed as part of her regular laboratory monitoring, and it was notable for a triglyceride level of 4369 mg/dL (49.3 mmol/L) (reference range, < 150 mg/dL [< 1.7 mmol/L]). One year prior, the patient's triglyceride level was slightly elevated to 243 mg/dL (2.74 mmol/L).

Diagnostic Assessment

In response to these levels, she was initiated on rosuvastatin 5 mg daily. She had previously been on simvastatin 80 mg daily that had been discontinued 7 months earlier, secondary to drug-drug interactions with posaconazole. It is unclear why it was not replaced by another lipid-lowering agent and why a fibrate had not been originally started. In the office, the patient was asymptomatic, denying nausea, vomiting, or abdominal pain. A repeat lipid panel was completed, which demonstrated a triglyceride level of 19 716 mg/dL (222.6 mmol/L). Her outpatient blood work was also notable for an elevated creatinine of 2.03 mg/dL (180 µmol/L) (reference range, 0.60-1.20 mg/dL (53-106 µmol/L) and hyponatremia with a sodium level of 120 mmol/L (reference range, 134-144 mmol/L]). She was subsequently admitted to the intensive care unit for treatment of severe hypertriglyceridemia. Pertinent laboratory tests on admission can be found in Table 1. Notably, the patient's

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Table 1. Laboratory results on morning of admission

Result	Value	Reference range
Glucose	230 mg/dL (12.7 mmol/L)	65-99 mg/dL (3.6-5.5 mmol/L)
Blood urea nitrogen	26 mg/dL (9.28 mmol/L)	8-20 mg/dL (2.85-7.14 mmol/L)
Creatinine	1.89 mg/dL (167 μmol/L)	.60-1.20 mg/dL (53-106 μmol/L)
eGFR	29 mL/min/1.73 m^2	>60 mL/min/1.73 m^2
Sodium	119 mEq/L (119 mmol/L)	136-145 mEq/L (136-145 mmol/L)
Potassium	4.2 mEq/L (4.2 mmol/L)	3.5-5.2 mEq/L (3.5-5.2 mmol/L)
Carbon dioxide	19 mEq/L (19 mmol/L)	22-32 mEq/L (22-32 mmol/L)
Osmolality	260 mOsm/kg (260 mmol/kg)	275-295 mOsm/kg (275-295 mmol/kg)
Alanine aminotransferase	64 U/L (1.07 μkat/L)	0-33 U/L (0-0.55 μkat/L)
Aspartate aminotransferase	58 U/L (0.97 μkat/L)	0-30 U/L (0-0.50 μkat/L)
Amylase	42 U/L (0.70 μkat/L)	0-105 U/L (0-1.75 μkat/L)
Lipase	22 U/L (0.37 μkat/L)	13-60 U/L (0.22-1.00 μkat/L)
Triglycerides	19 716 mg/dL (222.6 mmol/L)	<150 mg/dL (<1.7 mmol/L)
White blood cell	7.9 K/mm^3 (7.9 ×10^9/L)	4.0-11.0 K/mm^3 (4.0-11.0 ×10^9/L)
Hemoglobin	8.0 g/dL (80 g/L)	12.3-15.3 g/dL (123-153 g/L)
Platelets	279 K/mm^3 (279 ×10^9/L)	150-450 K/mm^3 (150-450 ×10^9/L)
Hemoglobin A1c	9.3%	4.7%-6.4%

hemoglobin A1c was 9.3% (reference range, < 6.5%), which was elevated from a baseline of 5.4% collected 1 year prior. Unfortunately, there were no additional hemoglobin A1c or fasting glucose trends between these 2 measurements. On admission, the patient remained asymptomatic and denied dyspnea, nausea, vomiting, or abdominal pain. On physical examination, the patient was afebrile, normotensive with blood pressure of 129/81 mmHg, tachycardic with heart rate 116 beats per minute, and had an oxygen saturation of 96%. Her weight was 58.1 kg and her body mass index was 21.3 kg/m^2.

Treatment

The patient was initiated on an insulin infusion at 0.3 units/kg/hour along with dextrose containing fluids to maintain normoglycemia with goal glucose 140 to 180 mg/dL for a total of 4 days. She was kept NPO for approximately 24 hours after admission, then transitioned to a low-fat diet with daily fat intake of < 50 grams per day. Plasmapheresis was not initiated, as there was no evidence of pancreatitis or features of end organ damage. Rosuvastatin was modestly increased to a dosage of 10 mg daily due to drug-drug interactions. She was also initiated on oral triglyceride-lowering medications fenofibrate 145 mg daily and prescription strength omega-3 acid ethyl esters 2 g twice daily. Review of her sirolimus drug level monitoring revealed that her levels were within therapeutic range or below for the 6 months prior to admission and were checked weekly during that time frame. Sirolimus was discontinued, and immunosuppression replaced with a tacrolimus challenge started prior to discharge.

Outcome and Follow-Up

By the time of discharge on hospital day 5, the triglyceride level had improved to 1772 mg/dL (20 mmol/L) from the peak of 19 716 mg/dL (222.6 mmol/L). She remained asymptomatic during her hospital stay. Hyponatremia was attributed to pseudohyponatremia from hypertriglyceridemia, and this improved as the triglyceride level trended downward. As she had no known history of chronic kidney disease (CKD), her acute kidney injury resolved and renal function returned to baseline prior to discharge. She was discharged with nutritional counseling to maintain a low-fat diet of less than 15 grams of total fat per day. Medication discharge therapy included fenofibrate 145 mg daily, rosuvastatin 10 mg daily, and prescription omega-3 acid ethyl esters 2 grams twice daily. She was counseled to return to the emergency room if she developed any symptoms of pancreatitis.

Her home medical regimen for diabetes management prior to admission included empagliflozin 10 mg daily, metformin 1000 twice daily, and insulin glargine 16 units nightly. Given that her hemoglobin A1c during admission was elevated, insulin aspart 5 units 3 times daily before meals was added to her home regimen on discharge.

The patient's triglyceride level was rechecked 2 weeks after discharge and had improved to 670 mg/dL (7.56 mmol/L). Sirolimus was not resumed and tacrolimus was continued for GvHD prophylaxis instead.

Discussion

Hypertriglyceridemia is often the result of secondary factors, and the Endocrine Society advises clinicians to search for and address reversible causes [4]. In this case, the patient had multiple secondary factors causing her severe hypertriglyceridemia, including the medication sirolimus and uncontrolled type 2 diabetes mellitus [5]. Although multifactorial, it was suspected that sirolimus was the primary driver of this patient's hypertriglyceridemia, which is evidenced by the sustained improvement in triglyceride levels after the medication was discontinued.

Sirolimus-induced hypertriglyceridemia is a well-known side effect of the medication [5-7]. While it is known that sirolimus is an mTOR inhibitor, there is an incomplete understanding of

the mechanisms by which sirolimus produces lipid abnormalities and multiple mechanisms have been described [2, 5, 8-12]. Evidence from genetically modified mTOR complex 1 (mTORC1) knockout mice has suggested mTOR is critical for regulating lipid metabolism and its absence results in enhanced, unregulated lipolysis [13]. Study of renal transplant recipients being treated with sirolimus similarly showed increased production of free fatty acids following the administration sirolimus [10]. Study of hepatic-specific mTORC1 knockout mice failed to produce comparable results, suggesting adipocyte, rather than hepatocellular, free fatty acid production is primarily contributing to sirolimus-induced hypertriglyceridemia [14]. Diminished activity of lipoprotein lipase (LPL) has also been implicated in sirolimus-induced hypertriglyceridemia, as sirolimus has been shown to decrease levels of apo-C III, a known inhibitor of LPL [10, 15].

Post-transplant diabetes is common following transplantation, and many immunosuppressive medications can potentiate insulin resistance and compromise glycemic control [16, 17]. Sirolimus has been associated with beta cell dysfunction, which could worsen dyslipidemias. In vitro study of human and murine beta cells has shown sirolimus depletes intracellular calcium stores and promotes mitochondrial dysfunction and apoptosis [18]. Insulin is an inhibitor of hormone-sensitive lipase and potentially counteracts the lipolysis-enhancing effect of sirolimus [19]. Transplant recipients with diabetes mellitus may be particularly at risk for sirolimus-induced dyslipidemias, and murine studies have suggested that co-treatment with metformin can prevent hypertriglyceridemia through its insulin sensitizing properties [11]. In addition to diabetes, CKD, which is associated with decreased free fatty acid metabolism through inhibition of LPL and the LDL-receptor, may also potentiate sirolimus-induced dyslipidemias [20, 21]. However, further study is needed to elucidate the impact of CKD.

Evidence suggests that sirolimus-induced hypertriglyceridemia is dose dependent [2, 8, 10]. Therefore, minimizing sirolimus doses may help to reduce hypertriglyceridemia if it develops. The half-life of sirolimus is roughly 63 hours, but its effects on triglycerides may linger for an additional 1 to 2 months following discontinuation [10, 22]. The reported incidence of hypertriglyceridemia in patients treated with mTOR inhibitors is 21% to 57% [23]. The FDA recommends that any patient treated with sirolimus should have regular monitoring for hyperlipidemia and that lipid-lowering therapy, including dietary and exercise modifications, should be initiated if necessary. While modest elevations in triglyceride levels are well documented in patients treated with sirolimus, extreme elevations, such as the initial blood level seen in this case, are not. Other case reports have documented lower levels of sirolimus-induced hypertriglyceridemia (3,000-10,000 mg/dL) resulting in complications, such as pancreatitis and hyperviscosity syndrome, that required treatment with plasmapheresis [3, 24-26]. For example, in one case report, a patient on sirolimus for immunosuppression after solid organ transplant required treatment with plasmapheresis for a triglyceride level of 9360 mg/dL (105.7 mmol/L) because he was symptomatic with central nervous system and cardiac manifestations [24]. In another case report, a patient required plasmapheresis for hyperviscosity syndrome attributed to hypertriglyceridemia related to sirolimus treatment for GvHD [25]. There was one recent case report of acute pancreatitis attributed to sirolimus-induced hypertriglyceridemia [26]. In contrast, the patient presented in this case was largely asymptomatic and did not require plasmapheresis.

There was concern regarding the accuracy of the triglyceride assay at the extreme value of 19 716 mg/dL (222.6 mmol/L) in this case. Our clinical laboratory utilizes the commercially available Beckman-Coulter triglyceride assay. Like other triglyceride assays, the Beckman-Coulter assay utilizes a multistep reaction that hydrolyzes triglycerides to glycerol, which is then converted to a chromophore that can be measured with quantitative spectrophotometry [27]. The assay has an analytical range of 10 to 1000 mg/dL, and samples above this range require manual dilution in normal saline. Triglycerides are poorly soluble in water, which raises the concern that error may be introduced during serial dilution of a potentially nonhomogenous sample [28]. It has also been suggested that highly lipemic samples can produce optical interference during spectrophotometry [27, 28]. Regardless, this patient's measured triglyceride value showed a relatively consistent downward trend upon discontinuation of sirolimus and the initiation of therapeutic interventions, suggesting that this assay must retain a clinically significant degree of reproducibility when measuring values above the analytical range. The patient also self-reported that her blood looked like "crème" at the time of the original blood draw, which further supported the severe triglyceride readings.

There is limited high-quality evidence to guide the management of severe hypertriglyceridemia in the inpatient setting. Most of the available evidence is from studying patients with hypertriglyceridemia-induced pancreatitis rather than severe hypertriglyceridemia alone [29]. One randomized controlled trial comparing insulin to plasmapheresis for the treatment of hypertriglyceridemia-induced pancreatitis found that while plasmapheresis lowered triglyceride levels more rapidly, its use was associated with a higher incidence of organ failure [30]. In this case, the patient showed evidence of acute renal insufficiency but did not display any signs or symptoms of pancreatitis or any other worrisome features. As a result, plasmapheresis was deferred, despite our facility possessing the capability to perform the procedure. This case represents the successful use of a conservative treatment strategy for very severe hypertriglyceridemia with end organ damage. It remains unclear whether end organ damage alone should necessitate the use of plasmapheresis or if its therapeutic benefit is primarily derived from mitigating the systemic inflammatory response of acute pancreatitis. Further research is needed to delineate the role of plasmapheresis in severe hypertriglyceridemia in patients with *and* without pancreatitis.

Learning Points

- Hypertriglyceridemia is an important side effect related to treatment with the immunosuppressive agent sirolimus.
- Patients treated with sirolimus need regular monitoring of blood lipid levels and prompt intervention is necessary if an abnormality is found.
- Sirolimus can rarely cause severe asymptomatic hypertriglyceridemia, and in some cases, close monitoring in the intensive care unit is necessary to prevent serious complications.

Contributors

S.S. and K.C. were involved in the diagnosis and management of this patient, in addition to contributing to all sections of the manuscript. J.S. helped to write the discussion section. J.C.

helped to write the case presentation and diagnostic assessment section. J.A. helped to write the introduction section. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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