Case Report

Hypertriglyceridemia Causing Continuous Renal Replacement Therapy Dysfunction in a Patient with End-stage Liver Disease

Abstract

Hypertriglyceridemia is infrequently reported as a cause of suboptimal delivery of dialytic therapy in critically ill patients. We report the case of a critically ill liver transplant patient in the Intensive Care Unit who was found to have recurrent filter clotting during continuous renal replacement therapy (CRRT). The patient had increased serum triglycerides (TGs), which was identified approximately 2 weeks into hospitalization and initially believed to be due to prolonged propofol use. The patient's elevated TGs ultimately caused her blood to become lipemic, causing the dialytic circuit to become nonfunctional and placed the patient in imminent danger due to hyperkalemia and metabolic acidosis. Therapeutic plasma exchange was emergently used to lower TG levels, and renal replacement therapy was resumed without any other issues. The patient's persistent hypertriglyceridemia was attributed to a combination of adverse effect of medications and liver graft failure. The high TG level and abnormal liver functions improved after a repeat liver transplantation.

Keywords: *Continuous renal replacement therapy, dialysis, hypertriglyceridemia, liver transplant*

D. C. McLaughlin, D. C. Fang[1], B. A. Nolot[2], P. K. Guru

Departments of Critical Care and [1]Laboratory Medicine and Pathology, [2]Department of Nursing, Apheresis, Mayo Clinic, Florida, USA

Introduction

Continuous renal replacement therapy is the most commonly used form of renal supportive therapy in critically ill patients with acute renal failure.[1] The continuous nature of the therapy necessitates close monitoring for filter clotting, dislodgement of the dialysis catheter, hemolysis as potential blood loss, and electrolyte and acid–base abnormalities. The optimal solute clearance and proper functioning of the filter to achieve the desired therapeutic goal depend on multiple patient- and machine-related factors. Recently, we encountered a patient with extreme acute elevation of triglycerides (TGs) leading to frequent filter clotting and electrolyte imbalances. The exact mechanism of the acute rise of TG is unclear; however, we hypothesize the multifactorial cause due to concomitant use of propofol, cyclosporine, and underlying liver graft dysfunction.

Case Report

A 40-year-old female patient underwent liver transplantation in February 2016 for cirrhosis secondary to nonalcoholic steatohepatitis. The patient's additional comorbidities included hypertrophic cardiomyopathy managed by myomectomy in 2013, hypothyroidism on replacement, Type II diabetes mellitus (controlled, HbA1c 5.4 g/dl), and chronic kidney disease (baseline creatinine 1.2 mg/dl). Her immunosuppressive regimen in the immediate posttransplant period included tacrolimus, mycophenolic acid, and prednisone. In July 2016, a diagnosis of possible tacrolimus-related posterior reversible encephalopathy syndrome was made on the basis of clinical and radiologic findings, and her immunosuppression was changed to everolimus-based therapy. In October 2016, the patient underwent liver biopsy, which showed severe acute cellular rejection and was managed with high-dose steroids and thymoglobulin. The patient was transitioned to cyclosporine for persistent clinical evidence of rejection.

In November 2016, the patient was admitted to Intensive Care Unit (ICU) for the management of adult respiratory distress syndrome and septic shock related to *Legionella pneumophila* pneumonia. Her ICU course was complicated by respiratory failure, including failed extubation, requiring more than 10 days of ventilatory support, acute on chronic renal failure requiring CRRT, and worsening graft

Address for correspondence:
Dr. D. C. McLaughlin, Department of Critical Care, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA.
E-mail: mclaughlin.diane@mayo.edu

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dysfunction requiring up-titration of immunosuppression. Propofol was used as the primary sedating agent along with opioids. She was continued on cyclosporine, which required aggressive up-titration due to subtherapeutic levels.

On day 13 of her ICU stay, the patient had issues with her CRRT filter clotting multiple times during the day shift, despite heparin infusion at set rate of 500 units/h with an activated partial thromboplastin time (aPTT) goal of 50–70 s. The anticoagulation was initially ordered for right radial artery thrombus but had helped prevent the patient's CRRT circuit from clotting until day 13. The patient's aPTT was stable between 48 s and 64 s and was therapeutic at the time of clotting on day 13. Due to the change in patient's response to propofol, in addition to the continuous 5 days of propofol infusion, a TG level was obtained and was found to be 3745 mg/dl. Six months prior, the patient's TG level was 156 mg/dl. Her filter and circuits were changed and propofol was discontinued. That evening, the patient had further clotting, and the bedside nurse noticed a change in color of the line and filter [Figure 1]. Her repeat TG level was found to be 3865 mg/dl with normal lipase level. She was also found to have rising serum potassium of 5.8 mmol/L, serum bicarbonate of 20 mmol/L, and pH of 7.2. Adjunctive therapy with intravenous insulin at the rate of 0.1 units/kg/h and heparin at the rate of 500 units/h was initiated, and the patient was planned for emergent therapeutic plasma exchange (TPE). TPE was initiated within 6 h of nonfunctioning CRRT circuits through the patient's hemodialysis vascular access [Figure 2] using 5% albumin as replacement fluid and a citrate anticoagulant to whole blood ratio of 10. CRRT was able to be resumed with a new filter following TPE and her acid–base balance and electrolytes normalized. She remained on heparin infusion at 500 units/h.

Despite being off of propofol in the days after, the patient continued to have elevated TG levels up to 708 mg/dl, with increasing serum lipase levels (peaking at 240 mg/dl) and complaints of abdominal pain concerning for pancreatitis. She subsequently required two additional TPE sessions, on day 16 (TG decreased from 708 to 186 mg/dl) and day 21 (TG decreased from 499 to 212 mg/dl) to maintain goal TGs <500 mg/dl. The patient was continued on cyclosporine with escalating doses due to persistent subtherapeutic serum levels and liver graft dysfunction. Both cyclosporine and underlying liver dysfunction were suspected as the culprits for her recurrent and persistent hypertriglyceridemia. She was also started on oral fibrate and fish oil as preventive measures to avoid pancreatitis. Approximately 8 weeks after the patient first required TPE for hypertriglyceridemia, she underwent combined liver–kidney transplant. She received propofol for sedation intraoperatively and remained on cyclosporine postoperatively. Immediately following the second transplant, her TGs level was 154 mg/dl, the lowest it had been since her baseline level months prior. Her TGs level has remained well-controlled despite continued use of cyclosporine.

Discussion

Elevated serum TG as a cause of CRRT circuit malfunction is sparsely reported. This is the fifth reported case of hypertriglyceridemia causing nonfunction of CRRT and electrolyte imbalance.[2-5] Table 1 summarizes the reported cases in the literature including the current case. Of note, three out of four cases reported previously occurred in transplant patients, similar to our patient, and receiving immunosuppression with a calcineurin inhibitor. All patients received infusion of an intravenous lipid emulsion. This is only the second case that required plasma exchange to rapidly decrease TGs and is the first case to demonstrate the success of TPE in maintaining CRRT function. Of the two patients who required plasma exchange, this is the first patient to survive despite having the highest reported TGs level. The effect of TPE on maintaining CRRT function could not be well assessed in the other case because the family withdrew support after 2 h of TPE.

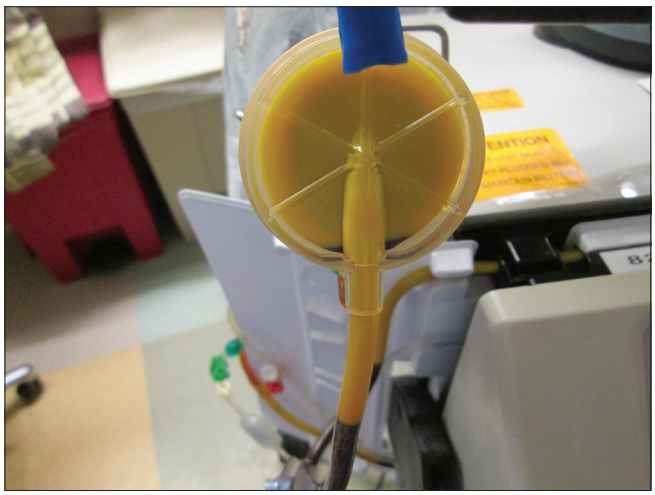

Figure 1: A clogged continuous renal replacement therapy filter secondary to lipemic blood resultant from hypertriglyceridemia

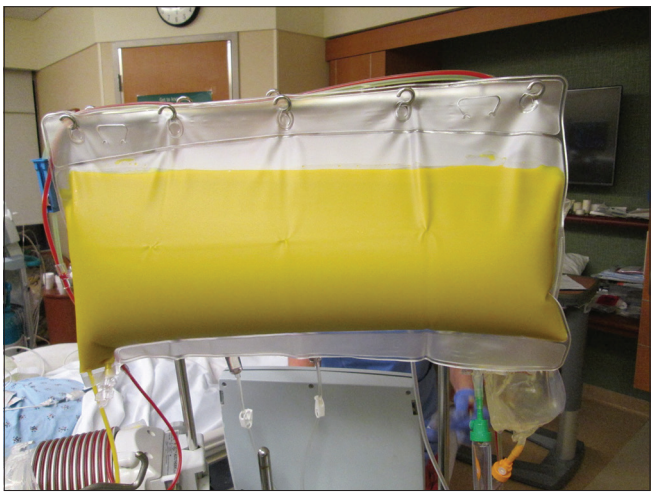

Figure 2: Plasma removed from the patient's blood during emergent apheresis treatment

Table 1: List of cases described in literature

Author/year	Age/sex	Clinical setting	Observations	Triglyceride level	Suspected agents	Interventions	Outcomes
Kazory, A. *et al*., 2008	34-year-old-male	Bone marrow transplant with pneumonia and septic shock	Filter clots every 2-6 h Lipemic blood	1743 mg/dl	Intralipid 20% emulsion	Discontinuation of intralipids	CRRT resumption
Rodriguez, B *et al*., 2014	26-year-old-male	Kidney transplant patients with drug overdose	Recurrent clots Lipemic blood	Not reported	Intralipid emulsion	Discontinuation of intralipids Therapeutic plasma exchange	Patient expired
Bassi, E *et al*., 2014	31-year-old-male	Motor vehicle accident with multiorgan failure	Recurrent clots Greasy blood	1772 mg/dl	Propofol	Discontinuation of Propofol	CRRT resumption
Kakajiwala, A *et al*., 2016	23 m/o male	Multivisceral transplant with sepsis	Recurrent clots Lipemic blood	988 mg/dl	Intralipid emulsion	Discontinuation of intralipids	CRRT resumption
Current case, 2017	40-year-old-female	Liver transplant with sepsis and ARDS	Recurrent clots Lipemic blood	3865 mg/dl	Propofol, cyclosporine and graft dysfunction	Discontinuation of propofol Therapeutic plasma exchange	CRRT resumption

CRRT: Continuous renal replacement therapy, ARDS: Adult respiratory distress syndrome

Hypertriglyceridemia in critically ill patients is often multifactorial. In the critical care practice, the most commonly cited agents responsible for elevated TGs are propofol and use of fat emulsion as part of total parenteral therapy. Besides familial predisposition and obesity, patients with pancreatitis, liver dysfunction, sepsis, hemolysis, and use of calcineurin inhibitor and antiretrovirals are at risk for the development of high TGs level.[6,7] Combination of increased synthesis and decreased catabolism is the primary mechanism responsible for the elevated TG levels. Our patient had several comorbidities, such as diabetes mellitus II, hypothyroidism, acute on chronic renal insufficiency, and liver graft failure that increased her risk of hypertriglyceridemia. The patient's hypertriglyceridemia initially worsened and then persisted, despite the discontinuation of propofol, leading to suspicion that cyclosporine and graft dysfunction were the likely underlying cause of TG elevation, with propofol contributing to the acute elevation. The normalization of TGs immediately following transplant and persistently normal levels of cyclosporine also suggests the importance of the role of the failed liver graft.

The exact mechanisms of CRRT circuit malfunction in cases of hypertriglyceridemia are unknown. Hyperviscosity due to elevated TG level, hypercoagulability due to elevated coagulation factors, mechanical obstruction of the hemofilter fibers by the lipid droplets, and altered fibrin structures are some of the factors incriminated for clotting and the shortened life span of the CRRT circuit.[4,8,9]

Elevated serum TG level is a well-known risk factor for cardiovascular disease. The most feared complication of extreme elevation of serum TGs, such as in our patient, is acute pancreatitis. The risk of developing acute pancreatitis is approximately 5% with TG >1000 mg/dl and 10%–20% with TG >2000 mg/dl.[10] A level below 500 mg/dl is thought to be a safer limit to prevent acute pancreatitis.[11] Therapy is primarily aimed at discontinuation of the inciting agents and prevention of acute pancreatitis and other systemic inflammations. TPE has been recommended as an initial therapeutic strategy in patients with extreme elevation of TG level.[12] TPE is useful in significantly decreasing serum TG levels as a short-term approach. However, perhaps due to the limited scope of reports in the literature, TPE is not currently included in the management recommendations of the 2012 Endocrine Society Clinical Practice Guidelines for hypertriglyceridemic pancreatitis[13] and is currently only a Category III (i.e., optimum role of apheresis not established) indication for TPE in the 2016 American Society for Apheresis guidelines.[14] Intravenous insulin with close monitoring of blood sugar is recommended as adjunctive therapy or in the absence of apheresis, in addition to antihyperlipidemic therapy such as fibrates. The role of heparin in management remains controversial.[15,16]

Conclusion

Hypertriglyceridemia in critically ill patients receiving immunosuppressive therapy is of multifactorial origin. These patients may be more prone to developing hypertriglyceridemia-related morbidity such as CRRT filter malfunctions and risk of superadded pancreatitis. Both

clinical hypervigilance and serial monitoring in at risk patients are necessary to avoid potential catastrophe. TPE remains a therapeutic option to rapidly lower the TG levels to decrease the risks pending the definitive treatment of the condition.

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Conflicts of interest

There are no conflicts of interest.

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