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Case Report

Hypertriglyceridemia-Induced Pancreatitis: A Case Report and Literature Review

Maarten Bulterys, MD; Melvin Willems, MD*; Agnes Meersman, MD

Department of Emergency Medicine, Jessa Hospital Hasselt, Stadsomvaart 11, 3500 Hasselt, Belgium

Corresponding author
Melvin Willems, MD
Department of Emergency Medicine, Jessa Hospital Hasselt, Stadsomvaart 11, 3500 Hasselt, Belgium; E-mail: melvin.willems@jessazh.be

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ABSTRACT

Hypertriglyceridemia is the third most common cause of acute pancreatitis. It typically occurs in patients with an underlying disorder of lipoprotein metabolism and the presence of a secondary condition. The risk and severity of acute pancreatitis increase with increasing levels of serum triglycerides. This case presents an atypical clinical presentation and one of the highest serum triglyceride levels ever reported. The early recognition of hypertriglyceridemia-induced acute pancreatitis can be complex due to lab interferences but is essential for appropriate management and prevention of recurrence. There is currently no approved treatment guideline available for managing hypertriglyceridemia-induced pancreatitis. Therefore, a literature review was performed. The initial management of hypertriglyceridemia-induced acute pancreatitis includes the treatment of acute pancreatitis with moderate fluid resuscitation, pain control, and nutritional support. The goal is to prevent necrotizing pancreatitis and organ failure by reducing serum triglyceride levels. Specific acute treatment options include insulin therapy, heparin therapy, plasmapheresis, and hemofiltration. Individual therapy should be tailored to each patient and their clinical condition. Diet and lifestyle modification, along with hypolipidemic drugs, prevent further episodes.

Keywords
Hypertriglyceridemia; Pancreatitis; Treatment; Hypolipidemic drugs; Diet and lifestyle; Metabolism.

INTRODUCTION

Acute pancreatitis (AP) is a life-threatening acute inflammatory process of the pancreas characterized by abdominal pain and elevated pancreatic enzymes. Gallstones and chronic alcohol abuse remain the leading causes of AP. Hypertriglyceridemia (HTG) is the third most common cause of acute pancreatitis.

Although hypertriglyceridemia only occurs in 9% of acute pancreatitis cases, patients with severe hypertriglyceridemia have a high incidence of acute pancreatitis (14%).[1]

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines categorize triglyceride (TG) levels as normal (<150 mg/dL), borderline high (150-199 mg/dL), high (200-499 mg/dL, and very high (>500 mg/dL).[2] The threshold level of fasting triglyceride levels of 150 mg/dL (1.7 mmol/L) is accepted by all medical societies.

The Endocrine Society has proposed the following criteria to classify serum TG level: normal (<150 mg/dL), mild HTG (150-199 mg/dL), moderate HTG (200-999 mg/dL), severe HTG (1000-1999 mg/dL), and very severe HTG (≥2000 mg/dL).[3] These definitions differ from the NCEP ATP III criteria to recognize the risk of pancreatitis associated with severe and very severe HTG (Table 1).

Table 1. *Classification of Triglycerides*[3]

NCEP ATP III			The Endocrine Society		
Normal	<150 mg/dL	<1.7 mmol/L	Normal	<150 mg/dL	<1.7 mmol/L
Borderline-high triglycerides	150-199 mg/dL	1.7-2.3 mmol/L	Mild hypertriglyceridemia	150-199 mg/dL	1.7-2.3 mmol/L
High triglycerides	200-499 mg/dL	2.3-5.6 mmol/L	Moderate hypertriglyceridemia	200-999 mg/dL	2.3-11.2 mmol/L
Very high triglycerides	≥500 mg/dL	≥5.6 mmol/L	Severe hypertriglyceridemia	1000-1999 mg/dL	11.2-22.4 mmol/L
			Very severe hypertriglyceridemia	≥2000 mg/dL	≥22.4 mmol/L

The etiology of hypertriglyceridemia-induced pancreatitis (HTGP) is divided into two categories: primary (genetic) and secondary disorders of lipoprotein metabolism. Pancreatitis secondary to HTG is typically seen in the presence of one or more secondary factors (e.g., uncontrolled diabetes, alcoholism, medications, pregnancy) in patients with an underlying common genetic abnormality of lipoprotein metabolism (i.e., familial combined hyperlipidemia or familial HTG). The mechanisms by which HTG causes acute pancreatitis fall outside the scope of this article.

A diagnosis of acute pancreatitis requires two out of three criteria: (1) abdominal pain consistent with pancreatitis, (2) a serum amylase or lipase three or more times the upper limit of normal, and (3) findings consistent with pancreatitis on cross-sectional abdominal imaging.[4]

No evidence-based definition of HTGP exists.[5] The diagnosis of HTGP is based on the following considerations: severely elevated TG level (at least >500 mg/dL, generally >1000 mg/dL), no alternative cause of pancreatitis based on history, imaging, and laboratory studies, and the presence of diabetes, pregnancy, obesity, or chronic hyperlipidemia supports this diagnosis.[6] The consensus in the literature seems to be that in a patient with pancreatitis, a triglyceride level >1000 mg/dL makes hypertriglyceridemia the likely cause.

Patients with higher TG levels appear to have a more severe hospital course with a higher incidence of complications (35-69%) and organ failure (20-35%). There is also a notification of prolonged hospitalization and higher mortality.[7] Twenty percent of the patients with severe hypertriglyceridemia experience at least one attack of AP.[8]

In the following case report, we discuss a patient presenting in the emergency department with very severe hypertriglyceridemia causing acute pancreatitis. The atypical clinical presentation and the normal serum lipase are interesting in this case, making the initial diagnosis difficult.

Stuart Blythe holds the Guinness world record for 'Highest triglyceride level'. On June 5, 2021, he had a triglyceride level of 13292 mg/dL. Our patient breaks this record by over 3000 mg/dL.[9] The discussion afterward will focus on the different treatment options.

CASE REPORT

A 42-year-old woman presented to the emergency department (ED) with an acute onset of sharp left thoracal pain. She had a loss of appetite but no other complaints. Her past medical history showed a cholecystectomy because of cholecystolithiasis (19 years ago). The patient had diabetes (non-insulin-dependent diabetes mellitus (NIDDM), first diagnosis 13 years ago), for which she was being treated with metformin 850 mg twice a day. The endocrinologist started atorvastatin 20 mg once a day three months ago because of a mixed dyslipidemia.

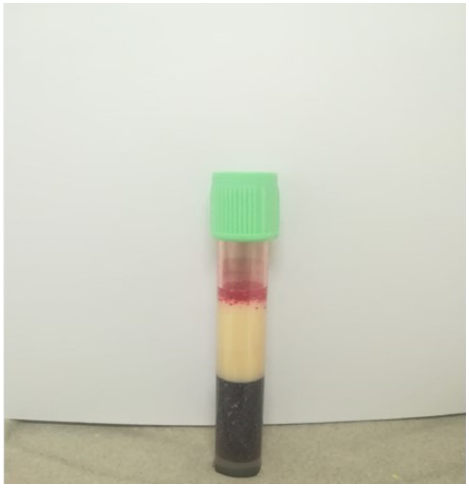
The patient was obese with a body mass index (BMI) of 29 kg/m^2, being 160 cm tall and weighing 75 kg, and having a body fat mass percentage of 47.5%. There was a fatty, unbalanced diet with lots of carbohydrates. Blood pressure was 181/109 mmHg. Electrocardiogram (ECG) showed a regular sinus rhythm of 114 bpm without repolarization abnormalities.

A physical exam revealed tenderness in the left upper quadrant. She had a chronic cough, her being an active smoker with 20 packyears. A corona virus disease polymerase chain reaction (COVID PCR) test was negative.

Lab biochemical parameters showed CRP 87.6 mg/L (reference 5 mg/L), leucocytes 19.05×10^9 /L (reference 4-10×10^9 /L) with 76% neutrophils, glucose 317 mg/dL (reference 55-100 mg/dL) and HbA1c 13.7% (reference 4.0-6.0%). The troponin level was normal.

The serum triglyceride (TG) level was higher than >4425 mg/dL (reference 150 mg/dL). HTG caused the serum to appear milky (Figure 1). Many other lab results, such as natrium, chloride, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and lipase, were interfered with. Serum lipase at presentation was 52 U/L (reference 13-60 U/L).

Figure 1. *Blood Sample from the Patient*



The triglycerides in the serum caused a milky coloration to the blood, leading to falsely normal lipase levels.

The clinical biologist was consulted to discuss the lab interferences. He performed lab testing after manual dilution 1/20 with NaCl 0.9%. This showed a serum TG level of 16616 mg/dL. Serum lipase was measured using the same dilution of 1/20 and showed <60 U/L (reference 13-60 U/L). The electrolyte exclusion effect on the lab testing machines (indirect potentiometry) explained pseudohyponatremia and hypochloremia. It was recommended that an arterial blood sample analysis be performed to interpret the electrolytes (direct potentiometry) correctly.

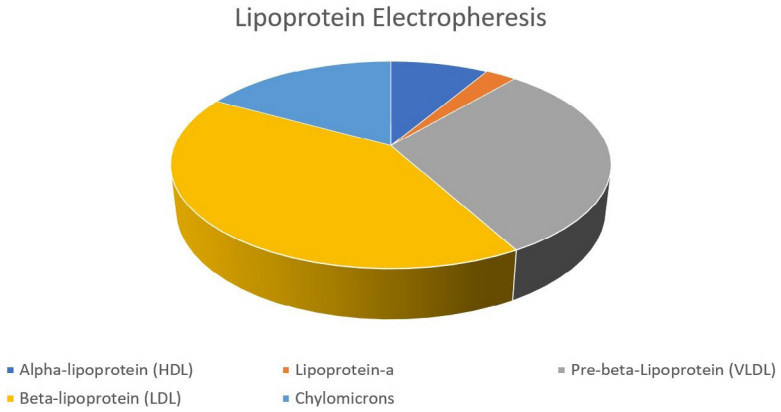
A computed tomography (CT) scan of the thorax showed no abnormal findings, and a CT scan of the abdomen showed characteristic findings of acute pancreatitis, mainly in the tail. Furthermore, there was no evidence of necrosis. No collections, no vascular complications, and no liver lesions were found, although there was important liver steatosis.

In the ED, the diagnosis of hypertriglyceridemia-induced acute pancreatitis was made, with uncontrolled diabetes being a critical trigger. The patient was treated with intravenous fluids and adequate analgesia. She was given an intravenous insulin infusion and intravenous potassium substitution. A risk stratification was made using the Apache II Score, widely used to predict the mortality of intensive care unit (ICU) patients. With three points, the risk was assessed as low. Plasmapheresis was not performed because of the low-risk assessment. The patient was admitted to the endocrinology ward.

A focused oral lipid-lowering therapy was initiated with atorvastatin 80 mg once a day and fenofibrate 267 mg once a day. Lab testing 24 hours after admittance showed a serum TG level decreased from 16616 mg/dL to 5702 mg/dL. In the following days, there was a clinical and biochemical remission. The patient was discharged after eight days of observation. Lifestyle counseling was provided, and regular follow-up was planned.

A lipoprotein electrophoresis showed mainly chylomicron and very low-density lipoproteins (VLDL) (Figure 2). Hyperlipidemia was classified as a type five phenotype in the Fredrickson Classification of Hyperlipidemia.

Figure 2. *The Lipoprotein Electrophoresis*



DISCUSSION

As mentioned in the presented case, hypertriglyceridemia-induced lipid interference may interfere with specific lab results.

Serum triglyceride levels >500 mg/dL may cause a falsely normal lipase level.[10] The lipase level at presentation could be normal and should be interpreted cautiously due to calorimetric interference of lipemic serum. Repeat lipase levels should be performed with severe dilutions.[11] In most cases, lipemia can be removed from the sample, and measurement can be done in a transparent sample without interference.

Early aggressive hydration is widely recommended for managing acute pancreatitis, but evidence for this practice is limited. A randomized trial involving patients with AP concluded that the early treatment with aggressive fluid resuscitation compared with moderate fluid resuscitation led to a higher-risk volume overload and did not improve clinical outcomes.[12]

The treatment of HTGP is an ongoing source of discussion. The following paragraphs will discuss different treatment options and their current evidence.

Insulin lowers TG levels by 50-75% over two to three days and appears to be a safe and effective therapy, even in non-diabetic patients.[6] Insulin may rapidly reduce free fatty acid levels *via* mechanisms independent of triglyceride levels.[13] It is unclear when to stop the insulin infusion; many authors advise continuing until the triglyceride level is <1000 mg/dL.

Frequent blood glucose measurements should be performed to avoid undetected hypoglycemia, and if needed, dextrose infusion should be started to maintain euglycemia.

Heparin has also been used in management alone or combination with insulin therapy, though its role is controversial. The decrease in triglycerides is transient, and there is a concern about rebound hypertriglyceridemia and the risk of hemorrhage into the pancreas during acute pancreatitis on a continuous heparin infusion.

Plasmapheresis should be considered in patients with severe HTG-AP with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥8 since mortality rates are high and reported to be around 10-39%.[14] High-volume hemofiltration (HVHF) should be considered in patients with

severe hypertriglyceridemia-acute pancreatitis (HTG-AP) with an APACHE II score >15 where plasmapheresis is not available.[15]

A single plasmapheresis session has been reported to lower triglyceride levels by 50-80%.[14] Plasmapheresis drastically lowers lipid levels within hours compared to conservative therapy, which usually takes days. However, this requires central venous access, which is costly and not easily available.

Plasmapheresis does not appear to improve outcomes in uncomplicated cases of HTGP.[16]

Ipe et al. advise plasmapheresis in patients with HTGP with worrisome features (hypocalcemia, lactic acidosis, signs of worsening systemic inflammation or organ dysfunction, and/or multi-organ failure), referring to the critical updates in the 7th edition of the American Society for Apheresis (ASFA) guidelines.[17]

In one large series of patients with HTGP undergoing plasmapheresis, anticoagulation with heparin was associated with a 10-fold higher mortality compared to patients treated with citrate (11% *vs*. 1%).[14]

The ASFA considers plasmapheresis's use in treating HTG-AP a grade 2C recommendation (the individualized decision is necessary, the unclear role of therapy).[18] There is no consensus on the treatment's endpoint. Due to the lack of randomized and controlled trials, it is currently unknown if plasmapheresis may improve morbidity and mortality in the clinical setting of HTG-AP.

There are no comparison studies evaluating insulin *versus* conservative therapy. One randomized controlled trial (RCT) has been performed to compare plasmapheresis *versus* insulin. This was a prospective RCT involving 66 patients with HTGP who were randomized to receive plasmapheresis *versus* insulin.

They concluded that plasmapheresis lowers TG levels more efficiently than insulin therapy but is not superior in clinical outcomes and costs.[19] Published data suggest that early removal of TG and toxic free fatty acids (FFA) may be advantageous. However, high-quality evidence is still missing. FFA are probably essential, but we cannot measure them in routine clinical practice. ELEFANT is a randomized, controlled, multicenter, international trial testing the concept that early elimination of TGs and FFAs from the blood is beneficial in HTG-AP.[20] The study will be organized between February 2020 and December 2025.

The goal of drug treatment of HTG is to reduce the risk of pancreatitis in patients with severe hypertriglyceridemia and cardiovascular disease in those with moderate hypertriglyceridemia. Suppose an adult patient with moderate hypertriglyceridemia has poorly controlled significant risk factors for atherosclerotic cardiovascular disease (ASCVD) and a 10-year risk of ASCVD ≥7.5% by the pooled cohort equations (PCE). In that case, initiating or intensifying statin therapy is reasonable.[21] The Task Force of the Endocrine Society Clinical Practice Guideline recommends that statins not be used as a monotherapy for severe or very severe hypertriglyceridemia.[3]

ATP-3 guidelines conclude that fibrates remain the drug of choice for severe HTG (TG >500 mg/dL) with niacin as adjunctive therapy.[2] Fibrates are the most effective in lowering TG levels in all antihyperlipidemic drugs.

The 2018 American Heart Association (AHA)/ American College of Cardiology (ACC)/multi-society cholesterol guidelines recommend that if triglycerides are persistently elevated or increasing, it is reasonable to further reduce triglycerides by the addition of prescription omega-3 fatty acids and, if necessary, to prevent acute pancreatitis, fibrate therapy.[21]

The 2019 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias recommend considering the use of TG-lowering drugs in high-risk patients with TG >200 mg/dL when lifestyle measures fail to lower TG levels.[22]

CONCLUSION

Hypertriglyceridemia (HTG) is an important but underestimated cause of acute pancreatitis (AP) and recurrent acute pancreatitis. The prompt recognition of hypertriglyceridemia in acute pancreatitis is essential in initial and long-term management. The presented case is a reminder that measuring a triglyceride level should be considered in all patients suspected of pancreatitis. Currently, there is no approved treatment guideline available for the management of HTGP. Therapy should be targeted towards the concomitant disorder. Diabetic patients should be treated with intravenous insulin infusions to obtain and maintain euglycemia rapidly. Insulin lowers triglyceride levels and is a safe and effective therapy, even in non-diabetic patients. However, it is unclear when to stop the insulin infusion; many authors advise continuing until the triglyceride level is <1000 mg/dL. Insulin infusion is safer, more easily initiated immediately, and probably clinically more effective than plasmapheresis. Plasmapheresis is still experimental, and better-designed studies are needed to clarify its role in the management of HTGP. Insulin may be used in mild HTG-AP, and plasmapheresis should be considered only for severe HTG-AP. Fibrates are the most effective in lowering triglyceride levels in all antihyperlipidemic drugs. Non-pharmacological treatment involves lifestyle modifications such as diet, exercise, weight reduction, limiting alcohol intake, and smoking cessation.

INSTITUTIONAL BOARD PERMISSION

This study has been approved by the Institutional Review Board (IRB).

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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