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Case report

Acute Pancreatitis Secondary to Hypertriglyceridemia: Case Report

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Abstract

Acute pancreatitis is characterized by a reversible inflammatory process affecting the pancreas. The most common causes include biliary tract obstruction and alcohol consumption. However, between 4% and 10% of cases are linked to hypertriglyceridemia, with serum triglyceride levels exceeding 1,000 mg/dL. While the exact pathophysiology remains unclear, prevailing hypotheses suggest two main mechanisms: the direct toxic effect of free fatty acids on pancreatic tissue and vascular obstruction caused by chylomicrons due to reduced genetic expression of lipoprotein lipase (LPL). Treatment focuses on lowering triglyceride levels to below 500 mg/dL. Although few interventions have proven effective, insulin therapy and anticoagulation are generally recommended. This report presents the case of a young male patient diagnosed with acute pancreatitis associated with hypertriglyceridemia, along with a review of the underlying pathophysiology and management strategies for this condition.

Keywords

Pancreatitis, hypertriglyceridemia, insulin.

INTRODUCTION

Acute pancreatitis is a reversible inflammatory process of the pancreas; the most common causes are bile duct obstruction and alcohol consumption[1]. In Colombia, the prevalence is similar between men and women, with the condition affecting more individuals between the ages of 50 and 70. In this population, approximately 50% of cases are of biliary origin, and 19% of cases have no identifiable cause. Mortality in severe cases can reach up to 8%[1,2].

Hypertriglyceridemia is the third most common cause of acute pancreatitis (APHTG), contributing to 10% of cases. It is estimated that this percentage may rise to 50% during pregnancy, making it one of the main etiologies in this population group[3,4]. The link between hypertriglyceridemia and acute pancreatitis was first identified by Speck in 1865, and since then, numerous studies have explored this relationship[5].

Complications associated with APHTG have been found to be more severe than those caused by other forms of pancreatitis[6]. Therefore, early and aggressive management is crucial. The main treatment described involves insulin infusion to reduce serum triglyceride levels through its action on lipoprotein lipase and hormone-sensitive lipase[7].

CLINICAL CASE

This is a 38-year-old male patient with a history of dyslipidemia, overweight (body mass index [BMI]: 26.8 kg/m^2), and a previous episode of pancreatitis of undetermined

etiology. He was admitted for a 24-hour history of progressive abdominal pain, starting in the epigastrium and radiating in a band-like pattern, with no signs of peritoneal irritation, and associated with oral intolerance. Paraclinical tests showed a glucose level of 140 mg/dL, lipase of 8050 IU/L, amylase of 963 IU/L, and a normal liver profile. A biliary obstructive process was ruled out through a total abdominal ultrasound, and triglyceride levels were 5780 mg/dL. He was diagnosed with mild pancreatitis secondary to hypertriglyceridemia (APACHE-II score of 0 points).

A significant decrease in hemoglobin levels was observed, from 17.2 mg/dL to 8.9 mg/dL. However, no obvious cause of loss, such as gastrointestinal bleeding or signs of hemolysis, was identified, and thus, hemodilution was considered as a possibility. Treatment was started with insulin infusion at 0.5-1 IU/kg/h, maintaining blood glucose levels between 140 and 180 mg/dL, and enoxaparin 80 mg every 24 hours. Triglyceride levels were reduced by the second day of treatment (**Table 1**). The patient's symptoms gradually decreased, allowing for the restoration of oral intake. No complications associated with pancreatitis were reported.

Table 1. Laboratory reports

Laboratory test	Day 1	Day 2	Day 3	Day 4	Day 5
Triglycerides (mg/dL)	5780	1887	665	499	
Leukocytes (10^3/µL)	10.60	7.57		6.26	5.08
Hemoglobin (g/dL)	17.2	15.6		10.1	8.9
TB/DB (mg/dL)	0.7/0.2				
AST/ALT (U/L)	29/27	33/20			
Lactic acid (mmol/L)	2.10	1.40			
Amylase (IU/1)	963				
Lipase (IU/L)	8.050				

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DB: direct bilirubin; TB: total bilirubin. Table created by the authors.

ETHICAL CONSIDERATIONS

The patient's informed consent was obtained and completed to collect clinical and paraclinical data for the purpose of writing the article, ensuring the confidentiality of the patient's personal information.

DISCUSSION

Acute pancreatitis secondary to hypertriglyceridemia (APHTG) occurs when triglyceride (TG) levels exceed 1000 mg/dL; the time required for elevated triglycerides to cause pancreatic injury is not well established[8]. It primarily affects young patients, in contrast to those with pancreatitis from other etiologies[3,9]. It has been observed that men make up two-thirds of the total patients affected by APHTG[3,7,10].

When diagnosing APHTG, it is crucial to determine the etiology of hypertriglyceridemia. This can be primary (usually polygenic), including patients with hyperlipidemia from groups I (increased chylomicrons), IV (increased VLDL), and V (increased chylomicrons and VLDL), which are particularly associated with this disease; or secondary to conditions such as diabetes, obesity, human immunodeficiency virus (HIV), estrogen use, medications like tamoxifen, or pregnancy. The latter increases the risk of developing pancreatitis associated with hypertriglyceridemia (**Table 2**)[4,7,9,10].

Table 2. Primary and secondary causes of hypertriglyceridemia

Primary causes (genetic)	Secondary causes
Type I hyperlipidemia	Obesity
Type IV hyperlipidemia	Diabetes mellitus
Type V hyperlipidemia	Renal disease: nephrotic syndrome
	Pregnancy (second and third trimester)
	Viral hepatitis
	Hypothyroidism
	Excessive alcohol consumption
	Medications: estrogens, tamoxifen, chlorthalidone, thiazides, β-blockers (non-selective and cardioselective).

Table created by the authors.

The pathophysiological mechanism of APHTG is unclear. Under normal conditions, a substance involved in the removal of triglyceride-rich lipoproteins, called lipoprotein lipase (LPL), is produced in adipocytes and myocytes. LPL is matured by lipase maturation factor 1 (LMF1). After its release, it is transported to the capillary endothelium, where it acts on triglyceride-rich chylomicrons, hydrolyzing them into chylomicron remnants and hydrolyzing triglyceride-rich lipoproteins into fatty acids and glycerol. These products are then transported to the liver, skeletal muscle, myocardium, and adipocytes for utilization. A deficiency in LPL disrupts the plasma degradation of chylomicrons, leading to an increase in free fatty acids in the serum of these patients[4,9].

In the pathophysiology of APHTG, a first hypothesis is proposed: the increase in free fatty acids due to the reduced activity of LPL, causing direct damage to the pancreatic tissue. Under normal conditions, these fatty acids are not toxic when bound to albumin or hydrolyzed by LPL. However, in APHTG, the albumin's capacity for transport is exceeded, which increases toxicity, leading to enzymatic degradation of the pancreas by endothelial lipase and lysolecithin in the acinar tissue, resulting in hemorrhages. Cellular injury leads to an increase in intracellular calcium levels and inhibition of mitochondrial complexes I and V, promoting necrosis and inflammation[9].

A second hypothesis suggests that chylomicrons obstruct the distal circulation of the pancreas, causing ischemia, which exposes the tissue to pancreatic lipase and triggers the inflammatory cascade[4,6,7]. Additionally, all these conditions lead to the activation of trypsinogen, a precursor to trypsin, which damages pancreatic acinar cells and ultimately promotes the development of pancreatitis[3].

Recent studies have identified a third mechanism related to a genetic decrease in LPL, typically of an autosomal recessive nature. Mendelian randomization analyses have shown that variants of LPL, such as APOA5, APOC3, ANGPTL3, and ANGPTL4, are associated with elevated serum triglycerides and an increased risk of pancreatitis[9].

The clinical manifestations of APHTG are similar to those of any other etiology of acute pancreatitis, including abdominal pain, nausea, and vomiting. However, the suspicion that the cause is hypertriglyceridemic is supported by the presence of the previously described risk factors[11].

The diagnosis of APHTG is made following the same criteria used for other forms of acute pancreatitis. This involves identifying at least two of the following three factors: the presence of characteristic abdominal pain, elevation of pancreatic enzymes to more than three times the upper limit of normal (ULN), and radiologic evidence confirming pancreatitis. In the initial approach to pancreatitis, the use of contrast-enhanced computed tomography is indicated only in particular cases; therefore, it was not performed in this case (**Table 3**)[12]. It is important to note that in approximately 50% of patients with APHTG, serum or urinary amylase levels at the time of diagnosis may be low or normal. This is due to interference with colorimetric reading[7,9]. Therefore, amylase levels are not useful to confirm or rule out the diagnosis of APHTG[5,6,13,14].

Additionally, pseudohyponatremia may occur for the same reasons, which normalizes as triglyceride levels decrease[7,9].

The initial management of APHTG, as in any case of pancreatitis, includes several key interventions. First, fluid replacement with crystalloids is essential, with careful monitoring to avoid fluid overload[15]. Second, pain control, early initiation of oral intake as tolerated, and strict glycemic control (target range: 140 to 180 mg/dL) are crucial. Finally, emphasis is placed on the importance of reducing triglyceride levels[13,16].

There are various options to lower triglyceride levels, including the use of insulin, heparins, and plasmapheresis. The choice of therapy also depends on the severity of the patient's symptoms, assessed through the Revised Atlanta Classification and other severity scoring systems[7]. These therapies aim to reduce the development of complications such as necrotizing pancreatitis and organ failure, both of which significantly contribute to increased mortality[17].

Table 3. Indications for contrast-enhanced computed tomography scanning

Indications
1. The diagnosis of acute pancreatitis is uncertain.
2. Patients with hyperamylasemia, severe clinical pancreatitis, abdominal distension and tenderness, fever >38.8° and leukocytosis for screening complications.
3. Ranson score >3 or APACHE score >8.
4. Patients who do not improve after 72 hours of conservative medical therapy.
5. Acute change in clinical status, such as new fever, pain, and shock after initial successful medical therapy.

Adapted from: Busireddy KK, et al. World J Gastrointest Pathophysiol. 2014;5(3):252-70 [12].

Insulin

Intravenous insulin has been used for over a decade to lower serum triglyceride (TG) levels by enhancing lipoprotein lipase activity, which accelerates the metabolism of chylomicrons and VLDL into glycerol and free fatty acids for absorption[14]. Additionally, it decreases the activity of hormone-sensitive lipase, leading to reduced breakdown of adipocytes into triglycerides and, consequently, lowering the circulation of free fatty acids. The general regimen involves a continuous infusion of 0.1 to 0.2 units/kg/hour until triglyceride levels fall below 500 mg/dL, while maintaining serum glucose levels between 150 and 200 mg/dL in cases of hyperglycemia. Insulin is able to decrease triglyceride levels from 50% to 75% in 2 to 3 days[11,13,18].

Heparin

Heparin is used as a measure to lower triglyceride levels due to its ability to activate LPL. Reports describe the use of heparin either alone or in combination with insulin,

administered through different routes and at various doses. However, although heparin has been found to produce an initial increase in LPL levels, this is quickly followed by hepatic degradation of LPL, leading to a rise in chylomicron levels. Therefore, there are significant doubts as to whether these transient effects are truly beneficial[11,18].

The duration of heparin's action has been described as 30 to 120 minutes, based on studies in healthy patients using it as monotherapy. As a result, the combined use of intravenous insulin and heparin is recommended[19,20]. Subcutaneous heparin dosing is described as 5000 units every 12 hours[20].

Plasmapheresis

Plasmapheresis has been proposed as an effective and rapid measure to remove triglycerides from the serum if the patient does not have associated hyperglycemia and there are no contraindications such as hemodynamic instability or inability to obtain venous access. To achieve triglyceride levels <500 mg/dL, three days of plasmapheresis are required. It is important to note that this therapy is highly expensive and available only in specialized medical centers. In addition, there is no clear evidence regarding its impact on morbidity and mortality[11,16]. To date, there is limited published information on its use in cases of acute pancreatitis; however, a few reports suggest better outcomes in cases of severe APHTG, defined by triglyceride levels >2000 mg/dL[18]. Some authors even recommend albumin as an alternative to plasmapheresis to avoid complications associated with plasma infusion[13].

Traditionally, APHTG has been believed to carry a worse prognosis compared to pancreatitis of other etiologies. However, the evidence is not entirely clear. In a retrospective study, APHTG was found to be associated with a higher recurrence rate and a more severe clinical course[3,9].

Prevention

Long-term management of hypertriglyceridemia is very important to prevent the development of recurrent pancreatitis. Treatment strategies include the use of fibrates and long-term therapies with omega-3 fatty acids, in addition to dietary measures and strict alcohol abstinence.

Currently, other available options include pemafibrate, a selective synthetic agonist of the PPARα nuclear receptor. This compound has been shown to reduce plasma triglyceride levels by enhancing LPL activity, lowering triglyceride levels by 26% to 28% within the first four months of treatment[21].

Among molecular therapies, ANGPTL3 inhibitors are noteworthy. Under normal conditions, this protein acts mainly as an inhibitor of LPL and endothelial lipase. Evinacumab has been shown to be effective in reducing cholesterol levels by 47% and triglyceride concentrations by 51%[9,22].

Finally, a recently published meta-analysis evaluated the incidence of pancreatitis in patients receiving Volanesorsen®, an oligonucleotide targeting APOC3 messenger RNA to reduce triglyceride levels. Among patients who received the medication, no cases of pancreatitis were reported during the four-month follow-up period[23].

Future Perspectives

The supramolecular protein mTOR complex 1 (mTORC1) is essential for the production of VLDL-triglycerides, which are exported by the liver and delivered to peripheral tissues. High-fat diets activate the mTORC1/S6K1 pathway, leading to an autophagic response in pancreatitis. Although drugs such as sirolimus increase the risk of pancreatitis, rapamycin (the precursor of sirolimus), a TOR inhibitor, has been evaluated in pancreatitis models. It has been shown to restore autophagic flow and to reduce the adverse effects of hypertriglyceridemia. However, there is no human evidence supporting this effect[24].

CONCLUSION

Acute pancreatitis secondary to hypertriglyceridemia is a rare condition, which is why there are no established protocols for its diagnosis and treatment. A triglyceride level greater than 1000 mg/dL in the presence of pancreatitis should raise suspicion for this diagnosis. It is important to be familiar with the pathophysiology for the use of insulin and heparin in the management of this condition during the acute phase.

Conflicts of interest

None.

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