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Plasmapheresis as a therapeutic approach for hypertriglyceridemia-induced acute pancreatitis

Plasmaférese como modalidade terapêutica na pancreatite aguda por hipertrigliceridemia

ABSTRACT

Acute pancreatitis is an inflammatory condition that is clinically manifested by abdominal pain and elevated serum levels of pancreatic enzymes. Hypertriglyceridemia is the third most common cause of acute pancreatitis. The present report aimed to describe a case of hypertriglyceridemia-induced acute pancreatitis, where the therapeutic approach was plasmapheresis. A 48-year-old female patient was admitted to the hospital with complaints of "severe abdominal pain". She reported the onset of such symptoms as nausea, vomiting and abdominal pain with a burning feeling in the epigastric area. The patient denied having a fever. The initial examination revealed that she was obese, oriented, tachypneic, normotensive, tachycardic, dehydrated, afebrile, anicteric and acyanotic and had normal color. Her abdomen was distended with bowel sounds, tympanic and diffusely painful, which was mostly in the supramesocolic compartment. The

initial laboratory exams showed 10.932 mg/dL triglycerides, 1.548 mg/dL cholesterol, 226 mg/dL amylase and 899 mg/dL lipase. The abdominal computed tomography exhibited increased pancreatic volume (Balthazar E). The patient's condition worsened, and she was sent to the intensive care center. Plasmapheresis was performed with no complications. On the 14th day after admission, the patient was discharged from the intensive care center and was sent to the gastroenterology ward, where an oral diet was resumed with good acceptance. The patient progressed well and was discharged from the hospital on the 25th day after admission. High triglyceride levels are necessary to cause pancreatitis, and it is important to exclude the most common causes. Importantly, the therapeutic approach reduced the high hypertriglyceridemia quickly, thereby avoiding tissue damage.

Keywords: Pancreatitis; Hypertriglyceridemia; Plasmapheresis; Case reports

This study was conducted at the Antônio Pedro University Hospital, Universidade Federal Fluminense - UFF - Niterói (RJ), Brazil.

Conflicts of interest: None.

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INTRODUCTION

Acute pancreatitis is an inflammatory condition of the pancreas caused by the premature activation of its digestive enzymes, and this condition is clinically manifested by abdominal pain and high serum levels of the pancreatic enzymes. Hypertriglyceridemia is the third most common cause of this condition after alcohol and gallstones and is responsible for 1 to 38% of the cases.⁽¹⁾ Usually, serum levels of triglycerides (TG) $\geq 1,000$ mg/dL (10 mmol/L) are needed to induce acute pancreatitis.⁽²⁾ This report aimed to describe a case of hypertriglyceridemia-induced acute pancreatitis, where the therapeutic approach was plasmapheresis, which resulted in a good outcome.

CASE REPORT

The patient was a 48-year-old Caucasian female, who was married, born in Rio de Janeiro and had worked as a sales consultant but was unemployed at the time of the treatment. The patient reported the onset of symptoms, including nausea, vomiting and abdominal pain with a burning feeling, which began in the epigastric area and later spread to the whole abdomen but was concentrated in the left upper quadrant (LUQ). She sought emergency medical assistance, where exams were performed that ruled out an acute myocardial infarction (AMI). The patient denied having a fever or previous similar episodes. She was hospitalized for 48 hours, and when she had a new episode of malaise after food ingestion, which was followed by vomiting, she was subsequently referred to the Antônio Pedro University Hospital (APUH) emergency care.

Regarding her past medical history, the patient reported treatment for systemic lupus erythematosus for the previous 6 years, taking prednisone (60 mg daily), hydroxychloroquine (400 mg daily) and azathioprine (100 mg daily). The patient was hypertensive and diabetic for the previous 7 years, taking captopril and glyburide. The patient presented with metrorrhagia approximately 1 month before admission, which was associated with cramping and abdominal pain in the lower abdomen. The patient reported having smoked 1 pack of cigarettes a day for 14 years and having stopped smoking 14 years ago. The patient denied consuming alcohol. She reported 3 pregnancies, 3 births and 0 miscarriages.

The physical examination revealed that the patient was obese (body mass index (BMI) = 35.29), lucid, oriented with respect to time and space, normally colored and dehydrated (+/4+), afebrile, anicteric, acyanotic and showing facial erythema. Her blood pressure was 110 x 70 mmHg, her heart rate was 120 bpm and her respiratory rate was 32 breaths per minute. The cardiac auscultation showed a regular sinus rhythm with 2 normal sounds (primary heart sounds) without murmurs. The respiratory system examination showed decreased vesicular murmur at the bases, with crepitant rales in the middle third of the left lung. The abdomen was distended, obese and tympanic and had bowel sounds and a free Traube's space. It was also extremely and diffusely painful, primarily in the left upper quadrant, the left lower quadrant and the hypogastric area. The abdominal examination also indicated probable hepatomegaly, but the examination was impaired by the obesity. There were no periumbilical or flank ecchymotic lesions. The lower limbs did not present with edema and had free calves, and the peripheral pulses were palpable and symmetrical.

The initial abdominal computed tomography (CT) scan (Figure 1) at the time of admission showed increased

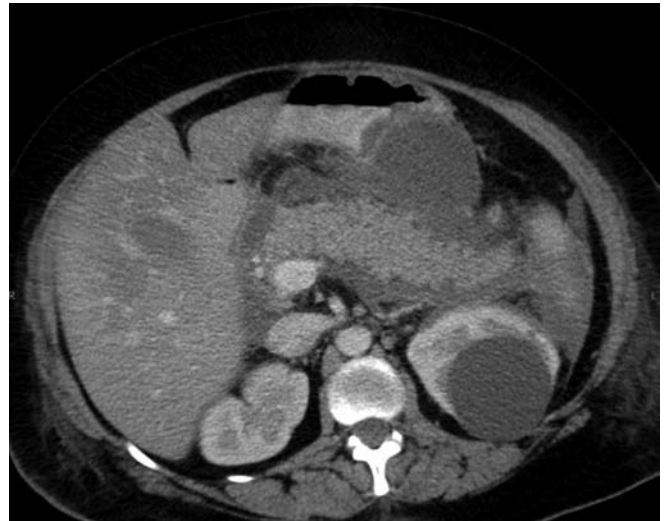


Figure 1 - An abdominal computed tomography scan showing a diffuse enlargement of the pancreas, densification of the peripancreatic fat and 2 free fluid collections.

pancreatic volume with a diffuse densification of the peripancreatic fat and 2 free fluid collections, which were located above the left renal fascia and between the pancreas and the liver. The CT also showed hepatic steatosis and an E score on the Balthazar CT severity index.

The initial exams included blood tests that showed hemoglobin level of 16.4 g/dL (reference range [RR] 12-17), hematocrit of 48% (RR 36-50), glucose level of 236 mg/dL (RR 40-80), creatinine level of 4.32 mg/dL (RR 0.6-1.2), lactate dehydrogenase level of 50 U/L (RR 240-480), total cholesterol level of 1,548 mg/dL (RR <200) and triglyceride (TG) level of 10,932 mg/dL (RR <150).

The patient experienced a worsening of her general condition and was sent to the intensive care center (ICC) on the same day of arrival at the AUPH. On day 1 of admission at the ICC, the patient was placed under a nebulization treatment with oxygen and a fasting regime. A deep venous access was established, and an adjuvant treatment with fibrates was initiated. On the next day, a 140-min plasmapheresis session was conducted with no complications. The hemodynamic pattern was not changed, and clinical stability was maintained. It was observed that within 48 hours, there was a reduction of approximately 65% in the TG levels.

On the 3rd day of hospitalization, total parenteral nutrition was initiated, and she received this type of nutrition for 1 week when an elemental enteral diet was introduced.

On the 8th day, an intravenous (IV) therapy with 4.5 g of piperacillin and tazobactam was started and administered every 6 hours because of the extension of the pancreatic

necrosis observed in the abdominal CT. The patient developed episodes of diarrhea without fever and with a slight increase in the level of serum lipase but with no exacerbation of the abdominal pain. However, this condition has proven to be self-limiting, lasting 4 days without any changes in the diet.

After 2 weeks, the patient was clinically stable and had no complaints, and the physical examination showed no changes. She was discharged from the ICC and transferred to a clinical gastroenterology ward. An oral hypolipidemic diet was introduced and was well-accepted by the patient. She progressed with stabilizations of the clinical condition, laboratory exams and CT scans.

On the 25th day, the patient was discharged from the hospital and referred to the gastroenterology clinic. She was taking 600 mg of genfibrozil orally (PO) twice a day. The pancreatic pseudocyst identified on the CT scan on the 21st day of hospitalization was monitored through observation, and the antibiotic therapy lasted 19 days.

The abdominal CT scan (on the 8th day) showed collections throughout the abdomen, with multiple foci of pancreatic necrosis and an E score in the Balthazar CT severity index. However, the abdominal CT scan on the 21st day showed that the pancreas had an increased volume and was heterogeneous. The pancreas also showed a regular hypodense lesion that was retrogastric, measured 9 cm, compressed the stomach and appeared to form a capsule around the stomach, which was suggestive of a pseudocyst. The CT scan also showed fluid around the pancreas, liver and hilum and a small bilateral pleural effusion.

Table 1 shows the results of laboratory tests that were conducted throughout the patient's hospitalization in the APUH.

Table 1 - The results of the initial laboratory exams

Exam	3 rd day	8 th day	13 th day	15 th day	21 st day
Glucose	299	136	320	262	223
Urea	23	13	17	20	8
Creatinine	0.58	0.45	0.59	0.64	0.54
Sodium	126	137	133	133	136
Potassium	4.2	3.1	4.9	4.5	3.4
Total protein	X	5.1	X	5.9	6.1
Albumin	2.0	2.0	X	2.5	3.2
Amylase	226	31	55	50	46
Lipase	899	271	475	437	423
TG	3866	405	543	533	537
TB	X	0.68	0.41	0.38	X
BU	X	0.23	0.16	0.13	X
ALP	108	90	X	92	52
LDH	50	241	x	188	x
AST	28	30	20	17	18
ALT	133	39	35	32	39
CRP	49.86	20.3	3.01	1.04	0.12
Calcium	5.8	7.9	X	8.7	X
TC	513	287	333	305	X
Hb	14.6	11.1	12.2	11.5	12
Hct	41	33.8	37.3	33.9	35.8
Leukocytes	10,600	10,600	8,800	7,300	2,700
Band cells	15	1	3	3	1
Segmented	68	70	78	55	55
APTT	100	X	X	31.8	X
PTT	1.01	0.97	X	15	29.4
INR	0.99	1.93	X	1.12	X
Platelet	190.00	196.00	239.00	276.00	X

Reference ranges: glucose 40-80 mg/dL; urea 10-50 mg/dL; creatinine 0.6-1.2 mg/dL; sodium 135-145 mEq/L; potassium 3.5-5.0 mEq/L; total protein 6.5-8.1 g/dL; albumin 3.5-5.0 g/dL; amylase 28-100 U/L; lipase < 60 U/L; Triglycerides (TG) < 150 mg/dL; total bilirubin (TB) 0.3-1.3 mg/dL; direct bilirubin (DB) 0.1-0.4 mg/dL; alkaline phosphatase (ALP) 35-104 U/L; lactate dehydrogenase (LDH) 240-480 U/L; aspartate transaminase (AST) 12-38 U/L; alanine transaminase (ALT) 7-41 U/L; C-reactive protein (CRP) < 0.5 mg/dL; calcium 8.5-10 mg/dL; total cholesterol (TC) < 200 mg/dL; hemoglobin (Hb) 12-17 g/dL; hematocrit (Hct) 36-50%; leukocytes 5000-11000/mm³; band cells 1-5%; segmented 45-70%; activated prothrombin time (APTT) > 70%; partial thromboplastin time (PTT) 26.3-39.4 s; international normalized ratio (INR) 1.0-1.4; and platelets 150,000-400,000/mm³.

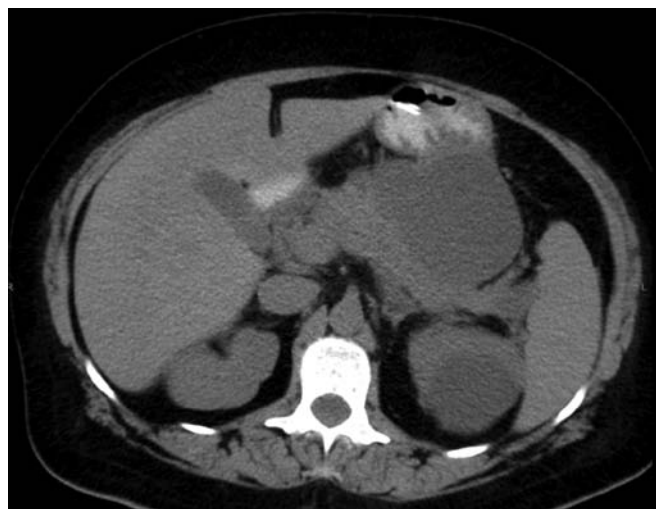


Figure 2 - An abdominal computed tomography scan showing a lesion suggesting a pancreatic pseudocyst compressing the stomach.

DISCUSSION

Acute pancreatitis may be initially suspected due to the clinical symptoms, which are characterized by a sudden and constant pain in the upper abdomen that ranges from a mild discomfort to debilitating pain, sometimes irradiating to the back, which is defined as a Chauffier's sign. The pain, which is relieved by flexing the torso over the abdomen, is often followed by nausea, vomiting and abdominal distension due to gastric and intestinal hypomotility. However, 5 to 10% of patients do not exhibit abdominal pain.⁽³⁾

Despite the clinical suspicion, laboratory and image tests are needed to corroborate the clinical diagnosis and to determine the underlying cause. In general, diagnosis of pancreatitis requires 2 of the following 3 criteria:

clinical signs consistent with pancreatitis, high levels of pancreatic enzymes and pancreatic alterations shown in the imaging tests.

In cases of acute pancreatitis, laboratory findings are characterized by an increase in serum amylase to 3 or more times its upper limit, which returns to its normal value within 3 to 5 days. Increased lipase occurs concurrently with the increase in amylase (within 2 to 12 hours after the crisis), but it is more specific for pancreatitis, and the decrease of lipase to normal values is slower, possibly remaining high for up to 14 days. The increase in TG may undervalue the lipase and amylase serum levels, which may be normal or slightly elevated, as in the described case.⁽⁴⁾

The mechanism of induction of pancreatitis is not yet fully known. Among the models exposed to triggering factors, only a small number develop the disease. Serum TG levels above 1,000 mg/dL have been demonstrated to be the primary risk factor for the development of acute pancreatitis, although a few cases with levels between 500 and 1,000 mg/dL have already been recorded.⁽⁵⁾ In general, patients with hypertriglyceridemia-induced acute pancreatitis have a pre-existing alteration in lipoprotein metabolism.⁽¹⁾ It has been described that TG hydrolysis by pancreatic lipase causes a local release of a toxic amount of free fatty acids, and this release is capable of damaging acinar cells. Concurrently, there is an elevation of chylomicrons in the pancreatic capillaries, resulting in capillary congestion and contributing to ischemia and acidosis. When direct cellular damage or duct blockage occurs, large amounts of pancreatic secretions are released. The secretions contain pre-activated proenzymes, such as active trypsinogen that is stimulated by an acidic environment, which is a critical step in the process that leads to pancreatitis.^(5,6)

The initial treatment of acute pancreatitis is based on rapid intravenous hydration, analgesia and parenteral nutrition that is free of lipid infusion when necessary. The primary intention of any treatment is to reduce the hypertriglyceridemia to levels below 500 mg/dL.⁽⁷⁾ Among several therapeutic approaches, the use of such drugs as fibrates (TG reduction of up to 50%) and nicotinic acid (TG reduction between 15 and 25%) exhibit notable results in countering dyslipidemia, with heparin and insulin infusions stimulating the lipoprotein lipase activity and accelerating the chylomicron degradation.⁽⁶⁻⁸⁾ Fibrates are the most commonly used drugs for the treatment of hypertriglyceridemia. Fibrates act on the nuclear receptor "peroxisome proliferator-activated nuclear receptor alpha" (PPAR- α). This

stimulus leads to an increased production and activity of lipoprotein lipase, which is responsible for intravascular TG hydrolysis. Usually, fibrates are recommended when there are shortcomings in non-pharmacological measures, or they are used initially when the TG levels are above 500 mg/dL along with non-pharmacological measures. In major hypertriglyceridemia (greater than 1,000 mg/dL), the use of fibrates may be considered, but the most recommended treatment is plasmapheresis.⁽⁹⁾

Piolot et al.⁽¹⁰⁾ described the use of this procedure in patients with severe primary hypertriglyceridemia and recurrent acute pancreatitis, as a way of preventing future episodes of pancreatitis. The mechanism of action of plasmapheresis is the extracorporeal purification of blood, which is designed to remove high molecular weight substances from the plasma, such as TG, in addition to active enzymes and inflammatory mediators from plasma by filtering and removing them from the blood.⁽¹¹⁾ The basic premise of this type of treatment is to reduce the tissue damage and reverse the pathophysiological process, thereby reducing the plasma hyperviscosity and hypertriglyceridemia in a few hours.⁽¹²⁾ Within 2 hours of therapy, the plasmapheresis reaches an acute reduction of the serum levels of TG and total cholesterol by 60 to 85%. The plasmapheresis session should be performed as early as possible for a greater effectiveness.⁽⁵⁾

Several studies reaffirm the use of plasmapheresis as a treatment for pancreatitis caused by hypertriglyceridemia, although these studies are case studies and clinical sessions. No randomized clinical trial was developed to corroborate this assertion yet.^(5,6) The therapeutic approach in pancreatitis due to hypertriglyceridemia, according to the American Society for Apheresis, 2007,⁽¹³⁾ is considered a class III in the indication for treatment with plasmapheresis, meaning that there is still no conclusive or inconclusive evidence about the use of this approach; however, there is a clinical indication in specific cases. Plasmapheresis has also previously been used with success as a preventive therapy for recurrent pancreatitis in patients with dyslipidemia. However, this method has limitations due to anaphylactic reactions, hypotension, hypocalcemia and transfusion-associated infections.⁽⁶⁾

Consecutive comparisons of the serum levels of lipids and plasma lipoproteins should be performed to confirm the progressive recovery of the pancreatic tissue.⁽⁷⁾

In the present report, the patient only underwent 1 session of plasmapheresis, in which a reduction in TG levels was observed from 10,932 mg/dL to 3,866 mg/dL after 3 days (64.6% reduction). Due to the scarcity of

case reports in the literature on this subject, the decision to carry out only 1 session was based on a major study by Yeh et al.,⁽¹⁴⁾ which showed that a simple exchange removed 66.3% of the TG, while a second session removed 83.3% of the serum TG. The procedure time was 2 hours and 10 minutes long because short sessions (lasting approximately 2 hours) were associated with a lower transmembrane pressure of the plasmapheresis filter and thus a better TG clearance (greater removal of TG from the plasma). The number of sessions, however, did not correlate with the clinical prognosis of the patient. Because of this result and considering that plasmapheresis is not free of complications, which include the inherent vascular risk (such as infections and bleeding), electrolyte imbalances and allergic reactions, including anaphylactic shock, and its high cost, it was decided that only a single session would be conducted. Although the patient maintained high levels of TG (3,866 mg/dL), given the above, it was decided to continue the treatment with fibrates and a hypolipidemic diet. Non-pharmacological measures, such as reducing alcohol intake, weight loss and diabetes control, were also encouraged because they are important supportive measures for decreasing the TG and cholesterol levels. It was also important that the patient had a balanced diet, which was monitored by a nutritionist, that aimed for a saturated fatty acid intake of less than 7% of the total daily energy intake and restricted trans fat and cholesterol intake. Nonrandomized studies demonstrated a clinical improvement with a reduction in laboratory parameters, such as the TG, amylase and lipase levels, and a reduction of cytokines released during the inflammatory process of the acute condition. Although there are no detailed protocol descriptions about the chronological application of this therapy in emergency situations in the literature, this therapy has proven to be beneficial for the clinical progress and for the prognosis of the patients.

Currently, hypertriglyceridemia is a common condition, due to such lifestyle habits as sedentarism, alcohol abuse and high-fat diet, which are habits that constitute a cardiovascular risk. However, these habits' association as the primary causes of pancreatitis is not commonly found because high TG serum levels are

required to start the process; therefore, this association should only be considered after excluding most common conditions, such as alcohol and gallstones. Hypertriglyceridemia is generally controlled with drugs, and there is occasionally refractoriness to the conventional treatment.

There are situations, such as in this case report, in which the TG levels are extremely high. These situations may present a risk to the patient. Plasmapheresis has been proven to be a good alternative for an abrupt reduction of hypertriglyceridemia.

RESUMO

Pancreatite aguda é uma condição inflamatória manifestada clinicamente por dor abdominal e níveis séricos elevados das enzimas pancreáticas. A hipertrigliceridemia é sua terceira causa mais comum. O presente relato teve por objetivo descrever um caso de pancreatite aguda por hipertrigliceridemia, cuja modalidade terapêutica utilizada foi a plasmaférese. Paciente, gênero feminino, 48 anos, apresentou-se ao hospital com queixa de "dor muito forte na barriga". Relatou início do quadro com náuseas, vômitos e dor abdominal do tipo queimação, iniciada em região epigástrica. Negou febre. Ao exame: obesa, orientada, taquipneica, normotensa, taquicárdica, normocorada, desidratada, afebril, anictérica, acianótica; abdome: distendido, ruídos hidroaéreos presentes, timpânico, doloroso difusamente, porém, principalmente em andar supramesocólico. Aos exames de admissão: triglicerídeo 10.932 mg/dL, colesterol 1.548 mg/dL, amilase 226 mg/dL, lipase 899 mg/dL. A tomografia computadorizada de abdome evidenciou pâncreas aumentado de volume (Balthazar E). Evoluiu com piora do estado geral, sendo encaminhada para o centro de terapia intensiva. Foi realizada plasmaférese sem intercorrências. No 14º dia, teve alta do centro de terapia intensiva indo para enfermaria de gastroenterologia, onde foi reiniciada dieta oral, com boa aceitação. Evoluiu bem, com alta hospitalar no 25º de internação. São necessários níveis elevados de triglicerídeos para causar pancreatite, sendo importante excluir causas mais comuns. A abordagem terapêutica utilizada foi importante para reduzir, rapidamente, a hipertrigliceridemia elevada, evitando, assim, danos tissulares maiores.

Descritores: Pancreatite; Hipertrigliceridemia; Plasmaférese; Relatos de casos

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