Diabetic ketoacidosis and pancreatitis secondary to peg-asparaginase

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ABSTRACT

Objectives: We present a rare case of diabetic ketoacidosis (DKA) and pancreatitis secondary to the use of PEG-asparaginase in a pediatric patient being treated for acute lymphoblastic leukemia (ALL) and draw attention to the signs that refer to these diagnoses.
Case description: A female adolescent, aged 10 years and 11 months, undergoing treatment for ALL, used PEG-asparaginase for 6 days prior to admission. She was hospitalized due to severe hypotensive shock and was then referred to the intensive care unit. Initially, the clinical condition was interpreted as septic shock. However, detailed anamnesis and results of laboratory tests led to the diagnoses of DKA and pancreatitis; hence, appropriate interventions were initiated. She was discharged after 30 days without the need for insulin therapy but received pancreatic enzyme replacement therapy.
Comments: Generally, diagnosing severely ill and leukopenic children with ALL is only attributed to sepsis, which is a priority diagnosis. However, in the group treated with PEG-asparaginase, the pediatric emergency specialist should consider differential reasoning in patients with DKA and pancreatitis, which can be quite difficult to assess initially. Alertness towards the differential diagnoses of septic shock, although rare, in the care of pediatric oncology patients, in addition to the correct and prompt identification of the condition and provision of appropriate management, directly correlates with treatment success and, in some situations, the improvement in patient's survival.

Keywords: PEG-asparaginase, Diabetic ketoacidosis, Pancreatitis, Acute lymphoblastic leukemia.

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INTRODUCTION

The introduction of L-asparaginase or its pegylated form (PEG-asparaginase) in treatment protocols for patients with acute lymphoblastic leukemia (ALL) has contributed considerably to the increase in therapeutic success rates and improvement in overall survival of these patients, especially in the pediatric age group[1,2].

Currently, PEG-asparaginase has been preferred over L-asparaginase, since the former has a long half-life and low immunogenicity[1-3]. However, both forms of this enzyme have potential adverse effects, such as liver injury, venous thromboembolic events, hyperglycemia, hypertriglyceridemia, and hypersensitivity reaction[3].

In some individuals, the use of L-asparaginase can cause diabetic ketoacidosis (DKA), a rare condition with an estimated frequency of 0.8% among those who use this chemotherapy drug[4-9]. Another potential adverse effect is pancreatitis, described in 2%–16% of the patients, the prevalence of which is correlated with the cumulative dose of the drug. These two conditions can coexist since DKA can result from the cytotoxic destruction of pancreatic islets mediated by pancreatitis[7]. Generally, these adverse events have a limited course and the patients may use the drug again in the future[10-11].

In the context of a pediatric emergency, the mechanism involved in the acute occurrence of abdominal pain and hypovolemic shock in neutropenic oncology patients remains unclear. It is not directly attributable to DKA and pancreatitis, leading the attending physician to interpret the event as septic shock, which frequently occurs in this context, and to intervene according to this diagnosis. A delay in the correct diagnosis and taking appropriate interventions can lead to a real increase in morbidity and mortality.

This report aimed to present a rare case of DKA and pancreatitis secondary to PEG-asparaginase treatment in a pediatric patient being treated for ALL and to draw attention to the signs and symptoms that may lead to these diagnoses. It is a rarely reported condition, potentially deadly, and generally not contemplated when diagnosing patients under oncologic treatment in the emergency setting.

CASE DESCRIPTION

A female patient, aged 10 years and 11 months, weighing 41.6 kg, was admitted to the pediatric urgency and emergency department of a tertiary hospital in DF, Brazil. The patient had a poor general condition, was torporous, and experienced severe abdominal pain, gastric fullness, and episodes of evacuation of pasty feces for 2 days prior to admission, associated with progressive respiratory distress and Kussmaul's pattern. The patient had type B ALL and was in phase 1 of the Berlin-Frankfurt-Munich Protocol II (2002)[12], adapted for medium-risk patients, and underwent PEG-asparaginase treatment 6 days prior to the occurrence of this complication.

Upon admission, the patient was in severe hypotensive shock, initially classified as septic. Volume expansion with crystalloid (total of 40 mL/kg, rapidly) and broad-spectrum antibiotic therapy with vancomycin and cefepime were initiated due to recent hospitalization and febrile neutropenia.

Results of the baseline laboratory tests are shown in Table 1. Findings showed severe leukopenia, thrombocytopenia, and metabolic acidemia with a high anion gap, normal lactate levels, and hyperglycemia.

The patient was transferred to the pediatric intensive care unit (PICU). She underwent fresh volume expansion and titration of intravenous adrenaline up to 0.4 mcg/kg/min but did not show adequate response. A higher dose of hydrocortisone (100 mg/m^2) was administered to manage shock as the patient was unresponsive to catecholamines.

In the PICU, the patient exhibited ketonic breath. Moreover, the mother reported that the patient developed polydipsia, polyphagia, and polyuria for 3 days before admission. During this period, the patient experienced weight loss. This clinical and biochemical context led to the diagnosis of DKA, and appropriate treatment was initiated according to the institution's protocol. On the following day, due to persistent abdominal pain and an increase in the serum amylase level (from 108 U/L to 778 U/L; reference: 28–100 U/L), computed tomography of the whole abdomen was performed, which showed findings compatible with those of acute pancreatitis (Figure 1).

A discretely enlarged pancreas is observed (blue arrow) with a small hypoechoic area on its tail, which is compatible with the features of acute pancreatitis, and a small area of necrosis (red arrow). The presence of peripancreatic fluid in the anterior pararenal spaces (green arrow) is visible.

The patient was then diagnosed with acute pancreatitis according to Suzuki et al.'s[13] criteria due to

Table 1. Laboratory test results of the patient.

Analyte	Admission	Day 1	Day 10	Reference values
Glucose	391 mg/dL	223mg/dL	62 mg/dL	Fasting: 70-99 mg/dL
Urea	27.2 mg/dL	14 mg/dL	21 mg/dL	8 -36 mg/dL
Creatinine	0.47 mg/dL	0.37 mg/dL	0.06 mg/dL	0.31 - 0.88 mg/dL
TGO (AST)	21.5 U/L	50 U/L	29 U/L	5 - 36U/L
TGP (ALT)	52.7 U/L	54 U/L	57 U/L	19 - 44 U/L
DHL	331 U/L	----------	703 U/L	250 - 500 U/L
Lactate	2 mmol/L	4.9 mmol/L	1.7 mmol/L	0.63 - 2.44 mmol/L
Sodium	131mmol/L	132 mmol/L	140 mmol/L	135 - 145 mmol/L
Potassium	3.9 mmol/L	2.2 mmol/L	4.3 mmol/L	3,3 - 4,6 mmol/L
Chlorine	108 mmol/L	103 mmol/L	101 mmol/L	97 - 106 mmol/L
Ionic calcium	0.88 mmol/L	0.99 mmol/L	1.13 mmol/L	1.13 - 1.32 mmol/L
Phosphorus	0.77 mmol/L	0.49 mmol/L	2.97 mmol/L	3.3 - 5.3 mmol/L
Magnesium	1.5 mg/dL	0.93 mg/dL	1.7 mg/dL	1.6 - 2.6 mg/dL
pH	7,00	7,27	7,48	7,35 – 7,5
Bicarbonate	8.8 mEq/L	13.4 mEq/L	28 mEq/L	22 - 29 mEq/L
Amylase	108 U/L	778 U/L	49 U/L	28 - 100 U/L
Albumin	2.4 g/dL	2.0 g/dL	2.15 g/dL	2.9 - 4.7 g/dL
HB/Hematocrit	13.8 g/dL / 41%.	13.3g/dL / 39%.	9.7 g/dL / 30.7%.	12-16 g/dL / 36-46%
Leukocytes	650	390	10.060	5,000 -10,000 cell/µL
Neutrophils	150	No reading	8.260	1.500 -6.000 cell/µL
Platelets	18,000/µL	42,000/µL	163,000/µL	140.000-400.000/ µL
CPR		6.8 mg/dL	1.75 mg/dL	< 0.5 mg/dL

Legend: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; HB: Hemoglobin; CRP: C-reactive protein;

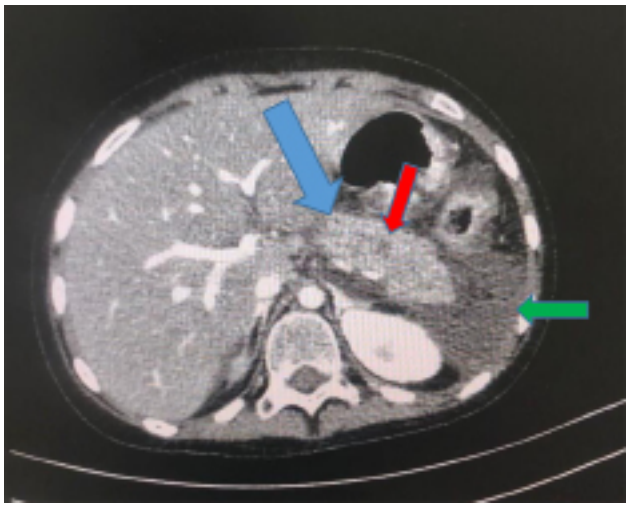

Figure 1. Computed tomography of the patient's abdomen after intravenous injection of the contrast medium

the presence of severe abdominal pain, hypovolemic shock, and vomiting; a significant increase in the amylase level; and typical radiological findings. An important aspect of asparaginase-induced pancreatitis is the absence of hyperamylasemia in the initial phase in half of the patients, which was observed on the first day of hospitalization. This event is attributed to the deficiency of protein synthesis induced by asparaginase[14].

Within this broad context, the patient was managed according to the protocols for treatment of acute pancreatitis, DKA, and severe hypovolemic shock adopted by the facility. The patient eventually recovered and was discharged from the PICU after 10 days with good glycemic control, without the need for insulin, without abdominal pain, and with an enteral feeding tube in place and showed spinal cord recovery after receiving chemotherapy. After 30 days of admission to the ward, she was discharged with oral feeding established but still under pancreatic enzyme replacement therapy. However, insulin therapy was not required.

At the end of hospitalization, consent and assent were obtained from the patient and guardian; subsequently, the consubstantiated opinion of the research ethics committee (CAAE 33296420.8.0000.0025) was obtained.

DISCUSSION

ALL is characterized as a massive proliferation of immature lymphoid cells in the bone marrow and is the most common type of cancer in the pediatric age group[3]. The cure rate currently recorded among pediatric patients with ALL is higher than 90% in several centers[6], owing to early diagnosis and current therapeutic protocols, with asparaginase being one of the main chemotherapeutic agents responsible for this response[1-3]. Asparaginase is an aminohydrolase enzyme that breaks the asparagine molecule down (by catalyzing the transformation of the amino acid L-asparagine into aspartic acid); this process is essential in triggering the

apoptosis of leukemic cells. This event occurs as these cells, unlike other cells in the body, cannot synthesize asparagine due to the lack of asparagine synthetase[3,15]. Without asparagine, leukemic cells do not survive, since this amino acid is necessary for protein synthesis to maintain cell function[8-9].

The asparaginase formulations available for the treatment of ALL are L-asparaginase derived from *Escherichia coli*, L-asparaginase derived from *Erwinia chrysanthemi,* and PEG-asparaginase (succinimidyl mono-ethoxy polyethylene glycol conjugate of *E. coli* L-asparaginase). Currently, PEG-asparaginase has been preferred over L-asparaginase as the former allows dosing with long intervals between doses due to its long half-life (5.7 ± 3.2 days compared with 1.3 ± 0.4 days, respectively, through intramuscular administration), besides its low immunogenicity[1-3,7,10]. However, both forms of this enzyme have potential adverse effects, such as hepatotoxicity, pancreatitis, venous thromboembolism, hyperglycemia, hypertriglyceridemia, and DKA[6-7]. Hyperglycemia and pancreatitis are relatively common[4,6,10-11,15] and may be present in up to 25% and 16% of pediatric patients, respectively. However, DKA is extremely rare and reported in 0.8% of children and adolescents using L-asparaginase, usually associated with the concomitant use of corticosteroids and presence of infection[4,9]. The occurrence of concomitant DKA and pancreatitis associated with the use of asparaginase in children and adolescents with ALL are extremely rare[6,16].

Among the pathophysiological mechanisms suggested to explain the development of DKA secondary to the use of asparaginase are the cytotoxic actions of the drug causing a decrease in insulin secretion, insulin resistance, and/or excessive glucagon synthesis[14,17]. DKA can also occur secondary to drug-induced pancreatitis. These processes are related to the disturbances in the intracellular signaling of Ca2+ ions induced by asparaginase in normal cells, causing decreased intracellular adenosine triphosphate concentrations and cell necrosis[18].

Since pancreatic beta-cells require asparagine for insulin synthesis[9] and the chronic use of corticosteroids can trigger insulin resistance[6,9], this therapy causes potential interference in insulin metabolism, which becomes critical in the context of pancreatitis.

Previous studies suggest that asparaginase-induced pancreatitis may occur within 3 days after the administration of L-asparaginase and 11 days after PEG-asparaginase[19]. According to the results of a cohort of pediatric patients with ALL and asparaginase-induced pancreatitis (n=465), who were followed up for over 20 years, the presence of metabolic complications, such as DKA and pancreatitis, and lethal outcomes correlated significantly with age, with a median age of 10.5 years for the group that developed complications and 6.1 years for the group without complications[19]. Only 2% of the patients died due to pancreatitis. This study also indicated that the maintenance of insulin therapy and recurrent abdominal pain were associated with pancreatic pseudocysts.

Although hyperamylasemia is a biochemical characteristic of pancreatitis, caution should be observed when interpreting the clinical picture, especially when the above-mentioned complication is not present in this group of patients; since asparaginase decreases the synthesis of this enzyme by the pancreatic acinar cells, the absence of hyperamylasemia does not rule out the diagnosis of pancreatitis in the early stages[14].

In the reported case, the patient presented pancreatitis and DKA secondary to PEG-asparaginase treatment, leading to severe hypovolemic shock, initially interpreted and treated as septic shock, a completely plausible condition and a real priority diagnosis in the context. However, the refractiveness of shock to the initial measures for sepsis led to the conduction of complementary and subsequent investigations that revealed persistence of severe acidemia, significant hyperglycemia, and ketonuria; the clinical picture described by the mother, who reported the occurrence of polyuria, polydipsia, and ketotic breath, and the presence of dehydration and glycosuria led to the diagnosis of DKA and the timely provision of therapeutic intervention.

The discussion of this rare clinical evolution in the emergency department for pediatric oncology patients is important for the possibility of its occurrence and a prompt investigation by the emergency physician. However, in order to evaluate this condition, it should be determined and included among the possible differential diagnoses. Generally, patients with shock admitted to the health facility due to immunosuppression and neutropenia are initially treated for septic shock. This is due to the prevalence of this diagnosis and high mortality due to sepsis in those individuals with

febrile neutropenia. However, it is very important to perform a complete evaluation of the patient's condition, including the possible adverse effects of ongoing pharmacological treatments, with the elaboration of an inclusive list of diagnostic hypotheses, especially in cancer patients with ALL using one of the forms of asparaginase. This initial approach allows a detailed diagnostic investigation and, consequently, a great possibility of early confirmation of the correct diagnosis and timely provision of the most appropriate intervention.

In this context presented by the patient, it is important to consider other signs that overlap the clinical and biochemical manifestations of septic shock, pancreatitis, and DKA, such as decreased general status, torpor, hypovolemia, respiratory hemodynamic instability, metabolic acidosis, and hyperglycemia. However, when present, there are aspects that lead to the possibility of DKA, such as the history of weight loss, polydipsia, polyuria in the presence of dehydration, perception of ketotic breath, significant ketonemia, and ketonuria. Pancreatitis is suspected when patients experience severe abdominal pain in the upper quadrants and exhibit abdominal guarding.

Thus, in the emergency care of patients receiving oncologic treatment using asparaginase, a broad laboratory investigation is indicated to evaluate pancreatic lesions and their metabolic consequences, such as glycemia, ketonemia, acidosis, amylasemia, lipasemia, calcemia, glycosuria, and ketonuria. These can be complemented by the clinical and biochemical findings on abdominal imaging (computed tomography).

The reported case illustrates the important aspects to be considered in the emergency care of children with cancer in shock since ALL is the most frequent neoplasm in pediatric patients, and PEG-asparaginase or L-asparaginase is among the treatment protocols used. In these situations, DKA and pancreatitis should be considered by the assistant physician as the differential diagnoses, and knowledge on the specific aspects of the manifestation and evolution of these conditions should be enhanced.

Exercising inclusive diagnostic suspicion and investigation is essential for expanding, qualifying, and providing medical care to children and adolescents undergoing cancer treatment who require evaluation in urgent and emergency settings.

CONCLUSION

Extra care should be taken when making a diagnostic hypothesis of DKA in cancer patients treated with PEG-asparaginase since the occurrence of shock and dehydration in those with pancytopenia usually leads to the diagnosis of septic shock. The differential diagnoses for DKA and pancreatitis, in this clinical context, may lead to the successful management of a pediatric oncology patient with a severe and difficult condition.

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Author contributions
1. Substantial contribution in the design of the study or interpretation of the data:
FRP, CAS, MBL, SHK, and LCGC
2. Participation in the drafting of the manuscript: FRP, CAS, MBL, SHK, and LCGC
3. Participation in the review and approval of the final version of the manuscript: FRP, CAS, MBL, SHK, and LCGC
4. Compliance in being responsible for the accuracy or completeness of any part of the study: FRP, CAS, MBL, SHK, and LCGC

Conflict of interest statement
The authors declare that they have no conflicts of interest

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Justification of the importance of the work
This study demonstrates the rarity and importance of the diagnosis of diabetic ketoacidosis and pancreatitis in cancer patients who use PEG-asparaginase. Most of them arrive at the health facility presenting with shock and neutropenia, being diagnosed only as having septic shock. However, the above differential diagnoses must be taken into consideration to provide the most appropriate management to these already immunosuppressed patients.

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