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Case Report

Ketosis Diabetes and Hypertrygliceridemia Induced By L-Asparaginase Administered For the Treatment of Acute Lymphoblastic Leukemia (ALL)

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Abstract

Asparaginase (ASP) is an effective chemotherapy agent extensively used in children with acute lymphocytic leukemia (ALL). There has been a recent interest in using ASP in adults with ALL. We present the case of a 23-year-old patient who presented with fatigue, polyuria, polydipsia associated to a bronchial syndrome and fever with vomiting and abdominal pain. The patient was on chemotherapy for his acute lymphoblastic leukemia (ALL). Blood and urine examination confirmed the diagnosis of diabetic Ketosis. A hypertriglycedemia was also found. The etiology for this both complications was most likely a result of oral glucocorticoid therapy combined with asparaginase therapy. The patient was rehydrated with saline, and antibiotics were administered to treat his infection. He was then slowly brought to euglycemia with sub cutanous insulin injections. Although these complications are relatively rare during the treatment of ALL (prevalence of 10%), frontline providers should be aware of these side effects because delayed diagnosis may lead to a more severe complications such as ketoacidosis or hyperosmolar hyperglycemia with risk of hypovolemic shock and death.

Keywords: Leukemia, Asparaginase, Ketosis, hypertriglyceridemia, HTG.

INTRODUCTION

L-Asparaginase (ASP) has been a key component of the chemotherapy regimens used for acute lymphocytic leukemia (ALL) in children for 50 years [1]. L-asparaginase is reported to cause hyperglycemia in approximately 10% of patients treated for acute lymphoblastic leukaemia (ALL) [2]. There has been a recent interest in using ASP in adults with ALL, particularly the less toxic pegylated formulation: PEG-ASP (a long-acting formulation). Unfortunately, in our case, this formulation was not available. The literature on ASP toxicities is mainly from the pediatric population, with just few reported cases in adults. ASP-related toxicity includes: pancreatitis, liver toxicity, thrombosis, hyperglycemia, hypersensitivity reactions, hyperviscosity syndrome, osteonecrosis and lipemia retinalis [1, 3]. Asymptomatic hypertriglyceredemia (HTG) has also been reported [4, 5], but with just few case reports in adults [6, 7]. Here, we present a case of severe hyperglycemia with diabetic ketosis and HTG secondary to L-asparaginase.

CASE PRESENTATION

A 23-year-old man with acute lymphoblastic leukemia (ALL) presented to the emergency department with asthenia, polyuria, and polydipsia for 4 days, complicated with vomiting and abdominal pain. A cough and fever were also reported. His chemotherapy regimen included vincristine, aracytin, doxorubicin, vinblastine, methrotexate, cyclophosphamide and ASP. He was also taking high-dose corticosteroids (oral prednisone 60 mg/day) that he stopped progressively two weeks before. He had also reported the occurrence of polyuria and polydipsia after his first ASP dose, with spontaneous regression few days later. He had no personal or family history of dyslipidemia, diabetes or thyroid disorders. On examination, temperature was 36.9°C; heart rate 113 beats/min; respiratory rate 20 breaths/min; blood pressure 120/86 mm Hg, capillary blood glucose was elevated to 4,5g/l with ketonuria and glucosuria. Blood assessment showed a normal level of serum creatinine, uremia, bicarbonates, natremia, and kaliemia. Blood glucose was elevated as well as The C-Reactive Protein and triglycerides. There was no clinical or biological evidence of pancreatitis (Table-1). The cytobacteriological exam of urines, abdominal ultrasound, and chest radiography were normal. He received intravenous normal saline. Insulin therapy was started: 10 U of subcutaneous regular insulin. Paracetamol, ceftriaxone, anti emetic and a gastric protection was also administered. He was also continued on insulin therapy: glargine 12 units and insulin aspart units: 08 ui -10- 10ui before each meal. The patient refused to take fibrate for his HTG. After

discharge, the patient TG level decreased to 1g/l after 10 days. Insulin was ceased after a month. To date, the patient remains euglycaemic does not require insulin therapy and is continuing his chemotherapy without ASP.

Table-1: Blood assessment of the patient

Blood assessment	Results	Normal Range
Glycemia	4g/l	0,7 et 1,09
Sodium	139 mmol/l	135-145
Potassium	4.1 mmol/l	3,5-4,5
Bicarbonate	24mmol/l	22-27
Urea nitrogen	0, 38 g/l	0,25-0,48
Creatinine	9mg/l	7- 12
Lipase	16u/l	<60
Triglycerides	7g/l	0,35-1,5
Complete blood count (CBC):		
White blood cell count:	4500/µl	4000-10000
Hemoglobin	14.5 g/dl	12-16
Platelet count	341,000/µL	150000-450000
Lymphocyte	630/µl	1000-4000
C-Reactive Protein	343mg /l	0-5

DISCUSSION

Medication induced diabetes (MID) has been well described in children receiving therapy for ALL [8]. This complication is attributed to specific chemotherapeutic agents, such as L-asparaginase causing pancreaticβ-cell dysfunction, and glucocorticoids leading to insulin resistance [8, 9]. In adults, persistent hyperglycemia is associated with reduced induction success rates [10].

L-asparaginase is extracted from cultures of *Escheria coli* (*Leunase*) and *Erwinia carotovora* (*Porton Asparaginase*). Our patient received *E. coli* derived L-Asparaginase, which maybe more diabetogenic than *Erwinia* L-asparaginase.3. The prevalence of MID during ALL therapy in childhood has been reported to be between 9.7 and 20.4% [11, 12]. The most likely mechanism for hyperglycemia during L- asparaginase therapy is inhibition of insulin production due to L- asparagine insufficiency, as pancreatic beta cells require three L-asparagine molecules to generate each insulin molecule. Alternatively, there may be excessive degradation of existing insulin supplies and hyperglucagonaemia [13]. Our patient presented a cetosis associated to a pulmonary infection occurring in a context of lymphopenia that could be complicated to an acidosis, if he did not consult early. And also could have been avoided if there have been a systematic checking of his glycemia. Specially that he reported a polyuria and polydypsia after the administration of his first asparaginase dose. Eventhough it s is a quite common perturbation and it is self resolving in most cases, it is still unknown whether its occurrence carries any long-term metabolic implications. Specially that a higher prevalence of features of the metabolic syndrome have been shown in adult cancer survivors [14]. This predisposition for the metabolic syndrome further increases the cardiovascular risk experienced by survivors of ALL, caused by the known cardiovascular impact of chemotherapy. The mechanisms and risk factors leading to the development of features of the metabolic syndrome are not well understood. A single study in pediatric patients confirmed impaired pancreatic β-cell function in ALL survivors [15]. In order to assess the relationship with previous development of MID during treatment and metabolic implication, a study that observed a relatively high frequency of impaired glucose tolerance in adolescents with a previous history of MID, most of who are not considered overweight based upon their BMI. Therefore, they recommend a closer monitoring for metabolic diseases in this group of patients when they reach young adulthood [16].

Our Patient Presented Also a HTG that had Spontaneously Regressed

ASP-induced HTG has also been previously reported but mainly in the pediatric literature with just few reports in adults [6, 7]. In a study of 40 adults treated with L-ASP, the overall incidence of HTG was 12.5% (n: 5/40). Most studies have demonstrated a transient and asymptomatic course without pancreatitis, even in patients with severe HTG (TG > 10 g/L) [4]. Overall, pancreatitis is uncommon and affects < 10% of adults treated with PEG [3]. Rare, but more severe, complications of ASP-induced HTG have also been reported such as: hyperviscosity syndrome, thrombo-embolism, osteonecrosis, and transaminitis and lipemia retinalis [17].

The proposed mechanisms of ASP-induced HTG are decreased lipoprotein lipase activity [18]. Which may result in elevated exogenous chylomicrons [19] and increased endogenous very-low-density lipoprotein (VLDL) synthesis [5].Additionally, it's been suggested that ASP may cause a disturbance in lipoprotein metabolism [20]. Whether glucocorticoids

(GC), commonly used in ALL's chemotherapy regimens, or ASP are responsible for the TG elevation has been debatable. Steroids also induce VLDL production in the liver; yet they also increase LPL activity, with may be sufficient enough to prevent severe HTG [18].

We suggest checking baseline TG levels before starting ASP or PEG or during therapy in these patients. In cases of severe HTG (TG > 10 g/ l), it is suggested to hold ASP/PEG [3]. Close monitoring for spontaneous resolution can be attempted in mild or moderate HTG cases [19]. Re-challenging with ASP/PEG has been shown to be well tolerated, but this decision should be made on a case-by-case basis and when TGs have normalized [3, 21]. Immediate dietary modifications and drug therapy is recommended for severe HTG (TG > 10 g/l) to prevent pancreatitis [4]. Dietary interventions should always be considered as first line therapy for HTG. Decreasing total fat (< 10-15% of total calories) and preferring complex carbohydrates, rich in dietary fiber, is recommended [4]. Drugs for long-term management include: fibrates – considered as first-line drug –, omega-3 fatty acids, or niacin [4]. Lashkari and cols. reported four children treated with statins for ASP-induced HTG. The authors questioned its benefits as some patients may have showed TG normalization with just observation [21]. In cases of severe HTG or HTG-induced pancreatitis, in which an immediate decrease in TG is needed, Insulin infusion should be considered – particularly if accompanied by hyperglycemia [22]. Insulin activates lipoprotein lipase (LDL) leading to chylomicron degradation, thus increasing TG clearance.

In HTG patients treated with insulin infusion, a mean TG reduction of 40% was reported within the first 24 hours. But in those patients that were fasting and treated with insulin infusion, the TG reduction was 87% [22]. Cancer patients receiving chemotherapy usually have poor nutritional status and oral intake. So, it is crucial to monitor patients with normoglycemia given their higher risk for hypoglycemia. Plasmapheresis is another costlier option that has also been successfully used in patients with severe HTG (TG > 20g/l) and HTG-induced pancreatitis [23, 24]. The literature review showed limited evidence in adults. As seen in other cases, patients who develop PEG-induced HTG tend to be asymptomatic and respond to conventional therapies for HTG as well as discontinuation of PEG.

CONCLUSION

We therefore encourage clinicians to monitor blood glucose, and triglycerides rate regularly, during treatment with L-asparaginase. Blood ketone levels should also be checked if hyperglycemia develops. Preferential use of Erwinia-derived rather than E. coli derived L-asparaginase should be considered. Even though these reported side effects are rare and self resolving, but informing the patient about the possibility of their occurrence remains important. This will avoid any delay of the diagnosis that may make the prognosis worse in the context of these patients.

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