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Case Report

Asparaginase and Steroids-induced Extreme Hypertriglyceridemia in a Child with Acute Lymphoblastic Leukemia

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Asparaginase has been used in the treatment of childhood acute lymphoblastic leukemia (ALL) for more than 30 years. It is combined with steroids in most pediatric ALL treatment protocols and hyperlipidemia is a common side effect. However, severe hyperlipidemia is rare. Risk of major clinical complications increases significantly when serum triglyceride level is greater than 1,000 mg/dl. Here, we report a child with ALL who developed extreme hypertriglyceridemia without clinical symptoms during reinduction of maintenance therapy. Following administration of oral gemfibrozil, her triglyceride and cholesterol levels gradually fell to within normal range. Further treatment of ALL was not altered and her hyperlipidemia resolved without sequelae.

Keywords: acute lymphoblastic leukemia, asparaginase, hyperlipidemia, hypertriglyceridemia

Introduction

Asparaginase is an effective drug in the treatment of childhood acute lymphoblastic leukemia (ALL) and has been an important component of most childhood ALL regimens for more than 30 years[1]. Asparaginase can cause a variety of side effects, including hypersensitivity reactions, pancreatitis, hyperglycemia and hypoglycemia, as well as increased risks of both bleeding and thrombosis. Asparaginase and steroids are often used together in children with ALL and both have profound effects on lipid metabolism. Therefore, hyperlipidemia is common in these patients. Mild hyperlipidemia is rarely associated with severe complications. However, the risk of major clinical problems, such as pancreatitis and neurological complications, increases significantly when triglyceride (TG) level is greater than 1,000 mg/dl[2]. Here, we report a patient with ALL who developed extreme hypertriglyceridemia without clinical symptoms during reinduction of maintenance therapy. Following administration of oral gemfibrozil, her TG and cholesterol levels gradually fell to within normal range and further treatment of ALL was not altered.

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Case Report

A previously healthy 13-year-old girl (weight 75th percentile, height 75th percentile, body mass index 22.1) displayed symptoms of fever and epistaxis for 2 weeks. The complete blood count revealed an elevated leukocyte count (92.41×10^9/l) with circulating blasts (84%). Platelet count

and hemoglobin were 28×10^9/l and 13.2 g/dl, respectively. The diagnosis of B-precursor ALL was made after bone marrow examination and cytogenetic analysis of the bone marrow blasts showed 46,XX, der(19) t(1;19)(q25;q13.1)[10]/46,XX[4]. She did not have a family history of lipid disorders. The initial serum levels of fasting glucose, cholesterol and TG were within normal range.

Five-week induction was implemented based on the Taiwan Pediatric Oncology Group ALL 2002-High Risk protocol with prednisolone, vincristine, epirubicin, and asparaginase[3]. She completed induction chemotherapy without significant side effects and complete remission was achieved. Further, she received four courses of high dose methotrexate (5 g/m^2) with 6-mercaptopurine and triple intrathecal therapy as consolidation treatment according to the protocol. Although there were two episodes of leukoencephalopathy, which may have been associated with the use of methotrexate, the girl was quite well without any neurological symptoms at the beginning of maintenance therapy.

There were no prior hyperglycemic episodes. Asparaginase (10,000 U/m^2) was administrated on day 1 of the 3rd week of maintenance therapy with daily 6-mercaptopurine. Dyspnea with Kussmaul respirations and poor oral intake were noted on day 5. Laboratory evaluation showed hyperglycemia (glucose level 703 mg/dl) and metabolic acidosis with the presence of urinary ketones, which met the criteria for diabetic ketoacidosis (DKA). Elevation of TG (989 mg/dl) and cholesterol (358 mg/dl) levels was also found. There were no other concurrent events, such as infections. With insulin use and adequate fluid management, she recovered quickly without any sequelae or the need for additional medication. She continued to receive chemotherapy according to the protocol without any alterations. Serum lipid and glucose levels returned to within normal range.

Fig. 1 A heparinized tube of blood from the patient described in this case report demonstrating the lactescence of the plasma.

Three-week reinduction was started at week 7 of maintenance therapy. She was scheduled to receive weekly vincristine (1.5 mg/m^2) and three-times-weekly asparaginase (6,000 U/m^2), as well as epirubicin (30 mg/m^2) on days 1 and 8 and oral dexamethasone (8 mg/m^2) on days 1-8 and 15-21. On day 15, routine laboratory evaluation revealed extreme hypertriglyceridemia (8,462 mg/dl) and high serum cholesterol level (1,143 mg/dl) without any clinical symptoms. Markedly lactescent blood was noted (Fig. 1). Her fasting glucose level was 80 mg/dl. There was no evidence of pancreatitis and amylase and lipase concentrations were normal. Magnetic resonance image of the brain showed no vascular thrombosis. Moreover, her apolipoprotein E genotype was normal (E3E3). Due to the absence of associated clinical manifestations, only an antilipidemic agent (gemfibrozil) was used and her TG and cholesterol levels gradually returned to within normal range. On regular antilipidemic medication during maintenance therapy, she completed therapy without alterations in the protocol. She is now in complete remission and doing well without any medication. Follow-up laboratory examinations were normal.

Discussion

Asparaginase and steroids are commonly used in combination to treat ALL. Although both agents have been implicated in aberrant lipid metabolism, severe hyperlipidemia is rare. Parsons et al. demonstrated that 67% of children with ALL have fasting TG levels above 200 mg/dl during asparaginase therapy and only 19% have levels above 1,000 mg/dl[4]. The mean peak TG level in that study was 465 mg/dl. More recently, Cohen et al. reported a 72% incidence

of hypertriglyceridemia in pediatric patients with ALL during asparaginase therapy, with only 12% of patients with TG level greater than 1,000 mg/dl[5]. Our patient developed extreme hypertriglyceridemia during reinduction therapy. We have not previously found such a high TG level (8,462 mg/dl; normal range 20 to 110 mg/dl) in a patient receiving asparaginase therapy without clinical symptoms.

The mechanisms underlying asparaginase-induced hyperlipidemia are manifold. There are no clinical or laboratory features that distinguish patients who are at risk while receiving therapy[5,6]. No correlation has been found between increased TG levels and age, gender, or risk factors of leukemia. As apolipoprotein E polymorphism has been found to be associated with dyslipidemia in many disease states[7-9], the patient underwent apolipoprotein E genotyping to search for a genetic predisposition to severe hypertriglyceridemia. E3E3 genotype was normal. From published case reports and studies, most patients with high TG levels during induction therapy are associated with the long-term use of steroids[10]. Our patient developed extreme hypertriglyceridemia during reinduction of maintenance therapy after complete resolution of DKA. We speculated that the cause of hyperlipidemia in this case was impairment of lipid metabolism from subclinical insulin deficiency or insensitivity after DKA, even though all laboratory parameters had returned to within normal range.

There is no consensus on the management of asparaginase-associated hyperlipidemia in children with ALL. Several reports have suggested plasmapheresis to treat symptomatic severe hypertriglyceridemia[11, 12]. Administration of insulin or heparin has been used to reduce TG concentrations[6, 13]. Asymptomatic patients usually receive conservative treatment only[5]. Due to many unidentified factors, there is no useful parameter to distinguish patients who will experience serious events from those whose hypertriglyceridemia will resolve on its own. Considering the risks of further increase in TG levels and development of severe complications, oral gemfibrozil was given in our patient. Further treatment of ALL was not altered, and her hyperlipidemia resolved without sequelae.

Treatment of severe hyperlipidemia in patients with ALL depends on the clinical symptoms and TG levels. In patients with extreme hypertriglyceridemia, treatment can prevent further increase in TG levels and development of severe complications. Given the serious nature of the underlying disease and the value of asparaginase and steroids in the treatment of ALL, no modification of the antileukemic therapy should be contemplated for patients with asparaginase-induced hyperlipidemia.

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