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# **CASE REPORT**

### L-ASPARGINASE INDUCED SEVERE HYPERTRIGLYCERIDEMIA: UNUSUAL COMPLICATION AND TREATMENT

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#### Abstract:

L-asparginase is an integral part of various multi-modality pediatric inspired protocols in the management of acute lymphoblastic leukemia in young adults. Severe hyperlipidemia is uncommon but occasionally a dangerous complication of L-asparginase in the treatment of acute lymphoblastic leukemia. Because L-asparaginase associated hyper triglyceridemia (TG) is usually asymptomatic and resolves after drug discontinuation, its importance has been largely overlooked in the medical literature. However, increased awareness of the possibility of L asparginase-associated hyperTG may help alleviate serious complications of hyperTG including acute pancreatitis and neurological symptoms owing to hyper viscosity we hereby report two such cases and our experience in treating them.

Keywords: L-asparginase, hyper triglyceridemia, case report

#### **INTRODUCTION:**

Young adults diagnosed with acute lymphoblastic leukemia are treated withpediatric inspired intensive treatment protocols. Our institute uses the BFM 90 protocol which includes multiple chemotherapeutic agents like prednisolone, vincristine, daunorubicin, l-asparginase, cytarabine, 6-Mercaptopurine, cyclophosphamide, high dose methotrexate and includes prophylactic cranial irradiation in moderate and high risk patients. L-asparginase is an integral part of this regime and is used in the induction as well as delayed intensification phases. Common side effects of L-asparginase include gastrointestinal symptoms like nausea, vomiting, and abdominal pain. While rare but life threatening side effects include anaphylactic reaction, acute pancreatitis and acute thrombo-embolic phenomenon. Severe Hypertriglyceridemia along with hyperglycemia in the absence of pancreatitis is a very rare event with only few anecdotal case reports. Two of our patients experienced severe hyperlipidemia with hyperglycemia requiring GPI(glucose potassium insulin infusion) and were successfully managed conservatively. We recommend monitoring of serum lipid levels especially when patients are on corticosteroids with L-asparginase and early and timely intervention.

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#### CASE 1

26 year old male presented with a twoweek history of fever and petechie, CBC revealed pancytopenia (Hb – 5.9 gm/dl ,Wbc – 700 cells/cmm ,Platelet count – 10,000/cmm ), peripheral smear examination revealed 90 % blasts. Baseline renal, hepatic and coagulation functions werenormal .Tumourlysis(TLS) profilewas normal. Hepatitis B surface antigen test was positive, however hepatitis B e antigen was negative. Lamivudine was started. Ultrasound of the abdomen was normal. Bonemarrow aspiration and immunophenotyping was suggestive of pre B cell Acute Lymphoblastic Leukemia. Cytogenetic study revealed Ph chromosome positivity on FISH analysis. He was started on BFM 90 induction protocol with Prednisolone. Vincristine, Daunorubicin, Imatiniband prophylactic IT Methotrexate were added on day 8 of protocol, and L-Asparginase was added on day 12 as per protocol.Patient was tolerating chemotherapy well, with objective response in the form of increased Hb, platelet count and disappearance of blasts from peripheral blood. He received his 7<sup>th</sup> dose of L- asparginase and was due for day 29 of induction protocol, when he presented to our institute with severe body ache, high grade fever and abdominal pain, which was deep seated and boring in character. Clinical impression of L Asparginase induced pancreatitis was made. He was kept nill by mouth(NBM), started on I.V Fluids and I.V antibiotics. Investigations revealed normal counts, renal and liver function. Sr.Lipase was 61 U/L (Nupto 60 U/L), serum electrolytes were normal.. CT scan of abdomen revealed normal Pancreas, mild hepatomegaly and left sided basal patchy consolidation. However the pathologist noted a highly lipemic sample and advised lipid profile.Sr.Lipids revealed severe Hypertriglyceridemia( 3751.7 mg %) {N < 150 mg % ), with increased Sr.Cholesterol (466.4 mg %, N < 160 mg %, random blood sugar( RBS) was 301 mg/dl. Abdominal pain, severe bodyacheand fever persisted. Antibiotics were stepped up, and patient was started on a Glucose potassium insulin drip (GPI drip) for hypertriglyceridemia (starting with 2 units/hr, in dextrose solution with 2 ampoules of potassium chloride, RBS charting was done rigorously, and insulindextrose titrated to maintain RBS between 100 - 150 mg/dl).Over next 90 hours lipid profile dramatically improved to Sr.TG to 296 mg% and Sr.Cholesterol to 173 mg%. Symptoms of bodyache, which was later attributed to possibly hyper viscosity subsided and fever eventually responded to anti fungal agents. He was shifted to oral antibiotics, antifungals and fenofibrates. Lipid profile and RBS normalized .Further monitoring of lipid profile over the next few months was normal. His family was screened to rule out familial autosomal dominant type 5 hyperlipidemia, which was negative. He was shifted to the less intensive MCP 841 protocolwith the exclusion of L Asparginase in view of life threatening fungal pneumonia. At present he is on maintenance phase 3 of MCP 841 protocol and doing well.

#### CASE 2;

15 year old female presented with 10 days history of generalized weakness and low grade fever , CBC revealed pancytopenia (Hb 8.4 gm/dl , WBC 3,100/cumm , platelet count -17,000/cumm) , peripheral smear -27 % blasts ) baseline renal , hepatic and coagulation profile were normal. TLS profile was normal. X ray chest and USG abdomen were normal. Viral markers were negative. Bone marrow examination and Immunophenotyping was suggestive of pre B Acute lymphoblastic leukemia.Cytogenetic study was normal. She was started on BFM 90 protocol with steroids. Vincristine, Daunorubicin and intrathecal methotrexate were added on day 8 of

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protocol. L Asparginase was added on day 12 as per protocol. She was tolerating chemotherapy well, and responding in the form of improvement in Hb, Platelet count with disappearance of blasts from the periphery. Post day 22 of induction, on receiving her 6<sup>th</sup> dose of L asparginase, she was admitted with severe generalizedbodyache, malaise andabdominal pain. Clinical diagnosis of L asparginase induced pancreatitis was made. She was admitted and kept nill by mouth and I.V fluids and supportive treatment was administered. Investigations revealed Hb -7.6 gm/dl, WBC - 2,300 /cumm, platelet count - 1,30,00 /cumm. Hepatic, Renal and Coagulation parameters were normal. Sr.Lipase was normal (21 U/L, N <60 U/L). RBS was normal (81 mg/dl). Ultrasound abdomen was suggestive of mildly bulky pancreas. Sr.Lipids revealed severe hypertriglyceridemia and hypercholesterolemia (Sr.TG - 873 mg/dl , - 250 mg/dl.) In view of persistence of symptoms and no response to Sr.Cholesterol conservative management. She was started on GPI (Glucose potassium insulin drip) for the next 72 hours. Her symptoms resolved. Her lipid profile steadily improved over the next 4 days (Sr.Cholesterol 196 mg/dl, Sr.TG - 100 mg/dl) . She was shifted to oral fenofibrates. L Asparginase was avoided from her protocol. She was continued on BFM 90 protocol and is currently on BFM maintainence protocol M4 and her last lipid profile was normal.

### DISCUSSION

L Asparaginase (LA), an effective drug in the treatment of childhood ALL, has become an important component of most childhood ALL regimens during the remission induction or intensification phases of treatment. The drug depletes the blood of asparagine, a nonessential amino acid on whichmany cells depend for normal metabolic processes. Whereas normal cells compensate by synthesizing L-asparagine from aspartic acid and glutamine via the enzyme, asparagine synthetase, selected malignant lymphoid cells have low levels of the synthetic enzyme and depend on intracellular pools of L-asparagine for protein synthesis and cell functioning<sup>1,2</sup>. LA treatment is associated with acute side effects that include unpredictable toxicities such as allergy (20%), thromboembolic events (2% to 11%), and severe pancreatitis  $(4\% \text{ to } 7\%)^{3,4}$ . LA has been reported to cause abnormalities in lipid metabolism, ranging from hypercholesterolemia and hypotriglyceridemia to hypercholesterolemia and hypertriglyceridemia during asparaginase therapy<sup>5</sup>

The pathogenic mechanism seems to be due to an increase in the endogenous synthesis of verylow-density lipoprotein (VLDL) during LA administration and a decrease in lipoprotein lipase (LPL) activity with a consequent decrease in the removal of TGs from plasma<sup>6,7</sup>.LPL is the ratelimiting enzyme for the removal of TGs from the circulation; the fasting plasma concentration of TGs correlates with LPL activity<sup>8</sup>. In addition to the effects of LA on lipid metabolism, both the diagnosis of ALL and the use of other chemotherapeutic agents, notably corticosteroids, have been associated with alterations in lipid synthesis and clearance<sup>7,9</sup>. During treatment with corticosteroids, an extensive production of TG-rich lipoproteins occurs<sup>10</sup>. On the other hand, corticosteroid treatment results in increased LPL activity, which is thought to be sufficient to prevent extreme hypertriglyceridemia in patients treated with corticosteroids alone<sup>10</sup>

In order to determine the incidence of LA associated hyperTG, Parsons et al<sup>7</sup> evaluated a group of 37 paediatric patients with ALL treated with L- asparaginase. Their mean peak TG level during L-asparaginase therapy was 465mg/dL, compared with 108mg/dLpre-treatment. Thirteen

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patients (35%) had no TG elevation. Sixty-seven percent of newly diagnosed patients had fasting TG levels greater than 200mg/dL, 42% had levels greater than 400mg/dL, and 19% had levels greater than 1000mg/dL during L- asparaginase therapy. Similarly, Cohen et al<sup>11</sup> found that 72% of 42 newly diagnosed children with ALL had TG levels above 200mg/dL, 29% had levels higher than 400mg/dL, and 12% had TG levels above 1000mg/dL. None of the patients in either study with severely elevated TG level greater than 1000mg/dL developed pancreatitis. They suggested that it usually has a benign course and does not warrant treatment , while there are multiple case reports of LA induced hyperTG induced pancreatitis. One of our patients with a TG level greater than 3000mg/dL did not have clinical or laboratory evidence of pancreatitis. Not all pancreatitis is associated with hyperTG, and not all hyperTG is associated with pancreatitis

There are no guidelines for the treatment of LA-associated hyperTG, in part because there is no single typical clinical course of hyperTG after LA therapy. A patient's clinical course may vary depending on the maximum TG elevation and a number of unidentified factors. HyperTG sometimes, but not always, leads to serious sequel, including pancreatitis, clotting issues, and hyper viscosity of the blood. However, there is currently no way to distinguish patients who will experience serious events from those whose hyperTG will resolve on its own. Similarly, there are no reports of clinicians restarting asparaginase therapy after discontinuing therapy because of hyperTG. Steinherz<sup>12</sup> reports the only case in which LA was administered for 3 doses past the occurrence of severe hyperTG, but was discontinued due to "concerns about the persistent lethargy and hyperlipemia."

Both insulin and heparin decrease serum TGs by stimulating LPL activity, which degrades TGs into fatty acids and glycerol. Insulin and heparin treatment have been used together to successfully reduce plasma TG concentrations. Jain and Zimmerschied<sup>13</sup> report a case where a 54-year-old male presented with hyperTG-induced acute pancreatitis. His serum TG level decreased by 50% within 24 hours of initiation of insulin and heparin infusion. Similarly, Mongaet al<sup>14</sup> report a 51-year-old man with hyperTG-associated pancreatitis. His treatment with heparin and insulin was accompanied by reduction in serum TG levels and resolution of pancreatitis in 5 days. The authors of these reports conclude that heparin and insulin can be considered as a safe treatment modality for reducing TG levels in patients with hyperTG-associated pancreatitis

Treatment of asparaginase-associated hyperTG varies from conservative therapy—observation, discontinuation of asparaginase therapy, and dietary fat restriction—to more intensive treatment ranging from fibrate therapy to insulin infusion to plasmapheresis<sup>15</sup>

We report two cases of hyperTG and hyperlipidaemia in young adults on BFM 90 protocol in induction phase therapy for ALL. Severe lipemia was noted after 6<sup>th</sup> and 7<sup>th</sup> doses of LA respectively. Both the patients presented with non-specific symptoms. Neither had biochemical evidence of pancreatitis. Decision to treat was made in view of persistence of symptoms on watchful expectancy. Both patients were treated with insulin infusion drips, glucose and potassium were added as per standard practices to counteract insulin induced hypoglycaemia and hypokalaemia. Although plasmapheresis appears to lower serum TG levels more rapidly than insulin and heparin infusions, it does require placement of large bore venous catheters and availability of an apheresis machine. As our patients did not have signs or symptoms of

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pancreatitis, we elected to treat them initially with insulin infusion rather than plasmapheresis. We decided to forego heparin therapy in our patient with acute leukemia to lessen their risk of bleeding complications.

#### CONCLUSION

L-asparaginase-associated hypertriglyceridemia (TG) is a common asymptomatic abnormality with protean presentations ranging from accidental discovery by pathologist to rarely life threatening events. It usually resolves after drug discontinuation, its importance has been largely overlooked in the medical literature. We recommend close monitoring of lipid profile while on L Asparginase therapy and treat those patients who are symptomatic or have life threatening complications of hyperlipidaemia .Increased awareness of the possibility of L asparginaseassociated hyperTG may help alleviate serious complications including acute pancreatitis and neurological symptoms owing to hyper viscosity

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