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Pegylated L-Asparaginase Induced Cholestatic Jaundice and Treated with Oral L-Carnitine; A Case Report

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Abstract

Various chemotherapeutic regimens are available for the treatment of acute lymphoblastic leukemia (ALL). While providing improved cure rates these regimens are also associated with various systemic toxicities including hepatotoxicity. L-Asparaginase is a commonly used drug in various combination regimens for the treatment of both adult and childhood ALL. Most observed side effect is hypersensitivity followed by liver injury. 85% of all the patients treated with L-Asparaginase develop hepatic steatosis whereas Cholestatic jaundice is infrequently seen. Timely identification and management of this entity can prevent progression to fatal liver failure. We, here, describe a patient of acute lymphoblastic leukemia diagnosed on bone marrow biopsy and immunophenotyping who developed Cholestatic jaundice after induction chemotherapy using L-Asparaginase, Vincristine, Daunorubicin and Dexamethasone. He was identified earlier and was given a good supportive management along with holding chemotherapy. He recovered within a span of two weeks and is on maintenance chemotherapy doing well on last follow up.

Keywords: Acute lymphocytic leukemia, asparaginase, l-carnitine

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Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous clonal malignancy which affects lymphoid progenitor cells. The peak age of presentation is 2-5 years however, it can be presented in both children and adults.[1] ALL is treated with different range of intensive combination chemotherapeutic regimens; currently available regimens show cure rate of 40-50% in adults and 85-90% in children.[2] Advancement in understanding of the genetics of the disease may help in development of targeted. However, currently available majority of the chemotherapeutic drugs are associated with systemic toxicities. L-asparaginase is a commonly used drug in combination chemotherapy for ALL. *Normal cells can produce their own asparagine (amino acid) whereas malignant cells (e.g. lymphoblast) acquire asparagine from blood to support their own growth. L-asparaginase aids to deaminate asparagine into aspartic acid, hence, deprives the tumor cells from essential amino acid.* Three types of L Asparaginase formulations are commercially available. It is a bacterial enzyme which can be obtained from two different types of bacteria i.e. *Escherichia coli* and *Erwinia carotovora. Native E-coli asparginase and pegylated asparginase (PEG asparaginase) both are obtained from E-coli. Erwinia asparginase is obtained from Erwinia carotovora.*[3-4] *Frequently observed side effects of* conventional L-asparaginase therapy are hypersensitivity, thrombosis, pancreatitis, hepatotoxicity and hyperglycemia. PEG preparation has a long serum half-life, so it produces prolonged depletion of asparagine and shows less frequency of immunological and non-immunological reactions.[3] Erwinia asparaginase preparation is used as a second line treatment when patient develops hypersensitivity to other types of asparaginases.[5] Hepatic injury induced by asparaginase can present as mild to moderate Cholestatic jaundice, macro vesicular steatosis or fatal hepatic failure.[6] We here describe a patient who developed Cholestatic jaundice after induction chemotherapy for B-Acute lymphoblastic leukemia where PEG Asparaginase (Oncasper) was used along with other chemotherapeutic agents.

Case Report

A-30-years old male presented with a history of fever, generalized weakness, and bone pains on and off for the past two months. No symptoms and signs related with bleeding tendency were seen. He was recently diagnosed diabetes mellitus for which he has been taking insulin (Humulin 70/30). His past medical history was significant for renal calculi and was being operated for deviated nasal septum 15 years back. He belonged to a middle-class socio-economic status. His baseline workup was done, and he was diagnosed as B- Acute lymphoblastic leukemia on bone marrow biopsy and immunophenotyping. He had no evidence of central nervous system (CNS) disease at

the time of the presentation. Induction chemotherapy was started by using UK ALL Protocol XI with Daunorubicin, Vincristine, Pegylated L-Asparaginase and corticosteroid. CNS prophylaxis was given in the form of intrathecal administration of Methotrexate, Cytosar and Hydrocortisone as per protocol.

Baseline workup at the time of induction chemotherapy was as follows: Table I & II.

Table I: Complete Blood Count

Parameter	Results
Hemoglobin	8.6 g/dl
Total leukocyte count	31.3 x10^3/ l
Platelets	13 x 10^3/ l
Neutrophils	04 %
Lymphocytes	08%
Blasts	88%

Table II: Bone Marrow Findings

1. Trephine biopsy findings: Bone marrow is diffusely infiltrated with blast cells with markedly suppressed normal hematopoiesis.	
2. Immunohistochemistry:	
CD Markers	**Interpretation**
Tdt	Diffuse positive in blast cells
PAX-5	Diffuse positive in blast cells
CD 10	Diffuse positive in blast cells
CD20	Diffuse positive in blast cells
CD3	Negative in blast cells
MPO	Negative in blast cells
3. Bone marrow cytogenetics: 20 Metaphases were counted, and 06 cells showed Monosomy 10 (45 chromosomes); whereas the remaining 14 cells showed 46 number of chromosomes.	
4. RT – PCR: BCR- ABL1 p190 –Not detected	

Based on these baseline investigations the diagnosis of B-Acute lymphoblastic leukemia was made. Further workup was done before starting chemotherapeutic regimen. Biochemical profile including liver function tests and renal function tests were unremarkable except for serum LDH which was raised as shown in Table III.

Ultrasound whole Abdomen: Spleen size 16 cm and shows normal appearance, liver size 18 cm parenchyma shows normal echo texture.

His course of chemotherapy remained stable except for complaints of nausea, anorexia and lethargy. He received PEG Asparaginase (Oncasper) on Day 3 of induction chemotherapy along with other chemotherapeutic agents like Vincristine, Daunorubicin and Corticosteroid. Concurrently he also received intravenous Tazobactum, Pipperacillin and Amikacin for febrile neutropenia and oral Fluconazole as a fungal prophylaxis. Meanwhile his LFTs were checked after every 2 – 3 days interval. However, on Day 13 of induction he developed jaundice, right upper quadrant tenderness and pedal edema. His total billirubin elevated to 5.5 mg/dl and rose up 15.9 on day 15 of chemotherapy. There was gradual rise in ALT and GGT were also observed as shown in Table IV.

Table III: Biochemical profile and viral screen.

1. **LFTs**		
Parameter	**Results**	**Normal Ranges**
Total bilirubin	0.3	(0.2-1.2mg/dl)
Conjugated bilirubin	0.1	(less than 0.5mg/dl)
Unconjugated bilirubin	0.2	(0.1-1.0mg/dl)
ALT	31	(less than 55 U/L)
AST	28	(5-34 U/L)
Alkaline Phosphatase	156	(less than 500 U/L)
GAMMA GT	85	(10-64 U/L)
Total Protein	7.2	(6.0-8.5 G/dl)
Albumin	3.3	(3.5-5.0 G/dl)
Globulin	3.9	(1.8-3.5 G/dl)
Albumin/Globulin Ratio	0.8	(1.0-2.2)
RFTS:		
Urea	22	10-50 mg/dl
Creatinine	0.9	0.7-1.3 mg/dl
3. LDH	743	120-220 U/L
4. S/Amylase	26	25-125 U/L
5. Viral screen		
HBsAg	**Non-reactive**	
Anti-HCV	**Negative**	
Anti-HIV 1 and 2 antibodies	**Negative**	

USG Abdomen was done at the time of jaundice which revealed enlarged fatty liver 18 cm in size and spleen of 16 cm. It ruled out biliary obstruction.

Treatment: His dose of Vincristine and L-Asparaginase was held and he was started on supportive management which included oral L- Carnitine 990mg twice a day, oral Ursodiol 500 mg twice a day, I/V Omeprazole 40 mg once a day, I/V Drotaverine 40 mg four times a day, Inj. G-CSF 300 mg S/C once a day, Inj. Vitamin K 5 mg I/M once a day. These all above mentioned drugs were given for a week.

Meanwhile he also received red cell and Platelet transfusions for the correction of anemia and thrombocytopenia respectively. In addition, he was given intravenous fluid support with Normal saline 1000ml at the rate of 50ml / hour / day.

Table IV: Serial LFTs.

Parameters	Day +13	Day +14	Day +15	Normal Ranges
Total bilirubin	5.4	11.4	15.9	(0.2-1.2mg/dl)
Conjugated bilirubin	3.8	8.5	10.5	(less than 0.5mg/dl)
Unconjugated bilirubin	1.6	2.9	5.4	(0.1-1.0mg/dl)
ALT	85	83	101	(less than 55 U/L)
AST	58	28	29	(5-34 U/L)
Alkaline Phosphatase	131	271	492	(less than 500 U/L)
GAMMA GT	132	158	229	(10-64 U/L)
Total Protein	3.6	3.9	4.2	(6.0-8.5 G/dl)
Albumin	1.9	1.8	1.9	(3.5-5.0 G/dl)
Globulin	1.7	2.1	2.3	(1.8-3.5 G/dl)
Albumin/Globulin Ratio	1.1	0.9	0.8	(1.0-2.2)

Outcome and Follow-Up: Patient showed gradual improvement over a period of 10 days. His jaundice, right upper quadrant tenderness and pedal edema were settled. His total bilirubin was reduced to 2.3 mg/dl after 10 days of withholding chemotherapy. Gradual decrease in Alkaline phosphatase, ALT and GGT were also observed.

As we ruled out all other potential causes of Cholestatic hepatic injury we concluded our diagnosis as L-Asparaginase induced Cholestatic jaundice. The patient is on maintenance chemotherapy and was doing well on the last follow up.

Discussion

Chemotherapeutic drugs are associated with a wide range of systemic toxicities including hepatotoxicity. Hepatic steatosis can be seen in up to 85% of patients treated with L-asparaginase but Cholestatic jaundice is a less frequently seen entity.[7] Potential causes of Cholestatic jaundice must be ruled out before concluding chemotherapy related liver toxicity; as reactions to analgesics, antibiotics , pre-existing problems like hepatitis viruses, veno-occlusive disease, parental nutrition, and immune suppression may all lead to hepatic injury.[8] In 1960s overall survival of children with ALL was <30% and it has markedly improved up to 90% over the years and that is at least in part contributed by addition of L-asparaginase to the combination chemotherapy regimens. However, not all the patients receive full course of asparaginase due to associated toxicities.[9] Mild hepatic injury like hepatic steatosis or Cholestatic jaundice if managed promptly can save the patient from progression to fatal liver failure. Although literature reviews show rare cases of fatal hepatotoxicity, it is still an existent entity. A Japanese case report shows development of fulminant hepatic failure by therapy with L-asparaginase during induction chemotherapy in a patient with acute lymphoblastic leukemia.[10] Similarly another case has also been reported as fatal hepatic failure after being treated with L-asparaginase for adult ALL; this patient progressed to multi organ failure from mild micro vesicular hepatic steatosis and mixed liver injury.[6]

Drug induced steatohepatitis and Cholestatic jaundice resolves with good supportive care as is shown in several case reports. A 52-years-old male treated with L-asparaginase for ALL developed steatohepatitis during neutrophils recovery phase and was managed with antioxidants successfully.[11]

Micro vesicular steatosis, macro vesicular steatosis and Cholestasis are caused by accumulation of unoxidized substances (i.e. fatty acids) in the hepatocytes which in turn is caused by mitochondrial dysfunction. Thus, administration of mitochondrial co-factors aids in resolving these conditions.[12] Vitamin B- complex when administered along with L- Carnitine (mitochondrial co-factor) improves recovery period for steatohepatitis.[13] In addition L-Carnitine also has a potential to improve hepatotoxicity caused by L- asparaginase in patients with preexisting liver disease.[14] Additional supportive measures include administration of intravenous fluids, low fat diet and analgesia.[15] A group of experts gathered in London in 2019 for a roundtable discussion regarding management of toxicities induced by treatment with asparaginase in ALL patients. The suggestions were to reduce dose of L-asparaginase during hyperbilirubinemia and later give full dose in addition to supportive management. [16]

Conclusion

Cholestatic jaundice is an infrequently seen adverse effect of L-Asparaginase therapy. Timely identification, with holding chemotherapy drugs and good supportive care can prevent worsening of the condition as well as help in prompt recovery of the patient.

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