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An Interesting Case Of Intermittent Unconjugated Hyperbilirubinemia In A Child With Acute Lymphoblastic Leukemia

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Abstract

Chemotherapy for acute leukemia may sometimes result in hyperbilirubinemia in the absence of liver dysfunction. We report a 13 year old female with relapsed T-cell acute lymphoblastic leukemia (ALL) who had intermittent, reversible and transient indirect hyperbilirubinemia during chemotherapy. Indirect hyperbilirubinemia was transient and reversible during first remission, but it was not reversible to normal levels during induction of second remission and thus she was investigated for underlying autoimmune vs. chronic hemolytic anemia. As no evidence of hemolysis was observed, thus uridine diphosphate-glucuronyl transferase 1A1 (UGT1A1) assay was done that suggested minimal enzyme activity. Hence, Gilbert syndrome (GS) should be considered as a cause in unexplained cases of indirect hyperbilirubinemia among patients undergoing chemotherapy.

Keywords: Gilbert's syndrome, bilirubin, chemotherapy

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood accounting for 80% of all pediatric cancers. The use of more intensive chemotherapy regimens have improved outcome of children with ALL during the last decades, albeit at the expense of more toxicity. Children with ALL frequently present with hepatomegaly and mild liver functional impairment. Mild hyperbilirubinemia due to liver damage secondary to chemotherapy is frequent but usually transient[1]. In most chemotherapy protocols, hyperbilirubinemia above certain thresholds is a parameter that dictates modifications in schedule and dosage of chemotherapeutic agents. Isolated elevation of unconjugated bilirubin is an uncommon event in individuals receiving chemotherapy. We present an interesting case of intermittent indirect hyperbilirubinemia in a child with acute lymphoblastic leukemia and also discuss the challenges in management.

Case Presentation

A 13 year old female child, follow up case of relapsed T- cell ALL was noticed to have mild unconjugated hyperbilirubinemia (1.2 mg/dl) at the time of relapse. During induction of remission, her unconjugated bilirubin levels increased to 2.4 mg/dl. This increase in bilirubin was initially attributed to chemotherapy. The levels returned to normal after induction. However, during consolidation phase she again developed hyperbilirubinemia (total bilirubin/ indirect bilirubin 3.8/3.0 to 7.4/6.2) following intermediate dose methotrexate (2.5gm/m²/dose). Hence, further chemotherapy was deferred. In follow up, as she had persistent mild hyperbilirubinemia (total bilirubin/ indirect bilirubin 2.5/1.9) her medical records were reviewed. She was found to have similar intermittent transient, unconjugated

hyperbilirubinemia episodes (ranging from 1.1 mg/dl to 2.2 mg/dl) without any evidence of liver dysfunction during first remission also. Of note her transaminases and other liver functions were always normal. As the levels of bilirubin were higher this time the child was again investigated for causes of liver dysfunction. Her viral hepatitis work up that is HbsAg, anti HCV IgM, anti HAV IgM, anti HEV IgM were normal. Also, she had normal liver enzymes, serum albumin, alkaline phosphatase, PT/ aPTT/ INR and ultrasound abdomen. As no cause could be found and she had indirect hyperbilirubinemia, she was investigated for cause of underlying hemolysis. She had normal serum LDH, high performance liquid chromatography (HPLC), osmotic fragility, G6PD level and negative Coombs test. General blood picture was suggestive of normocytic normochromic blood picture with reduced total leucocyte count and a normal platelet count. As no evidence of hemolysis or liver dysfunction could be ascertained, UGT1A1 estimation was done. She was found to have two extra bases (TA) in the promoter region of UGT1A1 and had a (TA)7TA sequence, known as UGT1A1*28 resulting in minimal enzyme activity. Hence Gilbert syndrome was established as a cause of intermittent hyperbilirubinemia in this case.

Discussion

Gilbert's syndrome is a hereditary bilirubin mechanism disorder due to decreased activity of uridine diphosphate-glucuronyl transferase 1A1 (UGT1A1) causing intermittent unconjugated hyperbilirubinemia with otherwise normal transaminases and liver function tests in the absence of structural liver disease or hemolysis[2]. It is an autosomal recessive condition, mainly associated with variations in gene for UGT1A1[2]. In our patient UGT1A1*28/28 genotype was detected and she was homozygous for A(TA)7TAA genotype suggestive of Gilbert syndrome. UGT1A1 is the enzyme required for conjugation and clearance of bilirubin. Gilbert syndrome is one of the common genetic but benign cause of unconjugated hyperbilirubinemia with a population frequency of 5-10% worldwide[3]. There is scarcity of adequate literature on GS in pediatric population in indian subcontinent[3]. The incidence of GS in hematological malignancy has been scarcely studied worldwide. In a case series of 159 pediatric ALL patients by Berrueco et al[4], 2015 the frequency of GS (homozygous for UGT1A1*28 allele) was reported to be 14.5%. In another study by Nomura et al[5], 2016 in Japanese pediatric leukemia patients biallelic variation in UGT1A1gene was associated with chemotherapy induced hyperbilirubinemia.The present case report demonstrated that when patients receiving chemotherapy show unconjugated hyperbilirubinemia without any signs of liver dysfunction, the possibility of a UGT1A1 mutation should be considered after ruling out hepatocellular injury and hemolysis.

Unconjugated hyperbilirubinemia during chemotherapy is considered as an adverse event (AE) which results in suspension of chemotherapy. However in a study by Nomura et al[5], 2016 where they studied 25 Japanese pediatric ALL patients with and without hyperbilirubinemia each and concluded that hyperbilirubinemia without evidence of liver dysfunction and hemolysis was due to underlying UGT1A1 mutation, hence it is not necessary to cease or modify chemotherapy in such patients. Berrueco et al[4], 2015 studied children with ALL having jaundice, retrospectively to assess toxicity, outcome and treatment modification among who were diagnosed with GS. They found that patients with GS had statistically higher hyperbilirubinemia during all treatment phases however, no relevant toxicity or delays in treatment or differences in outcome were found .

Conclusion

In the light of above case, if a child comes with isolated unconjugated hyperbilirubinemia on several occasions in the absence of hemolysis or underlying liver disease, Gilbert syndrome should be considered as an important differential diagnosis. In most protocols of chemotherapy, hyperbilirubinemia above certain thresholds is a parameter that decides drug modification. Individuals with GS on chemotherapy hyperbilirubinemia is secondary to its impairment in glucuro-conjugation of bilirubin and this can lead to an unnecessary reduction of drug doses, delays and even withdrawal of the administration of some drugs. As the incidence of Gilbert's syndrome in pediatric leukemia is very rare and there are no definite guidelines for tailoring chemotherapy and hence the management poses challenges.

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Table 1. Laboratory investigations for unconjugated hyperbilirubinemia

Lab Tests	Normal range	Values
Hemoglobin (gm/dl)	13 - 16	10.8
RBC(cells/mm^3)	4,500,000-5,300,000	369,200
WBC(cells/mm^3)	45,00-13,000	3200
Platelets (cells/mm^3)	150,000-450,000	280,000
Packed Cell Volume (%)	37.0-49.0	30.2
Reticulocyte count (%)	0.5-2.5%	3.5
Aspartate Aminotransferase (U/L)	10-55	53.3
Alanine Aminotransferase(U/L)	10-40	42.1
Albumin (mg/dl)	3.3-5	4.2
Alkaline Phosphatase (U/L)	15-350	126
Globulin (mg/dl)	1.9-4.1	2.69
Total Bilirubin (mg/dl)	0.0-1.0	7.4
Direct Bilirubin (mg/dl)	0.0-0.4	0.8
LDH(IU/L)	105-333	242.9
G6PD level(units/gram)	5.5-20.5	13.44
Direct coombs test		Negative
Hepatitis B Surface Antigen (HbsAg) &		Negative

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Hepatitis C Virus antibody (HCV)		
High performance liquid chromatography (HPLC)		Normal
Osmotic fragility		Normal
USG abdomen		Normal, liver normal

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