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Short Reveiw

Severe Liver Steatosis from L-Asparaginase May not Recur Following Drug Re-Challenge

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Introduction

A 33 year old man was commenced on L-asparaginase based chemotherapy for acute lymphoblastic leukaemia that had been newly diagnosed at our center. Over 14 days, 7 doses of L-asparaginase were administered in combination with prednisolone, daunorubicin, vincristine, and intrathecal methotrexate. Serum liver biochemistry became abnormal from day 3 following administration of the first dose. L-asparaginase was administered at day 0, 2, 4, 6, 8, 10, and 15. Serum liver biochemistry reached a peak Alanine Aminotransferase (ALT) of 265 IU/L (day 26), peak bilirubin of 97 micromol/L (day 21), peak Alkaline Phosphatase (ALP) of 504 IU/L (day 26) and peak Gamma-Glutamyl Transferase (GGT) of 1959 IU/L (day 26). Serology for viral hepatitis, autoimmune liver disease, and genetic liver disease was negative. An ultrasound performed on day 21 found moderate fatty infiltration with a smooth liver contou. Liver biopsy performed on day 23 revealed severe mixed microvesicularand macrovesicular steatosis with minimal hepatocyte necrosis (Figure 1&2). On the basis of clinical presentation and histology, L-asparaginase was determined the most likely cause of liver injury. Liver biochemistry normalised over 3 months following cessation of L-asparaginase., which was not re-trialled for this patient. The patient had no significant risk factors for fatty liver disease beyond an elevated body mass index of 29.4 kg/m2. Other potentially hepatotoxic drugs, including vincristine and daunorubicin, were not thought to be the primary cause of hepatotoxicity in this case. These drugs typically cause mild transient biochemical derangement and there are no record of them being associated with jaundice. It is possible that other medical therapies, including undisclosed or over-the-counter remedies, may have been a factor in this patient's presentation, however this is not likely.

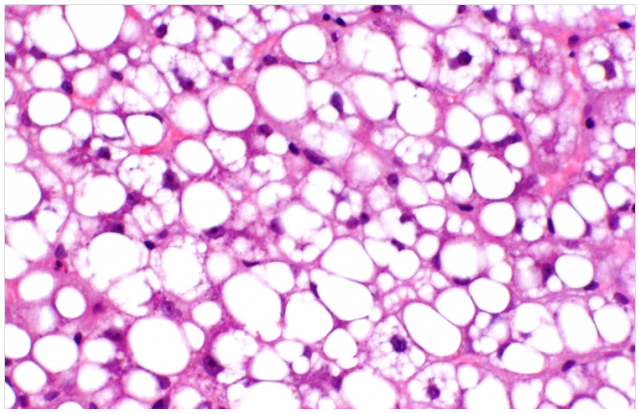

Figure 1: Hematoxylin and eosin staining demonstrating severe pan-lobular steatosis.

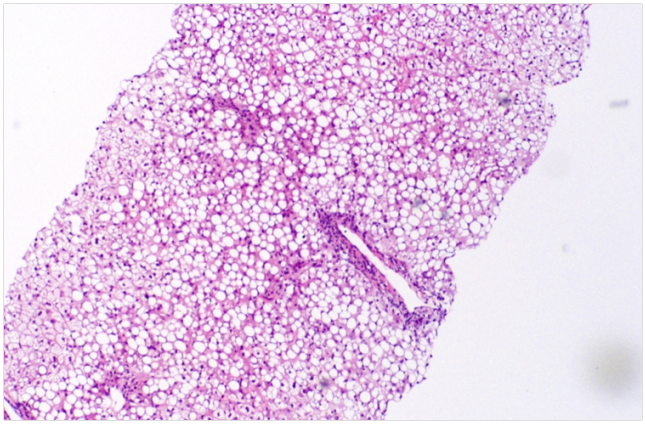

Figure 2: Hematoxylin and eosin staining demonstrating severe pan-lobular steatosis.

L-asparaginase, a bacterially derived enzyme, is an important therapy in the treatment of acute lymphoblastic leukaemia. Drug Induced Liver Injury (DILI) occurs as grade 3-4 elevation in liver transaminases and grade 3-4 hyperbilirubinaemia in 54-65% and 23-34%, respectively [1,2]. Most episodes are self-resolving, however, fulminant hepatic failure has been reported [3]. Liver histology typically shows moderate to severe diffuse micro- or macro-steatosis with minimal inflammatory changes [4].

A retrospective cohort study investigating all adult patients who received L-asparaginase based chemotherapy for 5 years preceding

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this case at our institution identified 10 patients (median age 46 years, 8 males) who received a total of 19 cycles of L-asparaginase based chemotherapy. Nine of 19 (47%) cycles were complicated by ALT rise greater than 5 times the Upper Limit of Normal (ULN), consistent with the US DILI network definition of significant DILI [5]. Five patients were rechallenged with L-asparaginase and three had recurrence of hepatotoxicity; however none of these repeat exposures were associated with an ALT rise greater than 5 times ULN. Of the nine cases of hepatotoxicity, one case was hepatocellular injury (R factor > 5), four were mixed (R = 2-5), and four were cholestatic (R< 2). Mean time to peak value of ALT following first dose was 23.1±7.8 days, time to peak bilirubin was 17.3±5.0 days. All cases of hepatotoxicity resolved over time and there were no cases of fulminant hepatotoxicity or death from liver failure.

This is one of the largest cohort of patients recorded in the literature with L-asparaginase related DILI. A prior report from the DILI-Network reported 7 adults from 5 centres who had liver injury secondary to asparaginase(as either L-asparaginase or PEG-asparaginase form); all recovered post cessation of the drug. Only one patient was re-trialled on asparaginase and re-developed less severe liver injury [6].

L-asparaginase induced liver injury is well described in the paediatric literature, however there is a paucity of literature of its use in adult population. Our series is the largest of its kind and highlights that despite the severity of liver biochemical and histologic reactions to L-asparaginase, complete resolution following drug cessation is typical. Omission of L-asparaginase from acute lymphoblastic leukaemia chemotherapy regimens is associated with a significant reduction in cure rate.We have demonstrated that re-trial of L-asparaginase following an episode of hepatotoxicity is usually safe and may not precipitate recrudescence of hepatotoxicity; this finding may help inform future treatment with this drug.

Author's Contribution

Patient identification and case description by TW, MG, and AT, study design and protocol development were done by TW, AN, and JL. Ethics approval was obtained by TW. Histology analysed by PH, data collection done by TW. Data interpretation and analysis were undertaken by TW, AT, MG, AN, and JL. All authors contributed to the manuscript preparation and revision and have approved the final version.

Conflict of Interest Statement

None declared for all authors.

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