Post-treatment Fulminant Hepatic Failure in an Infant with Visceral Leishmaniasis: Immune Injury or Stibogluconate Toxicity?

Sir,

Fulminant hepatic failure (FHF) is a rare occurrence in Visceral leishmaniasis (VL).[1] FHF developing after successful leishmanicidal therapy is further rare with only one case reported till date.[2] We report an infant with VL who developed fatal FHF towards end of stibogluconate treatment after satisfactory response.

An 1-yr-old girl presented with fever, palpable hepatomegaly (3cm) and splenomegaly (6.5cm). Investigation showed hemoglobin 78g/L, TLC 4.2×10^9/L (N20L80), platelet count 77×10^9/L, normal coagulogram and serum biochemistry. A diagnosis of VL was made on demonstration of Leishmania-Donovani bodies (+++) on bone marrow studies. She was put on intramuscular stibogluconate (20mg/Kg/day) and discharged for domiciliary therapy. On day 26, she was readmitted with complaints of malena and fever. Examination revealed fever, tachypnoea, tachycardia, jaundice, bilateral chest crepitations, hepatomegaly (same as before), but splenomegaly had reduced by 1.5cm. Investigation showed: hemoglobin 100g/L, TLC 12×10^9/L (N63L37), platelets 117×10^9/L and coagulopathy (PT 18 ", control 14"; aPTT 45 ", control 36"). Except for abnormal liver functions (bilirubin 3 mg/dL, AST/ALT 1346/1020 IU/L), rest of the biochemistry including Alkaline Phosphatase was normal. CXR showed bilateral infiltrates, but cultures were sterile. Repeat bone marrow examination did not show Leishmania-Donovani bodies. HBV, HCV, HAV and HIV serology were negative; HEV serology, serum ceruloplasmin, copper and auto-antibodies assessment were not available. Stibogluconate was discontinued. She became afebrile 48 hours after intravenous co-amoxiclavunate. Blood products were transfused as per need. On day 7 of admission, jaundice deepened and she developed alteration in sensorium and hyperventilation. CXR was normal and neuroimaging showed diffuse cerebral edema. Despite all supportive measures including mechanical ventilation and antibiotics for possible nosocomial sepsis, her condition worsened and she died of refractory shock. Autopsy could not be performed.

Here direct parasite-induced liver injury causing acute hepatocellular failure during 4th week of apparently successful therapy seems unlikely due to initial clinical improvement, reduction in splenomegaly, normalization of blood counts and clearance of parasites from marrow. Prompt response of pneumonia to antibiotic therapy rules out sepsis as a cause of hepatic dysfunction. Hepatitis E, autoimmune hepatitis and Wilson's disease seem less likely for young age. A similar case reported in literature also progressed dramatically to fatal FHF after initial clinical improvement within 2 weeks of antimony therapy.[2] Immunemediated injury[3] and/or antimony toxicity[4] may be possible mechanisms.

Hepatic inflammation and necrosis are universal in VL, which has been shown to deteriorate further with leishmanicidal therapy— increased swelling and ballooning degeneration of hepatocytes, cytosol edema, dilatation and disruption of endoplasmic reticulum.[3] Immune-mediated injury has been considered for persistence/worsening of hepatocytic injury despite clearance of parasites,[3] as VL results in suppression of cell-mediated immunity which improves with successful leishmanicidal therapy.[5] Antimony-toxicity has been reported to cause about 10 times elevation in transaminases and impaired functional metabolic capacity,[4] however levels >25 times upper reference level as seen in the index case has not been documented. Likelihood of both mechanisms operating simultaneously in the already inflamed liver cannot be ruled out.

Present case highlights the possible development of FHF even after successful treatment for VL. Immune-mediated hepatic injury due to reconstitution of immunity following therapy with/without antimony toxicity may be the underlying mechanism. There is a need for evidence creation and guidance development for monitoring of liver functions in VL patients, especially younger ones.

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[DOI-10.1007/s12098-009-0265-0]

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Scientific Letters to the Editor

Bovine Colostrum in Pediatric Respiratory Diseases: A Systematic Review

Sir,

Colostrum is the first natural species-specific food produced by female mammals during the first 24–36 hours after giving birth. Chemically, it is a very complex fluid, rich in nutrients, antibodies and growth factors. The antimicrobial components like lactoferrin, lysozyme and lactoperoxidase [1-3] and the immunoglobulins provide passive immunity to the newborn, and the growth factors stimulate the growth of the gut. Whole bovine colostrum and immunoglobulin-enriched colostrum (hyperimmune bovine colostrum; HBC) fractions have been used in infants and immunocompromised adults to treat or prevent enteric infections.[4,5]

The precise role of bovine colostrum (or HBC) in respiratory infections and other (immune –mediated) diseases like atopy/asthma in children is not well defined. We undertook a systematic review of the literature to look at the potential use in respiratory illnesses in children. We searched PubMed, Cochrane database (Cochrane Central Register of Controlled Trials: CENTRAL)) with key word "bovine colostrum" for studies in human (clinical trials, RCTs, reviews) in children 0-18yr. Comprehensive electronic searches and hand searching of the bibliographies of all the clinical trials were electronically retrieved. The numbers of citations using the key word 'bovine colostrum' retrieved with limits applied (humans, age 0- 18 yr, clinical trials/ RCTs/ reviews) were 55. On removing the age limits, 123 citations were retrieved and abstracts were reviewed. Thirty five studies including those in adults, animals and children were reviewed. Cohort studies were also reviewed.

We could not identify any published randomized controlled trials (RCT) evaluating the role of bovine colostrum in respiratory illnesses in children. There were 3 RCTs on beneficial effect of bovine colostrum in diarrheal diseases including one in immuno-compromised adults[6], one in children[7], one in juvenile rheumatoid arthritis.[8] There was only one study[9] which partly satisfied the inclusion criteria. In this open, multi-centric, non-comparative, post-marketing study, a total of 605 children of either sex between 1 to 8 yr of age were enrolled. The study was conducted involving 133 pediatricians across India. Children having recurrent episodes of URTI (defined as >6 episodes of URTI during the period 6 months prior to enrollment in the study) or having recurrent episodes of diarrhea were included in the study. Children, having any abnormalities of the respiratory tract, those having >3 episodes of lower respiratory tract and infections requiring hospitalization in the past 6 months or those children receiving corticosteroids (systemic or topical), immunomodulators or when parent/guardian did not give informed consent, were excluded. All children received bovine colostrum (Pedimune®, Mfg. by Merck India Ltd.) 3 g (one teaspoonful) with a glass of water once daily for a period of 12 wk.

Primary outcome measure was reduction in the number of episodes of upper respiratory tract infections (RTI) occurring during the study period (time from enrollment to 12 weeks of bovine colostrum therapy) as compared to the 6 months prior to enrollment in the study. Frequency of hospitalization required for RTI and diarrhea during study period as compared to 6 months prior to enrollment was also compared. The results of 551 patients who completed the study were analyzed. The number of episodes [Mean ± S.D.] of URTIs occurring 6 months prior to bovine colostrum therapy was 5.94 ± 3.88 which reportedly decreased significantly to 1.60 ± 1.74, 0.99 ± 1.20 and 0.52 ± 0.91