Toxic hepatitis-associated aplastic anaemia after dual homeopathic remedies and Gymnema sylvestre use

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SUMMARY

Hepatitis-associated aplastic anaemia (HAAA) is a rare condition characterised by onset of acute hepatitis which is followed by development of severe pancytopenia due to bone marrow failure within 6 months. This syndrome can be precipitated by acute viral infections, but the aetiology remains unknown in the majority. Drug-induced HAAA is extremely rare and has been reported with nutritional and dietary supplements in current literature. We report the first cases of ayurvedic herbal and homeopathic remedies-associated HAAA in two patients which proved fatal in both. Evaluation of patients with acute hepatitis and severe pancytopenia must include a detailed evaluation for complementary and alternative medicine use.

BACKGROUND

Hepatitis-associated aplastic anaemia (HAAA) is a rare and distinct type of aplastic anaemia which is characterised by pancytopenia occurring after the development of acute hepatitis. The HAAA, a variant of acquired aplastic anaemia, seen predominantly among adolescent males, has been defined as that which occurs within 6 months (average 2–3 months) of onset of acute hepatitis and was first reported by Lorenz and Quaiser in 1955.[1] The incidence of HAAA among patients with aplastic anaemia is 1%–5% and is more commonly encountered in hepatitis prevalent regions, such as the Asian subcontinent.[2] Multiple studies have suggested that an immune-mediated, antigen-driven T cell expansion within the liver, followed by the bone marrow results in the HAAA syndrome. Several hepatotropic and non-hepatotropic viruses such as hepatitis A, B, C, E and G and others such as parvovirus B19, human herpes viruses (HHV), Ebstein-Barr virus (EBV) and cytomegalovirus (CMV) are associated with HAAA.[3] Nonetheless, only 6% HAAA cases have an identifiable viral aetiology, while the majority are idiopathic cases without clear aetiology of liver injury.[4] To date only two reports of HAAA secondary to toxic hepatitis due to consumption of muscle building protein and work-out supplements are reported in literature.[5 6] In this report, we present two novel cases of HAAA following probable homeopathic remedies and ayurvedic herbal drug-induced toxic hepatitis.

CASE PRESENTATION

Case 1

A man in his early 30s without comorbid illnesses and in the absence of significant alcohol use was diagnosed to have asymptomatic renal stones and grade 1 fatty liver on routine ultrasound imaging as part of an executive health check. At the time of his routine evaluation, blood investigations including complete haemogram as well as liver and kidney function tests were within normal limits. For the management of incidentally detected renal stones and radiologically detected fatty liver, he consulted a homeopathic practitioner who prescribed him tinctures (figure 1A) of Sarsaparilla Mother Tincture -Q potency (MT-Q, *Hemidesmus indicus* or Nannari root, 15 drops two times a day with warm water) and Berberis MT-Q (*Berberis vulgaris* or common barberry, 15 drops two times a day with warm water) for 1 month duration. The patient did not consume other prescription medications or additional complementary and alternative medicines (CAMs) during this period. Two weeks later, he developed progressive, severe loss of appetite and lethargy associated with jaundice, without pruritus or other constitutional symptoms and was admitted for further evaluation including a liver biopsy. Three weeks after the initial presentation of acute hepatitis, the patient had recurrence of severe lethargy along with high grade fever with chills and rigours and was found to have severe pancytopenia in the presence of new onset deranged liver function tests. He was admitted for additional investigations, including a bone marrow biopsy.

Case 2

A man in his late 50s with severe lethargy, polyuria and polydipsia was recently diagnosed to have diabetes mellitus after initial work up revealed haemoglobin A1c (glycated haemoglobin, HbA1c) 10.3%. Fearing insulin injections for the rest of his life, he consulted a nearby ayurveda practitioner, for 'safer alternatives', who prescribed him powdered herbal extract of *Gymnema sylvestre* (GS; cowplant or sugar-destroyer, 'gurmar' in India; 4 g in two divided doses; figure 1B). One month after initiation of GS, the patient noticed severe itching of both palms and soles of his feet followed by development of jaundice, without other constitutional symptoms. The patient denied alcohol use, over the counter prescription drug use and other CAMs. He was admitted for further evaluation, including a liver biopsy test. Four months after the initial presentation of severe cholestatic liver injury, the patient presented with new onset lethargy, severe weight loss and loss of appetite. Repeat evaluation revealed severe anaemia, leucopenia and thrombocytopenia along with deranged liver tests without jaundice. The patient was admitted for additional investigations inclusive of bone marrow studies.

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Figure 1 Retrieved homeopathic remedies (A) and Gymnema sylvestre powder (B) from patients who developed acute hepatitis-associated aplastic anaemia.

INVESTIGATIONS

Baseline investigations had revealed normal haemogram, but severely deranged liver tests in both the patients. The detailed baseline investigations of both patients are shown in table 1. The type of liver injury in the first and second cases were hepatocellular (R factor 19.4) and cholestatic (R factor 0.6), respectively.[5] Investigations for bacterial infections were negative and cross-sectional contrast imaging of the abdomen in both patients did not reveal biliary obstruction, mass lesions or evidence of cirrhosis and portal hypertension. Complete work up for all acute and chronic hepatotropic as well as non-hepatotropic viruses including hepatitis E, dengue virus, parvovirus B, HHV, HIV, CMV and EBV was unremarkable. Investigations for leptospirosis, malarial infection and complete autoimmune liver disease panel were negative.

In the first patient, the liver biopsy revealed balloon degeneration of hepatocytes, occasional acidophil bodies, areas of confluent hepatic necrosis, moderate lobular and perisinusoidal inflammation composed of predominantly lymphocytes and areas of hepatocyte drop out. In the second patient, liver biopsy revealed portal inflammation with severe canalicular and hepatocellular cholestasis, and areas of spotty necrosis, both suggestive of drug-induced liver injury (DILI) in the absence of negative staining on the liver tissue for hepatitis B, herpes and CMV. The Roussel Uclaf Causality Assessment Model scores for establishing causal relationship between a substance and liver damage were suggestive of probable DILI in both patients.[6] Hence a diagnosis of homeopathic remedies and ayurvedic herb-induced liver injury deemed most likely after extensive evaluation and exclusion of other causes of liver injury (figure 2).

DIFFERENTIAL DIAGNOSIS

Three weeks after the acute hepatitis presentation, in the first patient, in the event of new onset high grade fever and pancytopenia, further evaluation was undertaken. The haemogram during repeat admission revealed haemoglobin 10.5 g/L (6.58 mmol/L) (normal 13–16 g/dL; 7.45–11.17 mmol/L), total leucocyte count 1500/µL (normal 4000–11 000) and platelets 35 000/µL (150 000–450 000). Extensive work up for new onset pancytopenia was initiated. The peripheral smear revealed normocytic normochromic anaemia with leucopenia, severe neutropenia, lymphocytopenia and thrombocytopenia. Levels of vitamin B12 and folic acid were within normal range and work up for haemolytic anaemia including Coombs tests was non-contributory. Similar findings were notable in patient 2. In the first patient, the bone marrow aspiration study demonstrated

Table 1 Pertinent work up and baseline investigation results of two patients developing homeopathic remedy and ayurvedic herb Gymnema-induced acute hepatitis with aplastic anaemia

Parameter (normal)	Patient 1: homeopathic remedy	Patient 2: ayurvedic herbals
Haemoglobin	C: 16 (12–18 g/L) SI: 9.93 (7.45–1.17 mmol/L)	C: 12.3 SI: 7.63
Total leucocyte count	C: 4.6 (4.5–11×10^3/µL) SI: 4.6 (4.5–11×10^9/L)	C: 5.3 SI: 5.3
Red blood cell count	C: 5.0 (4.7–6.1×10^6/µL) SI: 5.0 (4.7–6.1×10^{12}/L)	C: 6.1 SI: 6.1
Platelet count	C: 60 (150–450×10^3/µL) SI: 60 (150–400×10^9/L)	C: 125 SI: 125
Total bilirubin	C: 23.8 (<1.2 mg/dL) SI: 406.98 (<21 µmol/L)	C: 15.6 SI: 266.76
Direct bilirubin	C: 18.1 (<0.3 mg/dL) SI: 309.57 (<5.1 µmol/L)	C: 10.5 SI: 179.55
Aspartate aminotransferase	C: 2007 (10–40 U/L) SI: 33.45 (0–0.58 µKat/L)	C: 181 SI: 3.02
Alanine aminotransferase	C: 2655 (7–55 U/L) SI: 44.25 (0–0.58 µkat/L)	C: 79 SI: 1.32
Alkaline phosphatase	C: 133 (44–148 U/L) SI: 2.22 (0.73 to 2.45 µkat/L)	C: 244 SI: 4.07
Gamma glutamyl transferase	C: 246 (5–40 U/L) SI: 4.1 (0.07–1 µkat/L)	C: 488 SI: 8.13
Albumin	C: 3.6 (3.5–5.5 g/dL) SI: 541.67 (527–782 µmol/L)	C: 3.4 SI: 511.58
Prothrombin time	15.1 (11–13.5 s)	15.6
International normalised ratio	1.2 (<1.1)	1.34
Lactate dehydrogenase	C: 459 (140–280 U/L) SI: 7.65 (1.67–3.17 µkat/L)	C: 342 SI: 5.7
Blood urea	C: 21 (5–20 mg/dL) SI: 3.49 (1.8–7.1 mmol/L)	C: 14 SI: 2.33
Creatinine	C: 0.6 (0.7–1.2 mg/dL) SI: 53.04 (62–106 µmol/L)	C: 1.1 SI: 97.24
Uric acid	C: 7.2 (3.4–7 mg/dL) SI: 428.3 (208.3–428.4 µmol/L)	C: 6.8 SI: 404.5
Immunoglobulin G	C: 1384 (700–1600 mg/dL) SI: 92.32 (46.9–107 µmol/L)	C: 1626 SI: 108.4
ANA, ASMA, anti-LKM-1, anti-LC-1, AMA	Negative	Negative
COVID-19 antigen, SARS-CoV-2 PCR	Negative	Negative
IgM (HAV, HEV, HSV-1, HSV-2, CMV, EBV, Parvovirus B, Dengue, Leptospira), Dengue-NS1, Varicella zoster virus	Negative	Negative
HBsAg, anti-HCV, HIV-1, HIV-2	Negative	Negative
PCR: HBV DNA, HCV RNA, EBV	Not detected	Not detected
Malaria antigen, thick and thin smear	Negative	Negative
Peripheral smear	Normocytic normochromic, thrombocytopenia, no atypical cells	Normocytic normochromic, mild reduction in platelets, no atypical cells
Ferritin	C: 2876 (20–250 ng/mL) SI: 2876 (15–200 µg/L)	C: 1678 SI: 1678
Triglyceride	C: 270 (<150 mg/dL) SI: 3.05 (<1.8 mmol/L)	C: 198 SI: 2.23
Liver histopathology	Cytolytic hepatocellular injury, confluent hepatic necrosis in zone 3, acidophil bodies with balloon degeneration, moderate inflammation with lymphocytic predominance in lobules and perisinusoidal areas, mild pan-portal inflammation, mild interface hepatitis	Focal, spotty necrosis in zone 3, moderate to severe hepatocellular and intracanalicular cholestasis with bile plugs and bile infarcts, mild portal and lobular inflammation with lymphocytes and neutrophils

Continued

Table 1 Continued

Parameter (normal)	Patient 1: homeopathic remedy	Patient 2: ayurvedic herbals
Bone marrow aspiration and biopsy	Markedly hypocellular marrow with trilineage hypoplasia consistent with aplastic anaemia	Markedly hypocellular marrow with trilineage hypoplasia consistent with aplastic anaemia
Bone marrow failure syndrome gene panel	Negative	Negative
PNH panel	Negative	Negative
R factor (type of liver injury)	19.4 (hepatocellular)	0.6 (cholestatic)
RUCAM score (DILI causality)	7	8

AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; C, conventional unit; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Ebstein-Barr virus; HAV, hepatitis A virus; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; IgM, immunoglobulin M; anti -LC-1, antibody to liver cytosol-1; anti -LKM-1, anti-liver-kidney-microsomal antibody; PNH, paroxysmal nocturnal haemoglobinuria; RUCAM, Roussel Uclaf Causality Assessment Method; SI, international system of units.

hypocellular marrow with trilineage hypoplasia and the biopsy was suggestive of markedly hypocellular marrow consistent with aplastic anaemia in the absence of infiltrates, atypical cells, granulomas, haemophagocytosis and fibrosis. Similar findings on bone marrow studies were confirmed in patient with ayurvedic herb-induced liver injury who presented with similar clinical symptoms 4 months after initial presentation of acute hepatitis. Immunophenotyping of bone marrow aspirate in both cases was suggestive of lymphocytopenia with reduced ratio of CD4:CD8 T cells. Comprehensive cytogenetic testing for bone marrow failure syndromes as well as paroxysmal nocturnal haemoglobinuria (PNH) panel for PNH clone were negative in both patients, which was suggestive of acquired aplastic anaemia. Finally, a diagnosis of toxic (drug-induced) HAAA, due to two different CAMs was arrived on.

OUTCOME AND FOLLOW-UP

In the first patient, acute hepatitis was treated with corticosteroids (40 mg/day for 21 days). In the second patient, ursodeoxycholic acid (at 10 mg/kg body weight/day in divided doses) along with supportive symptomatic care was initiated and stopped over 8 weeks after complete resolution of cholestatic hepatitis and associated symptoms. After development of aplastic anaemia, both patients underwent best supportive care with blood and blood product transfusions for the correction of symptomatic anaemia and thrombocytopenia. The first patient was restarted on corticosteroids, but haemogram parameters did not improve. After 21 days of initial presentation with acute hepatitis and with the development of aplastic anaemia, over the next 3 weeks, the first patient developed multiple episodes of infections and symptomatic thrombocytopenia requiring hospital admission and corrective efforts. Immunosuppression therapies were withheld in view of recurrent infections. While on supportive care and work up for bone marrow transplantation, he died of progressive bone marrow failure and intercurrent sepsis-related multiple organ failure 7 weeks after diagnosis of HAAA. The second patient developed progressive pancytopenia not responding to immunosuppressive drugs including cyclosporine. During his work up for bone marrow transplantation, he developed worsening hepatitis, multidrug resistant sepsis and died of multiple organ failure 5 months after the initial presentation of acute hepatitis.

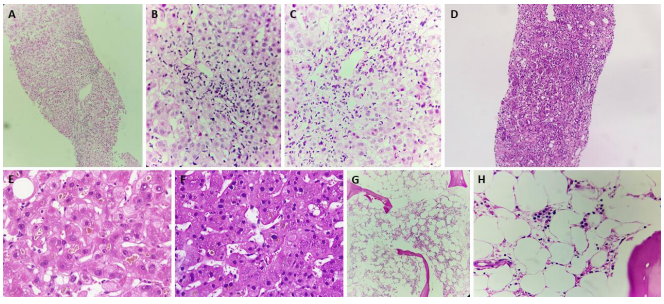

Figure 2 Liver histopathology—showing areas of lobular disarray, predominant lobular inflammation (A, H&E 10×); lymphocytic inflammation of the lobular and perisinusoidal areas (B, H&E 40×); hepatocyte fallout (cytolysis) and necrosis in zone 3 (C, H&E, 40×); spotty necrosis and lobular disarray in second patient (D, H&E 10×); intracanalicular (E) and hepatocellular cholestasis (F) noted in second patient (H&E, 100×); bone marrow biopsy showing hypocellularity and trilineage hypoplasia without haemophagocytosis or fibrosis, consistent with aplastic anaemia.

DISCUSSION

HAAA is a rare but well-documented type of AA more prevalent in adolescent males, characterised by onset of bone marrow failure (pancytopenia) after development of acute hepatitis, usually within 6 months of disease onset. Several viral infections are documented to be associated with HAAA. Nonetheless, in many cases, a causative agent cannot be identified.[1 4] HAAA is a potentially lethal disease and treatment follows similar protocol as with classical AA. This includes restrictive transfusion approach to correct life-threatening anaemia (irradiation-depleted and leucoreduced packed red cells) and thrombocytopenia; use of broad-spectrum antimicrobials in febrile neutropenia; immunosuppressive therapy (anti-thymocyte globulin, cyclosporine) and definitive treatment with allogenic bone marrow transplant.[4 7] HAAA secondary to CAMs such as ayurvedic drugs or homeopathic remedies has never been reported. In a report from the USA, a young male presented with acute hepatitis after consumption of muscle building protein supplements and anabolic steroids for 6 months. Liver biopsy revealed severe inflammation of the portal and lobular areas with sinusoidal lymphocytosis and centrilobular spotty necrosis. More than 4 months after the initial hepatitis episode, he developed severe pancytopenia associated with bone marrow failure. Immunosuppression therapy with prednisolone, anti-thymocyte globulin and cyclosporine stabilised AA and the patient remained disease-free at 3 years.[7] In another case, a young male consuming a 'pre-workout' supplement developed hepatitis after 4 months of intake, leading to AA 2 months after resolution of hepatitis episode. Liver biopsy revealed predominantly lymphocytic lobular inflammation with mild portal and pericellular fibrosis with multiple areas of hepatocyte dropout.[8] In our report, both the patients had similar clinical course and liver histology patterns. Box 1 includes a list of compounds found in medical literature to be associated with HAAA. Added to this in box 1 is a list of compounds found in the homeopathic and ayurvedic herbal remedies the two patients gave us for analysis. Analysis included inductively coupled plasma—optical emission spectrometry for heavy metals and gas chromatography-tandem mass spectrometry and Fourier transform infrared method for volatile organic and inorganic compounds.

In our investigations of the two patients, the homeopathic mother tinctures were found to contain industrial solvents such as methyl benzoate, butyl phenol and a host of plant-derived

Box 1 Contents and components of nutritional and dietary supplements described in literature and chemical and toxicology analysis of homeopathic remedies and ayurvedic herbal drug discussed in current report

Body building supplement (Qureshi *et al*, 2014)

Alanine, arginine, aspartic acid, cysteine, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, whey protein isolate, soy protein isolate, Lipobolic containing jumby pepper, caralluma fimbriata, forslean (coleus forskohlii), coffea arabica, olive extract, caffeine, evening primrose oil, conjugated linoleic acid, lax seed powder, borage seed oil powder, and omega-3 complex, lecithin, malic acid, acesulfame potassium, sucralose and citric acid.

Pre-work out supplement (Bastola *et al*, 2020)

Beta Alanine, L-taurine, L-carnitine tartarate, citrulline malate, N-acetyl tyrosine, betaine anhydrous, agmatine sulfate, L-norvaline, Di-caffeine malate, hordenine, N-methyl tyramine, MaxxEndure XT (capsaicin analogue, stearoyl vanniylamide).

Homeopathy remedy—Sarasaparilla/Nannari root (current report)*

Methyl benzoate, capric acid methyl ester, 2,4-di-tert-butyl phenol, lauric acid, methyl ester, megastigmatrienone, benzoic acid, myristic acid, palmitic acid methyl ester, methyl stearate, obacunone, betamethasone acetate, erucylamide, sarsasapogenin 3-tosylate, diosgenin, ethyl acetate, acetaldehyde, methanol (0.0014%), ethanol (16.09%).

Homeopathy remedy—Berberis (current report)*

n-caprylic acid, lauric acid, methyl ester, myristic acid, caprylone, palmitic acid, methyl ester, methyl stearate, phthalic acid, neotigogenin, sarsasapogenin, diosgenin, n-propyl linoleate, ethyl acetate, acetaldehyde, methanol (0.001%), ethanol (19.54%).

Ayurvedic herbal drug—Gymnema sylvestre (current report)*

2-methoxy-4-vinyl phenol, decanoic acid, asarone, turmerone, myristic acid, lauric anhydride, palmitic acid, methyl ester, estafiatin, columbin, campesterol, stigmasterol, sarsasapogenin, lupeolo-sitosterol, a-amyrin, o-sitostenone, borneol, n-caprylic acid, lead (in mg/kg)—2.1, mercury—6.84, arsenic—1.59, cadmium—0.14.

* Heavy metal analysis performed using inductively coupled plasma—optical emission spectrometry, organic and inorganic analysis performed using Fourier transform infrared and triple-quadruple gas chromatography–mass spectrometry.

chemicals such as sarasapogenin, obacunone and diosgenin along with traces of methanol and high ethanol content. Analysis of the ayurvedic herbal drugs revealed high levels of mercury, lead and arsenic along with various phytochemicals with unknown clinical benefits and potential for toxicity. We did not find pesticide or insecticide residues in the drugs analysed. Chemicals such as industrial solvents, pesticides and insecticides and drugs associated with AA include sulfonamides, chloramphenicol, antituberculosis agents, phenylbutazone, non-steroidal anti-inflammatory agents and heavy metals such as arsenic and benzene derivatives.[9–11] In our patients, the drug analysis revealed heavy metals and industrial solvents with the potential to cause hepatitis and bone marrow injury. Triterpenoid glycosides and saponins found in the Gymnema herb, such as gymnemic acids and gurmarin, have been found to have cytotoxic and immunostimulatory activities—a possible explanation for idiosyncratic and immune-mediated liver and bone marrow toxicity.[12 13] Furthermore, CAMs are well known to cause idiosyncratic hepatitis and immune-mediated systemic toxicities that can affect renal and haematological systems.[14 15] Various immune mechanisms triggered by various acute insult have been elucidated as the cause of bone marrow failure following an episode of severe acute hepatitis. These include increased activation and a broad skewing pattern of T cell fractions such as circulating cytotoxic T cells which infiltrate and accumulate in the liver (with notable inflammation on liver biopsy), defective monocyte to macrophage differentiation, CD8+ Kupffer cell-mediated liver and bone marrow toxicity, increase in interferon-gamma and interleukin-2-mediated organ damage in liver and bone marrow—all of which are driven by hapten/antibody-mediated inflammatory cascade after the initial insult.[16 17] Similar immune mechanisms, immune dysfunction and adaptive and innate immune changes (direct or indirect toxicity due to antibody or secondary metabolite generation) have been described in DILI, possibly explaining common pathophysiological mechanisms that result in HAAA syndrome development.[18–20] In conclusion, CAMs such as ayurvedic herbals and homeopathic remedies have the potential to cause acute severe hepatitis that can be associated with secondary aplastic anaemia which may result in poor clinical outcomes.

Learning points

- Hepatitis-associated aplastic anaemia (HAAA) is a rare condition characterised by acute hepatitis followed by features of bone marrow failure within 6 months.
- The aetiology of HAAA is usually unidentifiable in the majority, but can be precipitated by acute viral infections.
- Drug-induced HAAA is extremely rare and has been reported with nutritional and dietary supplements.
- We report the first cases of ayurvedic herbal and homeopathic remedies-associated HAAA in two patients which proved fatal in both.
- Evaluation of patients with acute hepatitis and concomitant or follow-up severe pancytopenia must include a detailed evaluation for complementary and alternative medicine use.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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REFERENCES

1 Rauff B, Idrees M, Shah SAR, *et al*. Hepatitis associated aplastic anemia: a review. *Virol J* 2011;8:87.

2 Locasciulli A, Bacigalupo A, Bruno B, *et al*. Hepatitis-associated aplastic anaemia: epidemiology and treatment results obtained in Europe. A report of the EBMT aplastic anaemia Working Party. *Br J Haematol* 2010;149:890–5.
3 Cudillo L. Aplastica anemia and viral hepatitis. *Mediterr J Hematol Infect Dis* 2009;1:e2009026.
4 Alshaibani A, Dufour C, Risitano A, *et al*. Hepatitis-associated aplastic anemia. *Hematol Oncol Stem Cell Ther* 2020;336.
5 Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990;11:272–6.
6 García-Cortés M, Stephens C, Lucena MI, *et al*. Causality assessment methods in drug induced liver injury: strengths and weaknesses. *J Hepatol* 2011;55:683–91.
7 Qureshi K, Sarwar U, Khallafi H. Severe aplastic anemia following acute hepatitis from toxic liver injury: literature review and case report of a successful outcome. *Case Reports Hepatol* 2014;2014:1–7.
8 Bastola S, Kc O, Khanal S, *et al*. Hepatitis-associated aplastic anemia from workout supplement: rare but potentially fatal entity. *SAGE Open Med Case Rep* 2020;8:2050313X2090193.
9 Aksoy M, Erdem S, Dinçol G, *et al*. Aplastic anemia due to chemicals and drugs: a study of 108 patients. *Sex Transm Dis* 1984;11:347–50.
10 Asif Syed M, Rahman AAU, Siddiqui MI, *et al*. Pesticides and chemicals as potential risk factors of aplastic anemia: a case-control study among a Pakistani population. *Clin Epidemiol* 2021;13:469–75.
11 Shallis RM, Ahmad R, Zeidan AM. Aplastic anemia: etiology, molecular pathogenesis, and emerging concepts. *Eur J Haematol* 2018;101:711–20.
12 Khan F, Sarker MMR, Ming LC, *et al*. Comprehensive Review on Phytochemicals, Pharmacological and Clinical Potentials of *Gymnema sylvestre*. *Front Pharmacol* 2019;10:1223.
13 Tiwari P, Mishra BN, Sangwan NS. Phytochemical and pharmacological properties of Gymnema sylvestre: an important medicinal plant. *Biomed Res Int* 2014;2014:830285.
14 Philips CA, Paramaguru R, Joy AK, *et al*. Clinical outcomes, histopathological patterns, and chemical analysis of ayurveda and herbal medicine associated with severe liver injury-A single-center experience from southern India. *Indian J Gastroenterol* 2018;37:9–17.
15 Asif M. A brief study of toxic effects of some medicinal herbs on kidney. *Adv Biomed Res* 2012;1:44.
16 Boqari DT, Al Faraj S, Arafah M, *et al*. Herb-induced acute bone marrow intoxication and interstitial nephritis superimposing glomerular C1q deposition in a patient with paroxysmal nocturnal hemoglobinuria. *Saudi J Kidney Dis Transpl* 2015;26:572–9.
17 Tufekci O, Ozdemir H, Malbora B. Hepatitis-Associated aplastic anemia: etiology, clinical characteristics and outcome. *J Pediatr Hematol Oncol* 2021.
18 Ju C, Reilly T. Role of immune reactions in drug-induced liver injury (DILI). *Drug Metab Rev* 2012;44:107–15.
19 Liu W, Zeng X, Liu Y, *et al*. The immunological mechanisms and immune-based biomarkers of drug-induced liver injury. *Front Pharmacol* 2021;12:723940.
20 Gerussi A, Natalini A, Antonangeli F, *et al*. Immune-Mediated drug-induced liver injury: immunogenetics and experimental models. *Int J Mol Sci* 2021;22:4557.