



Herbal Immune Booster–Induced Liver Injury in the COVID-19 Pandemic

We read with interest a case series of drug-induced liver injury (DILI) cases in COVID 19 pandemic, entitled “Herbal Immune Booster–Induced Liver Injury in the COVID-19 Pandemic—A Case Series” by Nagral A *et al.*¹ We have observed two similar cases at our center which were having complementary alternative medicine (CAM)–associated liver injury during COVID 19 pandemic. Both the patients were having no prior comorbidity, and all confounding diagnoses were ruled out. There was no history of any other new drug that could explain the presentation. Diagnosis of DILI was biopsy proven with the Roussel Uclaf causality assessment method (RUCAM) score and was suggestive of DILI (Table 1). Both the patients have received giloy kadha and giloy preparations in high doses for COVID prevention. Competing etiologies were ruled out. Hepatitis serology (A/B/C/E), ceruloplasmin, and serology for the Epstein-Barr/herpes simplex/cytomegalovirus were negative, and hepatic Doppler ultrasound was normal. Autoimmune markers showed antinuclear antibody (ANA) positive with high IgG levels in both cases, and possibility of autoimmune hepatitis (AIH) was considered vs. DILI. Biopsy was performed for both the cases and was not suggestive of AIH, and there were areas of perivenular necrosis and mild portal infiltrate, no interface hepatitis, paucity of plasma cells, no rosettes, and relatively mild-moderate inflammatory infiltrate, predominantly with eosinophils, consistent with DILI; both our cases were biopsy proven.

The patient was treated with steroids in tapering doses, ursodeoxycholic acid (15 mg/kg), and liver biochemistry was normalized after 10–12 weeks. In the absence of other etiologies, bland cholestasis on liver biopsy, and an RUCAM score of 7 and 9 (the second case has h/o of self-induced re-challenge, which resulted in fluctuating jaundice), which are consistent with DILI, DILI was confirmed with liver biopsy and AIH was ruled out.

Ayurvedic herb-related hepatotoxicity and liver injury can present as asymptomatic minor transaminase elevations, to acute liver failure requiring transplantation.² *Tinospora cordifolia*/giloy is an herbaceous vine of the family menispermaceae, used as an immune booster in the Indian subcontinent. DILI has emerged as a side effect after its prevalent use in the present time in various forms as a tablet and kadha to prevent COVID 19 infection. The major misconception in the Indian society is that “herbs are safe”, which results indigenous use of the potentially lethal CAM/herbs in high doses. Often patients use them along

with prescription drugs, without knowing the potential interactions and side effects of CAM. This results likely as a

Table 1 Basic Laboratory and RUCAM Parameters of Two Cases.

Parameter	Case 1	Case 2
Hemoglobin in g/dL	12.5	11.3
Total leukocyte count/ μ L	6.5	8.5
Differential count, %	N78, L12	N82, L14
Platelets/ μ L $\times 10^3$	180	2.43
Blood urea nitrogen in mg/dL	12	15
Creatinine in mg/dL	0.60	0.73
Total/direct bilirubin in mg/dL	0.93	8.9
Aspartate transaminase (AST) (<40 U/L)	119	679
Alanine transaminase (ALT) (<40 U/L)	78	436
Alkaline phosphatase (SAP) (30–120 U/L)	69	142
Gamma-glutamyl transferase, GGT (8–38 U/L)	70	68
Protein in g/dL	6.37	6.4
Albumin in g/dL	3.78	3.8
International normalized ratio (INR)	1.29	1.1
Hospitalization	Required	Required
Alternate causes and risk factors	Negative	Negative
Other concomitant drugs or potential hepatotoxins	Not present	Not present
Liver chemistry before starting CAM/Kadha	Normal	Normal
Latency period in days	21	14
Liver injury pattern	Hepatocellular	Hepatocellular
RUCAM score	7	9
Liver biopsy	Done	Done
DILI severity index	Mild, grade1	Moderate to severe, grade 3
Course and outcome	Recovered	Recovered

Abbreviations: N, neutrophils, L, lymphocytes, DILI, drug-induced liver injury; NA, Not available; RUCAM, Roussel Uclaf causality assessment method.

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result of inhibition of drug-metabolizing enzymes (e.g., cytochrome P450) or other unknown pathways, as CAMs are not studied well so far, and underlying mechanisms are not known. Despite this, a standard system for prediction of drug-herb interaction is still not present.³ In our cases, CAMs were taken to boost immune response for COVID 19 prevention. The regulations of these CAMs are not standardized, dosing is erratic, and there is emergence of liver injury related to CAM intake during COVID as the excess use of CAM may exceed the capacity of the liver to metabolize them and results in toxicity and immune dysregulation, resulting in DILI. One should observe utmost precautions to use these remedies without supervision.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Mukul Rastogi: Conceptualization, Methodology, Writing – original draft, Writing - review & editing. **Rakesh K. Jagdish:** Writing – original draft, Writing - review & editing. **Vivek Vij:** Supervision, Writing – original draft, Conceptualization. **Nalini Bansal:** Study of biopsy images and interpretations.

CONFLICTS OF INTEREST

The authors have none to declare.

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