Immune Boosting Gone Wrong? A COVID-Concoction-Conundrum

Sir

We read with interest the case series by Nagral A et al.[1] The authors highlight a vexing predicament brought to the fore amidst the frequent usage of "immune boosters" during the COVID-19 pandemic. In this context, we share our experience and delve into certain key issues.

Case 1: A 39-year-old female with no comorbidities presented with progressive noncholestatic jaundice for one month. She gave a history of consumption of *Tinospora cordifolia* (TC) plant twigs boiled with water once in three days for one month before presentation. On evaluation, she was icteric [peak bilirubin 20.1 mg/dl, alanine transaminase (ALT) 697 IU/L aspartate transaminase (AST) 645 IU/L, alkaline phosphatase (ALP) 155 IU/L] and coagulopathic [International normalized ratio (INR) 2.8]. Conventional (hepatitis A, B, C, and E virus) and atypical (Herpes Simplex, Cytomegalovirus, Epstein Barr virus) viral serologies were negative. The autoimmune panel was positive for antinuclear antibodies (ANA) (3+ Titre, 1:100), antismooth muscle antibodies (ASMA) (4+ Titre, 1:40), and an immunoglobulin G level of 1740 g/L (ULN1.6 g/L). Liver biopsy was suggestive of drug-induced liver injury (DILI) with autoimmune features (AI-DILI) (Figure 1a, b)[Simplified autoimmune hepatitis (AIH) Score 7, Council for International Organizations of Medical Science/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) score 5]. Based upon the findings, she was started on oral prednisolone 60 mg (1 mg/kg) with gradual taper with which there was a biochemical improvement (Bilirubin 2.1 mg/dl, AST 56 ALT 54) and symptom resolution and remains on follow up.

Case 2: A 53-year-old female with h/o bronchial asthma presented with noncholestatic jaundice for one month. She revealed having consumed TC as commercially available juice for one month every alternate day as an immune-boosting measure to protect from COVID-19. On evaluation, the patient was icteric (Bilirubin 15.1 mg/dl, ALT 591 IU/L AST 543, IU/L ALP 126 IU/L). Conventional and atypical viral serologies were negative. The autoimmune panel was positive for ANA (2+ Titre, 1:100) with an IgG level of 2200 g/L. Liver biopsy showed features consistent with AI-DILI (Figure 1c, d) (Simplified AIH Score 7, CIOMS/RUCAM 5). She was managed with oral prednisolone 50 mg/day with a gradual taper and supportive measures, which gradually improved her liver functions.

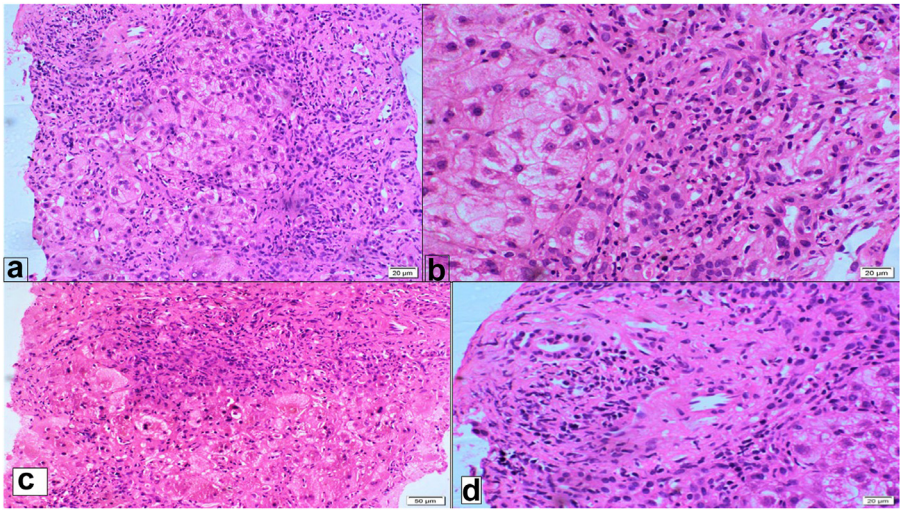

Figure 1 Photomicrograph shows the expanded portal tracts and interphase hepatitis by moderate mixed inflammatory infiltrates comprising neutrophils, eosinophils, plasma cells, and lymphocytes. (a) Patient 1 H&E stain; 200 ×. (b) Patient 1 H&E stain; 400 ×. (c) Patient 2 H&E stain; 200 ×. (d) Patient 2 H&E stain; 400 ×.

Abbreviations: AIH: Autoimmune hepatitis; ALT: Alanine Transaminase; ANA: Antinuclear antibodies; ASMA: Anti-smooth muscles antibody; AST: Aspartate Transaminase; CIOMS: Council for International Organizations of Medical Science; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; Ig G: Immunoglobulin G; INR: International normalized ratio; HSV: Herpes simplex virus; RUCAM: Roussel Uclaf Causality Assessment Method

https://doi.org/10.1016/j.jceh.2021.09.022

The use of herbal supplements and their potential for liver injury is a phenomenon well recognized.[2] In light of the findings of Nagral et al.[1] corroborated with our observations, a closer look into the immune-modulating properties of TC is warranted. The crux of the issue lies in differentiating a spontaneous AIH flare against AI-DILI physiology. Immunostimulatory herbal supplements such as TC are known to exacerbate preexisting autoimmune disease or precipitate autoimmune disease in genetically predisposed individuals.[3] Multiple mechanisms have been proposed for the same, although exact pathways need further elaboration.[3] Causalty assessments scores in the cases reported by Nagral et al.[1] and ours do implicate TC as an offending agent. However, certain inherent limitations of causalty assessment, especially in AI-DILI remain debatable. To add to the challenge, unless there is a presence of extensive background fibrosis, there are no absolute differentiating points on histopathology.[4] In this context, we re-enforce the need for a detailed mechanistic, toxicological and botanical analysis of such cases in conjunction with public awareness about the potential association.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

HG: Writing – original draft, NN: Resources and Visualization, SS: Writing – original draft, AR: Conceptualization, Writing – review & editing, RKD: Supervision, Writing – review & editing

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Nagral A, Adhyaru K, Rudra OS, Gharat A, Bhandare S. Herbal immune booster-induced liver injury in the COVID-19 pandemic - a case series. *J Clin Exp Hepatol*. 2021 Jul 2 https://doi.org/10.1016/j.jceh.2021.06.021.
2. de Boer YS, Sherker AH. Herbal and dietary supplement–induced liver injury. *Clin Liver Dis*. 2017;21:135–149.
3. Lee AN, Werth VP. Activation of autoimmunity following use of immunostimulatory herbal supplements. *Arch Dermatol*. 2004;140:723–727.
4. Febres-Aldana CA, Alghamdi S, Krishnamurthy K, Poppiti RJ. Liver fibrosis helps to distinguish autoimmune hepatitis from DILI with autoimmune features: a review of twenty cases. *J Clin Transl Hepatol*. 2019;7:21.

Himanshu Gupta
Department of Hepatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Neha Nigam
Department of Pathology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Surender Singh, Akash Roy, Radha K. Dhiman
Department of Hepatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Address for correspondence: Prof Radha K Dhiman, Director, Professor and Head, Department of Hepatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.
E-mail: rkpsdhiman@gmail.com (R. K. Dhiman)

1 September 2021.