

# Corticosteroid Responsive Herbal Medicine Induced Severe Cholestatic Liver Injury in an Elderly Female

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## ABSTRACT

Drug-induced liver injury (DILI) possesses a difficult challenge to clinicians because of its unpredictable course and the varied presentation. Herbal and alternative medicines are notorious to cause severe liver injury. We report a case of a 72-year-old rural lady who developed severe DILI after intake of unknown herbal drugs that she consumed for a month for grade III osteoarthritis. She presented to a tertiary care hospital in Gangtok, Sikkim for generalized pruritus and clay coloured stool. Her clinical examination revealed jaundice and laboratory reports were suggestive of severe hyperbilirubinemia with serum bilirubin of 27 mg/dL. There was mild elevation of liver enzymes (SGOT- 62 IU/L, SGPT- 50 IU/L, ALP- 230 IU/L and GGT-30 IU/L). Her viral markers were negative and autoimmune workup was also normal. Abdominal Ultrasound showed only grade I fatty liver without any evidence of portal hypertension. Liver biopsy performed at a higher tertiary centre was suggestive of DILI. Despite intensive supportive management and three sessions of plasmapheresis, bilirubin persisted around 17 mg/dL, and living donor liver transplantation was considered. Oral prednisolone 40 mg/day was initiated as a salvage therapy, leading to dramatic clinical and biochemical recovery with complete normalization of liver function tests within one month. This case highlights the importance of recognizing herbal medication-associated DILI and, a must trial of corticosteroid before considering liver transplantation.

## KEY WORDS

*Cholestatic hepatitis, Corticosteroids, Drug-induced liver injury, Herbal medicine, Plasmapheresis, Prednisolone*

## INTRODUCTION

Drug-induced liver injury (DILI) also termed as drug-induced hepatotoxicity, is an acute or chronic response to a natural or artificial compound.<sup>1</sup> It can be classified as hepatocellular, cholestatic, or mixed based on mechanism of hepatotoxicity, histological appearance and clinical presentation.<sup>2</sup> Although it's not a very common cause of acute liver failure, it's important to diagnose this potentially treatable condition. Diagnosis of the condition is challenging in view of its variable presentation, spectrum of which ranges from asymptomatic elevation of liver enzymes to clinically evident jaundice and severe acute liver failure. The true incidence is unknown as most of the causes are undetected or underreported. An intrinsic or dose-dependent, and idiosyncratic reaction to a drug is responsible for hepatotoxicity. Laboratory tests include elevated aminotransferases in hepatocellular and, raised

alkaline phosphatase (ALP) in cholestatic injury. A liver biopsy is helpful to rule out other causes of hepatotoxicity. The most important treatment is immediate withdrawal of the offending agent, which usually leads to recovery.<sup>3</sup> Sometimes, this remains refractory to the treatment and may be complicated by prolonged cholestasis.<sup>4</sup> Many cases of DILI are being reported off late as a result of consumption of over-the-counter and herbal drugs.<sup>5</sup> Herbal drugs usually cause cholestatic DILI and commonly present with jaundice and pruritus.<sup>6</sup> Females and elderly individuals are more vulnerable because of altered pharmacokinetics.<sup>7</sup> Though the role of corticosteroids is controversial but the isolated reports of its beneficial role, especially in refractory cholestatic DILI are available in the literature.<sup>1,8</sup> We report a case of severe cholestatic DILI related to herbal medication use in an elderly female. She remained symptomatic

with refractory cholestasis despite discontinuation of the offending drug, supportive therapy and plasmapheresis. Eventually a remarkable response to corticosteroid therapy was seen with full recovery.

## CASE REPORT

A 72-year-old female presented to a tertiary care hospital in Gangtok, Sikkim with generalized itching of approximately two weeks' duration. She had stable vitals with unremarkable general and systemic examination except for deep icterus and excoriation marks secondary to pruritic. Her history revealed consumption of herbal medications one month prior to the onset of symptoms which she took for almost a month for her osteoarthritis. She had normal BMI (22.2 kg/m<sup>2</sup>) and was neither diabetic nor hypertensive with no history chronic liver disease, alcohol consumption, or hepatotoxic drug intake apart from the herbal preparations.

Laboratory investigations revealed severe hyperbilirubinemia with total bilirubin of 27 mg/dL. There was mild elevation of liver enzymes (SGOT- 62 IU/L, SGPT- 50 IU/L, ALP- 230 IU/L and GGT-30 IU/L), suggestive of predominantly cholestatic liver injury. Complete blood count, renal function tests, coagulation profile, and serum electrolytes were within normal limits. Viral markers for hepatitis A, B, C, and E were negative. Autoimmune workup including antinuclear antibody, anti-smooth muscle antibody, and other autoimmune markers were negative.

Ultrasonography of the abdomen showed grade I fatty liver with no evidence of biliary obstruction, portal hypertension, or ascites. Other investigations were unremarkable.

A diagnosis of severe cholestatic drug-induced liver injury secondary to herbal medication use was considered after exclusion of other etiologies. The suspected herbal medications were discontinued immediately and she was managed conservatively with ursodeoxycholic acid, antihistamines, nutritional support, and hepatoprotective measures. However, despite approximately 30 days of supportive treatment, bilirubin levels remained markedly elevated with persistent severe pruritus. She was subsequently referred to a higher tertiary care institute where liver biopsy was performed which confirmed drug-induced liver injury. Therapeutic plasmapheresis was performed on three occasions in view of persistent severe hyperbilirubinemia. Despite these interventions, serum bilirubin remained markedly high at around 17 mg/dL with persistent pruritus. Owing to the prolonged cholestatic course and poor biochemical response, living donor liver transplantation was discussed with the family. As a desperate salvage measure, oral prednisolone 40 mg/day was initiated. Following initiation of corticosteroid therapy, the patient experienced rapid symptomatic improvement with marked reduction in pruritus and gradual decline in jaundice. Serial liver function tests showed progressive

normalization of bilirubin and liver enzymes. Prednisolone was gradually tapered over one month with complete normalization of liver function tests.

At two month follow-up, the patient remained asymptomatic with normal biochemical parameters.

## DISCUSSION

DILI is a diagnosis of exclusion and probably one of the most difficult conditions encountered in clinical practice.<sup>6,9</sup> One of the important culprit drugs are herbal and dietary supplements which have gained a lot of popularity of late.<sup>5,10</sup> The risk is more in view of a lack of strict regulation and incomplete understanding of the constituents.<sup>10</sup>

Our patient developed severe cholestatic DILI after intake of herbal medications for osteoarthritis. The temporal association between herbal medication use and onset of symptoms, exclusion of alternative causes, and liver biopsy findings strongly supported the diagnosis. Although liver biopsy is not routinely required, it can be valuable in atypical or severe cases to exclude other mimicking conditions and to assess the pattern of liver injury.<sup>6</sup>

The markedly elevated bilirubin with only mild transaminase elevation, was consistent with cholestatic DILI. Pruritus was the initial manifestation and remained a major disabling symptom throughout the illness.

Management of DILI primarily involves early identification and immediate withdrawal of the offending agent.<sup>6,4</sup> The mainstay of treatment being the supportive care. This includes the use of ursodeoxycholic acid and antipruritic drugs although the evidence is limited.<sup>6</sup> Steroid and ursodeoxycholic acid combination is also proposed.<sup>8</sup> Cholestatic DILI usually has a prolonged course compared with hepatocellular one and may persist for weeks or months even after discontinuation of the offending drug.<sup>11,12</sup> Extracorporeal liver support systems including plasmapheresis have been attempted in severe refractory cases, with variable results.<sup>13</sup>

Our patient remained symptomatic with persistent pruritus and elevated bilirubin levels despite undergoing three sessions of plasmapheresis. In view of the poor response, living donor liver transplantation was considered. But to our surprise, corticosteroid therapy led to dramatic clinical and biochemical improvement.

The role of corticosteroid in DILI is controversial and not universally accepted. The latest recommendation is limited to the cases associated with hypersensitivity reactions or autoimmune-like features.<sup>4,6</sup> Some case reports and emerging evidence have suggested the beneficial role of steroids in selected patients of severe cholestatic or immune-mediated DILI.<sup>8,14</sup>

The underlying mechanism behind this steroid responsiveness yet to be fully understood. Reduction of

inflammatory cytokines, suppression of immune-mediated bile duct injury, and restoration of hepatocellular transport function are some proposed theories.<sup>14,15</sup> A prompt reduction in bilirubin following initiation of prednisolone therapy in our patient strongly favours a positive therapeutic response rather than spontaneous recovery per se.

Many important clinical lessons are to be learnt from our case. Firstly, cautious use of herbal drugs should be advocated in view of their potential hepatotoxicity.<sup>5,10</sup> Secondly, marked transaminase elevation may not be seen in severe cholestatic DILI.<sup>11</sup> Lastly, corticosteroids may

be considered as a rescue therapeutic modality in some refractory cases after excluding autoimmune and infectious hepatitis.<sup>8,15</sup>

Herbal medication-induced cholestatic DILI may mimic progressive liver failure with severe cholestasis requiring transplantation. This case highlights dramatic recovery with steroid therapy after failure of supportive management and plasmapheresis. Corticosteroid treatment may be considered in carefully selected refractory cholestatic DILI cases after excluding competing etiologies.

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