Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.62.009719

Ashwagandha-Associated Acute Liver Injury: A Case Report and Literature Review

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ARTICLE INFO

Received: June 04, 2025

Published: June 12, 2025

Citation: Zhuang D, Zhang D, Paulus F, Waring D and Riordan SM. Ashwagandha-Associated Acute Liver Injury: A Case Report and Literature Review. Biomed J Sci & Tech Res 62(2)-2025. BJSTR. MS.ID.009719.

ABSTRACT

Ashwagandha is an over-the-counter herbal supplement that has been implicated in inducing liver injury. We report a case of a 77 year old female presenting with jaundice, dark urine and pruritis after using ashwagandha for three weeks. She reported no intercurrent or past medical history and no other recent medication use. Initial results revealed a high serum bilirubin level with a mixed cholestatic/hepatitic pattern of liver enzyme derangement. Testing for an extensive range of viral-, metabolic- and immune-mediated causes of liver injury proved to be negative. Liver and biliary imaging with dynamic phase computerised tomography and magnetic resonance imaging, including cholangiopancreatography, demonstrated no abnormality. A provisional diagnosis of ashwagandha-associated liver injury was made. Liver biopsy was performed on day 11 after ashwagandha withdrawal, at the peak of progressive liver biochemical derangement. This revealed bland cholestasis. Disturbed liver biochemistry, along with symptoms, slowly resolved after 4 months. Bland cholestasis is most commonly associated with anabolic steroid use and oestrogen therapy. Our case is important in highlighting that ashwagandha may also account for this histological pattern of liver injury, emphasising the importance of obtaining a thorough drug history, including for the use of this over-the-counter herbal agent, in patients with otherwise unexplained liver injury.

Keywords: Ashwagandha; Liver injury; Withania; DILI; HILI; Case Report

Introduction

Ashwagandha (Withania somnifera) is a herbal supplement [1,2] that is being increasingly used as an over-the-counter purported remedy for stress, anxiety and impaired muscle strength [3-8]. Several case reports have flagged the potential hepatotoxicity of ashwagandha. Few patients have subsequently undergone a liver biopsy to identify the histological pattern of liver injury related to this supplement. Here, we report a case of ashwagandha-induced liver injury and demonstrate that one of its histopathological patterns of liver injury is omit bland cholestasis.

Case Report

A 77 year old female presented to hospital with a 10 day history of painless jaundice, dark urine and pruritis. There was no history of abdominal pain, nausea or vomiting, diarrhoea, weight loss, bleeding or bruising. The patient was otherwise healthy, without any intercurrent of past medical history. There was no family history of liver disease. There was no history of alcohol use. She had commenced an ashwagandha supplement in pastille form three weeks prior to presentation in order to assist with sleep. Physical examination revealed jaundice and scleral icterus. There were no abdominal masses or tenderness. The remainder of the physical examination was normal. Liver biochemistry on admission demonstrated a bilirubin level of 132 micromol/L (normal <20 micromol/L), alkaline phosphatase (ALP) level of 270 U/L (normal <115 U/L), gamma-glutamyltransferase (GGT) level of 103 U/L (normal <35 U/L), alanine aminotransferase (ALT) level of 145 U/L (normal <40 U/L) and aspartate aminotransferase (AST) level of 67 U/L (normal <40 U/L). The serum albumin level was mild-

ly reduced at 31 g/L (normal >33 g/L). The international normalised ratio (INR) was normal. The full blood count, including haemoglobin level and platelet and white cell counts with white cell differential values, was normal. An extensive liver screen was performed, with no abnormality on testing for viral (hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, cytomegalovirus, Epstein Barr virus, adenovirus, parvovirus), autoimmune (smooth muscle antibodies, liver-kidney microsomal antibodies, anti-mitochondrial antibodies, anti-mitochondrial 2 antibodies, anti-soluble liver antigen antibodies, anti-sp100 antibodies, anti-gp210 antibodies, serum immunoglobulins) and metabolic (serum ferritin, serum alpha-1-antitrypsin, serum caeruloplasmin) aetiologies.

Liver and biliary imaging with dynamic phase CT and magnetic resonance, including cholangiopancreatography, demonstrated no abnormality. A provisional diagnosis of ashwagandha-related drug-induced liver injury was made. Serial measurements to track liver biochemistry demonstrated a progressive disturbance in liver enzyme values (Figure 1). Liver biopsy was performed on day 11 after ashwagandha withdrawal, at the peak of liver biochemical disturbance, demonstrating lobular cholestasis predominantly in a zone 3 distribution, with visible bile pigment in hepatocyte cytoplasm and bile canaliculi. There was minimal inflammation and no architectural changes of the liver parenchyma. Overall, the features were in keeping with a pattern of bland cholestasis (Figures 2a & 2b). Disturbed liver biochemistry, along with symptoms, slowly resolved after 4 months (Figure 1).

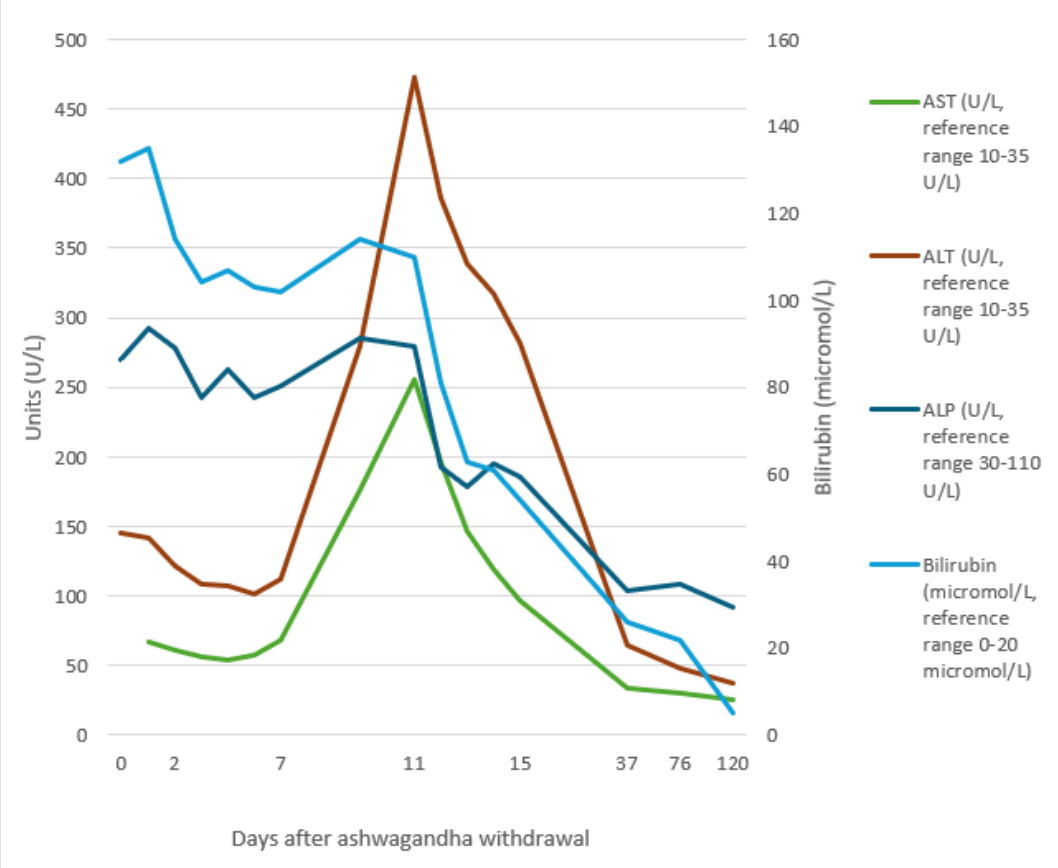

Figure 1: Trend of liver biochemical test results.

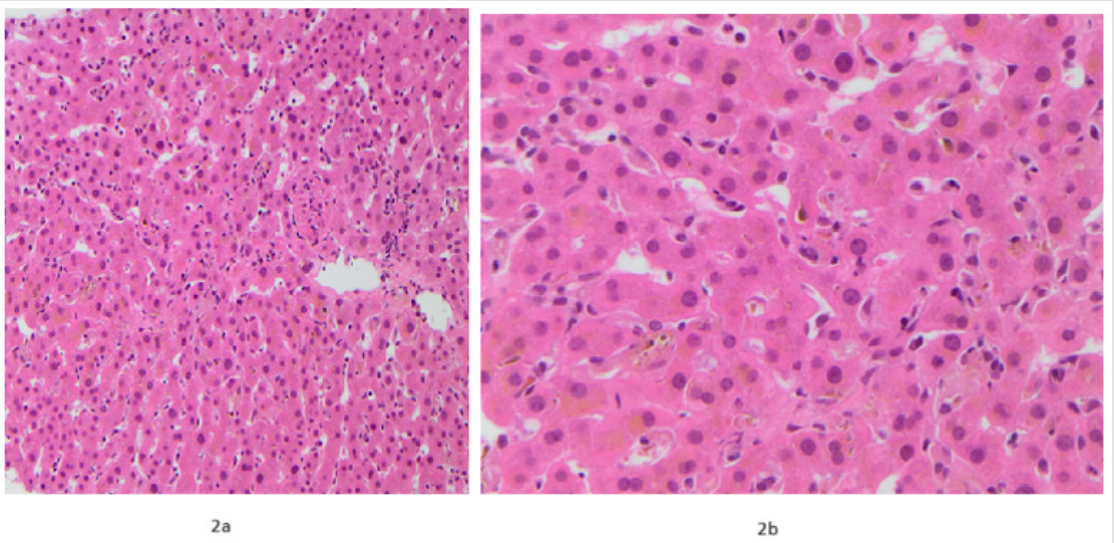

Figure 2: Liver histology at low magnification.
- **2a:** and at higher magnification.
- **2b:** Demonstrating bland cholestasis, including yellow bile pigment in hepatocyte cytoplasm and biliary canaliculi.

Discussion

Withania somnifera, more commonly known as ashwagandha or Indian ginseng, is a shrub that is native to parts of Asia, Africa, and the Middle East. Ashwagandha root, in particular, has been used in Ayurvedic medical practice for centuries [1]. Traditionally either the root or whole plant is used, and prepared in various forms like a decoction, paste, oil, or with clarified butter or ghee [1,2]. More modern preparations include capsules, tablets, and gummies. Studies have demonstrated its potential in several domains such as stress and anxiety, brain function, arthritis symptoms, and muscle strength and endurance [3-8].

The prevalence of complementary medicine use is reportedly to be as high as 50-70% [9-11]. There has been an increase in reported cases of associated liver injury including liver failure, both in Australia and worldwide [12-16]. The Drug-Induced Liver Injury Network registry recently reported that 16-20% of drug-induced liver injuries were due to herbal and dietary supplements [17].

Initial studies, although small, suggested that ashwagandha was not associated with apparent liver injury [8,18,19]. Since 2017, however, there have been 35 case reports of ashwagandha-associated liver injury, not including the case that we currently report [20-38]. Whether ashwagandha causes idiosyncratic or dose-dependent hepatotoxicity is unclear due to the variation of products, but the mechanism is postulated to be through DNA damage [39]. The biochemical pattern of reported liver injury is varied between cholestatic, hepatocellular, and mixed patterns [31]. Most patients with ashwagandha-induced liver injury present with jaundice and pruritus, as well as non-specific symptoms such as nausea, fatigue and general malaise. This was also true in our reported case. Whilst the majority of cases resulted in normalisation of liver biochemistry, there has been a case of ashwagandha-associated liver injury resulting in acute liver failure that required transplantation [40].

In February 2024, the Therapeutic Goods Administration (TGA) in Australia issued a safety alert after receiving 12 reports of liver injury potentially associated with ashwagandha use, four of which required hospitalisation [41]. At the time of writing, there were a substantial number of 405 products listed on the Australian Register of Therapeutic Goods (ARTG) containing Withania somnifera.

A liver biopsy is often not required to make a diagnosis of a drug-induced liver injury [15] but can be crucial in giving a clue as to the nature of a causative drug based on a known pattern of histological injury ascribed to its use. A liver biopsy was performed in our patient due to ongoing worsening of liver biochemical derangement 11 days post cessation of the postulated offending agent, at the peak of liver biochemical disturbance, and demonstrated bland cholestasis as the histological pattern of liver injury. Bland cholestasis has been reported in only a few cases of ashwagandha-induced liver injury to date [20,34,36]. In the realm of drug-induced liver injury, bland cholestasis is most commonly associated with anabolic steroid use and oestrogen therapy, although has also been rarely implicated with use of anti-metabolite drugs [15]. Our case is important in emphasising that ashwagandha may also account for this histological pattern of liver injury, highlighting the importance of obtaining a thorough

drug history, including of the use of over-the-counter herbal remedies often not considered as "drugs" by the general population, such as ashwagandha, in patients with otherwise unexplained liver injury.

In summary, increased patient and physician awareness of ashwagandha-associated liver injury is crucial in current clinical practice, especially due to the high prevalence of ashwagandha use as a readily available herbal supplement. Several known causes of drug-induced liver injuries that manifest as bland cholestasis include anabolic steroids and oestrogen therapy. Our case highlights that the herbal supplement, ashwagandha, should be added to this list. As part of the routine history taking and investigation of patients with otherwise unexplained liver injury, healthcare professionals should extensively enquire about the use of herbal supplements including ashwagandha.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.62.009719

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