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Innovations in medicine

Ashwagandha induced liver injury in a patient with chronic hepatitis C

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Abstract

26-year-old patient with three-year long alcohol abuse history was admitted to our hospital due to jaundice. She was previously well, didn't use medications but took an Ashwagandha supplement daily for a few months. Laboratory findings showed severely increased alanine and aspartate aminotransferases, biochemical signs of cholestasis and increased level of bilirubin. Moreover, anti-HCV was detected and viral hepatitis was confirmed with detection of HCV RNA. According to RUCAM score Ashwagandha could be linked as a culprit of liver injury. During hospital stay after observing rise in bilirubin levels the liver biopsy was performed. The following description highlights the challenges involved in establishing a diagnosis of drug induced liver injury and emphasises role of liver histopathology in claryfying diagnostic issues.

Streszczenie

26-letnia pacjentka z trzyletnim wywiadem nadużywania alkoholu została przyjęta do szpitala z powodu żółtaczki. Chora od kilku miesięcy przyjmowała suplement diety zawierający Ashwagandhę. W badaniach laboratoryjnych stwierdzono wysoką aktywność transaminaz, cechy biochemicznej cholestazy oraz podwyższone stężenie bilirubiny. Ponadto wykryto obecność anty-HCV a zakażenie HCV potwierdzono badaniem PCR RNA. Zgodnie z wynikiem uzyskanym w kwestionariuszu RUCAM uszkodzenie wątroby można było powiązać z przyjmowanym suplementem ziołowym. W trakcie hospitalizacji obserwowano narastające stężenie bilirubiny co przyczyniło się do decyzji o wykonaniu biopsji wątroby. Poniższy opis ilustruje jak dużym wyzwaniem jest rozpoznanie polekowego uszkodzenia wątroby oraz wskazuje na wysoką wartość biopsji w rozstrzyganiu problemów diagnostycznych.

Keywords *hepatotoxicity, ashwagandha, withania somnifera, hepatitis C virus, herbal medicine, chemical and drug induced liver injury, plant extracts/adverse effects*
Słowa kluczowe *ashwagandha, uszkodzenie wątroby wywołane substancjami chemicznymi i lekami, witania ospała, hepatotoksyny, wirus zapalenia wątroby typu C, ziołolecznictwo, wyciągi roślinne/działania niepożądane*

INTRODUCTION

The popularity of dietary supplements containing Ashwagandha is increasing. Unfortunately, although its benefit on general health and improvement of countless ailments is widely marketed, the negative aspects of this herb are obscure. Publications regarding Ashwagandha's hepatotoxicity began to emerge in the literature over the past several years [1]. In the following case we describe such a situation, nevertheless, overshadowed by competing aetiologies. We would like to show how liver biopsy, although not required for the diagnosis of drug/herbal induced liver injury (DILI/HILI), can provide critical information that allows determining the nature of a liver injury.

CASE PRESENTATION

A 26-year-old female was admitted to our hospital in January of 2025. She was well until the end of December 2024, when she started to experience abdominal pain. She was presented to the emergency department with jaundice and discoloured urine. She did not report any other symptoms. Her past medical history contained atopic dermatitis. The patient confessed to alcohol abuse. She had her last drink a day before the admission. The excessive consumption of alcohol lasted for approximately three years, with a minimum intake of 2 standard units per day and more on weekends. She did not smoke cigarettes; however, she was using about 15 heated tobacco inserts per day. She was not receiving any pharmacological treatment. However, she was self-

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administering a daily Ashwagandha supplement for several months to alleviate fatigue.

On physical examination her BMI was 19,6kg/m2, arterial blood pressure was elevated (159/106mmHg), she had tachycardia (141 beats per minute), dry mucous membranes, jaundice and appeared anxious and agitated. Her abdomen was soft, without symptoms of hepatosplenomegaly or palpable masses.

Initial laboratory tests have shown markedly elevated alanine transaminase (ALT 2673 U/l), aspartate transaminase (AST 2529 U/l), alkaline phosphatase (ALP 472 U/l), gamma glutamyl transpeptidase (GGT 1216 U/l) and total bilirubin (9,89mg/dl), but without coagulopathy (INR 1,13) or hypoalbuminemia (4,57 g/dl) (Table 1). The R factor of 19.0 indicated a hepatocellular pattern of this liver injury.

	Refference range	Day 1	Day 3	Day 8	Day 70	Day 130
ALT (U/l)	5-31	2673	1838	688	21	10
AST (U/l)	5-31	2529	772	223		
ALP (U/l)	35-104	472	375	224		
GGT (U/l)	0-40	1216	621	391		
Bilirubin (mg/dl)	0.30-1.20	9,89	12,7	5,75	0.61	
INR	0.9-1.2	1.13	1.1	0.99		
Albumins (g/dl)	3.5-5.2	4.57				
IgG (mg/dl)	610-1616		982			
Ceruloplasmin (mg/dl)	16.0-45.0		27.5			
WBC (10^3/ul)	4.5-10.0	7.05	5.79	5.43	3.84	6.1
RBC (10^6/ul)	4.2-5.4	4.83	4.32	4.1	4.66	4.7
HBG (g/dl)	12.0-16.0	15.3	13.4	12.6	14.6	14.4
MCV (fl)	81.0-94.0	91.7	92.1	93.7	89.3	87.9
PLT (10^3/ul)	150-400	258	179	284	249	361

Table 1 *Laboratory results.*

Abdominal ultrasound revealed a liver of normal size and echogenicity, without focal lesions. There were no signs of cholelithiasis. Liver perfusion was normal. The portal vein was patent with hepatopetal flow and preserved spectral pattern. There was no thrombosis in hepatic veins. Enlarged lymph nodes were found in hepatoduodenal ligament.

DIFFERENTIAL DIAGNOSIS

According to the patient's medical history, aetiologies including drug induced liver injury or alcoholic hepatitis were the initial suspects. Despite heavy drinking in recent years, the clinical presentation was not coherent with the latter. The magnitude of aminotransferase elevation was not characteristic for alcoholic hepatitis. Moreover, the AST/ALT ratio (de Ritis) was not consistent with alcoholic liver disease.

Nonetheless, it was crucial to consider other possible causes of liver injury. Even in the case regarding a strong suspicion of DILI, the diagnosis can only be made by exclusion. Differential diagnosis for this patient must be focused on an established pattern of liver injury. To perform work-up we followed AASLD Drug, Herbal, and Dietary Supplement–induced Liver Injury Guidelines algorithm [2].

In this case we must remember to perform a screening for viral hepatitis, autoimmune hepatitis and Wilson's disease. Ischemic aetiology was not plausible, as there was no history of hypotension or signs of impaired liver perfusion in the ultrasound examination. The hepatic veins or portal vein thrombosis were excluded as well.

COURSE OF HOSPITALIZATION AND LIVER BIOPSY

We ordered additional laboratory tests for viral and autoimmune hepatitis to be conducted. Hepatitis A virus (HAV) and hepatitis B virus (HBV) serology were negative, but anti-hepatitis C virus (HCV) antibodies were present, prompting us to run real-time polymerase chain reaction (RT-PCR) for HCV RNA. Antinuclear (ANA), anti-smooth muscle (ASMA), liver kidney microsomal t.1 (LKM1) and antimitochondrial (AMA) antibodies were negative. Ceruloplasmin and IgG levels fell within normal range (Table 1,2).

	Result
Anti-HAV IgM	Negative
Anti-HBc total	Negative
HBsAg	Negative
Anti-HCV	Positive
HCV RNA	5,512,000 IU/ml
ANA screen	Negative
Anti-LKM1	Negative
Anti-SMA	Negative
AMA M2	Negative

Table 2 *Serological tests results.*

During the hospital stay the bilirubin concentration continued to rise (12,7mg/dl on day 3). The unclear clinical picture as well as the possibility of overlapping multiple aetiologies led us to perform a percutaneous liver biopsy. The procedure, using a trucut 14G needle, was completed with no complications. In the following days aminotransferase and bilirubin levels started to spontaneously decline. The patient was discharged for further evaluation in the outpatient clinic.

In a week we received a positive HCV RNA result, confirming hepatitis C and the result of histopathological evaluation, which stated that the histological picture most likely corresponds to changes observed in the course of toxic liver injury: mild cholestasis, moderate polymorphic lobular and portal inflammation with eosinophils, minimal steatosis (5%). Conversely, it is vital to note the observation of moderate fibrosis.

The further evolution of the patient was favourable with normalization of liver tests within 2 months (Table 1). To assess the causality, we used Roussell-Uclaf Causality Assessment Method (RUCAM) score. The outcome of the assessment was a score of six (Table 3). The result presented that Ashwagandha was a probable cause of this particular liver injury.

DISCUSSION

After summarizing the medical history and additional test results, it was undeniable that this patient presented various potential causes of liver injury. A particular concern was the rising level of bilirubin, marking the possibility of the beginning liver failure; that placed the patient under close monitoring of laboratory parameters and signs of hepatic encephalopathy or ascites, to determine whether liver transplantation should be considered. All aspects mentioned above highlight the complexity of given case and diagnostic dilemma considering this patient.

The clinical presentation itself suggested the possibility of alcoholic hepatitis, acute viral hepatitis or DILI. As previously mentioned, the former didn't comply with laboratory results. According to the

LiverTox database, Ashwagandha is a likely cause of apparent liver injury. Although typically it results in a cholestatic or mixed pattern, cases of hepatocellular injury caused by this herb have also appeared in literature [3].

During diagnostic workup of a young female with high transaminase levels, it was of utmost importance to check for autoimmune hepatitis (AIH). In our case it was ruled out due to absence of typical antibodies, normal IgG levels (982mg/dl), not characteristic liver histology and spontaneous remission achieved in the following weeks [4].

Categories	Score
1. Time to onset	Compatible (+1)
2. Course	Highly suggestive (+3)
3. Risk Factors	Ethanol Present (+1)
4. Concomitant drug(s)	None (0)
5. Exclusion of other causes of liver injury	Five or 4 causes of Group I ruled out (0)
6. Previous information on hepatotoxicity of the drug:	Reaction published but unlabeled (+1)
7. Response to readministration:	Not done or not interpretable (0)
Total	**6 - probable**

Table 3 *RUCAM Causality Assessment*

It remains essential to remember that acute viral hepatitis could have a similar biochemical pattern. However, the presence of both HCV RNA and HCV antibodies indicates chronic viral hepatitis. Furthermore, moderate liver fibrosis seen on liver histology cannot be attributed to acute liver injury (neither toxic nor viral) and presumably is a sequel of chronic hepatitis C.

The final diagnosis was acute liver injury caused by Ashwagandha ingestion in a patient with undiagnosed chronic hepatitis C.

CONCLUSION

Excessive use of herbal and dietary supplements, including Ashwagandha, contribute to the rising incidence of drug induced liver injury prevalence. In complicated cases, as the one presented above, in which multiple aetiology occurs, liver biopsy remains a gold standard for both establishing the diagnosis and evaluating the level of liver damage and prognosis.

FOLLOW UP

After one month, the patient's laboratory results were within normal range. Two months after discharge, she initiated the treatment with direct-acting antivirals (DAA) for chronic hepatitis C. The 12-week treatment regime with sofosbuvir and velpatasvir was completed without complications. The patient is currently well, waiting for the confirmation of HCV cure (sustained virological response 12 weeks post treatment; SVR12).

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