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Case Report

Ayurvedic treatment induced severe alcoholic hepatitis and non-cirrhotic portal hypertension in a 14-year-old girl

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Abstract

We report a novel and as yet undescribed clinical scenario in a young girl with liver failure, in whom, the liver histopathology was suggestive of alcoholic hepatitis in the background of hepatoportal sclerosis and incomplete septal cirrhosis. An extensive clinical and investigational evaluation revealed chronic consumption of multiple Ayurvedic herbal medications for seizure disease. Six months after stopping herbal medicines, the repeat liver biopsy demonstrated resolution of alcohol-related changes but persistence of classical features of non-cirrhotic portal hypertension. Analysis of the retrieved agents, including state of the art chemical and toxicology analysis, using gas chromatography and mass spectroscopy methods demonstrated multiple organic and inorganic toxins associated with acute alcohol and arsenic poisoning related hepatoportal sclerosis/incomplete septal cirrhosis in the young girl.

INTRODUCTION

Alcohol consumption, heavy or otherwise, in the short or long duration, in predisposed individuals, can lead to the spectrum of alcoholic liver disease (ALD) comprising of alcoholic fatty liver, alcoholic steatohepatitis, fibrosis and cirrhosis. Fatty liver, the earliest and most common imaging and pathological finding in ALD, develops in persons consuming at least four standard drinks (14 g of pure ethanol) per day over decades but can also develop in binge drinkers (up to five drinks in a single sitting, over 2 hours). Steatosis in ALD is not a benign condition and leads to fibrotic liver disease in the long term. Alcoholic hepatitis (AH) is the most severe form of ALD in which, histologically, balloon degeneration of hepatocytes with apoptosis, neutrophilic lobular inflammation and presence of Mallory-Denk bodies (MDB) with pericellular fibrosis become evident in the presence of clinical jaundice and complications of portal hypertension and encephalopathy [1]. It was recently reported that complementary and alternative medications (CAMs) with alcohol as a known or unknown constituent or adulterant could also promote severe ALD without actual alcohol consumption in predisposed individuals [2, 3]. Non-cirrhotic portal hypertension (NCPH, or recently coined portosinusoidal vascular disease) is a syndrome characterized by portal hypertension in the absence of chronic liver disease, advanced fibrosis or cirrhosis. It is associated with immunological disorders such as connective tissue diseases, inflammatory bowel syndrome and common variable immunodeficiency syndrome, chronic infections and genetic syndromes with familial aggregation, such as Turner disease and prothrombotic state, such as inherited thrombophilia and myeloproliferative diseases and also rarely, exposure to certain drugs such as azathioprine. Heavy metals, especially arsenic, have been shown to promote the development of NCPH, skin diseases and associated dermatological and hepatic malignancies [4, 5].

In this report, we present the novel and as yet undescribed clinical scenario of the case of a young girl with jaundice and ascites in whom the liver histopathology was suggestive of severe AH with additional findings of dense fibrosis localized mostly to the portal regions. An extensive clinical evaluation revealed chronic consumption of multiple Ayurvedic medications for seizure disease from 9 years of age. After 6 months of stopping the CAMs, a repeat liver biopsy demonstrated resolution of AH but the persistence of classical features of 'hepato-portal sclerosis', a variant of

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Figure 1. Ayurvedic medications—retrieved Ayurvedic medication from the young girl with ALD and NCPH.

NCPH. In-depth analysis of the retrieved agents, including state-of-the-art chemical and toxicology analyses, clinical exome studies, gas chromatography (GC) and mass spectroscopy (MS) studies, demonstrated multiple hepatotoxins associated with acute alcoholic- and arsenic poisoning-related hepatoportal sclerosis in the young girl.

CASE REPORT

A 14-year-old girl was referred to our treating unit with complaints of progressive, painless and non-cholestatic jaundice associated with loss of appetite and lethargy for 3 weeks. There was no history of fever or prodrome preceding jaundice. The patient was diagnosed with possible Gilbert's syndrome (total bilirubin: 4.2 mg/dl, direct bilirubin: 0.8 mg/dl) in November 2013 during a workup for seizure episodes. At the time, she was started on phenytoin to control seizures, which she took for 3 months. During this period, she developed breakthrough seizures on phenytoin after which additional antiepileptics were advised. Due to concern for 'excessive use' of antiepileptic medications in a girl child, the family turned toward 'safer, natural' alternative medicines to control seizures. At the age of 9 years, she was started on multiple herbal medications (Fig. 1) in May 2014 ('CNS Ayurveda Chikitsalayam and Research Center, Palakkad, Kerala, India') for control of seizures which was continued until the presentation to our department. On examination, the patient was conscious and oriented, without flapping tremors and had a hyperpigmented facial and upper body. She was icteric with firm hepatomegaly, splenomegaly and Grade 2 ascites. Contrast-enhanced computed tomography imaging of the abdomen revealed hepatomegaly with mild undulating margins and an enlarged spleen with mild ascites. Oesophagogastroscopy revealed Grade 2 varices without red color signs. Blood investigations revealed anemia, thrombocytopenia, predominantly direct hyperbilirubinemia, aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio > 2, hypoalbuminemia and hyponatremia with raised prothrombin time. Liver stiffness measurement (Shearwave Elastography, Logiq E9, GE, USA) was 28.8 kPa, and hepatic venous pressure gradient (HVPG) was 12 mm Hg. The baseline (at admission) and follow-up investigations are shown in Table 1. A transjugular liver biopsy showed features of macro- and microvesicular steatosis with lobular neutrophilic inflammation, extensive ballooning of hepatocytes with MDB and pericellular fibrosis in the presence of lobular distortion due to the formation of irregular incomplete nodules of hepatocytes surrounded by thick fibrous bands at the portal areas with extension to peri-portal areas with enhanced and dilated portal venules (Fig. 2A–D). A diagnosis of severe AH was considered associated with incomplete cirrhosis. The Ayurvedic medications were retrieved from the patient and subjected to extensive chemical and toxicology analyses. Heavy metal concentration was performed by inductively coupled plasma (ICP) atomic emission spectrometer (Thermo Electron, IRIS Intrepid II XSP Duo, Munich, Germany). Methodology, chemical standards, reagents and vials were acquired per standards set by the US Environmental Protection Agency, methods 5021A, 8015, 8021 and 8260. Hepatotoxic volatile organic compounds' (VOC) qualitative analyses were performed using GC coupled to tandem mass spectrometry (MS) method (GC/MS–MS; Thermo Fisher Scientific, USA). Pesticide residue analysis was also performed using the triple quadruple GC–MS/MS (GC TRACE 1300 with TSQ EVO 8000 MS). For qualitative corticosteroid analysis, 1 μl of the extract was injected into Gas Chromatograph, and qualitative identification of all possible peaks of steroids available in the GC/MS–MS temperature programming method (350°C max) was made and noted. Further augmentation of the detection process was done using the Salkowski and Lieberman Burchardt tests. Further to these tests, 1 μl of the sample extract was injected into a gas chromatograph, and qualitative identification of all possible peaks of organic compounds available in the GC–MS/MS temperature programming method was performed so as not to miss all identifiable substances in the drug sample. For alcohol analysis and quantification, GC coupled to Mass Spectrophotometer using procured and defined standards. Similarly, using the GC–MS/MS standardized technique, VOC were detected and identified using the equilibrium-based static headspace method for solid samples and the purge-and-trap method for liquid samples. The analysis revealed extremely high levels of arsenic in multiple

Table 1. Investigations at baseline and on follow-up in the young girl with Ayurvedic medicine related dual liver disease

Investigation	Baseline	Follow-up (6 months)
Hemoglobin (g/l)	9.8	12.2
Total leucocyte count ($\times 10^9$/l)	16.8	6.7
Platelet counts ($\times 10^3$ per μl)	68	100
Total bilirubin (mg/dl)	12.8	1.2
Direct bilirubin (mg/dl)	8.8	0.6
AST (IU/l)	188	32
ALT (IU/l)	54	34
Alkaline phosphatase (IU/l)	214	198
Gamma-glutamyl transpeptidase (IU/l)	164	102
Serum albumin (mg/dl)	2.6	3.2
Serum globulin (mg/dl)	4.2	3.4
Blood urea (mg/dl)	34	18
Serum creatinine (mg/dl)	0.8	0.6
Serum sodium (mmol/l)	134	141
Serum potassium (mmol/l)	3.6	4.4
International normalized ratio	2.8	1.1
Shearwave elastography (kPA)	28.8	11.8
HVPG (mm Hg)	12	9
Discriminant function	62.4	-

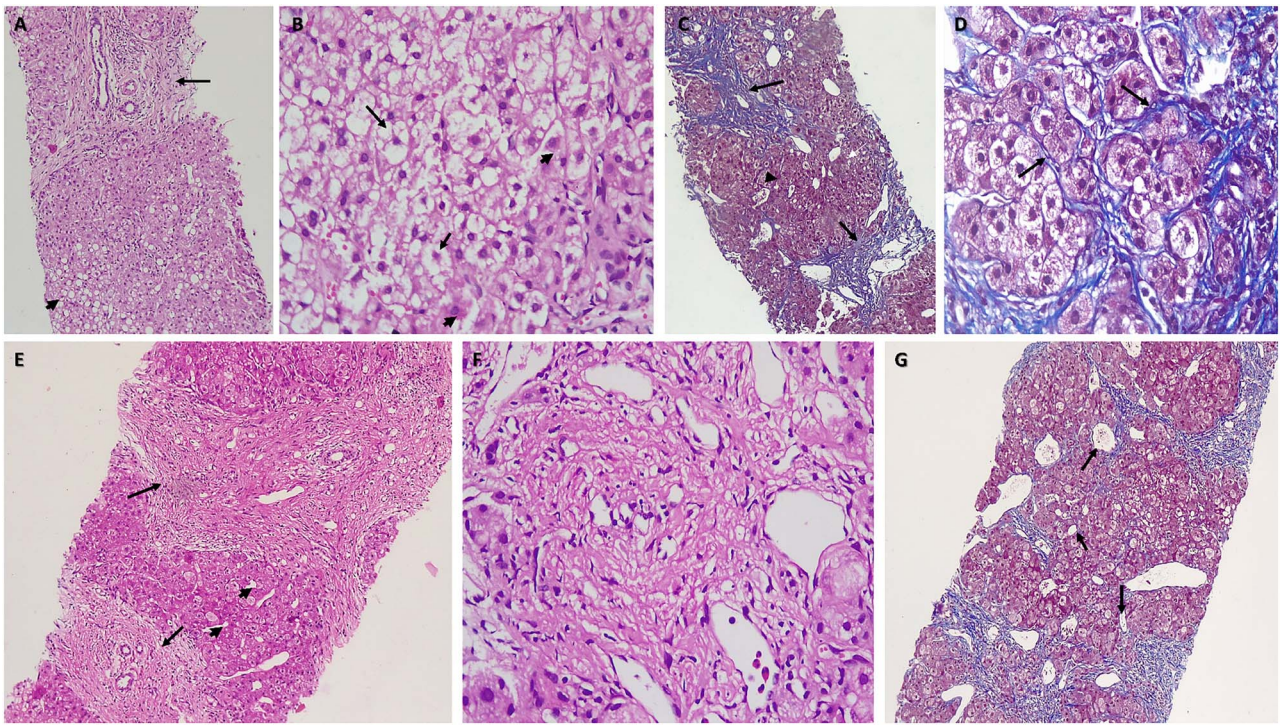

Figure 2. Baseline and follow-up liver histology; (**A**) liver biopsy at admission showing macro- and microvesicular steatosis (arrowhead), lobular distortion, neutrophilic lobular inflammation and dense portal fibrosis (arrow; H&E stain, 40×); (**B**) extensive ballooning of hepatocytes (arrows) associated with MDB (arrowheads) and neutrophilic inflammation surrounding ballooned hepatocytes (H&E stain, 400×); (**C**) dense portal fibrosis with thin septal portal to portal bridging fibrosis (arrows), dilated periportal veins and incomplete hepatocyte nodule formation (arrowhead; MT stain, 40×); (**D**) extensive pericellular fibrosis (arrows) of AH (MT stain, 400×); (**E**) follow-up liver biopsy showing dense portal fibrosis (arrows), portal vein dilatation, numerous collateral veins (arrowheads) in the periportal region and incomplete nodule formation (H&E stain, 100×); (**F**) representative image of hepatoportal sclerosis with portal vein sclerosis and dilatation of distal venules and periportal collateral formation (H&E stain, 400×); (**G**) dense portal and periportal fibrosis with thin septal extension of fibrosis toward adjoining portal areas, incomplete hepatocyte nodule formation, focal dilatation of sinusoids (arrows) and venule/radicle dilatation seen in hepatoportal sclerosis and incomplete septal cirrhosis (MT stain, 40×). H&E; hematoxylin and eosin; MT, masson-trichrome.

herbal formulations, the cumulative alcohol content of 26% v/v and adulteration with clonazepam and volatile industrial solvent compounds (Table 2). After halting all the Ayurvedic medicines for 6 months and starting corticosteroid therapy (prednisolone at 40 mg per the first week, tapered and stopped over 28 days), it was noted that, on follow-up, the thrombocytopenia, jaundice, ascites and coagulation failure resolved with the persistence of mild hypoalbuminemia. Repeat elastography was 11.8 kPa and

Table 2. Analysis of retrieved Ayurvedic medications using GC–MS and ICP-optical emission spectrometry methods

Details of ayurvedic drugs analysis									
Parameters	**Kalashadi Kashayam (liquid)**	**Pippalyasavam (liquid)**	**Aravindasavam (liquid)**	**Jeerakadi Churnam (powder)**	**Braigen (granules)**	**Triphala Churnam (powder)**	**Vachadi Churnam (powder)**	**Nirgunadhi Khritham (thick liquid)**	**Chukkum Tippalyadi Guliga (tablet)**
Lead	BDL	BDL	BDL	BDL	BDL	BDL	0.34	BDL	18.41
Cadmium	0.05	0.05	BDL	BDL	0.05	0.04	BDL	BDL	0.42
Arsenic	0.43	BDL	0.48	44.26	73.43	67.21	246.08	46.31	1982.4
Nickel	0.14	0.59	0.193	0.12	3.34	4.39	4.28	BDL	7.22
Mercury	0.04	0.114	0.96	0.019	0.460	0.58	0.41	0.99	BDL
Alcohol (% v/v)	ND	12.1	14.1	ND	ND	ND	ND	ND	ND
Other compounds (qualitative)	Benzoic acid	Eugenol Mono-palmitin Pentadecenyl phenol	ND	Enoborneol Isoborneol Eugenol Asarone Thymol Ethanolamine Bornanone Terpinyl acetate Camphene	Benzenamine Homopterocarpin Piperine d-Sesamin Spirojatamol Refractomide Squalene Lupeol Benzodioxole Camphesterol Sitosterol Stigmasterol Camphor	Thymol Dimethyl phenol Tocopherol Tocospiro Citrostenol Sitostenone Lupenone	Piperine Glabridin Methoxyphenyl oxime Dihydroxy chalcone	Laurin Palmitin Glycidyl palmitate Monostearin Distearin	ND
Adulterants (qualitative)	ND	ND	ND	ND	Clonazepam	ND	Clonazepam	ND	ND

Heavy metals quantification in mg/kg; BDL, below the detection limit; ND, not detected.

HVPG 9 mm Hg. Repeat percutaneous liver biopsy revealed the persistence of dense fibrosis of the portal areas with portal vein sclerosis, segmental portal vein dilatation, peri-portal collateral formation, thin incomplete septae and vague nodularity in the absence of steatosis, inflammation or pericellular fibrosis (Fig. 2E–G). Nail and hair clippings of the family members (father, mother and a sibling) and the patient were gathered at this time and analyzed for arsenic content which was non-contributory (below detectable range, the minimum detection being 0.1 mg/kg) and suggestive of the absence of systemic toxicity in the former but remarkable in the latter (nails—2.8 mg/kg, hair—4.3 mg/kg). Even though the clinical, investigational and special analyses pointed toward a diagnosis of drug-induced AH with NCPH (hepatoportal sclerosis with incomplete septal cirrhosis) due to arsenic poisoning, we wanted to ensure the liver disease was not due to known genetic causes even in the absence of a significant family history of liver disease. Mutation analysis of genes associated with heritable causes of chronic liver disease was performed with next-generation sequencing (NGS) panel (TruSight One, Illumina, California, USA) consisting of >4800 genes run on deoxyribonucleic acid (DNA) extracted from peripheral blood using the Illumina NextSeq platform. Bioinformatic analysis of genome sequencing was carried out within coding regions and along exon-intron boundaries on the genes (clinical exome analysis) which are associated with the hereditary chronic liver disease. All controls and quality metrics were performed to specification. NGS of DNA revealed the presence of heterozygous variants c.2930C > T (p. Thr977Met) and c.2029C > T (p. Pro677Ser) in the *NPHP4* gene; c.980G > A (p. Arg327His) in the *PEX12* gene and c.1490A > C (p. Gln497Pro) in the *HNF1B* gene. These variants were classified as insignificant based on the available evidence from the literature, analysis by *in silico* mutation prediction algorithms and status and in-house database and absence of associated clinical features in the child. Since the associated clinical features were lacking in our patient, known genetic causes for the underlying liver disease were essentially ruled out. Single-source exposure (Ayurvedic herbals) and heavy metal toxicity in only the exposed, i.e. the patient, not the rest of the family members, confirmed chronic arsenic poisoning and related clinical events. With clinical and investigational results, a final diagnosis of Ayurvedic medicine-related severe AH and background NCPH of the hepatoportal sclerosis variant due to chronic arsenic exposure was made. Written informed consent for publication of patient-related data, including pertinent images, were taken from the father of the child before the preparation of the manuscript.

DISCUSSION

The use of CAMs is on the rise world over. This is especially true in countries entrenched in the practice of CAM, with a collective thought among patients and their families that these alternative drugs are safer and free from adverse effects. In our region, the most commonly utilized alternative medicine is Ayurveda and is associated with traditional and proprietary herbal medications. Even though traditionally considered as safe, better awareness of the identification and availability of sophisticated analytical methods have demonstrated an increased incidence of Ayurvedic drug-related liver injury among the general population, leading to acute liver failure and patients with chronic liver disease, resulting in acute on chronic liver failure [6, 7]. Heavy metal contamination is well-known to be associated with Ayurvedic medicines. Saper and colleagues showed that one of five Ayurvedic drugs produced in South Asia and marketed in the USA contained potentially harmful levels of lead, mercury or arsenic and that consumers of such drugs were at risk for heavy metal toxicity. The same authors also found that one-fifth of US-manufactured and Indian-manufactured Ayurvedic medicines purchased over the Internet contain detectable lead, mercury or arsenic [8, 9]. Lead poisoning related to Ayurvedic medicine use has been reported by multiple authors, and large cluster series have also been reported on the same, shedding light on the importance of stringent regulatory policies on CAM use among the general and patient populations [10, 11]. Similarly, chronic arsenic poisoning leading to severe systemic effects has been reported with Ayurvedic medications [12]. Adulteration of Ayurvedic medicines with synthetic medicines to improve efficacy and mislabeling of herbal products have been reported in the literature. In our patient, we found adulteration with clonazepam (an add-on therapy for refractory epilepsy in adults) in the 'herbal antiepileptics', which was very concerning since the treatment provided and the principles followed were fraudulent and unethical [13, 14]. Nevens and colleagues demonstrated in eight patients, on treatment with arsenical solution, complications of NCPH and associated dermatological effects and malignancies on long-term follow-up. In their paper, evidence for NCPH in the absence of generalized systemic toxicity was described, which was noted in our patient. The emergence of chronic systemic toxicity apart from liver involvement could depend on the duration of exposure to arsenic and the time to toxicology analysis. The latter was late by 6 months in our patient since the diagnosis was made in retrospect [15]. Recently, Goel *et al.* described arsenicosis, possibly from contaminated groundwater, associated with NCPH. In their paper, only 10% of patients with portal hypertension had raised nail levels of arsenic, while skin changes were notable in 11% [16]. In our patient, we performed clinical exome analysis to identify the genetic causes for liver disease and found variants of clinical insignificance. Mutations of the *NPHP4* gene are typically associated with the autosomal recessive type of nephronophthisis with hepatic fibrosis. By contrast, those of the *HNF1B* gene are associated with monogenic diabetes, renal cyst and liver disease. The *PEX12* gene mutations are associated with abnormal peroxisome biogenesis associated with childhood onset, an autosomal recessive developmental disorder. All of these associated features were absent in our patient, and the possibility of genetic causes for liver disease was unlikely, with a high likelihood of Ayurvedic medicine-related dual liver pathologies [17–19]. Histologically, hepatoportal sclerosis (also called obliterative portal venopathy, non-cirrhotic portal fibrosis or idiopathic portal hypertension depending on the diagnosis region) encompasses a variety of portal vein abnormalities and bridging fibrosis. Portal vein involvement includes fibrous intimal thickening, sclerosis of the portal tracts, collateral vein formation in the periportal areas or replacement of portal vein by numerous small venous radicles. Bridging fibrosis between portal areas may be notable in the absence of nodule formation along with parenchymal atrophy due to portal perfusion abnormalities. Hepatoportal sclerosis is synonymous with incomplete septal cirrhosis even though the latter finding is better described in the context of regression of cirrhosis. Still, it has been well described in patients with chronic arsenic exposure [20, 21].

Certain limitations require deliberation. First, even though we have extensively worked up our patient to confirm the complex diagnosis beyond a reasonable doubt, the supposition that a pre-existing, undiagnosed pathology was already there and the

consumed medications only accelerated the process to reach fibrosis, and portal hypertension also remains a possibility. Second, the role of heavy metals, particularly arsenic, cadmium and nickel, as mitochondrial toxins contributing to micro and macrovesicular steatosis along with alcohol, could also have contributed to the final disease phenotype and not purely ethanol *per se*. Finally, as with every publication on multiherbal drug-induced liver injury, the specific dose/frequency/duration of numerous multiherbal products consumed over a long period was difficult to ascertain practically in our report. Hence, estimating the cumulative/daily dose the patient had of each toxic component over the course was not feasible.

Severe AH and NCPH of hepatoportal sclerosis and incomplete septal cirrhosis variety can be seen with Ayurvedic medicine. In the absence of known etiological exposures, a mandatory, detailed drug history is needed, especially in areas endemic to CAM use. Public education, especially regarding health-seeking behavior, and integration of health practices at the industry and Government level for better regulation and control of alternative medicine use among the population is the need of the hour. A strict and well-defined methodical general pharmacovigilance, including modern and alternative practices, is an unmet need. This would help prevent avoidable drug-related adverse events, especially among the pediatric population, as the latter remains our hope and future.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None to declare.

ETHICAL STATEMENT

All authors confirm that they are accountable for all aspects of the work (if applied, including full data access, the integrity of the data and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONSENT

A written informed consent to publish the de-identified patient data was taken from the parents of the patient.

GUARANTOR

Dr Cyriac Abby Philips.

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