

CASE REPORT

Ayurveda metallic-mineral 'Bhasma'-associated severe liver injury

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SUMMARY

Ayurveda Bhasma is a metallic-mineral preparation homogenised with herbal juices or decoctions and modified with heat treatment to apparently detoxify the heavy metals. It is widely recommended for the treatment of many disease conditions by practitioners of complementary and alternative medicine in the absence of good quality clinical trial evidence on its safety and efficacy. Heavy metal-induced liver injury is widely reported in the literature, and heavy metal adulteration of non-Bhasma-related Ayurveda and herbal products has been well described. We report a patient who developed severe liver injury requiring listing for liver transplantation for improved survival, after consumption of Bhasma for dyspepsia. This case describes the first documented case and toxicology analysis of Ayurveda Bhasma associated with severe drug-induced liver injury. Physicians must be alert regarding patient's use of supposedly safe Ayurveda Bhasma that may promote acute severe liver injury in the absence of other known aetiologies.

BACKGROUND

A large proportion of people, especially in the Asian continent and recently in the West, believe that Ayurveda and herbal medicines are completely safe and non-toxic, in contrast to modern medicines and utilise herbal medicine for long periods. The Ayurveda and herbal drugs used in the Indian subcontinent and China have been found to contain a higher concentration of heavy metals compared with other regions.¹ Saper and colleagues found that one out of five Ayurvedic herbal medical products produced in South Asia contained high levels of arsenic, mercury and lead.² Ayurveda practitioners prepare Bhasma encompassing different processes such as trituration and heating of raw materials (herbs, metals, minerals and decoctions) claiming that the final product thereby becomes non-toxic. Such processes also use cow urine and dung in the conversion of the herbo-metallic-minerals into ash (final form of the product), promoting microbial contamination where good manufacturing practices are not stringent.³ Even though Ayurveda texts and proponents of complementary medicine endorse proper detoxification processes in preparation of Bhasmas, no universal guidelines or quality studies on preparation exist, for homogenising preparation techniques world over, leading to disturbing differences in quality and contamination of such herbal products. In the absence of safety and efficacy

studies in the short, intermediate and long term, the use of Bhasmas in the current era remains a threat to public health. Safety and toxicity associated with lead-based traditional herbo-metallic preparations was described by Nagarajan and co-workers previously.⁴ Ayurveda Bhasma related to severe liver injury and its chemical analysis have not been documented in the literature. Ayurveda Bhasma is a very commonly used complementary drug that lacks stringent pharmacovigilance, manufacture practices and control of traditional healer-based treatments in areas entrenched in complementary medicine practice. Here we report the case of a patient who after consuming Ayurveda 'Dahanabhasma' for dyspepsia and improvement in appetite daily for a week developed acute severe liver injury requiring listing for liver transplantation for improved survival. We also discuss in depth, the toxicology and chemical analysis of the retrieved Bhasma sample.

CASE PRESENTATION

A previously healthy 54-year-old man was seen in the Hepatology emergency room with complaints of nausea, loss of appetite and general well-being for 1 week followed by yellowish discolouration of skin and darkening of urine for 2 weeks associated with severe itching all over the body, especially worse at night time in the absence of clay-coloured stools, abdominal pain and fever. The patient had consumed a multi-ingredient, unlabelled Ayurveda product called 'Dahanabhasma' for 2 weeks before symptomatic presentation (figure 1) for severe dyspepsia and loss of appetite. The product package did not disclose any components other than a multitude of symptoms for the drug use. He was taking two spoons of the product three times per day (approximately 350 g per week), after meals before the onset of current symptoms. He did not consume alcohol and did not abuse oral or injectable recreational drugs. His other medications included vitamin B complex and occasional calcium and vitamin D supplements, in the last 6 months. On evaluation, the patient had a body mass index of 29.2 and was deeply icteric with extensive scratch marks all over the body in the absence of other stigmata of chronic liver disease.

INVESTIGATIONS

Blood work revealed a total serum bilirubin level 28.8 (upper limit of normal, ULN 1.1 mg/dL), direct bilirubin 19.6 (ULN 0.2 mg/dL), aspartate aminotransferase 228 (ULN 36 U/L), alanine



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Figure 1 The Ayurveda Bhasma consumed by the patient associated with severe liver injury. Note that there are no content, component and adverse effect disclosures. The package also mentions dosing in children without clear evidence for safety and efficacy in a paediatric population.

aminotransferase 302 (ULN 45 U/L), alkaline phosphatase 324 (ULN 120 U/L), gamma-glutamyl transferase level 563 (ULN 35 U/L), albumin 3.1 (ULN 5.5 g/dL) and international normalised ratio 2.7 (normal <1.2). Aetiological workup was negative for viruses (hepatitis A and E virus immunoglobulin M, hepatitis B virus surface antigen and core antibody, hepatitis C virus antibody, cytomegalovirus DNA, Epstein-Barr virus immunoglobulin M, Herpes and Zoster virus immunoglobulin M) and negative autoimmune markers (antinuclear antibody, antiliver kidney muscle antibody type 1, antismooth muscle antibody and antimitochondrial antibody with normal serum gamma globulins). Renal function tests and complete blood counts were within normal range. A CT scan of the abdomen revealed hepatomegaly with steatosis, patent hepatic vasculature and normal biliary anatomy without evidence of portal hypertension. In the absence of known causes of liver diseases, drug-induced liver injury, secondary to Ayurveda Bhasma was considered, with a Roussel Uclaf Causality Assessment Method (RUCAM) score 8 (probable adverse drug reaction). Liver histopathology revealed

extensive periportal and perivenular necrosis (figure 2A). The portal tracts showed infiltration by neutrophils, lymphocytes and eosinophils (figure 2B) associated with marked cholangitis, hepatocytic ballooning, neutrophilic satellitosis (figure 2C, D) and severe canalicular and hepatocellular cholestasis (figure 2E). Masson Trichrome staining revealed extensive bridging fibrosis (figure 2F). No inclusion bodies or atypical cells were noted. We retrieved the Bhasma sample from the patient and subjected it to chemical analysis and toxicology. Heavy metals testing was done using inductively coupled plasma–optical emission spectrometry (ICP-OES, Agilent Technologies, Santa Clara, California, USA) and volatile organic compounds, chemical adulterants, pesticides and insecticide contamination were screened using triple, quadruple gas chromatography and dual mass spectroscopy (TQ-GC-MS-MS, Thermo Fisher Scientific, Waltham, Massachusetts, USA). We detected multiple undisclosed heavy metals such as barium, chromium, lead, vanadium, thallium and arsenic (table 1) in the Bhasma, but not volatile organic compounds, chemical adulterants, pesticide or insecticide residues.^{5 6}

TREATMENT AND OUTCOME

The patient was initially started on weight-based corticosteroid therapy (1 mg/kg) along with *N*-acetyl cysteine and nutritional support. After 3 days of treatment, he developed ascites without spontaneous bacterial peritonitis. Corticosteroids were withheld, and the patient was started on therapeutic plasma exchange (membrane plasma separation method); single volume plasma exchange; standard haemodialysis equipment in high flux ultrafiltration mode without cytopheresis (4008S Classix +fxClassix Filter, Fresenius Medical AG & Co. KGaA, Germany; replacement plasma volume – one-third with 5% human albumin and two-thirds with fresh frozen plasma; estimated plasma volume for removal calculated using formula= $0.065 \times \text{wt in kg} \times (1 - \text{haematocrit})$) with daily with monitoring of haemogram, renal and liver biochemistries, serum electrolytes, arterial ammonia and coagulation indices (prothrombin time, INR and serum fibrinogen) every 12 hours. After two sessions, clinical deterioration was evident with new-onset hepatic encephalopathy that was managed conservatively with ammonia-lowering therapies. The family was detailed regarding the grave prognosis and high short-term mortality associated with the disease and was advised for liver transplantation as definitive treatment. The patient was after that transferred with a referral to a liver transplant facility for emergency workup and listing but died during the workup due to multiple organ failure before a transplant could be offered.

DISCUSSION

We present a patient who developed acute severe liver injury secondary to Ayurveda Bhasma used for dyspepsia and appetite enhancement that eventually led to his death. Mohamed and co-workers demonstrated that heavy metal accumulation was associated with molecular and pathological perturbations in the liver of yellow-edged lyretail fishes in the Red Sea. Such good quality preclinical studies are ideal for gaining insights into tissue effects of traditional medicines such as Ayurveda Bhasma which is non-existent in the complementary medicine literature.⁷ Liver transaminase activity and bilirubin concentration increased significantly in male Wistar rats exposed to cadmium, lead and manganese and correlated positively with their respective blood levels in a study on effects of chronic exposure to lead, cadmium and manganese mixtures on oxidative stress in rat liver by Markiewicz-Górka *et al.*⁸

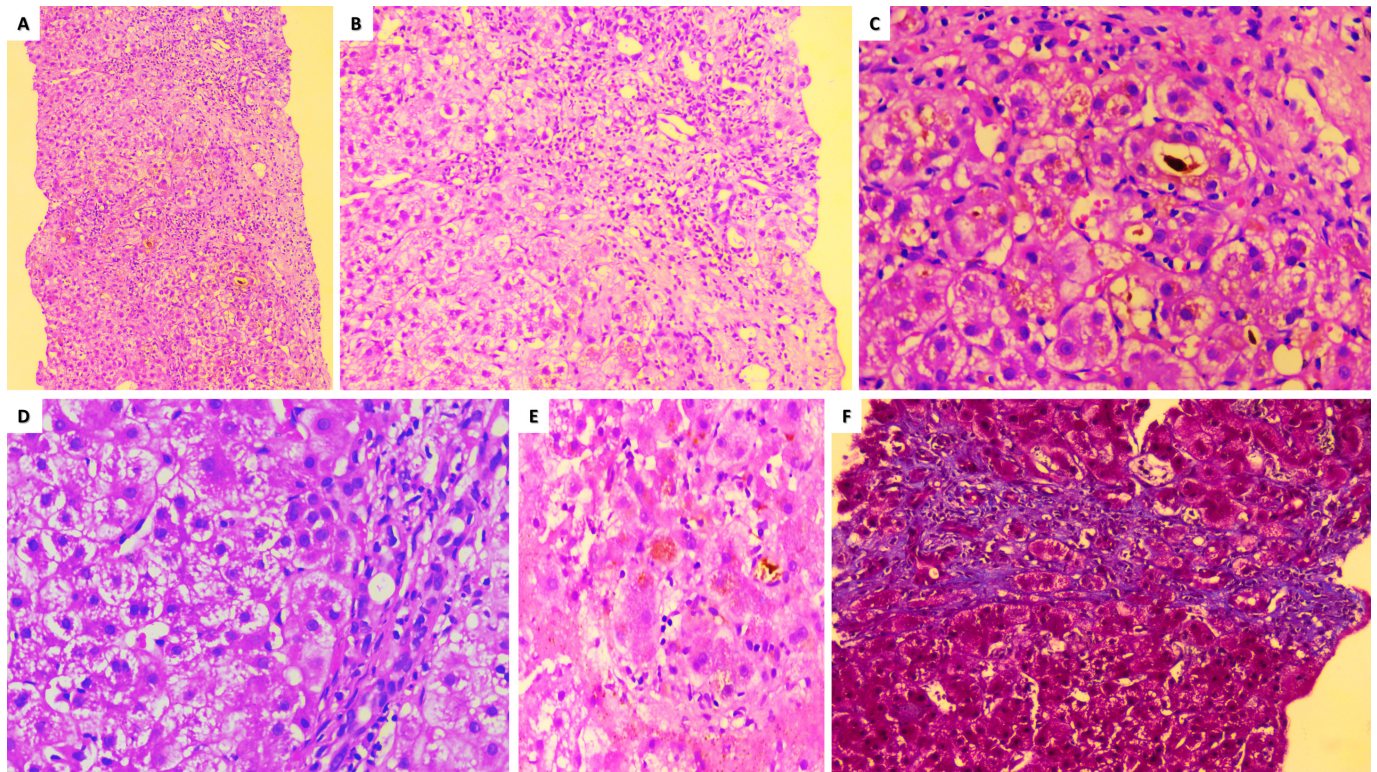


Figure 2 Liver histopathology of a Bhasma-poisoned case that revealed extensive periportal and perivenular necrosis (A; H&E, magnification 10×); infiltration of the portal tracts by mixed inflammatory cells (B; H&E, 20×) marked cholangitis, hepatocytic ballooning (C; H&E, 40×), neutrophilic satellitosis (D; H&E, 40×) and severe canalicular and hepatocellular cholestasis (E; H&E, 40×); extensive bridging fibrosis on Masson-Trichrome staining (F, 20×).

The hepatotoxicity induced by arsenic, cadmium, chromium, copper, lead and mercury, including histological injury, lipid peroxidation, glutathione depletion and mitochondrial dysfunction, are well documented in preclinical models.^{9 10} Lin *et al* showed the combined toxicity of eight common heavy metals (Pb, Cd, Hg, Cu, Zn, Mn, Cr and Ni), based on the daily amount of each heavy metal that a human consumed from fish. They also evaluated the combined cytotoxicity of multicomponent mixtures on human liver HL7702 cells and observed synergistic, antagonistic or additive effects of toxicity with different heavy metal mixtures suggesting that the combined effects should be considered in the risk assessment of heavy metal co-exposure—an important study aspect completely lacking in Ayurveda and its purported science.¹¹ Prystupa and co-workers provided insights into the fact that

disorders of metabolism of heavy metals were associated with patients with liver cirrhosis. Patients with underlying liver disease such as those with the fatty liver disease could develop severe liver injury with use of Ayurveda products rich in heavy metals, a scenario that could have led to severe liver disease in our patient.¹² Ayurveda practitioners believe that the various compounds of a heavy metal exert differential effects on organ systems which is true. For example, a cyanide form would be more toxic than its oxide form. However, this generalisation is not adequate. With complex Ayurveda medicinal mixtures, drug–drug interaction, pharmacokinetics and pharmacodynamics could be very different from what is theoretically considered and such demonstrations in preclinical and clinical studies are unavailable.¹³ Studies on effects of Bhasma in patients with and without liver disease lacks in the Ayurveda

Table 1 Results of chemical and toxicology of retrieved Ayurveda Bhasma sample

S No:	Heavy metals	Unit	Result	Provisional tolerable intake/recommended daily intake/toxic doses
1	Arsenic	mg/kg	0.25	0.015 mg/kg weekly (drinking water source), not allowed in food and drug products
2	Cadmium	mg/kg	0.083	0.025 mg/kg monthly
3	Barium	mg/kg	8.25	0.2 mg/kg daily
4	Chromium	mg/kg	2.85	Recommended dietary allowance is up to 0.05 mg/kg
5	Cobalt	mg/kg	0.13	0.005 mg/kg per day is average adult intake, safe cut offs not defined
6	Beryllium	mg/kg	Below detection limit	
7	Lead	mg/kg	0.73	0.025 mg/kg weekly
8	Vanadium	mg/kg	0.47	1.8 mg/day is allowed upper limit in adults; >2.5 mg per day is toxic
9	Thallium	mg/kg	0.13	1.5 mg/kg total dose can cause acute toxicity, 1 g in cumulative amounts can cause chronic toxicity
10	Mercury	mg/kg	Below detection limit	

literature even though the practice of prescribing such medicines for the treatment of diseases including severe liver disease is rampant. Ayurveda practitioners have reported on the utility of heavy metals in the management of liver disease and its complications without proper scientific evidence. However, in these reports, they continue modern medical management along with their alternative practices creating more of an illusion regarding the efficacy of treatments with heavy metals rather than conclusions.¹⁴ Chronic cadmium exposure has been shown to promote hepatic fibrosis, haemosiderosis, inflammation and steatosis in controlled observational studies.¹⁵ Similarly, consumption of water contaminated with arsenic has been shown to cause multiple organotoxicity including acute hepatitis previously.¹⁶ Recently, metabolomic studies on cadmium exposures demonstrated synergistic effects on pesticide-related hepatotoxicity. In developing countries, the use of pesticides and insecticides to increase crop productivity is burgeoning and concomitant use of Ayurveda drugs such as Bhasma could potentiate accelerated liver injury.¹⁷ Most of the heavy metal concentrations in the Bhasma were beyond permissible and tolerable levels. Apart from the heavy metals detected in the sample, complex herbal components, most of which remain unknown, and their phytochemical constituents could have heightened the severe hepatotoxicity seen in our patient.

There is no standard of treatment for patients with complementary and alternative medicine-related severe drug induced liver injury (DILI). Several studies have shown some benefit in using corticosteroids, ursodeoxycholic acid, N-acetyl cysteine, plasma exchange or liver assist devices to ameliorate liver injury in patients with severe DILI and in the presence of progressive liver failure, liver transplantation for curative intend, which is what we followed in our patient.¹⁸ Taking into consideration current available data in the scientific literature, we believe that

the severe DILI seen in our patient was strongly associated with the use of Ayurveda Bhasma. Even though we did not find volatile organic compounds, insecticides or pesticides in the retrieved sample, many more complex herbal components that remain undetected could have also added to the severe toxicity. Even though Ayurveda practitioners and unassuming patients believe in the safety and efficacy of Ayurveda Bhasma, it remains to be demonstrated in good quality preclinical and clinical studies. Until then, Ayurveda Bhasma use for prevention and management of a multitude of diseases remains a threat to public health.

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Learning points

- ▶ Ayurveda Bhasma is one of the most commonly prescribed complementary medicines for a wide variety of health conditions.
- ▶ Ayurveda practitioners and an unknowing public believe Bhasma use to be safe and efficacious for many disease conditions including liver diseases in the absence of high-quality scientific studies.
- ▶ Scientific literature is rich with preclinical studies and clinical observations on heavy metal-related liver toxicity.
- ▶ We present novel clinical and toxicology data on severe drug-induced liver injury in a middle-aged man secondary to Ayurveda Bhasma use.
- ▶ Ayurveda Bhasma use for prevention and treatment of diseases should be considered a threat to public health until good quality scientific evidence demonstrates its clinical safety and efficacy.

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