Controversy on a Newly Published Case of Assumed Acute Liver Failure One Day after Kava Use: Issues of Confounders, Causality, and an Undetermined Cause

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Abstract: In a recent case report from the Michigan State University, acute liver failure (ALF) was diagnosed one day after the alleged use of an unspecified herbal product possibly containing kava (*Piper methysticum* Forst.). The available details are insufficient for a formal causality assessment and remind us of pitfalls often associated with the diagnosis of herb induced liver injury: incomplete collection of data relevant for the diagnosis, disputable interpretation of clinical features, and ignoring of variables that confound the diagnosis. Considering the published case, the diagnosis of ALF is likely not correct. It is not based on mainstream criteria and shows a long list of confounding variables: comedication with the potentially hepatotoxic amitriptyline and cannabinoids, hypovolemic shock secondary to massive retroperitoneal hemorrhage, shock liver, extensive mesenteric ischemia with pneumatosis throughout the bowel walls and the liver, sepsis with septic shock, and acute renal failure. Causality assessment was attempted in the published report using the Naranjo method, which is unsuitable for liver injury cases. The use of a robust diagnostic algorithm like RUCAM (Roussel Uclaf Causality Assessment Method) was missing. In essence, the disease is best classified as multiorgan failure of undetermined etiology rather than as ALF caused by kava.

Keywords: Herb induced liver injury, RUCAM, acute liver failure, multiorgan failure, hemorrhagic shock, shock liver, sepsis, kava, acetaminophen, amitriptyline, cannabis.

1. INTRODUCTION

Abundant cases of herb induced liver injury (HILI) have been published, assessed for causality by RUCAM (Roussel Uclaf Causality Assessment Method) [1,2]. This is a diagnostic algorithm launched in 1993 [3], with an updated version published in 2016 [4]. In terms of case numbers, 12,068 RUCAM based cases of HILI have been published worldwide [2] including 11,160 RUCAM based cases of HILI by traditional herbal medicine presented by authors from the Asian region [1]. RUCAM was also used in 46,266 cases of drug induced liver injury (DILI) published worldwide from 2014 to early 2019 [5]. All these data suggest that RUCAM is part of the mainstream approaches assessing causality in liver injury cases. RUCAM outperforms other tools in terms of case numbers.

The diagnosis of HILI was established for most published cases [1,2]. There were rare exemptions for cases of HILI by selected herbs such as kava (*Piper methysticum* Forst.) [2]. A major controversy emerged around alleged HILI by kava with much scientific and clinical interest triggered by the German regulatory agency BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte). However, the regulatory claim related to liver injury by kava was not based on a robust causality assessment method. When re-assessed, the regulatory conclusion of a causal association between liver injury and kava use could not be substantiated in most cases [6], findings subsequently confirmed [7,8]. Recently, a new case report was published, claiming the occurrence of acute liver failure (ALF) with an assumed causal relationship to kava used one day before admission to the hospital [9]. Easily recognizable flaws of this published case report call for re-assessment of case details and a critical analysis.

In this viewpoint article, we critically analyze the published case details with associated fragile conclusions and provide our opinion on the case. This could help avoid diagnostic misconceptions and risky interpretations in future cases of HILI.

2. CONDENSED CASE NARRATIVE

The case of a man aged 40 years old is reported who developed ALF after use of kava one day before presentation [9]. Medical history included depression, anxiety and the use of amitriptyline. He was found unconscious with a so called down time of >24 hours. He was hypotensive, hypothermic, bradycardiac, and bradydyspneic upon admission and was classified with

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a Glasgow Coma Scale of 3. Urine drug screen was positive for cannabinoids and tricyclic antidepressants, with a negative drug panel for alcohol and salicylate. Acetaminophen levels were reported as "normal", whatever this means. Reported were also acute renal failure, metabolic and respiratory acidosis, septic shock, rhabdomyolysis, shock liver with alanine transaminase (ALT) >10,000, likely expressed in U/L, and elevated troponins, while his creatine phosphokinase and ALT levels started to normalize. Infectious, metabolic, and autoimmune causes were reported as excluded. The day after admission, the patient developed hypovolemic shock secondary to a retroperitoneal hemorrhage extended into the right thigh. Computed tomography of the abdomen showed extensive mesenteric ischemia with air throughout the bowel walls and the liver. In an attempt to assess causality for kava, the Naranjo scale was used. The final outcome was lethal. There was obviously little interest of an autopsy to clarify some of the open questions. Information is lacking whether this case was presented to the US regulatory agency.

3. SPECIFICITIES OF THE ASSUMED ACUTE LIVER FAILURE CASE BY KAVA

Some critical comments are warranted on the case report published by Dr. Raziq from the Michigan State University [9].

3.1. Kava Product Identification

Elements necessary for reporting cases of liver injury were missing in the case report [9]. Such reports normally should include the implicated herb or drug with generic name, dose and regimen of administration [1,10,11]. This was also proposed in a publication by the first author Fontana from the University of Michigan [11], the same university, which published the case report [9]. The kava product used was not identified [9], which is certainly a major omission in a case report of liver injury that normally would have been detected by skilled reviewers in a peer reviewing process, with the result of not endorsing publication. The information gap caused by omission of any details regarding kava exposure creates questions: it is unclear whether a kava product was consumed at all, whether a noble kava variety was used, and whether kava was prepared as an extract with ethanol, acetone, or water as solvent. There is also concern with the classification of the kava product as a dietary supplement for anxiety [9]. Anxiety is by no means a disease caused by any dietary deficiency requiring treatment by supplementation. In Germany, for instance, kava was an officially approved drug prior to its ban issued by the BfArM in 2002 and its removal from the market [6-8]. Kava is internationally used either for recreational drinks with relaxing effects or as a drug product. In the US, kava is favored as a drink in kava bars, or in form of "botanicals". The latter are barely supervised by the US FDA (Food and Drug Administration) and seem to be economically appreciated as tax generating products. However, they are not clearly designed to supplement patients who are on a normal balanced diet [12,13].

3.2. Kava Posology

Posology is an essential element in case reporting [10], but related questions remained unanswered in this case [9]. There was no discussion of a possible overdose of the kava taken 24 hours before admission [9]. Kava use in doses above those recommended is well documented in some published cases [6-8]. Based on clinical trials and according to regulatory recommendations in Germany, the usual daily dosage of kava, expressed as kavalactones, was 120 mg/d to be used for not longer than 3 months, was considered safe prior to the regulatory ban [7].

3.3. Multimorbidity

3.3.1. Depression, Anxiety

Depression and anxiety were mentioned as past medical history [9]. Both were likely not of short-term but rather long-standing diseases. Interestingly, kava is not effective in depressive disorders, it seems to work only for anxiety [6-8]. The patient reportedly used amitriptyline [9], a typical tricyclic antidepressant drug known for its established potency in causing liver injury, as assessed for causality by RUCAM [14].

3.3.2. Disputable Acute Liver Failure and Undetermined Cause

The multifaceted features of ALF in adult patients have attracted considerable interest with focus on pathogenesis, causes, and diagnostic criteria [15-23]. ALF is a clinical syndrome attributed to a loss of liver cells and liver function, typically associated with coagulopathy as evidenced by a prolonged INR (>1.5) and encephalopathy in a patient without preexisting liver disease or cirrhosis [15]. In this clinical context, features that are virtually unique to ALF include cerebral edema and swelling of the brain, detectable by computed tomography (CT) of the brain. This swelling may produce herniation of the uncus through the falx

cerebrum, leading to brain stem compression and death. In the case under consideration, however, neither an INR value was presented nor were there any results provided from a brain CT [9]. In addition, the typical interval from onset of symptoms to onset of encephalopathy is 1 or 2 weeks, or even up to 6 months [15]. This typical development does not concur with findings described in the published case of assumed ALF [9]. Instead, the lack of various typical criteria and clinical features essential to the diagnosis of true ALF raises concern on the validity of ALF as a realistic diagnosis. The described mental changes could well be ascribed to causes unrelated to ALF, such as overdosed cannabinoids or tricyclic antidepressants used by the patient. However, details of daily doses and duration of consumption were not provided [9]. Overall, discussions on possible causes are speculative and basically not warranted, because ALF as a diagnosis must be doubted.

There is also a large body of evidence from most published cohorts of adult patients with ALF showing that in many cases a cause for the disease could not be determined [15-23]: Percentages of ALF with no evident cause were 13% [15], 20-40% [16], almost 20%

Table 1: Selected Countries with Reports on Adult ALF of Undetermined Causes

Reporting Country	Year of Publication	ALF of undetermined causes	First author
UK	1989	19%	O'Grady [24]
US	1995	48%	Daas [25]
US	2000	28%	Shakil [26]
Japan	2001	62%	Kato [27]
US	2002	19%	Ostapowicz [28]
Canada	2002	27%	Tessier [29]
India	2003	7%	Khuroo [30]
Australia	2004	10%	Gow [31]
Pakistan	2006	4%	Sarwar [32]
Spain	2007	17%	Escorsell [33]
Sudan	2007	38%	Mudawi [34]
Sweden	2007	11%	Wei [35]
India	2008	7%	Bhatia [36]
Lithuania	2008	18%	Adukauskiene [37]
Germany	2008	28%	Hadem [38]
US	2008	14%	Lee [39]
UK	2009	2%	Marudanayagam [40]
Germany	2011	21%	Canbay [41]
Japan	2011	16%	Oketani [42]
UK	2012	43%	Germani [43]
Germany	2014	21%	Canbay [44]
US	2012	13%	Lee [45]
UK	2015	12%	Bernal [46]
UK	2017	3%	Donnelly [47]
Iran	2017	36%	Moini [48]
US	2018	11%	Ganger [49]
Australia	2019	10%	Hey [50]
India	2019	31%	Nabi [51]
India	2019	7%	Singh [52]
Thailand	2019	68%	Thanapirom [53]
Italy	2020	17%	Amoroso [54]

The undetermined causes are given as percentage of the whole analyzed study cohort of ALF.

Table 2: Open Case Related Questions

Selection of open questions	Answers
Evidence of kava ingestion?	Irrefutable
Role of antidepressants and cannabinoids evaluated?	No
Acetaminophen as contributing factor?	Possible
Viral infections could have been causative?	Yes
Is the multiorgan failure explained on the basis of kava alone?	No
Causality between kava and liver failure fulfils the robust criteria of RUCAM ?	No

The open questions represent a selection and relate to the published case [9].

[17], up to 50% [18], 30-50% [19], 11-32% [20], 15-20% [21], 20-45% [22], and 17-43% [23]. These rather high percentages of undetermined causes of ALF led to a more comprehensive examination of cases of ALF published between 1998 and 2020. The focus of this evaluation was on the reporting countries and their reported individual percentages of undetermined causes among the ALF cases (Table **1**) [24-54]. It is outside the scope of this report to analyze and discuss the background of the partially high percentages of undetermined causes in detail. This first approach does, however, underline the necessity for being cautious when it comes to conclusions drawn in case reports of ALF, especially when the report is as poorly documented as in the case discussed herein [9]. A selection of other open questions is listed (Table **2**).

3.3.3. Unconsciousness or Coma of Undetermined Cause

The patient was found in an unconscious state, a condition described in the hospital as coma attributed to assumed ALF. This diagnosis of ALF is highly questionable. Diagnostic criteria for a true ALF were not provided, and mainstream diagnostic essentials as proposed by others [15] were not followed [9]. There is no question that true ALF can cause coma or the less serious hepatic encephalopathy [15,16], but acute forms of coma may also be due other causes including cardiac arrest, primary cerebral lesions like intracranial hemorrhage and infections, or septic encephalopathy, intoxication, and epilepsy [55]. It seems that only few of these differential diagnoses were considered in this case [9].

3.3.4. Sepsis, Intestinal and Hepatic Pneumatosis, and Hypovolemic Shock

Sepsis leading to septic shock and a CT finding of the abdomen describing extensive mesenteric ischemia and intestinal and hepatic gas, usually known as pneumatosis, were mentioned in the case report [9]. Pneumatosis is caused most probably by gas producing bacteria [56]. All these conditions are to be classified as confounding variables and are not necessarily in support of ALF caused by kava.

The retroperitoneal hemorrhage extending into the right thigh was found the day after hospital admission [9]. This certainly does not rule out that the hemorrhage started when the patient was at home before he was found unconscious. He was described as hypotensive upon admission. The reported shock liver seems plausible with ALT values of >10.000 U/L [9]. In retrospect, shock liver was likely the correct diagnosis. Such high serum ALT activities were never reported in other patients who used kava for up to 24 months [7]. Among the published cases, there is also not a single patient who used kava for one day before uncomplicated liver injury or ALF was detected [7,8]. Evidently, there is no need to construct an ALF caused by kava.

3.3.5. Possible Role of Drug Overdose

Consensus exists that in most countries reporting on ALF, acetaminophen is responsible in the majority of cases. Frequently, acetaminophen is used either unintentionally or intentionally overdosed [15-23]. In this context, the vague note that in the reported patient the acetaminophen levels were reported as “normal” remains unclear. No details were given for the analyzed sample, the analytic method, and the detected quantity [9]. However, it obviously means that acetaminophen was detected. It would not be expected that Americans normally have a certain acetaminophen level, hence the finding should have been discussed. Acetaminophen may, in addition, already have largely disappeared from the patient’s body by the time of analysis. The report would have required more clarity regarding the time frame and dose concerning the use of acetaminophen. The diagnosis of ALF by acetaminophen requires a special diagnostic approach,

as outlined and discussed previously [13]. Other candidates for an intoxication are certainly the cannabinoids and tricyclic antidepressants, all tested positive in the urine of the patient but without reported quantification [9].

3.3.6. Virus Infections

In the case under discussion, infectious workup was reported globally as negative. The type of excluded infections was, however, not detailed [9]. This raises the question whether infections by HAV (hepatitis A virus), HBV (hepatitis B virus), HCV (hepatitis C virus), and HEV (hepatitis E virus) were all correctly excluded using specific PCR or antibody tests. Again, this is considered as essential elements in HILI cases requiring causality assessment for the implicated herb(s) [4]. There is particular concern regarding HEV infections, an element considered not always necessary to be excluded in the US, but an obligatory element in the updated RUCAM [4].

3.3.7. Multiorgan Failure

The clinical features described in the prefinal stage of the patient are best summarized as multiorgan failure of undermined etiology, because the initial triggering events cannot be identified upon retrospective analysis. Little support is provided that we are dealing with an ALF caused by a herbal product that may or may not have contained the herb kava.

3.4. Causality Assessment

The suspected cases of HILI claimed by the German regulatory agency BfArM have been heavily disputed. The major reason for the concerns was that the causality assessment leading to an indictment of kava was not based on a robust causality assessment method. The regulatory assessments were therefore questioned for most of the presented cases upon reassessment [6-8]. Specifically, the use of RUCAM provided negative causality gradings for most cases: In 18/26 cases, causality for kava was unassessable or excluded; among the remaining 8 cases, a probable causality grading for kava was attributed to 1 patient who adhered to the defined daily dose and maximum duration of the therapy, with another patient who received a highly probable causality grading for kava because of a positive result due to an unintentional re-exposure. For the remaining 6 cases variable causality gradings for kava ± comedicated drugs were found [7].

In the case report discussed herein, the Naranjo method was used in an attempt to assess causality [9], ignoring the fact that this method is not specific for liver injury cases. It is therefore classified as outdated [4]. Other authors from the US did in fact successfully use the robust RUCAM approach in the causality assessment of HILI cases [57-65], either in its original version [3] or now preferentially the updated RUCAM [4]. RUCAM has otherwise an excellent reputation worldwide for assessing cases of liver injury by herbs [1,2,4] and drugs [4,5]. We abstain using RUCAM for the case under consideration, because published case data were incomplete with missing essential elements required for a valid causality assessment. Raw case data were unavailable for re-assessment.

4. CONCLUSION

The prefinal features of the case under consideration can best be summarized as multiorgan failure of undetermined cause. The clinical picture includes retroperitoneal hemorrhage with hemorrhagic shock, shock liver, mesenteric ischemia with intestinal and hepatic pneumatosis commonly caused by gas producing bacteria, sepsis with septic shock, and acute renal failure. Mainstream criteria were not applied to diagnose true ALF, and uncertainties remained whether kava was used. It is also hard to believe that kava used the day before admission could have caused a severe liver injury such as the claimed ALF. In the published report, causality assessment was attempted by using the Naranjo method, which is unsuitable for cases of liver injury. Retrospective use of the robust RUCAM was declined by the authors of this analysis because the implicated herbal product was not identified, and the assumed ALF was not ascertained using standard clinical criteria. Case data as presented were incomplete, and raw case data were not available but provisionally an excluded or unlikely causality grading would be expected. In essence, since case data do not allow for a true ALF, there is no need to construct ALF caused by kava used one day before assumed ALF. The reported case is best classified as multiorgan failure of undetermined etiology.

AUTHORS' CONTRIBUTION

MS had the idea for this viewpoint article and provided a structure for the manuscript. RT wrote the first draft that was edited by MS. Both authors agreed on the final version to be submitted to JMMC.

CONFLICT OF INTERESTS STATEMENT

The authors state that they have no conflict of interests regarding this manuscript.

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