A rare cause of drug-induced hepatitis in an immunocompromised patient and the role of glutathione

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**Abstract**

The Food and Drug Administration (FDA) has issued a warning on numerous herbal drugs, including many popular products at General Nutrition Centers (GNC), regarding unstudied hepatotoxicity. There have been recent reports of GNC products such as hydroxycut and herbalife, causing drug-induced hepatitis. Herbal medications are over-the-counter products and are not investigated thoroughly by the FDA. Given that the most common outpatient laboratory abnormality is elevated liver transaminases, a sign of hepatocellular toxicity; it is not surprising that some of these products end up causing hepatic dysfunction, especially when taken in large volume. There are numerous herbal supplements that are hepatotoxic, however, these medications have a much more significant effect in human immunodeficiency virus (HIV)/acquired immune deficiency syndrome patients, which is secondary to depleted glutathione. We present a rare case of drug induced hepatitis secondary to herbal medications used to treat HIV and elucidate the role of glutathione depletion in immunocompromised patients.

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**Key words:** Glutathione; Human immunodeficiency virus; Acquired immune deficiency syndrome; Immunocompromised; Drug induced hepatitis; Hepatotoxicity; N-acetylcysteine; Herbal Medications

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**INTRODUCTION**

The Food and Drug Administration (FDA) has issued a warning on numerous herbal drugs, including many popular products at General Nutrition Centers (GNC), regarding unstudied hepatotoxicity. For example, there have been recent reports of GNC products such as Hydroxycut and Herbalife, causing drug-induced hepatitis. Herbal medications are over-the-counter (OTC) products...
and are not investigated thoroughly by the FDA. Given that the most common outpatient laboratory abnormality is elevated liver transaminases, a sign of hepatocellular toxicity, it is not surprising that some of these products end up causing hepatic dysfunction, especially when taken in large volume, which will be illustrated in our case presentation. There are numerous herbal supplements that are hepatotoxic (Table 1); however, these medications have a much more significant effect in human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) patients, which is secondary to depleted glutathione[2]. We present a rare case of drug induced hepatitis secondary to herbal medications used to treat HIV and elucidate the role of glutathione depletion in immunocompromised patients.

**CASE REPORT**

A 26-year-old African American male with a past medical history of HIV, with a recent CD4 count of 301, presented with yellow eye discoloration, dark colored urine, clay colored stools, nausea, malaise and fatigue of 2 wk duration. Pertinent physical examination findings revealed scleral icterus without evidence of anemia, ecchymosis, pruritus, asterixis, encephalopathy, and fetor hepaticus. Abdominal examination revealed non-tender hepatomegaly (liver span 14 cm). Laboratory findings revealed an albumin of 4.1, aspartate aminotransferase (AST) of 1301 (3 wk before AST = 432), alanine aminotransferase (ALT) of 1648 (3 wk before ALT = 609), alkaline phosphatase (ALP) of 154 (3 wk before ALP = 72), serum bilirubin of 10.4 (3 wk before bilirubin = 0.7), and a normal international normalized ratio. An acute hepatitis panel (hepatitis A, B and C) and serum acetaminophen levels were unrevealing. A workup for Autoimmune Hepatitis was also unrevealing. An abdominal computed tomography revealed nonspecific periporal edema and mild hepatomegaly. On further history, the patient was found to have increased his intake of herbal medications from 24 to 48 herbal pills per day, prior to his admission to treat his recently diagnosed HIV. His herbal medications included fucoidan, maya nut, and finger millet, to treat his recently diagnosed HIV. After discontinuation of his herbal HIV medications, his liver functions tests resolved within 2 wk and his symptoms dissipated.

**DISCUSSION**

Glutathione, a cysteine containing polypeptide, is essential for the function of all cells, but it is especially important in preventing oxidative stress and is involved in inflammatory cascades[3]. Additionally, glutathione becomes pivotal in HIV/AIDS patients[4]. In fact, low glutathione levels are linked with HIV disease progression and poor survival[3]. Glutathione levels are depleted in HIV patients and are correlated with depleted CD4 counts/decreased survival[3]. Thus, AIDS patients, more specifically, those with CD4 counts that are lower than 200, have even lower glutathione levels[3]. The depleted glutathione in HIV/AIDS patients is secondary to multiple mechanisms, such as excessive use of glutathione-depleting drugs, excessive natural production of proinflammatory cytokines such as TNF-α, and HIV gene dysregulation, leading to lower levels of superoxide dismutase[3]. Superoxide dismutase is an enzyme that prevents oxidative stress naturally and enhances the use of the enzyme glucose-6-phosphate dehydrogenase, which maintains glutathione stores[4].

Glutathione stores are critical in the metabolism of toxic free oxygen radicals that are created in drug detoxification[8]. For instance, the mechanism of fulminant hepatic failure in patients with severe acetaminophen overdose is fundamentally due to depleted glutathione stores[3]. Chronic alcoholics also have depleted glutathione stores due to the fact that alcohol directly depletes glutathione stores[3]. Alcohol toxicity is also more dangerous to the liver in the setting of depleted glutathione stores. Thus, this is the reason that alcoholics are more susceptible to free radical damage induced by Tylenol[3]. Similarly, there are many other drugs that can be toxic in the setting of depleted glutathione levels. Our patient had HIV/AIDS and thus, had depleted glutathione levels, which made him more susceptible to drug induced hepatitis.

The mechanism of the drug N-acetylcysteine (NAC) is to augment glutathione reserves in the body, and in combination with glutathione, directly binds to toxic metabolites that are created in drug metabolism[3]. The best example of this mechanism is the treatment of an Acetaminophen (Tylenol) overdose. Tylenol normally creates a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which is toxic to hepatocytes[3]. NAPQI is metabolized by glutathione, but in the setting of depleted glutathione levels (more likely in HIV/AIDS) accumulates to cause severe liver failure[3]. Similarly, this occurs in the metabolism of numerous other drugs as well, especially at higher toxic doses. The American Association for the Study of Liver Diseases recommended NAC for all cases of acute liver failure with exception of liver shock[4]. NAC was shown to improve transplant free survival in patients with early stage acute liver failure[4]. Similarly, NAC administration in HIV patients was shown to increase cysteine levels and thus, increase glutathione levels (cysteine derivative), which is associated with increased survival in HIV/AIDS patients[3]. As discussed above, herbal medications have their toxicities. Our patient was taking herbal medications including maya nut, fucoidan, and finger millet. The hepatotoxicities of these herbal medications are not well known, but in our patient, discontinuation of these medications led to the resolution of his symptoms. It is thought that these medications in tandem in the setting of an HIV/AIDS patient with depleted glutathione levels caused acute liver failure due to a similar mechanism of reduced glutathione levels, with glutathione preventing free radical damage. Finger millet
has been shown to be involved in free radical oxygenation pathways\[5\].

It is necessary to recognize hepatotoxic medications in any setting, but it is absolutely critical to identify hepatotoxic agents in HIV patients for many reasons. The most compelling reason would be in the setting of an HIV patient on highly active anti-retroviral therapy (HAART). Wrongly attributing hepatotoxicity to proven HAART therapy may subsequently alter the patient’s course as well as disease progression. Hepatotoxicity is one of the known side effects of HAART therapy and in some cases, is therapy limiting. HAART, unlike most therapeutic regimens, is specifically tailored to each individual patient based on drug resistance due to viral mutations, comorbidities, patient compliance, patient tolerance to side effects, toxicities, side effects, and disease progression or remission. Thus, it becomes even more monumental to elucidate occult use of herbal or OTC medications that are the true cause of hepatotoxicity and not prematurely discontinue patient tailored HAART therapy. Occult use of herbal medications or OTC medications that cause significant transaminase elevations in the setting of well managed HIV may cause cessation of effective treatment, which may lead to increased viral mutations/drug resistance. However, there are some impediments facing physicians to elucidating herbal medication use. For example, there is a stigma from a patients’ perspective that may facilitate concealing use of these medications from their healthcare provider due to the fact that they believe that their healthcare provider will not approve of this “alternative” regimen. Additionally, many patients do not list OTC and herbal medications as documented medications (medications they are taking) when asked by their healthcare provider. Lastly, patients that cease or decrease their HIV treatment (as seen in our patient) in favor of herbal medications; need to be warned of the risk of increased HIV viral mutations.

HIV treatment is further complicated by patient comorbidities such as hepatitis C (30%), hepatitis B (9%), HIV renal disease, and non-compliant patients\[6\]. Identifying hepatotoxic medications in HIV patients coinfected with Hepatitis C is also crucial. Hepatitis C and HIV coexist 50%-90% of the time in intravenous drug abusers\[8\]. Thus, another compelling reason to recognize occult herbal medication use and potential hepatotoxic medications is that hepatotoxicity would change the treatment regimen in patients with Hepatitis C. Pegylated interferon, the standard of care currently for Hepatitis C, could be limited in the setting of herbal medication use due to possible drug interactions or speculated hepatotoxicity (rare) in the absence of any attributable listed medications of the patient. Thus, treatment would be halted, leading to increased morbidity/mortality in HIV and hepatitis C patients. Even with the addition of the new protease inhibitors, Pegylated interferon is necessary (induction phase) for effective treatment and providers should have a complete understanding of occult use of herbal medications, as potential herbal drug interactions with the protease inhibitors may be therapy limiting.

Identifying hepatotoxic medications in HIV patients coinfected with Hepatitis B is also very important. Hepatitis B and HIV coexist 9% of the time, which is most likely due to the sexual transmission (listed as STDs by the CDC) of these viruses\[7\]. The treatment regimen for hepatitis B currently includes Tenofovir and Entecavir, which both have hepatotoxicity as a potential side effect and thus, treatment of Hepatitis B could be limited. This further exemplifies why healthcare providers need to be extremely meticulous in their initial/continued patient information intake regarding herbal medications.

Per the literature, it is known that HIV or immunosuppressed patients are more susceptible to drug induced liver injury due to depleted glutathione stores. In conclusion, we present a case of drug-induced hepatitis in an HIV patient due to herbal medications advocated to boost the immune system to treat HIV. We advocate that acute hepatitis in patients with HIV may be due to massive doses of herbal medication use, aside from the usual viral and drug induced hepatotoxicities. Close questioning of patients on OTC medications, and more specifically, herbal drug use, is paramount in the evaluation of patients with hepatitis, especially in the setting of immunosuppression.
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