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Gallbladder Perforation Associated with Consumption of Curcumin Case Report

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Abstract Curcumin is an herbal supplement that is consumed for its purported anti-inflammatory, antioxidant, and antitumor properties as well as the prevention of gallstone formation. There have been few studies that investigate its role in people with current or history of biliary obstruction. Herein we discuss an encounter of a patient who presented with a perforated gallbladder after having ingested 1500-2250mg of curcumin per day for four months. We shall also review the state of known literature on the pharmacokinetic and pharmacodynamic profile of curcumin and its role as an herbal supplement. Lastly, we will examine the pitfalls of taking high levels of herbal supplements.

Keywords: *Curcumin, adverse events, biliary obstruction, gallstone, perforation*

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1. Introduction

Curcumin is consumed worldwide as a nutritional supplement; with purported salutary effects on diabetes control, skin disorders, high cholesterol, Alzheimer disease, depression, HIV, upset stomach, joint pain, uveitis, osteoarthritis, rheumatoid arthritis, and generalized pain [1,2,3]. It is usually ingested in pill or powder form. There have been few adverse events recorded when curcumin was studied across a variety of diseases and diagnoses [1,2]. Despite being contraindicated in patients with biliary obstruction [4], its incidence and pathogenic mechanisms remain unclear. Gallbladder perforation (GBP) is considered a morbid condition because it is often diagnosed late [5]. The most common causes of GBP are gallstones and cholecystitis, and it is more common in elderly males within the Hispanic population [6,7]. Perforated gallbladders are a rare but serious complication of gallstones (2%-11%) [8]. Immediate surgical intervention is usually indicated, although some cases may resolve with supportive care [7]. We report a patient who ingested a large amount of curcumin and developed GBP.

2. Case Presentation

A 69-year old man came to the emergency department with non-exertional epigastric and chest pain, fever and diaphoresis for three days duration. The pain was described as 8/10 and radiated to his upper back bilaterally. On exam, he had mild epigastric tenderness to palpation. There was no costovertebral angle tenderness and he exhibited normal bowel sounds throughout. The cardiac and pulmonary exams were unremarkable. His past medical history included cholelithiasis, coronary artery disease and arterial hypertension. His medications include aspirin, rosuvastatin, fluoxetine, metoprolol succinate, and tamsulosin. He also attested to have been ingesting between 1500-2000mg of curcumin daily in powder and pill form for the last four months.

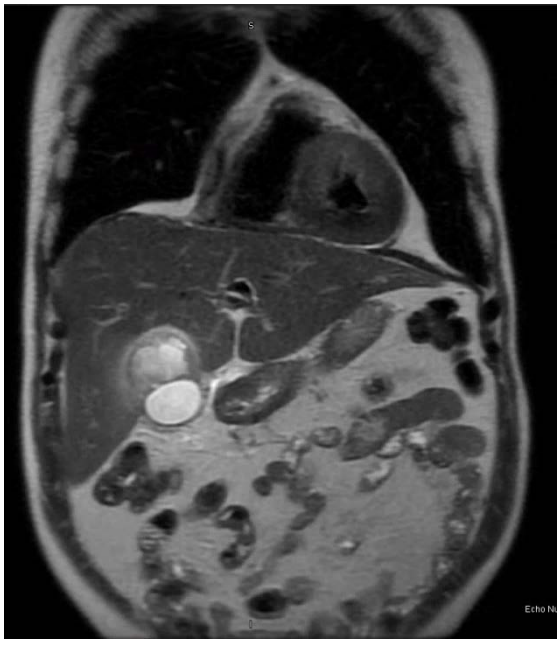

Figure 1. Coronal CT image of the patient showing a perforated gallbladder

His laboratory values were significant for a white blood cell count of $13.3x10^9$/L (normal $4.5\text{-}11x10^9$/L) and a CA19-9 of 239 U/mL (normal 0-37 U/mL). Computed tomography (CT) of the chest was performed to evaluate for aortic dissection instead showed an acute perforated gallbladder with fluid collection measuring 3.8cm x 4.5 cm and 1 cm calcified stone at the neck of the gallbladder (Figure 1). A subsequent magnetic resonance image (MRI) also demonstrated a 1 cm gallstone within the neck of the gallbladder. The superior aspect of the gallbladder contained a multicystic collection.

The patient was admitted for observation and given metronidazole 500 mg every 8 hours and levofloxacin 750 mg once daily. Over the next week, his pain improved and was discharged home on day 7 with a plan to complete his 14-day antibiotic regimen.

3. Discussion

Curcumin is consumed for its anti-inflammatory, antioxidant, and antitumor properties [2,3]. Curcumin is the main ingredient in turmeric. Turmeric is a perennial plant (*Curcuma Longa*) that is in the ginger family. It has been used for over 2000 years in China and India as a culinary supplement, medicine, cosmetic and fabric dye [3]. Johnson & Johnson currently manufactures curcumin band-aids in India [3]. Indian culture also uses it medicinally as "non-traditional medicine" by mixing it with boiled milk to suppress cough. It is even used for anti-hallucinatory effects against hashish [3].

Curcumin's anti-inflammatory effects are attributed to its inhibition of COX2, NF-κB, STAT3 and CRP [3,9-12]. NF-κB is a transcription factor that plays a critical role in regulating the transcription of signals that are involved in acute and chronic inflammation [3,9,10]. Some other important downstream targets of NF-κB include cyclin D1, adhesion molecules, BCL-2 and also tumor necrosis factor (TNF). Curcumin may work by quenching reactive oxygen species to inhibit NF-κB [10]. Another study also indicated that curcumin abolished the phosphorylation and degradation of inhibitor of nuclear factor kappa B (IKB) induced by TNF, suggesting that the step in the signal transduction pathway of NF-κB activation inhibited by this agent precedes the phosphorylation step of NF-κB [13].

Curcumin has also been shown to slow cancer progression in animal trials [3,9,14,15]. Curcumin reduces tumors induced by benz(a)pyrene and 7,12 dimethylbenz(a)anthracene and decreases tumor promotion induced by phorbol esters on mouse skin [3]. Curcumin has been shown to inhibit cancer development initiated by N-ethyl-N'-nitro-N-nitrosoguanide-(MNNG) induced duodenal tumors and reduces the multiplicity of esophageal tumors and preneoplastic lesions in rats with N-nitromethylbenzylamine induced esophageal carcinogenesis [3,9,14,15]. In bladder cancer, curcumin showed a cytotoxic effect against the MBP-2 tumor line in rats and the UMUC tumor cell line in humans [3,9,14,15].

Curcumin has shown significant antioxidant properties by increasing the activity of phase II enzymes such as glutathione transferase and UDP-glucuronosyltransferase [16]. Phase II enzymes detoxify carcinogens present in cells. Curcumin has shown to increase the effects of cyclophosphamide in rats who were fed curcumin for 7 days [16].

Curcumin has shown to increase human gallbladder motility by 29% with a 20mg dose [17]. The standard dose for a pill or powder is 1500mg-2000mg [18]. It is contraindicated in patients with gallstones but has also shown to decrease gallstone formation in patients without a history of gallstones [19].

There have been few adverse event reports despite considerable curcumin consumption (1500mg to 2500mg 1-2 times per day) in patients with a variety of conditions including colorectal cancer, pancreatic cancer, Crohn disease, rheumatoid arthritis, gastric ulcers, vitiligo, psoriasis, diabetes and much more [1,2]. Curcumin has demonstrated to have low bioavailability in patients consuming 2200 mg of curcuma extract per day for four months, suggesting that larger clinical trials of high dose curcumin administration are merited [20]. Parenteral administration of curcumin demonstrated considerably more activity, suggesting why high oral doses have been well tolerated [21]. At 3600 mg consumption of curcumin per day, pharmacologically efficacious levels were achieved with little distribution outside of the gut [22]. Efficacy was measured by adenoma reduction load in animals [23].

We hypothesize that the perforated gallbladder could have occurred due to overdose of curcumin while having a preformed gallstone. Since curcumin increases gallbladder motility [17], the gallbladder will have more difficulty releasing a preformed gallstone because there is less space in the biliary tree for the gallstone to be released. The buildup of pressure from repeated curcumin consumption/gallbladder contraction without gallstone release eventually ruptured the gallbladder.

The benign presentation of the patient could be attributed to the anti-inflammatory properties of curcumin. It has been shown to accelerate healing in perforated nasal septum in animal models [24] and inhibits COX2 and NF-κB [3]. FLLL32, a curcumin analog, demonstrated downregulation of proinflammatory cytokines TNF-α, IL-6 and the TLR9 signaling pathway [25,26,27]. These characteristics conceivably attenuated the inflammatory response by the patient, which helped him avoid surgery.

This case is important because it highlights the potential dangers on over ingesting herbal supplements. Herbal supplements typically circumvent drug regulatory agencies [28] and it is estimated that only 1/100 adverse events with herbal supplements are reported [29].

Learning Points

- Curcumin should be used cautiously, especially in patients with biliary disorders.
- Adverse events due to herbal supplement use should be rigorously and systematically reported.
- More studies are needed to investigate the benefits and risks of curcumin supplementation in humans.

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