

Ischemic colitis induced by the newly reformulated multicomponent weight-loss supplement Hydroxycut®

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do not disclose their use voluntarily to their physicians. Hydroxycut has to be considered as a potential trigger for otherwise unexplained ischemic colitis.

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Abstract

Ischemic colitis accounts for 6%-18% of causes of acute lower gastrointestinal bleeding. It is more often multifactorial and more common in elderly. Drugs are considered important causative agents of this disease with different mechanisms. In this paper, we describe a 37-year-old otherwise healthy female presented with sudden onset diffuse abdominal pain and bloody stool. Radiologic, colonoscopic and histopathologic findings were all consistent with ischemic colitis. Her only suspected factor was hydroxycut which she had been taking for a period of 1 mo prior to her presentation. Her condition improved uneventfully after cessation of hydroxycut, bowel rest, intravenous hydration, and antibiotics. This is a first case of ischemic colitis with clear relationship with hydroxycut use (Naranjo score of 7). Our case demonstrates the importance of questioning patients regarding the usage of dietary supplements; especially since many patients consider them safe and

INTRODUCTION

Ischemic colitis results from a sudden decrease of splanchnic blood flow to the colon. It occurs more often in the splenic flexure and rectosigmoid junction, which are also known as watershed areas of the colon. These two areas have limited collateralization between superior mesenteric artery and inferior mesenteric artery, and inferior mesenteric artery and internal iliac artery which supply splenic flexure and rectosigmoid junction of the colon, respectively. Therefore, these two areas are more prone to ischemic colitis^[1].

The mechanisms of developing ischemic colitis include hypoperfusion due to systemic hypotension secondary to sepsis, hemorrhage, cardiac failure or any other conditions that might cause hypotension. Vasoconstriction in the colonic vessels due to hypotension or certain substances such as cocaine and other sympathomimetic agents is another mechanism. The third mechanism is thromboembolism due to inherited or acquired hypercoagulable conditions such as antiphospholipid antibody syndrome. Also increased intracolonic pressure is another mechanism for ischemic colitis by causing decrease of the

blood flow into the colon which can occur after screening colonoscopy. Final mechanism is vasculitis involving colonic vessels such as polyarteritis nodosa^[1,2].

Advanced age, aortic surgery, diabetes mellitus, hypertension, and peripheral vascular disease have been also suggested to be predisposing factors for ischemic colitis^[1]. Hydroxycut is an over-the-counter herbal product that has been used for purpose of the weight loss, body building and as an energy enhancer. It is a multicomponent dietary supplement which has been reformulated twice after warnings from the food and drug administration (FDA). It has been linked to serious medical conditions, mostly acute liver toxicity. We describe here a case of ischemic colitis developed in a healthy young female after a month of hydroxycut consumption for purpose of weight loss in the absence of any other risk factors for ischemic colitis.

CASE REPORT

A 37-year-old otherwise healthy female presented with severe crampy abdominal pain. Pain was diffuse but more pronounce in left lower quadrant of her abdomen. The pain was also associated with nausea and one episode of non-bloody, non-bilious emesis. She had two bloody bowel movements at home and later on she had another two with blood clots in the stool at the emergency room. She denied fever, chills, urinary symptoms, similar symptoms in the past, recent travel, sick contact, or recent use of antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs). She had no significant past medical history. She had hysterectomy 4 years ago for repeated abnormal Pap smears. She was not on any prescribed medications. She denied smoking or using illicit drugs, but was drinking alcohol occasionally. She had no family history of major medical problems including gastrointestinal diseases or blood disorders.

The patient was afebrile with temperature of 98.2 F°, blood pressure of 106/63 without orthostatic hypotension, heart rate of 65 bpm, weight of 181 pounds, and body mass index of 29.2 kg/m². Her physical exam was remarkable for diffuse generalized abdominal tenderness, especially in left upper and left lower quadrants without guarding or rebound tenderness. Rectal exam was remarkable for blood on digital exam. The rest of exam including cardiopulmonary, skin, and extremities were unremarkable. Laboratory studies were unremarkable including complete blood count (hemoglobin of 15.9 g/dL), basic metabolic panel, liver function tests, urinalysis, urine toxicology, stool studies (except for positive blood), lipase, amylase, cholesterol profile, hemoglobin A1c, and thyroid function tests. Computed tomography (CT) scan showed a moderately severe colonic wall thickening in the descending colon extending into rectosigmoid area (Figure 1A, B).

Colonoscopy revealed erythematous and edematous colonic mucosa with multiple superficial erosions and ulcerations from the distal descending colon up to the mid-transverse colon which was consistent with moderately

severe ischemic colitis (Figure 2). Multiple biopsies were taken which were consistent also with ischemic colitis (Figure 1C, D). CT angiogram was performed and did not identify any stenosis, occlusion, or thrombosis in the intra-abdominal vessels.

On further questioning to determine the etiology of ischemic colitis in our patient, she reported taking hydroxycut in a recommended dose by the manufacturer for weight loss purposes for a period of one month prior to her presentation.

This temporal relationship between hydroxycut exposure and her symptoms, in the light of absence of other causes of ischemic colitis strongly raises the probability of hydroxycut as the potential trigger of ischemic colitis. This case scored a 7 on the Naranjo Nomogram for adverse drug reactions, indicating a probable association between hydroxycut exposure and the development of ischemic colitis (Probable: 5-8).

She was treated with intravenous fluids, bowel rest, intravenous antibiotics, and discontinuation of hydroxycut. Her hospitalization course was uneventful and she was discharged home 3 d later. She was counseled to stop hydroxycut consumption.

DISCUSSION

This case illustrates the importance of investigation for potential triggers for ischemic colitis when the classical risk factors are absent. The causes of ischemic colitis vary from systemic hypotension, aortoiliac surgery, atherosclerosis, thromboembolic events, vasculitis, to varieties of drugs^[3].

Drugs have been implicated in the development of ischemic colitis by different mechanisms including decreasing blood flow *via* systemic hypotension such as angiotensin-converting enzyme inhibitors, causing vasospasm such as pseudoephedrine, promoting thromboembolism such as oral contraceptives, causing vasculitis such as gold salts, and increasing intracolic pressure such as alosetron^[4]. The mechanism of some drugs reported to cause ischemic colitis has not yet determined. The Table 1 below shows a list of medications and their mechanisms for causing ischemic colitis^[4].

Many case reports have linked ischemic colitis and some commonly used medications such as NSAIDs and triptans, chemotherapy such as bevacizumab and irinotecan, hepatitis C therapy with pegylated interferon and ribavirin, following screening colonoscopy, scuba diving, flying, snake bite, acute carbonic monoxide poisoning, electrical muscle stimulation of the abdominal wall, following long distance running, herbal remedies such as ma huang (ephedra), and weight loss medications such as phentermine^[4].

A significant proportion of Americans and people all over the world are using herbal supplements for different purposes based on geographic, race, and cultural backgrounds. In a survey in 2007, 17.7% of adults in the United States and 3.9% of children were using some kind

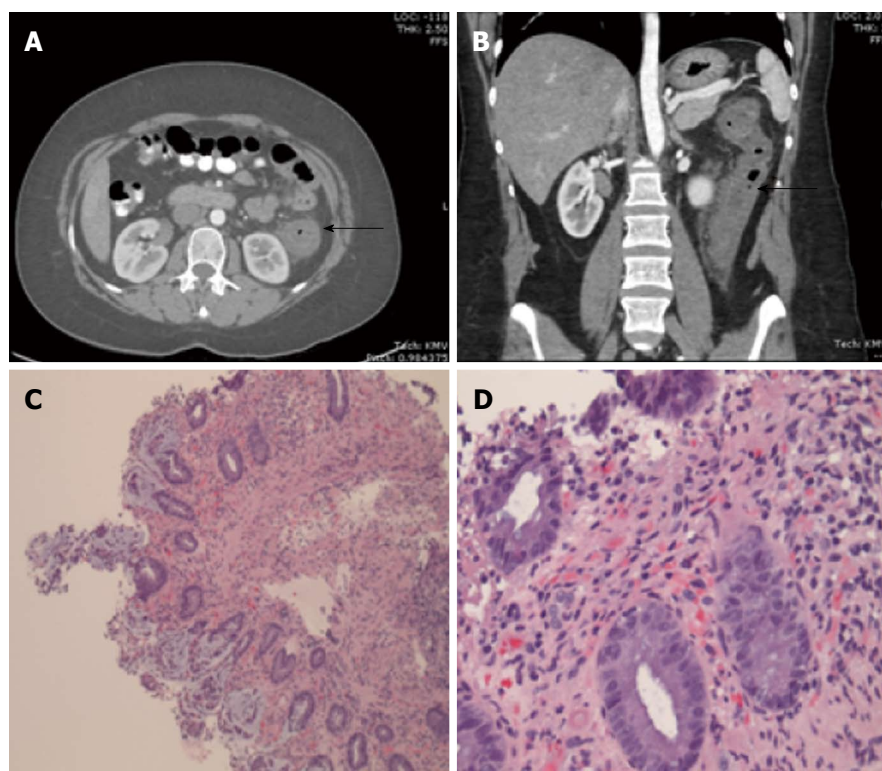


Figure 1 Computed tomography scan and histopathology. A, B: Computed tomography scan shows thickening of the colonic wall involving the descending colon (arrows); C, D: Histopathology shows: the overlying surface mucosa is eroded, the lamina propria is partially hyalinized with fibropurulent exudate and acute inflammation, consistent with ischemic colitis.

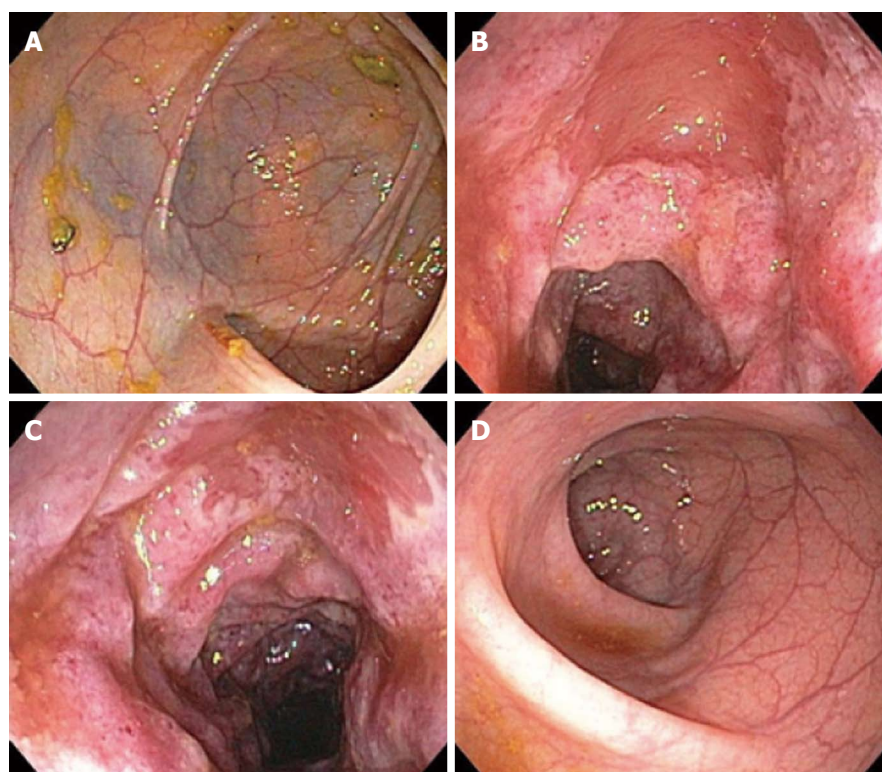


Figure 2 Colonoscopy shows. A: Normal mucosa of the right colon (hepatic flexure); B, C: Erythematous, edematous, erosive, and ulcerated mucosa of the splenic flexure of the colon, consistent with ischemic colitis; D: Normal mucosa of the sigmoid colon.

Table 1 Medications associated with ischemic colitis

Agent	Mechanism
Amphetamines	Vasoconstriction
Alosetron	
Catecholamines (epinephrine, norepinephrine)	
Cocaine	
Cyclosporine	
Digitalis	
Dopamine	
Ergot derivatives	
Nonsteroidal anti-inflammatory drugs	
Pseudoephedrine	
Triptans (Naratriptan, Rizatriptan, Sumatriptan)	
Vasopressin and vasopressin analogues	
Glycerin enema	Local vasospasm effect
Phosphosoda solution	
Angiotensin-converting enzyme inhibitors	
Antipsychotic (chlorpromazine)	Systemic hypotension
Beta blockers	
Barbiturates	
Diuretics	
Interleukin-2	Vasculitis
Tricyclic antidepressants	
Amphetamines	
Gold compounds	
Estrogens	Thrombotic lesion induction
Progestational agents	
Alosetron	Increased intracolic pressure
Danazol	
Glycerin enema	Undetermined
Carboplatin	
Flutamide	
Glutaraldehyde	
Hyperosmotic saline laxatives	
Interferon- α	
Mycophenolate mofetil	
Paclitaxel	
Simvastatin	
Tegaserod	

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of “non-vitamin, non-mineral, natural products” within the last 12 mo^[5]. Factors associated with herbal supplements use are middle age, female gender, uninsured persons, and higher education^[6]. Fifty eight percent of users do not disclose their use to their physicians^[6].

Among the most popular herbal supplements used in the United States are weight-loss products as obesity is becoming epidemic in the United States affecting more than one-third of population^[7]. These products are considered dietary supplements and are not regulated by the FDA^[8]. Dietary supplement manufacturers only need low-level of evidence for their efficacy and safety to get market approval, with most studies of small sample size for a short duration^[9]. In a systematic review of 19 human studies in 2009, the average number of participants was 64.4 (range: 24-153), and the average study duration was 15 wk (range: 2-36 wk)^[9,10]. Under Dietary Supplement Health and Education Act, once a product is marketed, it is the FDA's responsibility to prove it unsafe before with-

drawing or restricting its use, as opposed to conventional medications, for which pharmaceutical companies have to prove the safety of drug before marketing.

Hydroxycut is one of the most sold products among all weight-loss supplements. It is claimed to be a weight-loss aid, fat burner, and energy enhancer. Hydroxycut was introduced first containing ephedra as one of its components; however, after banning ephedra containing products by FDA in February 2004 for severe cardiovascular and neurologic toxicity, hydroxycut was withdrawn from the market and reformulated to exclude ephedra^[4,11]. In May 2009, FDA warned consumers to stop taking any hydroxycut products due to 23 reported cases of severe serious health events related to Hydroxycut, especially liver toxicity resulting in one death^[12].

The safety of hydroxycut (as well as its efficacy) is unstudied extensively and it is based on post-marketing case reports. Since 2004, after ephedra was withdrawn from hydroxycut, it has been reported 30 cases of serious medical conditions associated with hydroxycut ingestion including hepatotoxicity, in form of hepatocellular injury, immune-mediated hepatitis, or cholestasis patterns ($n = 26$), reversible cerebral vasoconstriction syndrome ($n = 1$), hypertensive retinopathy ($n = 1$), rhabdomyolysis ($n = 1$), atrial fibrillation ($n = 1$)^[13-24].

Prior to May 2009, its primary ingredients included *Gymnema sylvestre*, *Garcinia cambogia*, *Rhodiola rosea* extract, *Withania somnifera* extract, *Citrus Aurantium*, chromium, caffeine, and green tea extract (as *Camellia sinensis*), however; it has been reformulated again since then to have a variety of different herbal mixtures including Lady's mantle extract (as *Alchemilla vulgaris*), Wild olive extract (as *Alea europaea*), Komijn extract (as *Cuminum cyminum*), Wild mint extract (as *Mentha longifolia*), Acerola concentrate (as *Malpighia glabra*), Goji extract (as *Lycium barbarum*), blueberry (as *vaccinium corymbosum*), Pomegranate (as *Punica grantum*), Bilberry extract (as *Vaccinium myrtillus*), Brazilian acai concentrate (as *Euterpe oleracea*), Green coffee extract (as *Cunephora robusta*), Cayenne pepper (as *Capsicum annum*), Yohimbe extract (as *Pausinystalia yohimbe*), caffeine, many amino acids, vitamins and minerals^[25].

It has not determined clearly which substance(s) is responsible for reported toxicities. It has been suggested hydroxycitric acid, *Garcinia cambogia*, chromium, epigallocatechi-2-gallate (EGCG), green tea extract (as *Camellia sinensis*), and contaminated chemicals or bacteria as the cause of hepatotoxicity; however studies' results are conflicting^[13,16,20,26,27]. EGCG in Hydroxycut has been suggested as the suspected causative component for developing atrial fibrillation by blocking the atrial-specific *KCN45* potassium channel^[24].

The proposed mechanism for hydroxycut-induced ischemic colitis is the local vasoconstriction of vessels supplying the colon due to one or more substances. High dose of caffeine in hydroxycut has been suggested as a sympathomimetic agent causing vasoconstriction in the brain which might cause similar effects in other organs such as colon; however, it is unproven^[21,22,28]. Chromium

Table 2 Naranjo adverse drug reaction nomogram in our patient

	Yes	No	Our patient
1: Are there previous conclusive reports on this reaction?	1	0	0
2: Did the adverse event appear after the suspected drug was administered?	2	-1	2
3: Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	1
4: Did the adverse reaction reappear when the drug was readministered?	2	-1	0
5: Are there alternative causes (other than the drug) that could have, on their own, caused the reaction?	-1	2	2
6: Did the reaction appear when a placebo was given?	-1	1	1
7: Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	1	0	0
8: Was the reaction more severe when the dose was increased or less severe when dose was decreased?	1	0	0
9: Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
10: Was the adverse event confirmed by any objective evidence?	1	0	1

Definite: Score ≥ 9 ; Probable: 5-8; Possible: 1-4; Doubtful: ≤ 0 .

in prior formulas is another suggested substance to cause vasoconstriction by activating sympathetic nervous system^[23]. Other components are also possible causes by causing direct or indirect vasoconstriction in susceptible subjects; especially hydroxycut has multiple ingredients with limited known information regarding their precise mechanisms of action. Hydroxycut may work in serotonergic or adrenergic systems as many conventional weight-loss medications, however, it is difficult to identify the exact ingredient or mechanism by which hydroxycut works or causes its side effects.

While causation is impossible to confirm, the temporal relationship between initiation of this product and development of ischemic colitis, in the light of absence of other etiologies, raises the suspicion of hydroxycut as a potential culprit in this case. When applying Naranjo nomogram in our patient, a score of 7 was granted indicating a probable likelihood (Table 2).

Naranjo nomogram for adverse drug reaction consists of 10 questions to assess the cause-effect relationship between any potential offending drug and any event. The likelihood of a drug-event relationship is defined as definitive if score is 9 or greater, probable if the score is 5-8, possible if the score is 1-4, and doubtful if the score is 0 or less^[29]. It is considered a useful tool for evaluating the causality of any potential drug-induced event.

In conclusion, this is the first case report of ischemic colitis associated with ephedra-free weight-loss supplement hydroxycut. Our case demonstrates the importance of questioning patients regarding the usage of these supplements; especially since many patients consider them safe and do not disclose their use voluntarily to their physicians. Hydroxycut has to be considered as the potential cause for otherwise unexplained ischemic colitis.

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