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*RESEARCH ARTICLE*

# HEPATITIS AND COLITIS FOLLOWING COLOCYNTH INGESTION : A CASE STUDY

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## *Abstract*

**Introduction:** Colocynth is a commonly used remedy in some parts of the world to treat several conditions and most commonly to control diabetes.

**Case presentation:** 42-year-old gentleman, known case of diabetes, presented to ER with history of severe colicky abdominal pain, bloody diarrhea and nausea and vomiting for 6 hours, after ingestion of half piece of colocynth. Investigations showed a picture of pseudomembranous colitis and hepatitis along with diabetic ketoacidosis.

**Management and outcome:** He was admitted, treated conservatively and started on DKA protocol. Several investigations were done to clarify the causes of the colitis and hepatitis.

**Discussion and Conclusions:** In respect to his colitis, all possibilities were investigated thoroughly. Given the fact that colocynth toxicity is a well-known cause of colitis, order of events and absence of other causes, colocynth toxicity is the most probable cause. Regarding the hepatitis, there are several trials on animals and had controversy regarding colocynth as hepatotoxic or hepatoprotective material. Screening was done for our patient for all possible causes; viral, drug induced, hemolysis, and autoimmune. All came negative and the only possible cause was colocynth toxicity.



## Introduction :-

Colocynth (scientific name: citrullus colocynthis) is a plant used commonly in some parts of the world as a remedy for several medical conditions.[1]

It is known by several names in different languages and cultures; Bitter-apple or bitter-cucumber in English, Alhandhal in Arabic, Handal in Spanish, coloquite in French and tumba in Indian.[2]

Several extracts could be obtained from different parts of colocynth plant like leaves, flowers, stems, fruits and seeds. Of these extracts, several had biological activities such as the Methanolic, ethanolic, hydroalcoholic, aqueous, petroleumether, ethylalcoholic, hydromelthanolic extracts.[3]

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It has been known in alternative medicine for its antidiabetic [4-9] ,antihyperlipidemic [10,11] laxative [4,6,12],anti-inflammatory [12], analgesic [12],vermifuge [8], antibacterial [13], antifungal [13], and antioxidant properties. [14].
Historically, it has been used as a remedy to induce abortion. [15]

Colocynth have been placed amongst the top ten toxic plants [16] despite multiple debatable medical benefits.

Several studies suggested the role of its ethanol extract as an insulin secretogogoues [17-19] and one study suggested that the observed hypoglycemic effects of the pulp extract may be due to wounded intestine and injured renal proximal tubules and their subsequent reduced ability to regulate glucose transportation plus the impaired liver function and glucose metabolism. [20]

A patient with colocynth toxicity is not a common case to deal with, especially in Kuwait. There are no documented studies or reports of the same condition. Management of such challenging case starts from the moment the patient presents to the emergency department.

**Case Presentation**
Our patient is a 42-year-old Syrian gentleman, known case of diabetes mellitus type 1; presented with history of colicky abdominal pain, bloody diarrhea, nausea and vomiting of approximately 6 hours duration.
This started 2 hours after ingestion of a colocynth with its pulp as a remedy for his diabetes according an advice from one of his family members.
His symptoms started with severe lower abdominal pain, 10 of 10 on pain scale, squeezing in character, radiating to the upper abdomen, continuous and progressive, associated with abdominal distension and tenesmus. He experienced several episodes of bloody diarrhea. Then he started vomiting food content and stomach secretion. No history of heartburn, regurgitation, chest pain, SOB or fever. No history of any herbs or supplements other than Colocynth.

His past medical history is not clear since he was following up in his home country ; Syria. He was diagnosed with insulin dependent diabetes 4 years back and was on insulin. He was reluctant to talk about his diabetes and was not convinced of the necessity of the insulin as a treatment. He has done four lumbar disc surgeries on 2007 in Syria with no available reports. No previous medical records for the patient in our hospital.

He is a smoker. He smokes Shisha –Hubble Bubble-, 15 to 20 times per day for 20 years. He denies alcohol intake.

He works as a driver in a private company in Kuwait since 1993 and lives with his sister and her husband in an apartment. No pets at home. His family history was unremarkable.

Examination revealed an ill-looking middle-aged man, dehydrated and in pain. He was conscious, alert, oriented and vitally stable. Blood pressure was120/70 and his heart rate was 90 bpm. His abdomen showed generalized tenderness. Digital Rectal examination showed minimal fresh blood. A proctoscopy was done and there was no active bleeding. Other systemic examination was unremarkable.

Investigations initially showed increased hemoglobin and WBC count with normal liver function test and renal function tests. Lab investigations are summarized in table 1.

**Management and outcome:**
Mr. M was admitted initially under the care of the surgical team as a case of acute abdomen for investigations.

An urgent abdominal CT scan was done (see table 2 and pictures 1,2 and 3). Findings were in favor of diffuse extensive inflammatory process involving the colon with peri-colic fat planes changes raising the possibility of colitis. The differential diagnosis includes infectious colitis, inflammatory bowel disease. Also, Ischemic colitis was a possibility but less likely due to absence of vascular occlusion and no restriction to a vascular territory.

The patient was deemed not a surgical candidate and started on Conservative treatment including antibiotics in the form ciprofloxacin and metronidazole.

During his hospital stay, Mr. M developed DKA and was started on DKA protocol accordingly. He was shifted to the ICU for observation and stayed for 2 days.

He was seen and followed by the gastroenterology team and colonoscopy was done and showed the following: there was diffuse severe inflammation throughout the colon with yellowish exudate consistent with pseudomembranous colitis appearance. It was highly suspicious for C.dfficile colitis and washing was sent for PCR testing which came back negative. Other differential included inflammatory bowel disease.

A biopsy (see pictures 4,5 and 6) was taken from the Transverse colon biopsy and showed; Necrotic (fibrinoid) tissue with suppurative inflammatory cells exudate. No viable colonic epithelium present.

The features are in keeping with pseudomembranous colitis. Costridial organisms are the commonest cause in the proper clinical setting; however, other types of bacterial organisms can also sometime give similar morphology. Another differential is ischemic which can cause pseudomembranes. Rarely, iatrogenic and drug induced changes may also sometimes cause pseudomembranes. No viable colonic mucosa present to assess for viral inclusions and/or IBD changed.

Ciprofloxacin was stopped after receiving one dose only and he was shifted to oral Vancomycin instead due to suspicion of C. Difficile Colitis.

Mr. M's liver enzymes and bilirubin levels started to elevate markedly on day 3 of his admission (table1).

He was evaluated and observed by the gastroenterogists as "hepatitis for further work up".

Viral hepatitis profiles, toxicology screen, and autoimmune markers were all normal.

Mr. M's Hemoglobin was dropping slowly, hemolytic workup was sent and came negative, his Hemoglobin stabilized at the level of 100. This drop was attributed to his colitis.

Mr. M improved remarkably and gradually within 10 days after starting him on tapering course of prednisone; his diarrhea improved, abdominal pain subsided, Hemoglobin stabilized at the level of 100, blood sugar controlled and Liver enzymes normalized.

He was discharged and followed up as an outpatient.

Colonoscopy was repeated after 6 weeks and showed completely resolved inflammation in the transverse colon. There were ulcerations in patchy appearance in descending colon, sigmoid colon and rectum. No spontaneous bleeding. No polyps or masses seen. Biopsies were taken from ulcerations.

Histopathology report revealed the following:
Specimen taken from the descending colon had colonic mucosa with features of chronic inflammation including: crypts' architecture distortion, bifid glands, Paneth cell metaplasia and chronic inflammatory cell infiltrate. Acute inflammation is not seen. Specimens taken from sigmoid colon and rectum had no pathological findings.

## Discussion :-

Our patient was an unusual case, presented to our hospital with complications of colocynth ingestion as a remedy for his uncontrolled diabetes. It is a well-known traditional practice in his home country Syria to treat diabetes.

He ingested half piece of colocynth which according to him was in a size of a sweet melon.

As mentioned before, he had the symptoms 2 hours after ingestion and 72 hours later, developed high liver transaminases.

**Colitis**

In our explanation of the case we concluded that the colitis was a result of colocynth toxicity. Colocynth is well known to cause a colitis that mimics the picture of pseudomembranous colitis [21] [22]. This is supported by the fact of chronological order and timing of the pseudomembraneous colitis is consistent with Colocynth ingestion. Furthermore, all causes of Pseuodmembranous colitis were excluded including infections and drug induced. The chronicity of the disease on the subsequent colonscopy raised the possibility of IBD. However, spontaneous resolution of the inflammation is not expected in such severe inflammation. Goldfain et al, reported 3 cases of toxic acute colitis following ingestion of C. Colocythis. two to the cases had complete resolution of the colitis whereas the third case had chronic course but lost follow up.[21]

**Hepatitis**

In our patient, there are two possible causes for the hepatitis; ciprofloxacin toxicity vs. colocynth toxicity.

Ciprofloxacin induced liver injury occurs within a period of two days to two weeks following the initiation of antibiotic treatment.[23]

The pattern of drug induced liver injury can be cholestatic, hepatocellular, or mixed. The pattern of injury can be differentiated by the level of liver enzymes elevated.

If the ALP is elevated more than two times its upper normal limit or the ALT/ALP ratio is less than 2, this indicates cholestatic hepatitis. If the ALT/ALP ratio is between 2 and 5, then it is likely a mixed pattern. If the ratio is more than 5, this demonstrates hepatocellular injury [23-24]. If we calculate that for our patient, he has cholestatic liver injury.

In our case, the patient received only single dose of 500 mg of ciprofloxacin intravenously then stopped and shifted to oral vancomycin in suspicion of severe infection by C.difficile. He then developed the elevated liver enzymes within few hours.

Our points against ciprofloxacin as a cause are (1) the pattern of injury is cholestatic which needs a prolonged course of antibiotics [23, 25], (2) the very short duration between the ciprofloxacin intake and the elevation of liver enzymes along with (3) the rarity of ciprofloxacin induced liver injury.[23]

A research was conducted on 2006 in Shiraz, Iran, to study the histopathological changes of the liver after ingestion of citrullus colocynth in male rats. It was concluded that colocynth can have toxic effects on liver cells which may induce hepatocyte necrosis and liver fibrosis. [26]

A review of hepatic effects of Citrullus colocynthis was published on 2018 in the Journal of Pharmacognosy and Phytochemistry showed that few studies in literature discussed the effects of colocynth on liver through trials on animals; rats, rabbits, mice and Swiss rats. The review concluded that *Citrullus colocynthis* is hepatotoxic in doses more than 50-100 mg/kg. [27]

## Conclusion :-

Given the circumstances of our case plus the facts mentioned in the discussion from the literature, colocynth toxicity is the more probable cause of the both colitis and liver injury in our case.

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## A. Appendix [tables and figures]

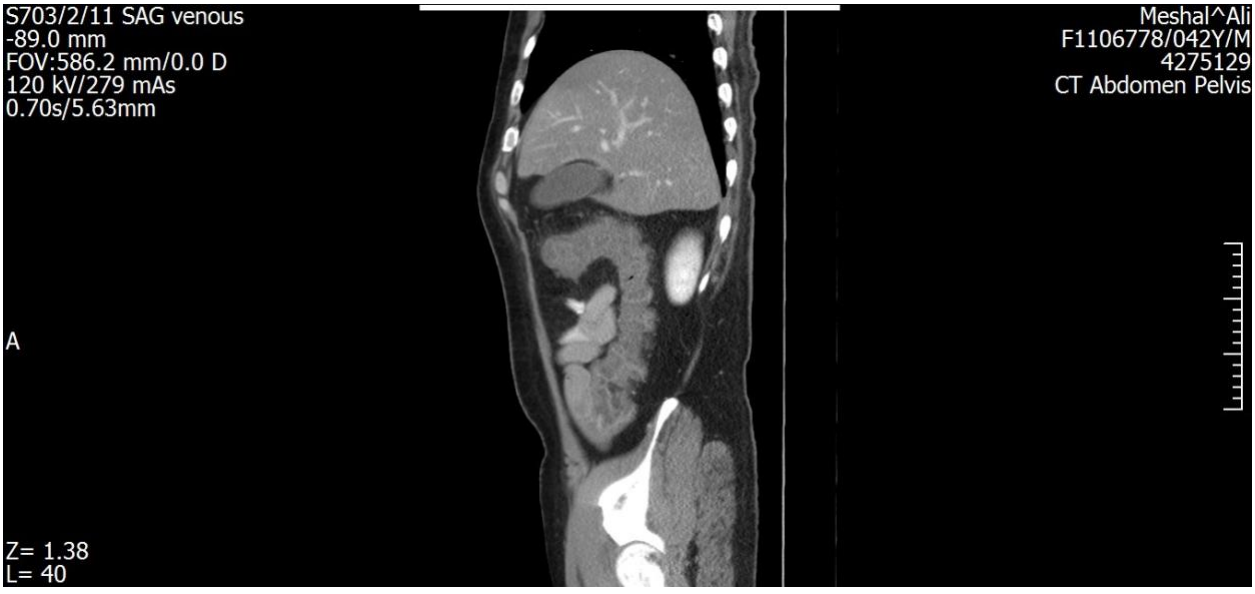
| Investigation | On admission | Day 5 | Day 10 | Normal range |
|---|---|---|---|---|
| ***CBC*** | | | | |
| WBC | 34.1 | 12.1 | 7.3 | 3.7 – 10 x 10^9 |
| Neutrophil count | 30.2 | 9 | 4.4 | 1.7 – 7.1 |
| Lymphocytes count | 1.6 | 1.7 | 2.1 | 1 – 3.2 |
| Monocytes count | 2.2 | 1.1 | 0.7 | 0 – 2 |
| Esinophils count | 0 | 0.2 | 0.1 | 0.1 – 0.5 |
| Basophils count | 0.1 | 0 | 0.1 | 0 – 0.3 |
| Hb | 200 | 135 | 101 | 130 – 170 g/L |
| Hct | 0.554 | 0.395 | 0.306 | 0.39 – 0.55 L/L |
| MCV | 85.1 | 89.8 | 96.5 | 82 – 98 fL |
| MCH | 30.7 | 30.7 | 31.9 | 27.3 – 32.6 pg |
| Platelets | 335 | 234 | 449 | 150 – 440 x 10^3 |
| Retics% | 2.3 | | | 0.58-3.26 % |
| ***Biochemistry*** | | | | |
| Glucose | 19.8 | 9.5 | 7.5 | 3.9 – 6.1 mmol/L |
| Urea | 5.6 | 2.8 | 2.4 | 2.5 – 6.4 mmol/L |
| Creatinine | 115 | 55 | 59 | 74 – 115 umol/L |
| Na | 134 | 135 | 137 | 136 – 146 mmol/L |
| K | 4.6 | 4.2 | 4.5 | 3.5 – 5.2 mmol/L |
| HCO3 | 17.8 | 22.8 | 22.2 | 22 – 30 mmol/L |
| ***LFT*** | | | | |
| ALT | 41 | 186 | 55 | 10 – 60 IU/L |
| AST | 19 | 188 | 27 | 10 – 42 U/L |

| | | | | | |
|---|---|---|---|---|---|
| Alkaline phosphatase | 62 | 279 | 90 | 53 – 128 | U/L |
| GGT | 33 | 561 | 129 | 12 – 64 | IU/L |
| Total Bilirubin | 48 | 378 | 37.2 | 3 – 20 | umol/L |
| Direct Bilirubin | 7 | >171 | 11 | 0 – 5 | umol/L |
| ***Coagulation Profile*** | | | | | |
| PT | 16 | - | - | 11.5 – 16 | seconds |
| APTT | 23.8 | - | - | 23.1 – 38.7 | seconds |
| INR | 1.17 | - | - | | |
| ***Inflammatory markers*** | | | | | |
| CRP | 225 | 20 | - | 0 – 8 | mg/L |
| ESR | 1 | - | - | 0 – 20 | mg/L |
| ***Others*** | | | | | |
| HBA1C | 11.2 | - | - | <6 | % |
| Amylase | 26 | | | 28 – 100 | U/L |
| Lipase | 36 | | | 13 – 36 | U/L |
| Haptoglobin | 2.18 | | | 0.16-2 | g/L |
| Blood Film | Neutrophilic leukocytosis, with toxic granulations, left shift, some reactive lymphocytes, relative monocytosis, RBCs and platelets are unremarkable | | | | |
| ***Stool investigations*** | | | | | |
| Routine | General: Brown soft. Direct wet mount. No ova, cyst or parasite<br>Pus cells: Excess RBC: Many | | | | |
| C. Difficile Toxin A, B | Not detected | | | | |
| Culture | Negative | | | | |
| Occult blood | positive | | | | |

**Table 1: Investigations on Day1, Day5 and Day 10**

| *Radiological investigations* | |
|---|---|
| CT Scan of abdomen | • Marked diffuse transmural wall thickening involving all the colonic segments, from the cecum down to the level of the rectum associated with marked hypo-attenuation that was noted likely due to marked mucosal and sub-mucosal edema as well as reduced delayed enhancement. There was also marked pericolic fat planes stranding with minimal pericolic fluid related mainly to splenic flexure and mild freefluid seen at the pelvis. Traces of water soluble contrast is seen trapped within the thickened mucosal and submucosal tissues (which shows nodular appearance) giving rise to "accordion sign", most appreciated at the right side of the colon.<br>• The liver is not enlarged, showing diffuse reduction of its parenchymal density consistent with diffusefatty infiltration. No focal or enhancing lesions. No intra or extra hepatic biliary dilatation.<br>• The portal vein and superior mesenteric veins and its branches are normally enhancing.<br>• The gallbladder shows irregular nodular polyps along its wall more appreciated at the level of its neck.The polyps are initially hyperdense with no significant post contrast enhancement.<br>• Both kidneys have normal size, shape and position with normal collecting systems and no abnormalmasses or renal calculi.<br>• Normal size and configuration of the spleen. No focal lesions.<br>• Normal CT features of the pancreas. No pancreatic duct dilatation.<br>• Normal aorta, celiac and superior and inferior mesenteric arteries.<br>• No obstruction or constricting bowel lesions are demonstrated.<br>• No ascites or abdominal lymphadenopathy.<br>• Normal volume of the urinary bladder with smooth wall thickness. |

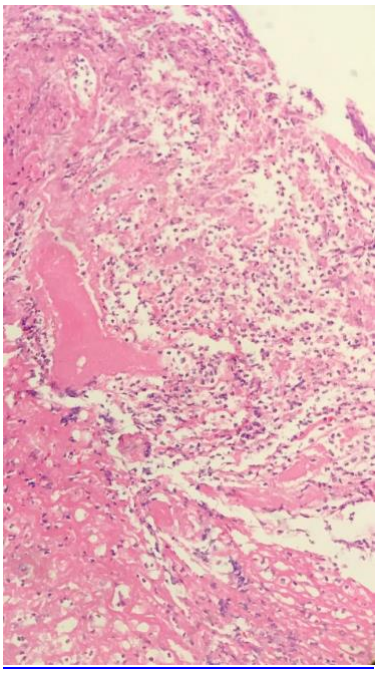
**Table 2: CT scan of abdomen**



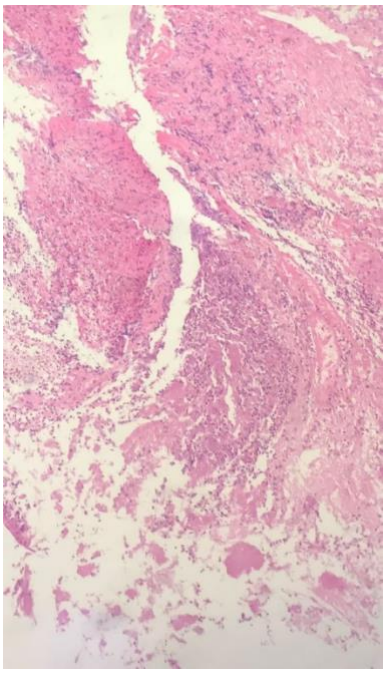

**Picture 1: Ascending colon**


**Picture 2: Transverse colon**

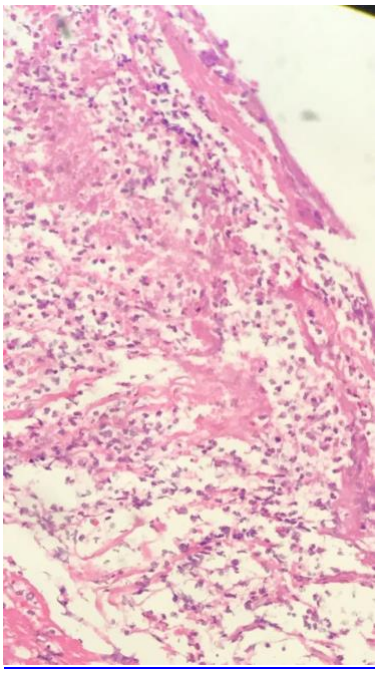

**Picture 3: Descending Colon**



**Picture 4**



**Picture 5**



**Picture 6**