Occult Colonic Adenocarcinoma as a Cause of Recurrent Hepatic Encephalopathy in Cirrhosis

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The prevalence of liver cirrhosis in the general population differs by country. In Great Britain there are 76.3 cases per 100,000 people. From 1992 to 2001, a 68% increase in prevalence of this disease was observed [1]. Portosystemic encephalopathy is a serious complication of liver cirrhosis. The most common precipitating factors are transjugular portosystemic shunt, variceal bleeding, infections, renal failure, hyponatremia, hypokalemia, and obstipation.

Many potential neurotoxins and neuromodulators play an important role in the pathogenesis. Some of them (e.g., ammonia) are direct products of gut bacteria. The incidence of colorectal carcinoma is similar in cirrhotic and non-cirrhotic patients and varies in European countries from 10 to 20 per 100,000 people [2]. Although not common, these two diseases may be present in one patient. In such a case, diagnosis and therapy may be problematic.

In this article we reported on a case of a cirrhotic patient with colon adenocarcinoma, which manifested itself as a series of hepatic comas.

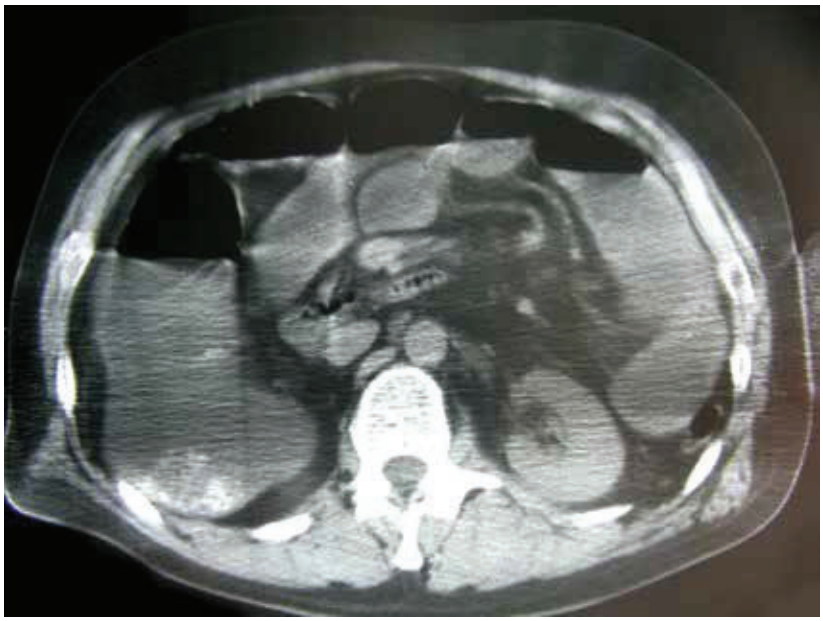
PATIENT DESCRIPTION

A 46-year-old male with known alcoholic liver cirrhosis was transferred to our department because of recurrent hepatic encephalopathy (HE). Before admission, the patient was hospitalized for 13 days in an intensive care unit due to a coma accompanied by nausea, vomiting, and abdominal colic. Laboratory results demonstrated alkalosis, hypokalemia, and dehydration. The diagnosis of coma based on metabolic disruption and electrolyte imbalance was set. On abdominal ultrasound and computed tomography (CT) images [Figure 1] visible signs of bowel paralysis were observed. These findings were thought to be secondary to metabolic and electrolyte imbalance, as both a barium study and CT of the abdomen did not show any intestinal obstruction. The level of consciousness temporarily improved after the correction of alkalosis, partial correction of hypokalemia. and antibiotic treatment. However, the patient again deteriorated to coma, with suspected variceal bleeding, which lead to the transfer to our department.

The Child-Pugh score at the time of admission was 9 points, despite hepatic coma. Chronic hepatitis (type B and C) was excluded by serology. In addition, the patient's history was significant only for esophageal varices Paquet II. The patient was receiving silymarin and essential phospholipids, H_2 blocker, lactulose, and metronidazole. At the time of admission, the patient was comatose (Glasgow Coma Scale 6). Physical examination showed vascular spiders and fresh blood in the mouth and oropharynx; however, the patient was hemodynamically stable. Palpation of the abdomen was performed with no pain, muscular defense, distention, or palpable resistance.

Results of a biochemical panel and blood gas analysis were consistent with the diagnosis of liver cirrhosis, with quite preserved

Figure 1. Distended colon with air suggestive of paralysis or obstruction



synthetic and excretory function (albumin 32 g/L, bilirubin 35 umol/L). Abdominal ultrasound showed diffuse hyperechogenic liver with nodulated margins. In a CT scan, the appearance of the liver was suggestive for cirrhosis. Esophagoduodenogastroscopy (EGD) visualized esophageal varices after a recent bleeding episode without a need for immediate endoscopic treatment.

The diagnosis of hepatic coma precipitated by bleeding from gastroesophageal varices was suggested. After standard conservative therapy including terlipressin, lactulose, and antibiotics, the state of consciousness improved and patient was discharged.

In the 7 weeks following discharge, the patient was stable. Routine checkups were performed where intermittent complaints of nausea, vomiting, loss of appetite, and irregular bowel movements with loose stools were noted.

After 7 weeks the patient was again hospitalized twice within one month because of HE with emesis and signs of bowel hypotonia. The cause of HE was uncertain. No clinical or laboratory signs of variceal bleeding or infection were observed. Poor compliance to the treatment regime and continued alcohol abuse was suspected. After a standard treatment regime including an increased dose of lactulose, the HE rapidly regressed and the patient was discharged. Seven days later, the patient was stable with only minimal signs of decreased consciousness and no subjective complaints.

However, 2 days after the previous checkup, the patient was again admitted to the hospital because of second degree HE (West Haven), which rapidly progressed to coma preceded by severe gastric vomiting with enteric content visible.

On physical examination, there were no clinical signs of peristalsis. Bowel sounds were absent; however, abdomen palpation was without peritoneal irritation or palpable resistance. Native X-ray of the abdomen showed pathologic air-fluid levels. Ultrasound showed distended small bowel and stomach, without colonic distension or ascites. According to the Child-Pugh classification, the cirrhosis progressed from stage B to stage C, ileus was deemed to be paralytic and secondary to the liver disease. After conservative treatment with parenteral hydration and nasogastric suction, the bowel paralysis and emesis regressed, but diarrhea appeared. Ultrasound checkup revealed continuing small bowel paralysis and colonoscopy showed a tumorous infiltration of colon transversum, with histology positive for intestinal type adenocarcinoma, grade 2–3.

After all necessary preparations, a right-sided hemicolectomy with ileo-transverse anastomosis was performed. The tumor peri-operatively was approximately 5 cm in size and was completely obstructing colon transversum. In the postoperative period, the patient was hemodynamically unstable, requiring catecholamine support and artificial ventilation. On the seventh day after surgery, the patient died.

COMMENT

All episodes of hepatic coma in this patient had a common and rather atypical appearance. Aside from one exception, each time the immediate precipitating factor was uncertain. The coma resolved rather quickly and other than coma, the cirrhosis was very well compensated. At the time of the first manifestation, the Child-Pugh score was only 9 points (B class), the highest points attributed by encephalopathy.

Among the most common manifestations of colonic carcinoma in the described location are rectal bleeding (49% of the cases), change in bowel habits (32%), anemia (11%), weight loss (12%), diarrhea (20%), and a palpable abdominal mass (3%). In later stages, symptoms of obstruction are noted. Unfortunately, most of these symptoms may be masked in patients with advanced liver disease. Moreover, bowel habits are significantly modified by administration of lactulose and antibiotics commonly used for treatment of portosystemic encephalopathy. Loss of appetite, in the setting of cirrhosis, could be caused by over-expression of certain cytokines (tumor necrosis factor alpha). Portal hypertension, through portal hypertensive gastropathy, and ascites also contribute to general dyspepsia. These complications could also cause vomiting by similarly induced disruption of gastric motility. Bowel obstruction is not a symptom, but a complication of advanced colorectal carcinoma.

Typical signs of colorectal carcinoma include colicky abdominal pain, abdominal distension, vomiting, and obstipation. Unfortunately, these symptoms are like those of bowel paralysis. Cirrhosis patients with ascites often include intestinal pseudo-obstruction.

Although the pathophysiology of acute intestinal pseudo-obstruction is not fully understood. It is thought to result from an imbalance in the regulation of colonic motor activity by the autonomic nervous system. An altered proximal small bowel motility has been observed in patients with cirrhosis and these disturbances appear not to be dependent on the presence of bacterial overgrow, but rather their severity correlates with more advanced liver disease. However, portal hypertension per se seems to be significantly related to small bowel abnormalities observed in patients with liver cirrhosis.

We found no studies showing evidence of bowel paralysis or ileus caused solely by liver cirrhosis through metabolic disturbances in the literature. In theory, however, there are a number of factors that could precipitate ileus in a cirrhotic patient. Electrolyte imbalances such as hypokalemia and hyponatremia could be one of them. Another potentially relevant factor is intestinal inflammation. This situation could start local production of several pro-inflammatory cytokines that subsequently inhibit enteric smooth muscle function.

As a result, in this case, the clinical picture of intestinal obstruction was blurred by the presence of liver cirrhosis. Moreover, the correct diagnosis was delayed by the negative results of imaging studies. Colonoscopy as the ultimate diagnostic method is used rather reluctantly in cirrhotic patients, especially with ascites, because of possible complications or induction of bacterial translocation that cause spontaneous bacterial peritonitis. Most of the ammonia is

produced by the action of bacteria on urea and ingested proteins in the colon. This ammonia is normally cleared by first-pass extraction in the liver but in cirrhosis, the liver can be bypassed by portosystemic shunts. Elevated plasma ammonia levels in cirrhosis can be improved by laxatives, antibiotics, and substances such as lactulose that decrease colonic pH. It is possible only to speculate that the rather fast recovery from coma in our patient was caused by liquefying the enteric content above the stricture and passing it, thereby removing the bacteria and their products from the intestinal lumen. But the standard treatment of portosystemic encephalopathy also included antibiotics for anaerobe gram negative flora of the gastrointestinal tract, which also might ameliorate symptoms of coma even though caused by colonic obstruction.

To date there are few reports of cirrhotic patients with concomitant colonic cancer-causing bowel obstruction and mimicking hepatic cause of coma. One patient was treated by implanting a soft metallic stent in the stenotic part of the colon because surgery was thought to be too risky [3]. The other case of pseudo-obstruction resolved quickly after administration of neostigmine. In another patient, the bowel obstruction was caused by massive fecal impaction and disappeared with disimpaction [4]. The treatment of colon adenocarcinoma is mostly surgical. The outcome of intra-abdominal operations in patients with liver cirrhosis is poor, as the mortality rate in Child-Pugh B and C are 30 and 82%, respectively [5]. In this case, despite the risk, there was an absolute indication for a surgery because of the acute bowel obstruction.

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Capsule

Matchmaking between virus and host

Coronaviruses not only include the deadly respiratory viruses, such as SARS and MERS, but also viruses that usually cause mild respiratory tract infections. However, mild coronavirus infections can cause severe complications in immunocompromised people. To infect cells, trimers of the coronaviruses' transmembrane spike glycoprotein bind to host receptors. **Tortorici** and co-workers determined the cryo-electron microscopy structures of the trimeric spike from human coronavirus HCoV-OC43 in isolation and in complex with a 9-*O*-acetylated sialic acid, a modification found on glycoproteins at the host cell surface. The ligand binds in a surface-exposed groove that is conserved in all coronaviruses.

Nat Struct Mol Biol 2019; 26: 481

Eitan Israeli

Capsule

Lipid droplets help anti-TB drug efficacy

Improving chemotherapies against intracellular pathogens requires understanding how antibiotic distribution within infected cells affects efficacy. **Greenwood** and colleagues developed an approach to visualize antibiotics in human macrophages infected with the tubercle bacillus. They showed that the antitubercular (anti-TB) drug bedaquiline accumulated in host lipid droplets. Lipid droplets seemed to act as an antibiotic reservoir that could be transferred to bacteria during host lipid consumption. Indeed, alterations in host lipid droplet content affected the anti-TB activity of bedaquiline against intracellular bacilli.

Science 2019; 364: 1279

Eitan Israeli

"Those who write clearly have readers, those who write obscurely have commentators"

Albert Camus (1913–1960), French philosopher, author, and journalist; won the Nobel Prize in Literature at the age of 44 in 1957, the second youngest recipient in history