Case Report

Chronic Diarrhea as First Manifestation of Liver Cirrhosis and Hepatocarcinoma in a Teenager: A Case Report and Review of the Literature

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INTRODUCTION

Hepatocellular carcinoma (HCC) is rare in children, accounting for approximately 0.5% of all pediatric malignances (1). It is the second most common hepatic malignancy in children after hepatoblastoma, with an incidence of 0.5% to 1.0% cases per million (2). HCC is closely associated with chronic hepatitis B virus (HBV) infection and occurs mainly in adults between 40 and 60 years of age (3–5). However, HCC may develop in children who live in hyperendemic areas as a consequence of vertical or horizontal HBV transmission (6). With the introduction of HBV vaccination programs, the incidence of HCC has declined markedly in many countries (3,5,7). In Brazil, the vaccination program began in 1990. Thus, there is still a sizable number of people with chronic HBV infection.

The symptoms of HCC are usually those of chronic liver disease and are generally nonspecific (8). Chronic diarrhea has been described as one manifestation of liver cirrhosis and HCC. Its pathogenesis is poorly understood and probably multifactorial. This report describes a patient with cirrhosis and HCC who presented with chronic diarrhea. Possible mechanisms leading to diarrhea are discussed.

CASE REPORT

A previously healthy 17-year-old boy was admitted to our hospital with a history of 45 days of diarrhea accompanied by lower abdominal cramping and mild pain. He reported six to seven clear to light brown, watery stools per day. There was no pus, mucus, or blood in the stools. Eating exacerbated diarrhea. No fever or significant weight loss was reported. Previous to admission, the patient had been seen at a primary-care center where complete blood count and differential examination were normal, and routine examination of stool for ova and parasites was negative. He had no history of alcohol or drug abuse and was not sexually active. There was no family history of liver disease or inherited disorders including Wilson disease, hemochromatosis, or alpha-1 antitrypsin deficiency.

On admission, blood pressure was 110/70 mm Hg, heart rate was 84 beats per minute, respiratory rate was 16 breaths per minute, and temperature was 36.5°C. His height (1.78 cm) and weight (60 kg) were appropriate by Brazilian standards. He was dehydrated and anemic with hematocrit (Hct) 34% and hemoglobin 10.8 mg/dL. There were no clinical signs of liver disease including jaundice, gynecomastia, vascular spiders, palmar erythema, ascites, fetor hepaticus, asterixis, or encephalopathy. There was no tenderness to abdominal palpation. No hepatomegaly or splenomegaly was detected during the initial physical examination. Repeated stool examinations at our hospital for infectious pathogens, ova, and parasites were negative.

On the day after presentation, he had an acute episode of hematemesis. Endoscopy revealed four medium-sized esophageal varices and portal gastropathy. Laboratory analyses then showed hemoglobin 6.1 mg/dL, Hct 19.2%, white blood cell count (WBC) 7,200/mm³, and platelets 147,000/mm³. Serum albumin was 2.2g/dL, aspartate aminotransferase 284 (normal 15–37) U/L, alanine aminotransferase 157 (normal 30–65) U/L, alkaline phosphatase 206 (normal 150–136) U/L, and γ-glutamyl transferase 410 (normal 5–85) U/L. The prothrombin time was 17 (normal 12) seconds, and the International Normalized Ratio was 1.3. Serum virologic markers for hepatitis B infection were positive.
including HBsAg, anti-HBcIgG, and HBeAg. His mother was also positive for HBsAg and anti-HBeAg, strongly suggesting a vertical transmission of HBV in this patient.

Five days later, he developed fever (39°C) and right lower quadrant abdominal pain. At that time his WBC was 6,700/mm³ with 45% band forms. The abdominal ultrasound and computed tomography (Fig. 1) showed a large mass occupying almost the whole right lobe of the liver. The spleen size was at the normal upper limit. Ascites was present. The α-fetoprotein level was elevated (2,789 μg/L), suggesting HCC. Spontaneous bacterial peritonitis (SBP) was diagnosed (700 WBC with 80% of PMN in the ascitic liquid). Empiric treatment with ciprofloxacin was begun. One of the ascitic fluid cultures was positive for Aeromonas hydrophila. One week after treatment, the patient was apparently well and no longer experienced any diarrhea.

Twenty-five days later, the patient died with portal thrombosis accompanied by a rapid clinical deterioration, making impossible any therapy for his HCC. Autopsy confirmed the diagnosis of HCC.

**DISCUSSION**

Chronic diarrhea has been described in some reports as a symptom of HCC in patients with liver disease (9–11). The reports indicate a prevalence varying from 3.7% to 50% in the largest case series. The mechanism of chronic diarrhea associated with HCC is not completely known, and existing reports have not been designed to determine the mechanism of diarrhea.

In a series of 211 patients with HCC, Lai et al. (10) reported chronic diarrhea in 21%. Diarrhea was attributed to the liver tumor because stool cultures were negative for infectious pathogens. Bruix et al. (11) observed that patients with HCC and diarrhea had higher bilirubin and alkaline phosphatase levels and worse hepatic function than those with HCC without diarrhea. Tumor size, vascular invasion, and degree of tumor differentiation were not related to chronic diarrhea.

A few case reports have clearly demonstrated that one of the causes of chronic diarrhea associated with HCC is paraneoplastic syndrome (12–14). The production of gastrin, vasoactive intestinal polypeptide, and prostaglandins in HCC has been demonstrated by immunohistochemical studies, and treatment with antagonists of these substances and tumor resection has led to the disappearance of diarrhea, thus corroborating this mechanism. Successful therapies of paraneoplastic diarrhea in HCC have included nonsteroidal anti-inflammatory drugs, described by Saban et al. (12) and Salinas et al. (13), and surgical ablation described by Steiner et al. (14).

A protein-losing enteropathy induced by intestinal lymphangiectasia secondary to cirrhosis has been proposed as another possible mechanism of chronic diarrhea associated with HCC (15). In this reported case, the diagnosis was confirmed by albumin scan, fecal α-1-antitrypsin, and biopsy of the duodenum. Control of diarrhea was achieved by the administration of subcutaneous octreotide.

Infectious disease is another potential etiology of chronic diarrhea. Because of associated immunocompromise, opportunistic pathogens such as Escherichia coli, Giardia, Cryptosporidium, Cyclospora, Microsporidia, and Isospora spp. should be considered (16,17).

At presentation, our patient had no clinical features of liver cirrhosis or HCC. The only complaint was chronic diarrhea without signs of infectious disease. However, during the evaluation, the diagnosis of liver cirrhosis and HCC was confirmed after an episode of upper gastrointestinal bleeding. The stool tests, including stool culture, were negative. Only after the diagnosis and treatment of SBP because of Aeromonas hydrophila did the diarrhea stop, leading us to suspect that this was the pathogen responsible for diarrhea.

Aeromonas hydrophila is a gram-negative bacillus of the genus Aeromonas (18). It has been regarded as an opportunistic pathogen in hosts with impaired local or systemic defense mechanisms (19). It has also been reported in immunocompetent patients (20–22). The clinical manifestations are generally those of an acute gastroenteritis. The diarrhea is caused by enterotoxin production (19–21,23,24). Aeromonas hydrophila has been reported as a cause of infections in cirrhotic patients, including SBP and septicemia, with a high incidence of fatal outcomes (25–28). Diagnosis is confirmed by culture (29,30). Fluoroquinolones are effective antimicrobial therapy (30–32). Other effective

![FIG. 1. Computed tomography showing hepatocellular carcinoma occupying almost the whole right hepatic lobe of the liver.](image-url)
drugs include trimethoprim-sulfamethoxazole, aminoglycosides, and third and fourth generation cephalosporns (18,33). In view of reports identifying Aeromonas hydrophila as a common cause of infectious disease in cirrhotic patients and the potential role of infection in increasing morbidity and mortality, empirical antibiotic therapy for these pathogens in patients with cirrhosis and HCC should be considered. The response of Aeromonas to antimicrobial therapy is variable in different geographic areas (34,35), and there appears to be a significant problem with inducible \beta-lactam resistance (18,33).

In conclusion, chronic diarrhea can be a symptom of HCC or liver cirrhosis. The mechanisms involved include paraneoplastic process and intestinal lymphangiectasia. However, the possibility of an infectious etiology, especially Aeromonas hydrophila, should be considered.

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REFERENCES