Case Report

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Relationship between portal HTN and cirrhosis as a cause for diabetes

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ABSTRACT

Our aim was to explore the relationship between liver cirrhosis (LC), portal hypertension (PH), and diabetes mellitus (DM). LC displayed hemodynamic alterations reflected by signs and symptoms of hypertension and hyperdynamic circulation. Portal hypertension also caused splenomegaly because of the blood flow into the spleen from the portal vessels and portal flow. The alcoholic cirrhosis displayed abnormal values (AST, ALT, AST/ALT, albumin, ammonia, bilirubin, blood platelet, erythrocytes, glucose, Hb, international normalized ratio (INR), PT, prothrombin index (PI), thymol test, white blood cell (WBC) count), which demonstrated the presence of portal hypertension, ascites, DM, infection, and coagulopathy. The evaluation of liver enzymes and other laboratories data helped to determine the severity of the condition and prognosis. Diabetes appeared to be less affecting the prognosis of patients with cirrhosis than LC itself, showing that hepatocellular failure was largely responsible for patients' mortality rather than diabetes and its complications. Patients displayed a BMI correlating obesity, although affected by concomitant diseases that commonly cause a severe weight loss. The elevated BMI in this case was accentuated by the presence of ascitic fluid, which is responsible for the increase in weight and the inaccurate BMI evaluation. Ascites affect patients' recovery from liver diseases. Obese patients with cirrhosis can be related to have a large amount of ascites and that physicians should be expecting to notice changes in their BMI pre- and postoperatively, subsequently making a prior classification as obese inappropriate. Disease severity could be assessed through the evaluation of PH stage, which was characterized by a significant depletion of WBC and as well as platelet counts.

Key words: coagulopathy, diabetes, hepatosplenomegaly, liver cirrhosis, portal hypertension

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INTRODUCTION

Liver cirrhosis (LC) is characterized by hemodynamic alterations that are displayed through hypertension and hyperdynamic circulation.[1] Hence, portal hypertension (PH) leads to the development of portosystemic collateral channels and abdominal wall collateral veins. PH is the result of the augmentation of intrahepatic resistance against portal blood flow because of hepatic architectural changes, accounting for the development of regenerative nodules surrounded by fibrotic septa, which are the histological peculiarities of hepatic cirrhosis. Hence, early stage of the disease characterization is by the increase in liver resistance to portal blood flow because of hepatic metaplasia, such as fibrosis and nodules.[2–5] Specifically, PH can be defined as a portal pressure gradient greater than 5 mmHg. Diabetes mellitus (DM) is usually developed before LC, characterized by the insulin resistance in muscular, hepatic, and adipose tissues as well as hyperinsulinemia.[6] Nevertheless, researchers debated that in the absence of other risk factors contributing to the development of metabolic syndrome, diabetes appears before LC. For example, this condition is frequently detected among patients with cirrhosis having viral, alcoholic, and cryptogenic etiologies. Moreover, the clinical interaction among alcoholic LC, DM, and PH remained poorly defined. Despite the first description that associated diabetes and alcoholic LC in 19th century, nowadays, this condition remained not fully described and is materialized by alterations

of organs functions, implying low life expectancy for patients.

CASE PRESENTATION

A 52-year-old female patient with BMI of 29 at admission was referred by local practitioner to regional hospital, where the patient was followed up because of mushroom poisoning and alcoholic LC, complicated by PH, ascites, and DM. **Anamnesis morbi:** Patient's medical history indicated 30 years of alcohol dependence and 10 years of smoking addiction. She presented a decompensated stage of LC since it initials diagnosis during a paradoxical episode 18 years ago. Twenty-four years ago, the patient displayed for the first time symptoms of chronic pancreatitis because of mushroom intoxication and alcoholism. At the moment of the event, doctor noticed an external secretory insufficiency of pancreas. Moreover, pancreatogenic diabetes developed secondary to pancreatic diseases. She suffered since 22 years of DM before developing symptoms of LC. The case exhibited in the past the presence of axial hiatal hernia and polyarthritis. In addition, forasmuch as a half year, she experienced cyclical period of upper abdominal pain, which radiated to the back after eating or drinking. Moreover, the patient presented symptoms and signs such as nausea, excessive thirst and fatigue, weight loss, diarrhea, and clay-colored stools. Chronic pancreatitis was diagnosed after the assessment of the results of endoscopic retrograde cholangiopancreatography (ERCP) and computed tomography (CT) scan of the abdomen, fecal fat test, increased serum amylase level, increased serum lipase level, and serum trypsinogen. The treatment focused on patient's state stabilization, reduction of pain, and improvement in digestive function. Therefore, a symptomatological treatment was implemented, which were composed of withdrawing of smoking and alcohol, dietary changes (low-fat, high-protein, high-calorie diet with fat-soluble vitamin (A, D, E, and K) supplements and drinking plenty of liquids), pancreatic enzyme supplements, insulin therapy (dosage was based on general insulin dosing guidelines as fixed for diabetes mellitus), glucagon-like peptide 1 (GLP-1, reduction of postprandial glucose), nonsteroidal anti-inflammatory drug (NSAIDs), proton pump inhibitor (PPI), corticosteroids, and IV fluid.[7] Digestive system investigation detected cavernous transformation of the portal vein, hepatosplenomegaly, chronic toxic hepatitis, chronic calculous cholecystitis, adhesive disease, and intestinal obstruction. She was operated in 2007, which consisted of resection of a segment of the colon, duodenal ulcer, erosive gastritis, and duodeno-gastric reflux. Instrumental investigation showed a clear liver contour with an increase of up to 3 cm in size, vena portae d = 10 mm, choledoctus d= 0.4 cm. The genito-urinary system medical history indicated the presence of a cyst on the right kidney followed by right-sided nephrectomy. A month before hospitalization, she noticed a deterioration of health condition through the appearance of diarrhea up to 5 times per day. **Anamnesis vitae:** At patient admission, signs and symptoms that were revealed through manual examination included ascites, tenderness of liver, chronic fatigue, general moodiness, feelings of despair, loss of appetite, nausea, bloating exacerbated after eating and exercise, liquid and tarry stools (feces), vomiting, fever, abdominal pain, stomach upset, jaundice, altered personality, hyperreflexia, insomnia, drowsiness, bruises, pedal edema, shortness of breath, breathlessness, caput medusa, blotchy palms, nosebleeds, and muscle cramps. Laboratory analysis showed abnormal values of complete blood count (CBC), blood chemistry, and liver enzymes components (Tables 1–5). During the

Table 1: Complete blood count, coagulation study, glucose, ammonia.

	Erythrocytes ($\times10^{12}$/L)	Hb (g/dL)	Blood platelet ($\times10^{9}$/L)	INR	PT (s)	PI (%)	Thymol test	Glucose (mmol/L)	Ammonia (µmol/L)
19.11.14	2.3	9	90	1.82	15.4			8.1	90
01.12.15	3.8	12.2	150	1.43	17	76	3	11.3	84
14.12.15					16.7	74	1.8	8	60
22.12.15	4.1	13.6	190	1.33	10.4	55	1.8	6.9	50

Hb: Hemoglobin; INR: international normalized ratio; PT: prothrombin time; PI: prothrombin index.

Table 2: White blood cell count, C-reactive protein, and erythrocyte sedimentation rate.

	WBC ($\times10^{6}$/L)	Neutrophil	Segmented neutrophil	Lymphocyte	CRP	ESR
19.11.14	20.3	13	80		4.5	35
01.12.15	7.4	3	72	33	2.1	25
14.12.15	3.3	7				
22.12.15	2.4	5	60	23	1.9	10

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cells.

period of hospitalization, patient displayed the following average values: fasting high-density lipoprotein (HDL) level < 45 mg/dL, fasting triglyceride level > 140 mg/dL, waist circumference > 92 cm, fasting plasma glucose > 5.6 mmol/L, and hypertension > 140/95 mm Hg throughout the different examination. Viral tests excluded the presence of viral hepatitis because the results of hepatitis screening were negative. Endoscopic examination indicated the presence of esophageal varices. In addition, ultrasound and magnetic resonance imaging (MRI) showed hepatosplenomegaly (+20 edges curves), spleen size (16.3*6 cm), with vena porta d = 19 mm, splenic vein d = 12 mm, and recanalization umbilical vein d= 14 mm. **Treatment:** Regimen palatine, diet N* (5 and 9), patient should visit once monthly the local dispensary for status checking; morning: insulin (short and long acting), aetropidi, protafan; evening: insulin (short and long acting), aetropidi, protafan, berlitioni, solution natrium 0.9%, enterogel; morning and evening: insulin (short and long acting), creonu, enterogermina, lacium, calcemin; thiotriazolini, reosirbilact, calcii, vitruni, lactovit, aevit, pimafucini, furamag, thiogamma, rheosorbilact, furosemide 1%, dibazol 1%, papaverine.

DISCUSSION

The patient presented depletion of CBC components and decrease in clotting time, which indicated coagulopathy (anemia). Following in-patient care, patient status improved through a sensible normalization of blood values (Table 1). In addition, prothrombin index (PI) could be used as a marker of liver deterioration, as it is decreased during the syndrome course, indicating the apparition of fibrous septa; PI ≤ 80% indicated LC.[8] Thymol test indicated liver dysfunction status without showing disturbed liver metabolism. White blood cell (WBC) count showed leucocytosis with shift to the left; these values later showed depletion of the number of neutrophils as patient infection state stabilizes (Table 2). Albumin and gamma-globulin showed an increase in values corresponding to the effect of alcoholic LC (Table 3). Elevated liver function enzymes and hyperammonemia at admission reduced after in-patient care (Tables 1 and 4). This clinical case presented mental and behavioral disorders caused by chronic alcoholism and confirmed by liver enzymes values and bilirubin levels.

As liver function was altered, the more frequent incidence of diabetes occurred and physicians could use this fact as a marker to determine liver failure stage. Therefore, in order to prevent the appearance of complication, antihyperglycemic agents and other diabetic treatments should be used carefully because of the complexity of liver insufficiency and the hepatotoxicity of some oral hypoglycemic drugs. Fasting glucose level confirmed that patient suffered from insulin-resistant diabetes (Table 1). In an another research patient was diagnosed with diabetes type 1, confirming the unlikely detection of DM (type 2) in patients with cirrhosis (Table 1).[6] Patient showed an increase glucose level, despite been on anti-diabetic medication (Table 1). Owing to cost and availability of technology, patient blood glucose was assessed only using blood sugar test; therefore, the data on glycated hemoglobin/hemoglobin A1c (HbA1c) are absent. Moreover, article reported that elevated HbA1c is associated with higher risk of cardiovascular failure in patients with DM. In order to prevent negative events, most patients should have a pre-meal blood glucose of 80–130 mg/dL and with individualized target. Hepatogenous diabetes appeared to be less affecting the prognosis of patients with cirrhosis than those with LC itself, showing that hepatocellular failure was largely responsible for patient mortality rather than diabetes and its complications. Prognosis factor in a study was demonstrated to be albumin, ascites, age, encephalopathy, bilirubin, diabetes, and platelet, which appeared to play an important role in determining the mortality.[6]

Clinical goals of diabetes therapy are to avoid symptoms related to glycosuria or hyperglycemia and ketonuria,

Table 3: Blood chemistries.

	Albumin (g/L)	Albumin alpha 1 (g/dL)	Albumin alpha 2 (g/dL)	Albumin beta 2 (g/dL)	Gamma (g/dL)
01.12.15	72.3	3.4	7.7	13	21.4
22.12.15	67	3.2	6.4	12.4	18.4

Table 4: Liver function tests.

	Total bilirubin (µmol/L)	Direct bilirubin (µmol/L)	AST (U/L)	ALT (U/L)	AST/ALT
19.11.14	151.2	119.7	74.3	32.9	2.3
01.12.15	24.2	8.6	14	6	2.4
14.12.15	23.2	5.2	16	16	1
22.12.15	23.8	6	18	9	2.0

ALT, alanine transaminase; AST, aspartate aminotransferase; AST/ALT: De Ritis Formula.

maintain an ideal BMI, and release patient from frequent or severe hypoglycemia event. Therefore, physicians prescribe one or two injections of insulin per day by mixing short-, intermediate-, and long-acting insulin. Throughout the treatment, a patient should be able to self-monitor his/her glucose level through blood or urine testing. Individualized meal plans and alimentary educational strategies should be established for each patients in order to adapt to the life style. In general, patients' calorie intake should be composed of 15–20% of the energy from protein, 30–35% from fat, and 50–55% from carbohydrates. Physician must recommend patients to abstain from alcohol and smoking and must also motivate them to perform a physical activity and visit a health care facility at least 4 times a year. Treatment goal in diabetes is for patient to have an HbA1c of <7%, a fasting blood sugar of 3.9–7.2 mmol/L, and a peak postprandial glucose of <10 mmol/L. During the medical visit, doctor must perform annual retinal examinations, urinary protein screening, and foot care. Hyperlipidemia is controlled with triglyceride level <150 mg/dL, HDL cholesterol >40 mg/dL, and by normalization of systolic and diastolic blood pressure, <130/80 mmHg.

Patients BMI showed the first stage of obesity, and it is also one of the conditions for the diagnosis of metabolic syndrome. In addition, she is a typical example of alcoholic liver damage with overweight. Metabolic syndrome was displayed in this case by an increase in abdominal girth, hypertension, hyperglycemia, and dyslipidemia. Moreover, the BMI, insulin resistance, and systemic hypertension are all features of metabolic syndrome and appeared independently to LC development.[9] She displayed a BMI correlating with obesity, although affected by concomitant diseases (diabetes, chronic pancreatitis) that commonly cause a severe weight loss. The elevated BMI in this case was accentuated by the presence of ascitic fluid, which is responsible for the increase in weight and the inaccurate BMI evaluation. A research confirmed the absence of correlation between BMI and ascites development in patients with cirrhosis.[10] Ascites affects the patients recovery from liver diseases. Scientists evaluated that the volume of ascites removed from obese patients was greater than that in non-obese and that most of the obese patients became non-obese postoperatively.[10] BMI is exaggerated by ascites during BMI pre-evaluation because ascites fluid is allegedly taken as fat. They concluded that pre-evaluation of BMI was not correlating with the values for ascites fluid or postoperative BMI, neither did it affect the average time of postoperative ventilation and critical care management period. Higher BMI are more subject to deterioration of lung function and bad postoperative prognosis. Obese patients with cirrhosis can be related to have a large amount of ascites and that physicians should be expecting to notice changes in their pre- and postoperative BMI, subsequently making a prior classification as obese inappropriate. Therefore, evaluation of the ascites volume should be done after surgery in order to reevaluate the BMI and determine if patient is still obese. The amount of ascites present in a patient reflects the level of deterioration of liver and kidney function. In addition, ascites influences the intraoperative events through albumin values, postoperative ventilation time, and others factors. Researcher point out that the development of ascites were associated with deterioration of blood components, proteins, and so on.[11] The end stage of LC is considered to be obese because of the elevated peritoneal fluid retention. Treatments of ascites should be promptly done by taking into account the side effect of diuretics and high probability of a patient to develop peritonitis or other infections.

PH is due to an increase in resistance of portal outflow and splanchnic blood flow.[12] In advanced stages, these two mechanisms induced the appearance of hyperkinetic circulation, featured by an elevated cardiac output and depletion of cardiac perfusion pressure as well as the reduction of systemic vascular resistance. Research showed the evidence of the interaction between PH and formation of portosystemic shunts from which esophageal varices originate.[13] Endoscopic detection of esophageal varices should be systematically used for the prevention of bleeding episode, and in case the bleeding already occurred, bleeding therapy should be induced.

Despite our current knowledge about PH, a lot remains to be discovered. Nevertheless, would it be possible for us to speculate that if we had a better knowledge of PH, we could predict the evolution of LC based on the spleno-renal shunt presence? Scientific knowledge indicated the presence of portosystemic collaterals circulation as a poor prognosis sign in patients with cirrhosis.[13,14] The increase in PH-induced inflation of collateral blood flow ultimately induces an elevation of cardiac output, which evolved into the occurrence of a cirrhotic cardiomyopathy.[13,15] The increase in splenic vein diameter (>10 mm) is a suggestive indication of PH. In addition, the Doppler examination demonstrated the presence of portosystemic collateral and can be used as a diagnostic tool for the confirmation of PH.[16–18] PH revealed itself by the appearance of major symptoms of portosystemic collaterals complications, which indicated the level of severity of PH and its future prognosis.[19–22] Disease severity could be assessed through the evaluation of PH stage, which is characterized by significant depletion of WBC (increasing the risk of developing infections) and platelet count (elevating the risk of hemorrhage). Late stage of PH are complicated by hepatic encephalopathy due to extensive alteration of liver detoxification function; therefore, toxemia occurred because of portal vein blockage.[23–25]

Diagnosis of alcoholic LC could be assessed using different imaging techniques such as CT, MRI, single photon emission CT, Doppler ultrasound technique, and also the percutaneous transhepatic portography, which appeared to be more efficient in detection and diagnosis of spleno-renal shunts.[26–29] Elastography and Fibroscan were not performed in this case, because of non-availability of technology at the hospital and high cost for patient, because she was not insured.

Conflict of Interest

Author has no conflict of interest to declare.

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