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ORIGINAL ARTICLE

Case Control Study

Gastric food retention at endoscopy is associated with severity of liver cirrhosis

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Abstract

BACKGROUND

Gastrointestinal symptoms are prevalent in patients with cirrhosis. Cirrhotic patients have a known predilection to delayed gastric emptying compared to those without cirrhosis. However, the contributing factors have not been fully elucidated. Retained gastric food on esophagogastroduodenoscopy (EGD) has been used as a surrogate marker for delayed gastric emptying with reasonably high specificity. Therefore, we hypothesize that the frequency of retained gastric food contents at EGD will be higher in a cirrhotic population compared to a control population without liver disease. Additionally, we hypothesize that increased frequency of gastric food contents will be associated with increased severity of cirrhosis.

AIM

To determine the relative frequency of delayed gastric emptying among cirrhotics as compared to non-cirrhotics and to identify associated factors.

of the authors have nothing to disclose.

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METHODS

We performed a retrospective case-control study of cirrhotic subjects who underwent EGD at an academic medical center between 2000 and 2015. Three hundred sixty-four patients with confirmed cirrhosis, who underwent a total of 1044 EGDs for the indication of esophageal variceal screening or surveillance, were identified. During the same period, 519 control patients without liver disease, who underwent a total of 881 EGDs for the indication of anemia, were identified. The presence of retained food on EGD was used as a surrogate for delayed gastric emptying. The relative frequency of delayed gastric emptying among cirrhotics was compared to non-cirrhotics. Characteristics of patients with and without retained food on EGD were compared using univariable and multivariable logistic regression analysis to identify associated factors.

RESULTS

Overall, 40 (4.5%) patients had evidence of retained food on EGD. Cirrhotics were more likely to have retained food on EGD than non-cirrhotics (9.1% *vs* 1.4%, $P < 0.001$). Characteristics associated with retained food on univariable analysis included age less than 60 years (12.6% *vs* 5.2%, $P = 0.015$), opioid use ($P = 0.004$), Child-Pugh class C (24.1% Child-Pugh class C *vs* 6.4% Child-Pugh class A, $P = 0.007$), and lower platelet count ($P = 0.027$). On multivariate logistic regression analysis, in addition to the presence of cirrhosis (adjusted OR = 5.83; 95%CI: 2.32-14.7, $P < 0.001$), diabetes mellitus (types 1 and 2 combined) (OR = 2.34; 95%CI: 1.08-5.06, $P = 0.031$), opioid use (OR = 3.08; 95%CI: 1.29-7.34, $P = 0.011$), and Child-Pugh class C (OR = 4.29; 95%CI: 1.43-12.9, $P = 0.01$) were also associated with a higher likelihood of food retention on EGD.

CONCLUSION

Cirrhotics have a higher frequency of retained food at EGD than non-cirrhotics. Decompensated cirrhosis, defined by Child-Pugh class C, is associated with a higher likelihood of delayed gastric emptying.

Key words: Child-Pugh; Cirrhosis; Endoscopy; Gastric emptying; Motility

Core tip: This is the first study to describe the frequency of retained gastric food contents on esophagogastroduodenoscopy (EGD) in a cirrhotic population. Our study reveals that cirrhotic patients are five times more likely to have retained food on EGD than controls. Additionally, this study investigates risk factors for gastric food retention in cirrhosis. Associated factors include age younger than 60, diabetes mellitus, opioid use, thrombocytopenia, and higher Child-Pugh class. A novel finding is the fact that gastric retention is associated with decompensated cirrhosis, as can be elucidated from the association with thrombocytopenia and higher Child-Pugh class.

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INTRODUCTION

Many patients with cirrhosis report gastrointestinal (GI) symptoms such as abdominal bloating, pain, and belching[1-6]. The prevalence of these symptoms has prompted investigation into abnormalities in GI function in cirrhosis. As suspected, cirrhotic patients have higher rates of gastrointestinal dysmotility, characterized by delayed gastric emptying and prolonged small bowel transit time, compared to those without cirrhosis[1,2,7-19]. While severity of cirrhosis has been associated with worsened small bowel motility, the relationship between gastric emptying and severity of liver disease has not been well established. Although some studies have correlated markers of

portal hypertension with delayed gastric emptying[7,9,14,20], those examining the size of esophageal varices[11], variceal pressure[16], and hepatic venous pressure gradient[21], have failed to demonstrate an association with impaired gastric motility.

The presence of retained gastric food on esophagogastroduodenoscopy (EGD) can be used as a surrogate for delayed gastric emptying with a reasonably high specificity[22]. Furthermore, the risk of retained gastric food contents at EGD is higher among patients with severe emptying delays compared to mild or moderate delays[22]. Using this method of evaluating for retained food at EGD, the prevalence of delayed gastric emptying is less than 1% in the general population[23].

Since patients with cirrhosis frequently require EGD for surveillance and treatment of esophageal varices, evaluation for retained gastric food contents at EGD could provide important clinical information in this population. Therefore, we conducted this study to characterize the frequency of retained gastric food contents at EGD in a cirrhotic population compared to a control population without liver disease and to elucidate factors predictive of retained food.

MATERIALS AND METHODS

We performed a retrospective case-control study of patients with cirrhosis who had an EGD for screening or surveillance of esophageal varices between 2000 and 2015. Cirrhotic patients who underwent EGD for an indication of screening or surveillance of varices were identified using the endoscopy electronic health record system, ProVation®, and the ICD-9-CM diagnosis codes 571.2, 571.5, or 571.6. A subsequent chart review confirmed a diagnosis of cirrhosis based on physician assessment. Patients younger than 18 years, those with intra-luminal tumor or mechanical bowel obstruction, those with a prior diagnosis of gastroparesis or prior esophageal, gastric or thoracic surgery, and those who had an EGD indication which could confound gastric emptying (food impaction, foreign body, active gastrointestinal bleed, abdominal pain, nausea, vomiting, dyspepsia, bloating, weight loss, early satiety, or post-prandial fullness) were excluded. Retained gastric food was defined as any EGD with retained food documented in the procedure note for a unique patient. A control group who underwent EGD for an indication of anemia was identified using ProVation® and the ICD-9-CM Diagnosis Codes 280.*, 281.*, or 285.9. Subsequent chart review excluded those with any known liver disease based on physician assessment. Anemia was chosen as the indication for EGD in the control group as it is unrelated to gastroparesis or its symptoms.

Demographic, clinical, laboratory, and endoscopic data were collected and managed using Research Electronic Data Capture tools hosted at Weill Cornell Medicine[24]. Demographic information included age, sex, ethnicity, and body mass index. Clinical data included documented symptoms of delayed gastric emptying in the six months preceding EGD (*i.e.*, bloating, nausea/vomiting, early satiety/post-prandial fullness, upper abdominal pain, or weight loss); current or past history of diabetes mellitus type 1, diabetes mellitus type 2, human immunodeficiency virus, neurological disorders (such as parkinsonism, multiple sclerosis, stroke, primary dysautonomias), infiltrative diseases (such as scleroderma or amyloidosis); causes of drug-induced gastroparesis (α-2 adrenergic agonists, tricyclic antidepressants, calcium channel blockers, dopamine agonists, muscarinic cholinergic receptor antagonists, octreotide, glucagon-like peptide-1 agonists, phenothiazines, cyclosporine, and any opioid); and use of prokinetic medications (metoclopramide, domperidone, erythromycin, or cisapride). Cirrhosis-specific details included model for end-stage liver disease score, Child-Pugh score, transient elastography results, liver biopsy results, hepatic venous pressure gradient, history of spontaneous bacterial peritonitis, history of hepatic encephalopathy (along with highest grade noted), history of esophageal varices (along with highest grade noted), history of ascites, history or development of hepatocellular carcinoma, and liver transplantation. Routine blood testing within 3 months of EGD was also obtained, including hemoglobin, platelets, sodium, blood urea nitrogen, creatinine, prothrombin time/international normalized ratio, total bilirubin, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, hemoglobin A1C, thyroid stimulating hormone, and anti-nuclear antibodies. Endoscopic information included total number of endoscopies completed per patient over the study period, maximal point of EGD insertion, endoscopic findings, presence of pyloric stenosis or other evidence of gastric outlet obstruction, interventions performed, presence of solid gastric food contents, qualitative amount of retained gastric contents, visualization during EGD and whether lavage was required, and endoscopic findings on subsequent EGD within one year.

The primary outcome of the study was the frequency of retained gastric solid food contents, as documented in the procedural report by the endoscopist, in patients with cirrhosis undergoing EGD as compared to patients without liver disease undergoing EGD for anemia. Secondary outcomes included the relationship between retained gastric food contents with severity of cirrhosis by Child-Pugh score; and the association between retained gastric food contents with complications of decompensated cirrhosis as defined by presence of esophageal varices, ascites, or hepatic encephalopathy.

Categorical variables were described as frequencies (percentages) and continuous variables as (mean ± SD). Characteristics of patients with and without retained food on EGD were compared using the Kruskall-Wallis test for non-parametric continuous variables and χ^2 or Fisher's exact test for categorical variables, as appropriate. A multivariable logistic regression analysis was performed including co-variates statistically significant on univariable analysis. Statistical significance was defined by a two-tailed P value of less than 0.05. The statistical methods of this study were reviewed by biostatisticians in the Biostatistics, Epidemiology and Research Design Core within the Weill Cornell Clinical and Translational Science Center. Statistical analysis was performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Between 2000 and 2015, 364 patients with confirmed cirrhosis, who underwent a total of 1044 EGDs for the indication of variceal screening or surveillance, were identified. During the same period, 519 control patients without liver disease, who underwent a total of 881 EGDs for the indication of anemia, were identified. Figure 1 shows the subject screening process and application of exclusion criteria.

Table 1 shows the baseline characteristics of these two groups. Cirrhotic patients had a mean age of 56 years as compared to 66 years in non-cirrhotic patients. Patients with cirrhosis were predominantly male (63%) compared to those without known liver disease who were predominantly female (55%). The vast majority of patients in both groups reported at least one upper gastrointestinal symptom within the six months prior to EGD. No patients had evidence of pyloric stenosis or other causes of gastric outlet obstruction on endoscopy. Well-established predisposing factors to gastroparesis, such as diabetes mellitus and opioid use, were similarly present in the two groups. Laboratory values demonstrated expected differences between the cirrhotic group and the non-cirrhotic, anemic group. Overall, 40 (4.5%) patients had evidence of retained food on EGD. Cirrhotics were more likely to have retained food on EGD than non-cirrhotics (9.1% *vs* 1.4%, adjusted OR = 5.83; 95%CI: 2.32-14.7, P < 0.001).

Table 2 demonstrates the results of univariate analysis of the relationship between patient characteristics and the presence or absence of gastric food retention. Age younger than 60 years was associated with retained food (12.6% *vs* 5.2%, P = 0.015). Diabetes mellitus types 1 and 2 showed a trend towards a significant association with retained food (P = 0.066). Opioid use was associated with retained food on EGD (P = 0.004). More severe thrombocytopenia, a marker of worse portal hypertension, was also associated with the presence of retained food (P = 0.027). Although no complications of decompensated cirrhosis were shown to be significantly associated, the presence of esophageal varices did show a trend towards significance (P = 0.084). On the other hand, severity of Child-Pugh class was associated with retained food on EGD (P = 0.007).

On multivariate logistic regression analysis, in addition to the presence of cirrhosis (adjusted OR = 5.83; 95%CI: 2.32-14.7, P < 0.001), diabetes mellitus (types 1 and 2 combined) (OR = 2.34; 95%CI: 1.08-5.06, P = 0.031), opioid use (OR = 3.08; 95%CI: 1.29-7.34, P = 0.011), and Child-Pugh class C (OR = 4.29; 95%CI: 1.43-12.9, P = 0.01) were also associated with a higher likelihood of food retention on EGD (Table 3).

DISCUSSION

This study is the first to describe the frequency of retained gastric food contents visualized on EGD in a cirrhotic population. Our study reveals that cirrhotic patients are five times more likely to have retained food on EGD than controls. In addition, more decompensated cirrhosis was associated with a higher likelihood of gastric food contents at EGD.

Cirrhosis has been associated with increased nitric oxide (NO) production, gut

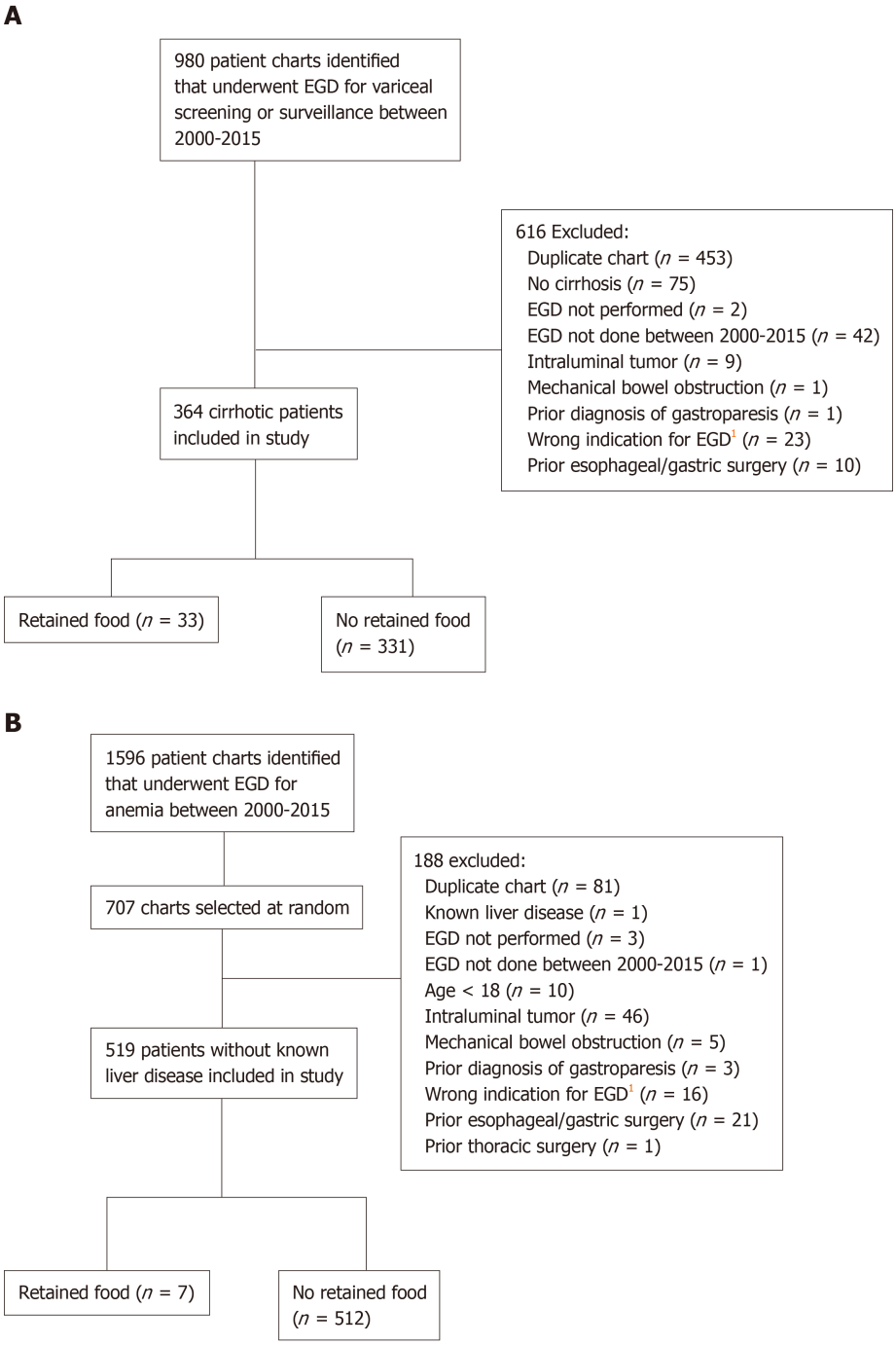

Figure 1 Flow chart of patient inclusion for cases (A) and controls (B). [1]Wrong indication for EGD includes food impaction, foreign body, melena, hematochezia, hematemesis, abdominal pain, nausea, vomiting, dyspepsia, bloating, weight loss, early satiety or post-prandial fullness. EGD: Esophagogastroduodenoscopy.

hormonal alterations, and autonomic neuropathy that can impact gastrointestinal motility[3]. Gut hormonal alterations related to insulin resistance, including hyperglycemia, hyperinsulinemia, and hypoghrelinemia can play a prominent role in the pathophysiology of delayed gastric emptying in patients with cirrhosis[17]. Portal hypertension has also been implicated as a potential mechanism given decreased postprandial portal blood flow resulting in congestion of the gastric wall as well as impaired antral compliance and motility[3]. Prolonged gastric emptying has been demonstrated in 24%-95% of patients with cirrhosis and upper gastrointestinal symptoms not attributable to other causes[1,2,4,5]. These often vague upper GI symptoms have been shown to contribute significant morbidity in the cirrhotic population through malnutrition[4], small intestinal bacterial overgrowth[4], psychological distress[6], and reduced health related quality of life measures[6].

The factors associated with gastric retention in the study population include age

Table 1 Baseline characteristics of patients with cirrhosis and without known liver disease

Variables	Mean ± SD or %		
	Cirrhosis (*n* = 364)	No known liver disease (*n* = 519)	*P* value[1]
Age (yr)	56 ± 11	66 ± 18	< 0.001
Sex			< 0.001
Male	227 (63)	232 (45)	
Female	133 (37)	287 (55)	
Presence of an upper Gastrointestinal symptom	357 (98)	505 (97)	0.457
Diabetes mellitus type I	2 (0.6)	1 (0.2)	0.572
Diabetes mellitus type II	112 (31)	142 (27)	0.271
HIV	22 (6)	17 (3)	0.049
Neurological disorders	7 (2)	59 (11)	0.001
Infiltrative diseases (scleroderma or amyloidosis)	7 (2)	9 (2)	0.836
Opioid use	46 (13)	52 (10)	0.223
Calcium channel blocker use	30 (8)	110 (21)	0.001
Other gastric anti-kinetic medications	19 (5)	58 (11)	0.002
Prokinetic medications	1 (0.3)	3 (0.6)	0.647
Hemoglobin (g/L)	129 ± 22	106 ± 22	< 0.001
Platelets (x 10^9/L)	97 ± 50	230 ± 87	< 0.001
Creatinine (μmol/L)	76 ± 21	83 ± 29	< 0.001
PT/INR	1.2 ± 0.1	1.1 ± 0.1	< 0.001
Total Bilirubin (μmol/L)	20.5 ± 13.7	10.3 ± 3.4	< 0.001
Albumin (g/L)	34 ± 7	37 ± 6	< 0.001
AST (IU/L)	58 ± 36	23 ± 7	< 0.001
ALT (IU/L)	39 ± 31	18 ± 8	< 0.001
Hemoglobin A1C	6.0 ± 1.3	6.2 ± 0.8	0.006
TSH (mU/L)	2.30 ± 0.40	3.47 ± 1.67	0.304

[1]χ^2 test or Fisher exact test for categorical variables and *t*-test/Wilcoxon rank sum test for continuous variables. HIV: Human immunodeficiency virus; PT/INR: Prothrombin time/international normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TSH: Thyroid stimulating hormone.

younger than 60, diabetes mellitus, opioid use, thrombocytopenia, and higher Child-Pugh class. Opioid use and diabetes mellitus are well described risk factors for gastroparesis. The association of diabetes with delayed gastric emptying lends further support to the role of insulin resistance in the pathogenesis of gastroparesis in cirrhotic patients, as previously described in Kalaitzakis *et al*[17]. Regarding the association of age and gastroparesis, it is unclear why gastric food retention was associated with younger age. Given that young age was associated with delayed gastric emptying on univariate analysis but not multivariate analysis, there are likely confounding factors at play. A novel finding is the fact that gastric retention is associated with decompensated cirrhosis as can be elucidated from the association with thrombocytopenia and higher Child-Pugh class. Additionally, there was a trend towards significance with the presence of esophageal varices that further supports an association between severity of cirrhosis, portal hypertension, and gastroparesis. Prior studies evaluating the association between severity of cirrhosis and gastroparesis have shown mixed results. The majority of studies have shown no association between severity of cirrhosis and gastroparesis[2,5,12,13,16,25]. However, the correlation between severity of cirrhosis and delayed gastric emptying seen in this study is similar to two previous studies[1,14]. Gumurdulu *et al*[1] demonstrated that Child-Pugh class correlated with delayed gastric emptying, as measured by scintigraphy, and Miyajima *et al*[14] concluded a similar association using measurements of autonomic function and portal blood flow *via* MRI. Despite the different methodologies used in those studies and the present study, the similar conclusions lend further credence to the results of the current study.

This study has several limitations. Given its retrospective non-interventional nature, no conclusions can be drawn regarding causality. Future studies should

Table 2 Relationship between patient characteristics and retained food in cirrhotics

	Retained food (*n* = 33)	No retained food (*n* = 331)	*P* value[1]
Age group			0.015
< 60 yr	12.6%	87.4%	
≥ 60 yr	5.2%	94.8%	
Sex			0.942
Male	9.3%	90.7%	
Female	9.0%	91.0%	
Diabetes Mellitus type I or II	13.2%	86.8%	0.066
Opioid use	21.7%	78.3%	0.004
Calcium channel blocker use	16.7%	83.3%	0.173
Child-Pugh class			0.007
A	6.4%	93.6%	
B	10.3%	89.7%	
C	24.1%	75.9%	
Alcoholic cirrhosis	13.0%	87.0%	0.201
Nonalcoholic steatohepatitis with cirrhosis	4.3%	95.7%	0.406
Lower platelet count (continuous)			0.027
Portal hypertensive gastropathy	10.9%	89.1%	0.292
Gastric varices	5.6%	94.4%	0.758
Esophageal varices	11.0%	89.0%	0.084
Hepatic encephalopathy	13.6%	86.4%	0.118
Ascites	10.6%	89.4%	0.471
SBP	13.3%	86.7%	0.640
Presence of an upper gastrointestinal symptom	12.9%	87.1%	0.248

[1]χ^2 test or Fisher exact test for categorical variables and *t*-test/Wilcoxon rank sum test for continuous variables. SBP: Spontaneous bacterial peritonitis.

consider prospectively recruiting patients to confirm these results, though time constraints might make prospective recruitment and longitudinal follow-up difficult. Since this is a single center study at an academic center, the results may also lack generalizability. Additionally, the presence of retained food on EGD is not the gold standard method for diagnosing gastroparesis; but, there exists strong evidence for correlation[22].

In conclusion, we demonstrate that cirrhotic subjects have a higher likelihood of delayed gastric emptying than non-cirrhotics, particularly in those with decompensation of their liver disease. Providers who care for cirrhotic patients should have a high index of suspicion for symptoms related to delayed gastric emptying, a condition which is vastly underrecognized in this patient group. Ultimately, a prospectively validated prediction tool would be useful for the detection of impaired gastric motility in cirrhotic patients. Future studies should evaluate the effect of delayed gastric emptying on patient reported outcomes, quality of life and health care utilization.

Table 3 Multivariate analysis for retained food in cirrhotic patients

	Adjusted odds ratio (95%CI)	*P* value[1]
Age		
< 60 yr	ref	
≥ 60 yr	0.49 (0.21-1.14)	0.098
Diabetes	2.34 (1.08-5.06)	0.031
Opioid use	3.08 (1.29-7.34)	0.011
Child-Pugh class		
A	ref	
B	1.43 (0.62-3.28)	0.403
C	4.29 (1.43-12.9)	0.010
Platelet count	0.99 (0.99-1.00)	0.117

[1]χ^2 test or Fisher exact test for categorical variables and *t*-test/Wilcoxon rank sum test for continuous variables.

ARTICLE HIGHLIGHTS

Research background

Many patients with cirrhosis report gastrointestinal (GI) symptoms such as abdominal bloating, pain, and belching. Cirrhosis has been associated with increased nitric oxide (NO) production, gut hormonal alterations, and autonomic neuropathy that can impact gastrointestinal motility. Portal hypertension has also been implicated as a potential mechanism given decreased postprandial portal blood flow resulting in congestion of the gastric wall as well as impaired antral compliance and motility. Prolonged gastric emptying has been demonstrated in 24%-95% of patients with cirrhosis and upper gastrointestinal symptoms not attributable to other causes. These usual vague upper GI symptoms have been shown to contribute significant morbidity in the cirrhotic population through malnutrition, small intestinal bacterial overgrowth, psychological distress, and reduced health related quality of life measures.

Research motivation

The prevalence of GI symptoms has prompted investigation into abnormalities in GI function in cirrhosis. Cirrhotic patients have higher rates of gastrointestinal dysmotility, characterized by delayed gastric emptying and prolonged small bowel transit time, compared to those without cirrhosis. While severity of cirrhosis has been associated with worsened small bowel motility, the relationship between gastric emptying and severity of liver disease has not been well established. The mechanisms for gastrointestinal dysmotility in cirrhosis are also not fully understood. Although some studies have correlated markers of portal hypertension with delayed gastric emptying, those examining the size of esophageal varices, variceal pressure, and hepatic venous pressure gradient, have failed to demonstrate an association with impaired gastric motility. Examination of the risk factors for delayed gastric emptying in patients with cirrhosis could provide further insight into the underlying pathophysiology and could help identify patients who may benefit from therapeutic interventions aimed at improving gastric motility.

Research objectives

The presence of retained gastric food on esophagogastroduodenoscopy (EGD) can be used as a surrogate for delayed gastric emptying with a reasonably high specificity. Since patients with cirrhosis frequently require EGD for surveillance and treatment of esophageal varices, evaluation for retained gastric food contents at EGD could provide important clinical information in this population. Therefore, we conducted this study to characterize the frequency of retained gastric food contents at EGD in a cirrhotic population compared to a control population without liver disease and to elucidate factors predictive of retained food. Specifically, we examined the relationship between retained gastric food contents with severity of cirrhosis by Child-Pugh score; and the association between retained gastric food contents with complications of decompensated cirrhosis as defined by the presence of esophageal varices, ascites, or hepatic encephalopathy.

Research methods

We performed a retrospective case-control study of patients with cirrhosis who had an EGD for screening or surveillance of esophageal varices between 2000 and 2015 at an academic medical center. Patients younger than 18 years, those with intra-luminal tumor or mechanical bowel obstruction, those with a prior diagnosis of gastroparesis or prior esophageal, gastric or thoracic surgery, and those who had an EGD indication which could confound gastric emptying (food impaction, foreign body, active gastrointestinal bleed, abdominal pain, nausea, vomiting, dyspepsia, bloating, weight loss, early satiety, or post-prandial fullness) were excluded. A control group who underwent EGD for an indication of anemia was identified as anemia is unrelated to gastroparesis or its symptoms. Three hundred sixty-four patients with confirmed

cirrhosis, who underwent a total of 1044 EGDs for the indication of esophageal variceal screening or surveillance, were identified. During the same period, 519 control patients without liver disease, who underwent a total of 881 EGDs for the indication of anemia, were identified. The presence of retained food on EGD was used as a surrogate for delayed gastric emptying. The relative frequency of delayed gastric emptying among cirrhotics was compared to non-cirrhotics. Characteristics of patients with and without retained food on EGD were compared using the Kruskall-Wallis test for non-parametric continuous variables and χ^2 or Fisher's exact test for categorical variables, as appropriate. A multivariable logistic regression analysis was performed including co-variates statistically significant on univariable analysis. Statistical significance was defined by a two-tailed *P* value of less than 0.05.

Research results

Overall, 40 (4.5%) patients had evidence of retained food on EGD. Cirrhotics were more likely to have retained food on EGD than non-cirrhotics (9.1% *vs* 1.4%, OR = 5.83; 95%CI: 2.32-14.7, $P < 0.001$). Characteristics associated with retained food on univariable analysis included age less than 60 years (12.6% *vs* 5.2%, $P = 0.015$), opioid use ($P = 0.004$), Child-Pugh class C (24.1% Child-Pugh class C *vs* 6.4% Child-Pugh class A, $P = 0.007$), and lower platelet count ($P = 0.027$). Diabetes mellitus showed a trend towards a significant association with retained food ($P = 0.066$). Although no complications of decompensated cirrhosis were shown to be significantly associated, the presence of esophageal varices did show a trend towards significance ($P = 0.084$). On multivariate logistic regression analysis, in addition to the presence of cirrhosis, diabetes mellitus (types 1 and 2 combined) (OR = 2.34; 95%CI: 1.08-5.06, $P = 0.031$), opioid use (OR = 3.08; 95%CI: 1.29-7.34, $P = 0.011$), and Child-Pugh class C (OR = 4.29; 95%CI: 1.43-12.9, $P = 0.01$) were also associated with a higher likelihood of food retention on EGD.

Research conclusions

This study is the first to describe the frequency of retained gastric food contents visualized on EGD in a cirrhotic population. Our study reveals that cirrhotic patients are five times more likely to have retained food on EGD than controls. In addition, more decompensated cirrhosis was associated with a higher likelihood of gastric food contents at EGD. The factors associated with gastric retention in the study population include age younger than 60, diabetes mellitus, opioid use, thrombocytopenia, and higher Child-Pugh class. Opioid use and diabetes mellitus are well described risk factors for gastroparesis. A novel finding is the fact that gastric retention is associated with decompensated cirrhosis as can be elucidated from the association with thrombocytopenia and higher Child-Pugh class. Additionally, there was a trend towards significance with the presence of esophageal varices that further supports an association between severity of cirrhosis, portal hypertension, and gastroparesis. Prior studies evaluating the association between severity of cirrhosis and gastroparesis have shown mixed results. However, the correlation between severity of cirrhosis and delayed gastric emptying seen in this study is similar to two previous studies. Gumurdulu *et al* demonstrated that Child-Pugh class correlated with delayed gastric emptying, as measured by scintigraphy, and Miyajima *et al* concluded a similar association using measurements of autonomic function and portal blood flow *via* MRI. Despite the different methodologies used in those studies and the present study, the similar conclusions lend further credence to the results of the current study. Clinicians should have a higher index of suspicion for upper GI symptoms related to dysmotility in those with more decompensated cirrhosis, so that these patients can undergo timely diagnosis and treatment.

Research perspectives

We demonstrate that cirrhotic subjects have a higher likelihood of delayed gastric emptying than non-cirrhotics, particularly in those with decompensation of their liver disease. Future studies should consider prospectively recruiting patients in multiple centers to confirm these results, though time constraints might make prospective recruitment and longitudinal follow-up difficult. Additionally, since the presence of retained food on EGD is not the gold standard method for diagnosing gastroparesis, prospective studies could utilize gastric scintigraphy, which remains the gold standard for diagnosis. Providers who care for cirrhotic patients should have a high index of suspicion for symptoms related to delayed gastric emptying, a condition which is vastly underrecognized in this patient group. Ultimately, a prospectively validated prediction tool would be useful for the detection of impaired gastric motility in cirrhotic patients. Future studies should evaluate the effect of delayed gastric emptying on patient reported outcomes, quality of life and health care utilization.

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CASE REPORT

Hepatotoxicity associated with *Garcinia cambogia*: A case report

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Abstract

BACKGROUND

Herbal supplements (HS) for weight loss are perceived to be "safe" and "natural", as advertised in ads, however, hepatotoxicity can be associated with consumption of some HS. Use of HS may be missed, as the patient may not report these unless specifically asked about these products, since they are often not thought of as medications with potential side effects or interaction potential.

CASE SUMMARY

We reported a case of a 21-year-old female with morbid obesity who presented with abdominal pain for 1 wk associated with nausea, vomiting, anorexia and myalgias. She denied smoking tobacco, drinking alcohol, usage of illicit drugs, hormonal contraceptives, or energy drinks. There was no significant past medical or family illnesses. Her laboratory workup revealed acute liver failure. The workup for possible etiologies of acute liver failure was unremarkable. She was using a weight loss herbal supplement "*Garcinia cambogia*" for 4 wks. This case demonstrates the association of acute liver failure with *Garcinia cambogia*.

CONCLUSION

Medical reconciliation of HS should be performed in patients with suspected acute liver failure and early discontinuation of HS can prevent further progression of drug induced hepatoxicity.

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Key words: Hepatotoxicity; Drug induced liver injury; Acute liver failure; Herbal supplements; *Garcinia cambogia*; Obesity; Case report

Core tip: Drug induced liver injury is a diagnosis of exclusion of possible etiologies of liver failure. Medical reconciliation of herbal supplements is important in these patients. The Council of International Organizations of Medical Sciences and Roussel Uclaf Causality Assessment Method "CIOMS/RUCAM" scale is a useful tool for the assessment of drug induced liver injury. A high index of suspicion is required for identification of patients with drug induced liver failure. Early discontinuation of offending agent may prevent progression of disease and results in rapid recovery.

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INTRODUCTION

In the United States, the prevalence of obesity is 39.8%, which is even higher among individuals aged 40 to 59 years old (42.8%)[1]. Individuals are using various modalities for weight loss including lifestyle modifications, pharmacologic, and surgical approaches. Herbal supplements (HS) have become a common method for weight loss due to accessibility without prescriptions, relatively low cost, and false perception of safety as widely advertised in the ads. Currently, there is lack of tight regulation of HS by the United States Food and Drug Administration (FDA) which raises a concern for safety. Every year millions of American use over-the-counter herbal products and most of them are unaware of the potential harmful effects of these products. Among these individuals, 58% failed to report use of HS to their primary care providers[2]. Since they are often not viewed as medications with potential side effects, usage of these HS may be missed because patients may not report their use unless specifically asked about these products. The United States Drug Induced Liver Injury Network (DILIN) noted increasing rates of hepatotoxicity due to HS in the past 10 years, ranging from 2%-16% of all reported liver injuries[3,4].

Garcinia cambogia (GC), a widely available "natural" HS, is found within a tropical fruit, commonly found in South Asia. Its extract is frequently used for weight loss and has been extensively marketed as such for the past decade. Herein we report a case of hepatotoxicity associated with use of the extract of GC.

CASE PRESENTATION

Chief complaints

A 21-year-old African American female with noted obesity (basic metabolic index 40.34 kg/m^2), without significant past medical history, presented with abdominal pain for 1 wk.

History of present illness

Her abdominal pain was described as 7 out of 10 on a pain scale, diffuse, and non-radiating. It was associated with nausea, multiple episodes of non-biliary and non-bloody vomiting, anorexia, and myalgias. She denied any jaundice, pruritis, change in bowel habits, urinary symptoms, or extremity swelling. There was no history of fever, sick contacts, or recent blood transfusions.

History of past illness

There was no significant past medical illness.

Personal and family history

She denied smoking tobacco, drinking alcohol, usage of illicit drugs, hormonal contraceptives, or energy drinks. She mentioned that she was taking a HS, GC (1400

mg daily), for weight loss since 4 wks. Family history was unremarkable.

Physical examination upon admission

Vital signs were notable for tachycardia (133 bpm). On examination, she had epigastric and right upper quadrant tenderness, without jaundice or hepatosplenomegaly.

Laboratory workup

Laboratory workup (Table 1) revealed elevated alanine aminotransferase (ALT) 981 U/L, aspartate aminotransferase (AST) 1062 U/L, alkaline phosphate 248 U/L, international normalized ratio (INR) 1.6, prothrombin time 19 s, and ammonia level 44 μmol/L. Acetaminophen and alcohol levels were negative, as was her urine toxicology. Testing for hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus, herpes simplex virus, cytomegalovirus, Epstein Barr virus, parvovirus, and rapid plasma regain were negative. Autoimmune work-up including antinuclear antibody, antimitochondrial antibody, and anti-smooth muscle antibody were also negative. Serologies for alpha-1 antitrypsin, ceruloplasmin, iron studies, alpha fetoprotein, and carcinoembryonic antigen were unremarkable.

Imaging examination

Abdominal ultrasound showed hepatosplenomegaly with heterogenous increased echogenicity compatible with fatty liver. Abdominal computer tomography (CT) scan showed hepatosplenomegaly with heterogeneous-appearing liver.

FINAL DIAGNOSIS

The final diagnosis of presented case is acute liver failure associated with GC.

TREATMENT

GC was stopped, and she was provided supportive care at the liver transplant center.

OUTCOME AND FOLLOW-UP

Patient's symptoms resolved, and liver enzymes improved gradually (Figure 1) by day 7 (ALT 125 U/L, AST 46 U/L, alkaline phosphate 248 U/L). Her liver function test returned to her baseline at 42 days follow-up from discharge.

DISCUSSION

Herbal and dietary supplements are the second most common cause of drug-induced liver injury (DILI), after antibiotic therapy, in the United States[5]. Americans spend an estimated $66 billion annually on weight loss products[6]. Approximately 10% of obese population are using over-the-counter weight loss products in the Unites States[7]. HS are increasingly used for weight loss in the past decade, as these products are easily available over the counter and considered natural supplements without potential side effects. GC is one of the HS which is increasingly being used in the United States for weight loss. It contains hydroxycitric acid which is considered to be a "magical ingredient" responsible for weight loss. It affects the metabolism of citric acid cycle and inhibits the *de novo* synthesis of fatty acid[8].

"Hydroxycut" is a weight loss supplement which was commonly used for weight loss about a decade ago. GC was one of the active ingredients in Hydroxycut supplement. In April 2009, the FDA reported 23 cases of severe hepatotoxicity attributed to Hydroxycut[9] and issued a public warning in May 2009 causing Hydroxycut product to be recalled by its manufacturer. A reformulated form of Hydroxycut without GC extract was manufactured and reissued within the market for weight loss. Since May 2009, multiple case reports have identified the causal relationship of GC with severe hepatotoxicity (Table 2)[7,10-16]. These case reports reinforce the potential toxic effects of GC contributing to hepatotoxicity.

Due to multitude of ingredients in the supplement formulations, it is difficult to establish correlation of hepatotoxicity with GC. The exact mechanism by which it causes liver failure is unclear. A rodent study revealed that GC may exacerbate steatohepatitis by increasing hepatic collagen accumulation, lipid peroxidation,

Table 1 Laboratory testing done to investigate acute liver failure etiology

Laboratory test	Reference range	Results
Liver function tests		
Alanine aminotransferase	15-41 U/L	981 (H)
Aspartate aminotransferase	3-34 U/L	1062 (H)
Alkaline phosphate	45-117 U/L	248 (H)
Total bilirubin	0.2-1.3 mg/dL	1.3 (N)
Conjugated bilirubin	0.0-0.30 mg/dL	0.73 (H)
Total Protein	6.3-8.2 g/dL	6.8 (N)
Albumin	3.5-5.0 g/dL	2.8 (L)
Ammonia level	0-32 μmol/L	44 (H)
Coagulation Studies		
Prothrombin time	10-13.5 s	19.0 (H)
International normalized ration	0.8-1.2	1.6 (H)
Viral serologies		
Hepatitis A, IgM	Nonreactive	Nonreactive
Hepatitis A, IgG	Nonreactive	Reactive
Hepatitis B, core IgM	Nonreactive	Nonreactive
Hepatitis B, surface antigen	Nonreactive	Nonreactive
Hepatitis C antibody	Nonreactive	Nonreactive
Human immunodeficiency virus 1 and 2 antibody/antigen	Nonreactive	Nonreactive
Herpes simplex virus 1 and 2 IgM	Negative	Negative
Cytomegalovirus, IgM	Negative	Negative
Cytomegalovirus, IgG	Negative	Negative
Epstein Barr virus, IgM	Negative	Negative
Parvovirus B19, IgM/IgG	Negative	Negative
Rapid plasma regain (RPR)	Nonreactive	Nonreactive
Influenza A, antigen	Negative	Negative
Influenza B, antigen	Negative	Positive
Autoimmune liver disease panel		
Antinuclear antibody	Negative	Negative
Antinuclear antibody titer	< 1.0 U	0.6 (N)
Antismooth muscle antibody	Negative	Negative
Antimitochondrial antibody, M2	< 0.1 U	< 0.1 (N)
Toxicology studies		
Acetaminophen level	10-30 mcg/ml	< 2
Ethanol level	0-3 mg/dL	< 3
Urine toxicology screen	Negative	Negative

H: High; N: Normal; L: Low.

oxygen free radical injury, and levels of proinflammatory cytokines like tumor necrosis factor-alpha and monocyte chemoattractant protein-1[17]. The pattern of liver injury caused by GC was noted to be hepatocellular and cholestatic in most of the case reports (Table 2). The most common symptoms of presentation are nausea, vomiting, abdominal pain, anorexia, jaundice, fatigue and generalized myalgias. The duration of GC use before onset of symptoms was ranged from 7 to 28 days however, it was found to be 2 days and 150 days in two case reports, respectively. In most patients, there was an improvement of symptoms and liver function with stopping GC and providing supportive care. Liver transplantation was required in 3 patients. In our case, the patient developed acute liver failure within 4 wks after starting GC. DILI is diagnosis of exclusion of other possible etiologies of acute liver failure, as was investigated in this patient.

To reduce the chances of overdiagnosis or misdiagnosis related to GC, The Council of International Organizations of Medical Sciences (CIOMS) and Roussel Uclaf Causality Assessment Method (RUCAM) scale is the "most commonly used scoring system to establish the etiology of DILI" (Table 3)[18]. The "CIOMS/RUCAM scale"

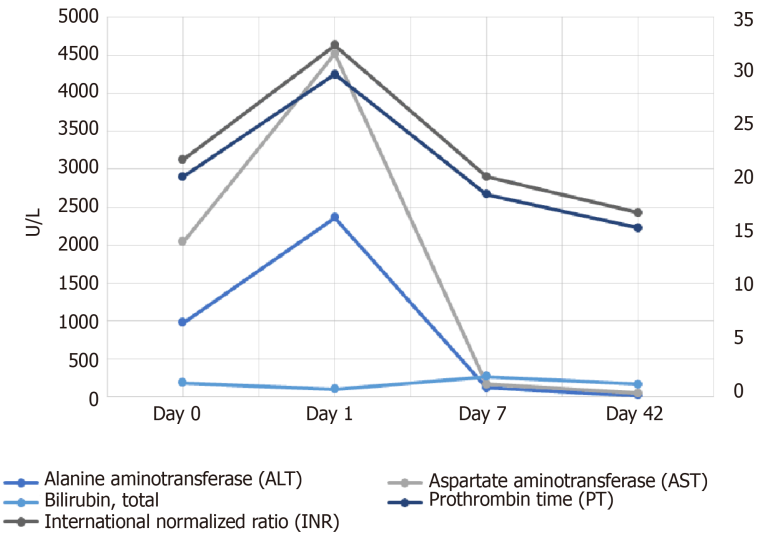

Figure 1 Trends of liver function test, prothrombin and international normalized ratio from day 0 to day 42.

grades DILI into definitive (score > 8), probable (score 6-8), possible (score 3-5), unlikely (score 1-2), or excluded (scores < 0). In this patient, a score of 9 was found and indicated acute liver failure secondary to use of herbal supplements. We excluded other possible etiologies of acute liver failure. Improvement in the patient's symptoms and liver function with discontinuation of GC also indicated correlation of hepatotoxicity with GC.

CONCLUSION

Early recognition and discontinuation of GC can prevent progression of drug-induced liver failure to fulminant hepatic failure and the potential need for liver transplantation if not investigated and stopped rather quickly. Therefore, a medication reconciliation of both prescribed and over-the-counter supplements are prudent on an ongoing basis. Ingredients of herbal and dietary supplements should be regulated by FDA for adverse health consequences and safety profile; however, this may prove to be a daunting task given the number of HS that are on the market and continue to be developed. Further clinical trials are needed to recognize the association between GC and hepatotoxicity and whether this ingredient needs to be closely regulated, given its high propensity for detrimental and potentially fatal complications.

Table 2 Case reports of hepatotoxicity related to non-Hydroxycut formulation of *Garcinia cambogia* since 2009

Case report	Year	Age	Sex	Duration of GC use	Clinical presentation	CIOSM/RUCAM score	Liver transplantation
Present case	2019	26	Female	28 d	Nausea, vomiting, abdominal pain, anorexia and myalgia	9	No
Sharma *et al*[15]	2018	57	Female	28 d	Vomiting and abdominal pain	11	No
Kothadia *et al*[14]	2018	36	Female	28 d	Fever, nausea, vomiting, abdominal pain, fatigue and jaundice	8	No
Lunsford *et al*[7]	2016	34	Male	150 d	Nausea, vomiting, abdominal pain and dark urine	NA	Yes
Smith *et al*[13]	2016	26	Male	7 d	Fatigue, icteric sclera and skin	6	Yes
Corey *et al*[12]	2016	52	Female	25 d	Fatigue, intermittent confusion and jaundice	7	Yes
Melendez-Rosado *et al*[11]	2015	42	Female	7 d	Nausea, abdominal pain, clamminess	NA	No
Lee *et al*[16]	2014	39	Female	2 d	Nausea, abdominal pain, anorexia, dyspepsia, fatigue and jaundice	9	No
Sharma *et al*[10]	2010	19	Male	NA	Fever, fatigue, myalgia, arthralgia, Nausea, Vomiting, abdominal pain and jaundice, erythematous skin rash lower extremities	7	No

GC: *Garcinia cambogia*; CIOMS: Council of International Organizations of Medical Sciences; RUCAM: Roussel Uclaf Causality Assessment Method; NA: Not-available.

Table 3 The Council of International Organizations of Medical Sciences and Roussel Uclaf Causality Assessment Method Scale

Criteria	Score
Time from drug intake until reaction onset	
5-90 d	+2
< 5 or > 90 d	+1
Time from drug withdrawal until reaction onset	
< 15 d	+1
> 15 d	0
Alcohol risk	
Present	+1
Absent	0
Age	
> 55 yr	+1
< 55 yr	0
Course of reaction	
> 50% improvement within 8 d	+3
> 50% improvement within 30 d	+2
Worsening or < 50% improvement in 30 d	-1
Concomitant therapy	
Time to onset incompatible	0
Time to onset compatible but with unknown reaction	-1
Time to onset compatible but known reaction Role proved in the case	-2 -3
None or information not available	0
Exclusion of non-drug related causes	
Ruled out	+2
Possible or not investigated	0
Probable	-3
Previous information on hepatotoxicity	
Reaction unknown	0
Reaction published but unlabeled	+1
Reaction labeled in the product's characteristics	+2
Response to re-administration	
Positive	+3
Compatible	+2
Negative	-2
Not available or not interpretable	0
Plasma concentration of drug known as toxic	+3
Validated laboratory test with high specificity, sensitivity, and predictive values positive	+3
Validated laboratory test with high specificity, sensitivity, and predictive values negative	-3
Interpretation of score for drug induced liver injury:	
> 8 definite drug induced liver injury	
6-8 probable drug induced liver injury	
3-5 Possible drug induced liver injury	
1-2 Unlikely drug induced liver injury	
< 0 drug induced liver injury excluded	

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CASE REPORT

Cholangiocarcinoma after flow diversion surgery for congenital biliary dilatation: A case report and review of literature

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Author contributions: Ataka R designed and wrote the manuscript; Ito T performed operation and edited the manuscript; Masui T, Seo S, Ishii T, and Ogiso S performed operation; All authors discussed the results and contributed to the final manuscript.

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Abstract

BACKGROUND

Pancreaticobiliary maljunction (PBM) can be classified into two categories, PBM with congenital biliary dilatation (CBD) or PBM without biliary dilatation, and the management of PBM is often controversial. The treatment for PBM with CBD is prophylactic flow diversion surgery, and some authors have reported that the incidence of cancer after extrahepatic bile duct excision is less than 1%. A very rare case of intrahepatic cholangiocarcinoma 6 years after flow diversion surgery for PBM with CBD is reported.

CASE SUMMARY

A 30-year-old man was diagnosed as having PBM with CBD, Todani classification type IVA, because of abnormal liver enzyme profiles. He underwent flow diversion surgery and cholecystectomy, and the specimen showed adenocarcinoma foci, pT1, pStage IA. Five and a half years passed without any recurrence of bile duct cancer. However, 6 years after his operation, computed tomography showed a gradually growing nodule in the bile duct. Fluorodeoxyglucose positron emission tomography showed high uptake, and magnetic resonance imaging showed restricted diffusion signals. On double balloon enteroscopy, the nodule at the posterior bile duct-jejunum anastomosis was directly visualized, and its biopsy specimen showed adenocarcinoma. The patient underwent right lobectomy and biliary reconstruction. The pathological diagnosis was intraductal papillary neoplasm with high-grade intraepithelial neoplasia, pTis, pN0, pStage 0. The patient's postoperative course was uneventful, and he has had no recurrence up to the present time.

CONCLUSION

This case suggests the necessity of careful observation after flow diversion surgery, especially when PBM with CBD is detected in adulthood.

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Core tip: Pancreaticobiliary maljunction (PBM) is one of the risk factors for biliary tract cancer. A rare case of intrahepatic cholangiocarcinoma 6 years after flow diversion surgery for PBM with congenital biliary dilatation (CBD) is presented. Careful follow-up after flow diversion surgery is important to detect cholangiocarcinoma in its early stage, especially when PBM with CBD is detected in adulthood, and when cancer has already developed in the bile duct.

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INTRODUCTION

Pancreaticobiliary maljunction (PBM) is an uncommon congenital anomaly defined as junction of the pancreatic and bile ducts outside the duodenal wall, allowing reciprocal reflux of pancreatic juice and bile, which is carcinogenic. Thus, PBM is a high-risk factor for biliary tract cancer, and preventive surgery is necessary. Congenital biliary dilatation (CBD), one type of PBM, is usually treated with prophylactic flow diversion surgery, and the extent of intrahepatic and extrahepatic bile duct resection is often controversial[1,2]. A rare case of a young man who developed cholangiocarcinoma 6 years after flow diversion surgery for PBM with CBD is described.

CASE PRESENTATION

A 30-year-old Japanese man was found to have liver dysfunction at a medical examination. He had no remarkable medical history, was not on any medications, and had no allergies to any food or drug. He visited a nearby hospital and was diagnosed as having PBM with CBD. His common bile duct showed cystic dilatation accompanied by intrahepatic bile duct dilatation, which was classified as Todani type IVA (Figure 1). In the same year, he underwent cholecystectomy and a flow diversion operation that consisted of excision of the extrahepatic bile duct, and biliary and Roux-en-Y reconstruction. According to the Union for International Cancer Control (UICC) 7th edition, the histopathological specimen showed adenocarcinoma foci, pT1, pNx, pStage IA. He did not have any adjuvant chemotherapy and five and a half years passed without any recurrence of biliary tract cancer.

MULTIDISCIPLINARY EXPERT CONSULTATION

However, six years after his operation, follow-up computed tomography (CT) showed a gradually growing nodule, about 10 mm in diameter, at the bile duct-jejunum anastomosis (Figure 2). Physical examination showed no abnormalities except for his previous operative scar. Laboratory tests were unremarkable, including liver and biliary enzyme profiles. Tumor markers were normal (carcinoembryonic antigen 0.8 ng/mL and carbohydrate 19-9 6.4 U/mL). Fluorodeoxyglucose positron emission tomography (FDG-PET) showed high FDG uptake, and magnetic resonance imaging showed restricted diffusion signals at the same nodular lesion. Double balloon enteroscopy showed the lesion directly. There were four holes anastomoses at the cholangiojejunostomy. A reddish and hemorrhagic tumor protruded from the posterior hole, and the other three holes were intact; the biopsy specimen showed adenocarcinoma (Figure 3).

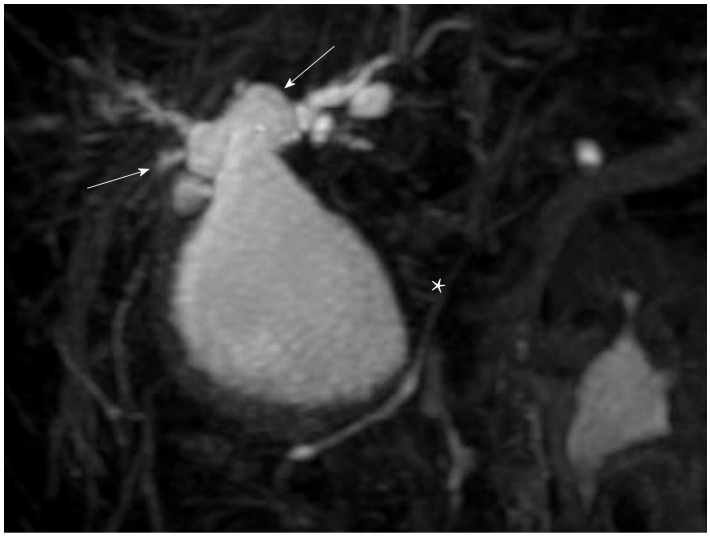

Figure 1 3D-reconstruction of magnetic resonance cholangiopancreatography shows an abnormally dilated common bile duct (white star). Both right and left hepatic ducts also show intrahepatic dilatations (white arrows).

FINAL DIAGNSIS AND TREATMENT

One month after percutaneous transhepatic portal embolization to prevent postoperative liver failure due to small remnant liver volume less than 30%, he underwent right lobectomy, biliary reconstruction, and regional lymph node dissection. At laparotomy, there were severe adhesions due to his previous operation. Right lobectomy was performed with dissection of the right hepatic artery, right portal vein, right hepatic vein, hilar bile ducts, and Roux-en-Y jejunum with cholangiojejunostomy. The remaining bile ducts in the hilar plate were three holes of B1, B2 plus B3, and B4. The biliary reconstruction was performed by new cholangiojejunostomy with a one-hole anastomosis. The Roux-en-Y reconstruction was also performed by a new jejunojejunostomy. The histopathological diagnosis was intraductal papillary neoplasm of the bile duct with high-grade intraepithelial neoplasia. There were no other abnormal findings in other intrahepatic bile ducts, including the anterior and posterior branches, with a negative bile duct margin. The dissected lymph nodes showed no evidence of malignancy. According to the UICC 8th edition, the pTNM classification was pTis, pN0, pStage 0 (Figure 4).

OUTCOME AND FOLLOW-UP

The patient's postoperative course was uneventful, and he was discharged on the 24th postoperative day. There has been no evidence of re-recurrence up to the present time.

DISCUSSION

PBM is a congenital anomaly defined as junction of the pancreatic and bile ducts outside the duodenal wall. Because of the abnormally located junction, the sphincter of Oddi does not work effectively. Reciprocal reflux of pancreatic juice and bile occurs, which introduces carcinogenic chemicals such as activated phospholipase A2 and secondary bile acids. These chemicals usually flow into the biliary tract because the hydropressure in the pancreatic duct is greater than that in the bile duct. The anomaly can also cause chronic cholangitis and chronic bacterbilia. As a result, patients with PBM have a higher risk of biliary tract cancer[3].

PBM can be divided into two categories: PBM with congenital biliary dilatation (CBD), which was previously called congenital choledochal cyst; or PBM without biliary dilatation (BD)[4]. Todani *et al*[5,6] classified this disease into five categories, and the Todani classification is now commonly used worldwide.

The essential management of PBM is prophylactic surgery to avoid carcinogenesis, and it should be performed immediately after the diagnosis of PBM[1]. Since bile stasis in the dilated biliary tract is the most important factor for the development of

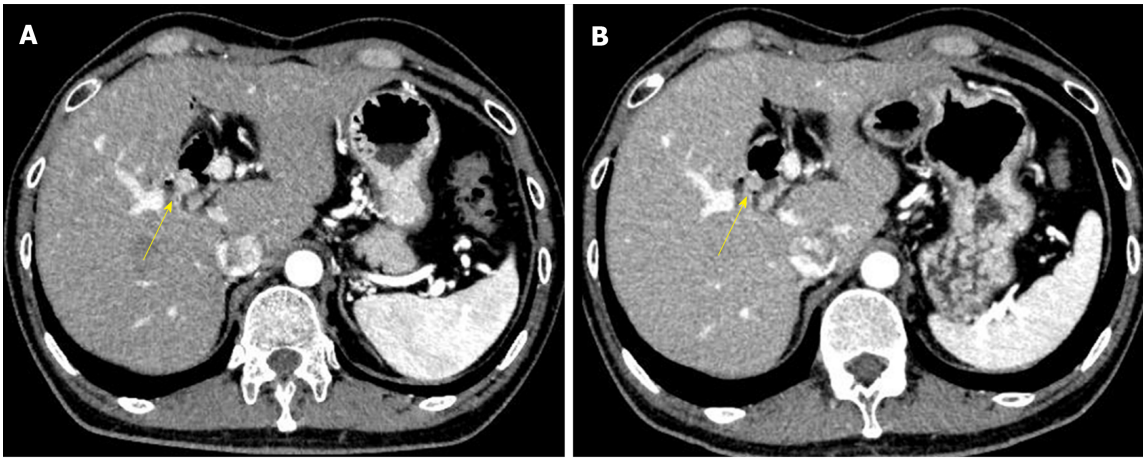

Figure 2 Abdominal CT images with contrast. A: Five and a half years after his first operation; B: Six years after his first operation. The images show a gradually growing nodule with contrast over a half a year (yellow arrow).

malignant changes in biliary epithelial cells[7], the treatment for PBM with CBD is prophylactic flow diversion surgery, and that for PBM without BD is prophylactic cholecystectomy. However, there is no consensus of opinion on whether intrahepatic dilated bile ducts should be resected for PBM with CBD, or whether extrahepatic non-dilated bile ducts should be resected for PBM without BD[1,8].

The present case showed a rare clinical course of PBM with CBD. Watanabe *et al*[9] reported that the incidence of cancer after extrahepatic bile duct excision is less than 1%. There seem to be two reasons for the carcinogenesis in this case. The first reason is that the flow diversion surgery left the dilated right hepatic duct in the hilar plate. In the first operation, the dilated left hepatic duct was removed, but the dilated right hepatic duct was used for cholangiojejunostomy. Since 30 years had passed before his diagnosis of CBD, there must have been some histological changes in the biliary epithelial cells, such as hyperplasia, metaplasia, and dysplasia. Damage and repair of the dilated biliary mucosa were likely to occur even after the first operation, resulting in carcinogenesis at the site of the cholangiojejunostomy. The second reason is that the reflux of intestinal juice at the cholangiojejunostomy probably played an important role in carcinogenesis. The stasis of bile and intestinal juice in the dilated biliary tract induces bacterial overgrowth and generation of unconjugated secondary bile acids[10]. The carcinogenic toxicity of secondary bile acids still remains unclear, but some authors report the following mechanism in mice and its relationship to humans. Secondary bile acids suppress the expression of chemokine ligand 16 (CXCL16), which recruits natural killer T cells, by liver sinusoidal endothelial cells. Then, the suppressed expression of CXCL16 weakens immunological defenses and leads to the development of malignancy and progression[11,12].

There have been 41 reported cases of biliary tract cancer after flow diversion surgery for PBM with CBD in the English literature from 1967 to 2016[7,13-41]. The characteristics of these patients are shown below (Table 1). Of the 41 cases reported, 35 reported details of the interval between age at flow diversion surgery and age at detection of biliary tract cancer. These 35 cases were divided into three groups by age (A, child group, 0-15; B, adolescent/young adult group, 16-30; and C, adult group, > 30 years old), and the interval times are shown in the figure (Figure 5). There were significant differences between Group A and Group B (median 26.5 *vs* 4.0 years, $P < 0.0001$), and between Group A and Group C (median 26.5 *vs* 8.5 years, $P < 0.0001$), with no difference between Group B and Group C. These data mean that patients who undergo flow diversion surgery in adulthood can develop biliary tract cancer earlier than patients who undergo it in childhood. In adulthood, furthermore, interval time does not always depend on age at flow diversion surgery, and it is short, most often less than 10 years. This fact suggests that the damage to the remaining biliary epithelial cells due to carcinogenic chemicals is greater in adulthood than in childhood. In adulthood, the interval time may depend on the size of the dilated bile duct, on the extent of reflux, on the flow diversion procedures, or on lifestyle. The details remain unknown, and further similar cases need to be studied.

In the future, the current patient has a high probability of re-recurrence of cholangiocarcinoma. Although Tsuchida *et al*[42] reported that chemoprevention can be effective for PBM to prevent postoperative carcinogenesis, this is still controversial.

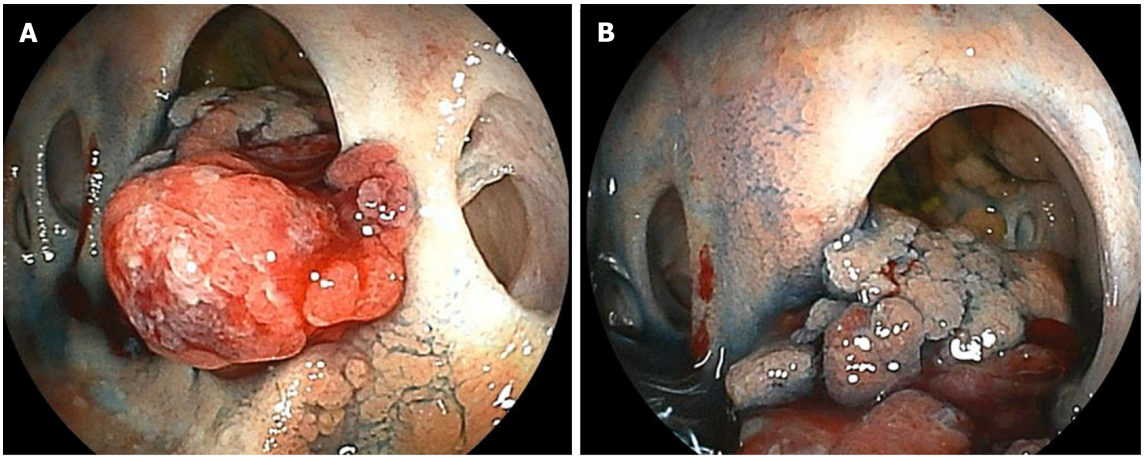

Figure 3 Double balloon enteroscopy shows the cholangiojejunostomy directly. A: There are four-hole anastomoses: Anterior hole, posterior hole, B2 plus B3 hole, and B4 hole, from right to left. A reddish and hemorrhagic tumor protrudes from the posterior hole; B: The tumor extends inside the posterior branch.

CONCLUSION

Follow-up throughout the life of a patient after flow diversion surgery is recommended[4], but this is difficult in some cases. This case suggests the necessity of careful observation after flow diversion surgery, especially when PBM with CBD is detected in adulthood, and when cancer has already developed in the bile duct.

Table 1 Characteristics of the patients with biliary tract cancer after flow diversion surgery

Variables		Number of Cases/years
Sex	Male	8
	Female	24
	NA	9
Todani classification	I	16
	IVA	16
	NA	9
Age at flow diversion surgery[1]		28.3 (0-68)
	NA	8
Age at detection of biliary tract cancer[1]		42.3 (20-70)
	NA	8
Interval time[1]		12.6 (1-35)
	NA	3

[1]Values are medians (range). NA: Not available.

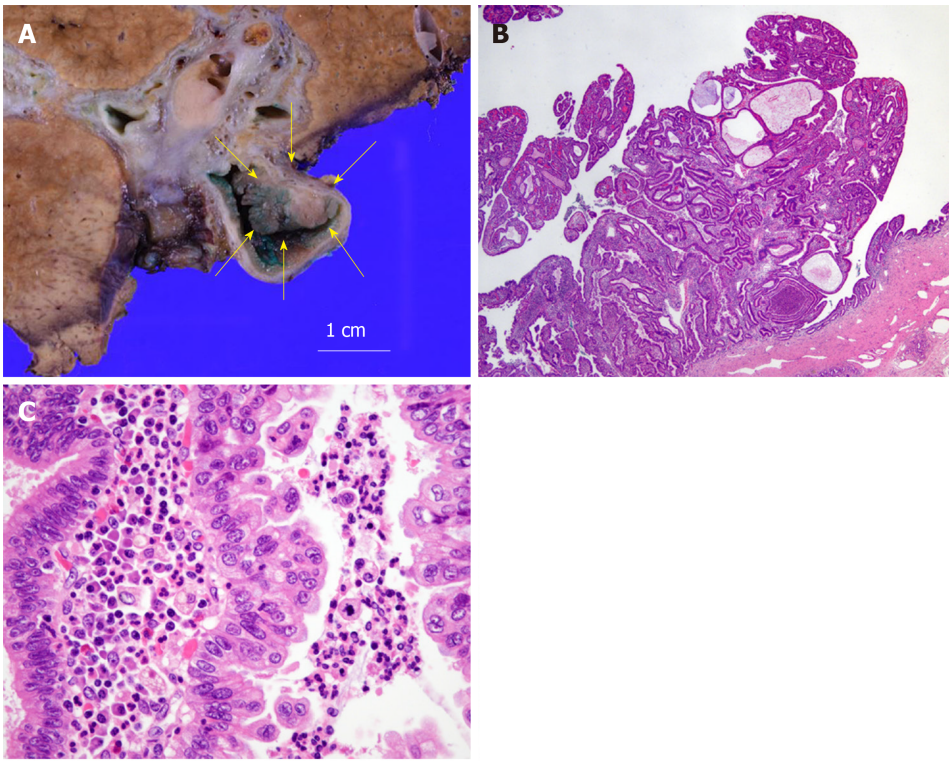

Figure 4 Histological analysis of the tumor. A: Macroscopic findings; B: Hematoxylin and eosin (HE) staining, × 20; C: HE staining, ×400. Histological studies show papillary growth and fibrovascular cores in the macroscopically nodular area (yellow arrow), comprising high-grade atypical epithelial cells. There is no invasive carcinoma associated with the intraductal neoplasm.

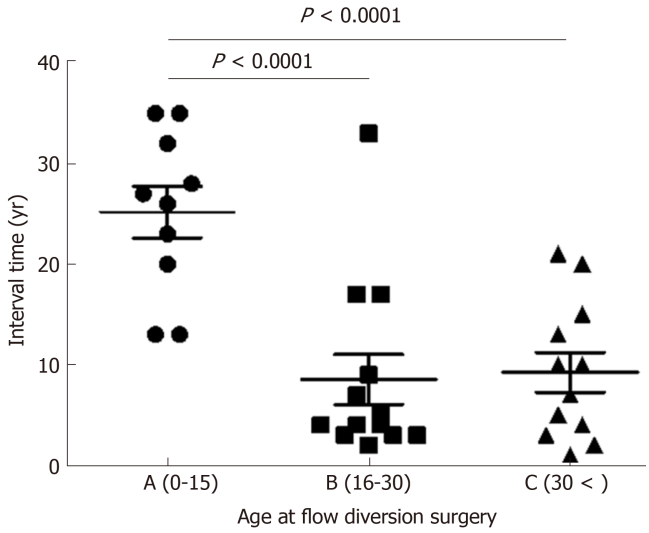

Figure 5 The graph shows the relationship between age at diversion surgery and interval time. Data represent means and standard deviation. $P < 0.0001$, one-way analysis of variance and Bonferroni's multiple comparison test.

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