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【 CASE REPORT 】

Gastroesophageal Varices and Hyperplastic Nodules of the Liver in a Patient with Anorexia Nervosa

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Abstract:

We report a case of anorexia nervosa (AN) with gastroesophageal varices (GEV) in a 36-year-old woman. The patient presented to our hospital with progressive bloating due to severe ascites. She had no history of alcohol intake. Esophagogastroduodenoscopy and enhanced computed tomography revealed GEV and multiple hepatic nodules, respectively. The histological examination of a liver biopsy specimen revealed similar features to nonalcoholic fatty liver disease and showed hyperplastic nodules that were suspected to be related to the uneven distribution of portal blood flow in the liver. In conclusion, patients with long-term AN should undergo abdominal imaging to detect signs of portal hypertension.

Key words: gastroesophageal varices, anorexia nervosa, AN, portal hypertension, hyperplastic nodules

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Introduction

Anorexia nervosa (AN) is an eating disorder characterized by a restriction of caloric intake relative to caloric needs, which leads to a significantly low body weight and severe damage to various organs, including heart failure, renal disorder, and liver dysfunction (1). Liver dysfunction is a common complication of AN that is reported seen in approximately 30% to 60% of cases (2-4). The histological liver findings of patients with AN sometimes reveal steatohepatitis, similar to those of patients with nonalcoholic fatty liver disease (NAFLD) (5-7). However, it is rare for patients with AN to develop gastroesophageal varices (GEV) due to advanced chronic liver disease. We herein report a case of GEV in a patient with AN in whom the histological examination of a liver biopsy specimen revealed characteristic findings.

Case Report

A 36-year-old woman presented at our hospital with a 2-month history of progressive abdominal bloating. The patient did not have fever or subjective gastrointestinal complaints. Her medical history included anorexia nervosa, binge-eating/purging type (AN-BP), which had been diagnosed 10 years previously based on abnormal eating behavior and her being significantly underweight. She had been repeatedly admitted to another hospital for psychotherapy and infusion therapy before her first visit to our hospital; however, her condition had not improved. She had no history of alcohol intake; however, she had a 5-year history of laxative abuse, and had taken more than 100 tablets per day until two years prior to her current presentation. Her vital signs were stable, with the exception of hypotension (91/50 mmHg). However, she had markedly low body weight (body mass index 14.0 kg/m^2) and abdominal swelling due to ascites. Laboratory tests showed iron-deficiency anemia, hy-

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Table 1. Laboratory Data on the First Visit.

White blood cell	5,900 /μL
Red blood cell	2.71 10^6/μL
Hemoglobin	6.3 g/dL
MCV	74.2 Fl
MCH	23.2 Pg
Platelets	140 10^3/μL
PT	89 %
PT-INR	1.05
Albumin	1.8 g/dL
Total bilirubin	0.8 mg/dL
AST	48 IU/L
ALT	32 IU/L
GGT	73 IU/L
BUN	14 mg/dL
Creatinine	0.55 mg/dL
eGFR	99.4 mL/min
Iron	19 μg/dL
UIBC	304 μg/dL
Vitamin B1	31 ng/mL
Vitamin B12	1,490 pg/mL
Folic acid	5.8 ng/mL
Ferritin	6 ng/mL
M2BPGi	(+) 1.04 COI
Hyaluronic acid	2,969.8 ng/mL
Type IV collagen 7S	18 ng/mL
TSH	4.560 μIU/mL
FT4	0.99 ng/dL
IgG	1,301 mg/dL
IgM	247 mg/dL
ANA	<40 Dil
AMA (M2)	(-)<1.5 Index
Tumor Makers	
CEA	7.2 ng/mL
CA19-9	7 U/mL
CA125	455 U/mL
Alphafetoprotein	6.0 ng/mL
DCP	41 mAU/mL
sIL-2R	522 U/mL
Infectious Makers	
HCVAb	(-)
HBsAg	(-)
HBsAb	(-)
HBcAb	(-)

PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, UIBC: unsaturated iron binding capacity, M2BPGi: Mac-2 binding protein glycosylation isomer, TSH: thyroid stimulating hormone, FT4: free thyroxin 4, IgG: Immunoglobulin G, IgM: Immunoglobulin M, ANA: antinuclear antibody, AMA: antimitochondrial antibody, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, CA125: carbohydrate antigen 125, DCP: des-c-carboxy prothrombin, sIL-2R: soluble interleukin-2 receptor, HCVAb: hepatitis C virus antibody, HBsAg: hepatitis B surface antigen, HBsAb: hepatitis B surface antibody, HBcAb: hepatitis B core antibody

poalbuminemia, elevated liver enzymes, and increased liver fibrosis markers. Serologic markers for hepatitis B and C were all negative (Table 1). Paracentesis was performed, and an analysis of the ascites revealed a high serum ascites albumin gradient (SAAG) of 1.5 g/dL. Esophagogastroduodenoscopy showed esophageal varices, classified as Li, F1, Cb, RC0, and TE0, according to the Japanese Research Society for Portal Hypertension (JRSPH) classification, and marked gastric varices, classified as Lg-f, F2, and RC0 according to the JRSPH classification (Fig. 1). Contrast-enhanced computed tomography (CT) revealed ascites, GEV with a gastrorenal shunt, and multiple hypervascular hepatic nodules. When percutaneous angiography was performed, these nodules showed hypoattenuation on CT during arterial portography, and hyperattenuation on CT during hepatic arteriography (Fig. 2a-d). Hepatobiliary phase images from gadolinium-ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced magnetic resonance imaging showed doughnut-like enhancement with relative hypointensity in the central portion, which suggested benign hepatocellular nodules, such as focal nodular hyperplasia (FNH)-like lesions or nodular regenerative hyperplasia (NRH) (Fig. 2e, f) (8, 9). Magnetic resonance elastography revealed a stiff liver (3.4-4.1 kPa; normal <2.1 kPa). On the other hand, portal vein thrombus and splenomegaly or irregularity of the liver, which would be suggestive of cirrhosis, were not observed in these images.

The patient was started on ascites treatment with diuretics and nutritional management with oral ingestion and intravenous supplemental feeding, which gradually increased the patient's caloric intake from 210 kcal/day to 1,200 kcal/day over two weeks, with careful attention towards refeeding syndrome (10). However, she developed bleeding from the GEV two months after her first visit. Endoscopic variceal ligation was performed for emergency hemostasis, and balloon-occluded retrograde transvenous obliteration (B-RTO) was added for more definitive management. The hepatic venous pressure gradient (HVPG) measured during B-RTO was elevated (16 mmHg; normal <10 mmHg) (11, 12). The patient's postintervention course was uneventful, and the GEV was well controlled. On the other hand, the liver damage did not improve, even at more than three months after the procedure. The histological examination of a liver biopsy obtained after the resolution of ascites showed mild steatosis in zone 3, mild chronic inflammatory cell infiltration, fibrosis in the expanded portal areas, and pericellular/perivenular fibrosis. Tissue obtained from one of the liver masses showed hyperplastic nodules on histology; thus, we diagnosed these masses as benign nodular hepatocellular lesions caused by abnormal hepatic circulation (Fig. 3).

Discussion

GEV is a serious complication in patients with advanced chronic liver disease and portal hypertension. Cirrhosis is the most common cause of GEV (13). The patient in the

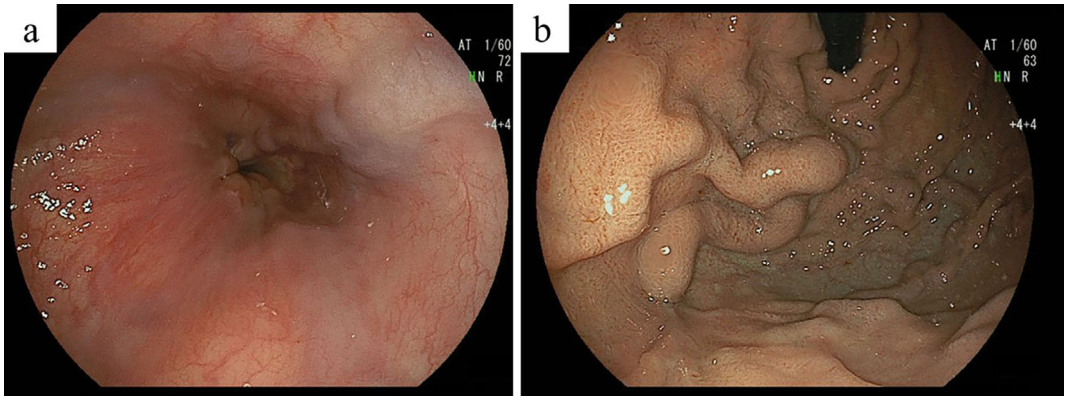

Figure 1. **Esophagogastroduodenoscopy showing esophageal varices, classified as Li, F1, Cb, RC0, and TE0, according to the Japanese Research Society for Portal Hypertension (JRSPH) classification (a), and gastric varices, classified as Lg-f, F2, and RC0, according to the JRSPH classification (b).**

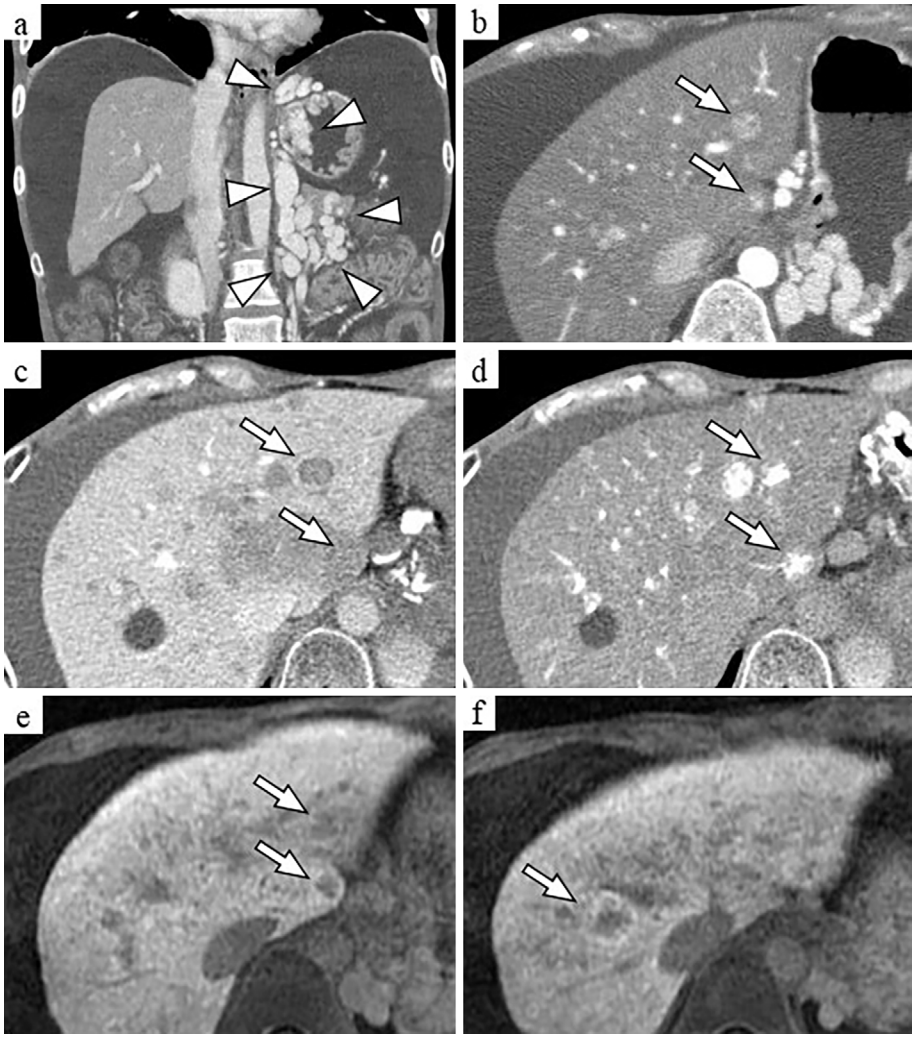

Figure 2. **Abdominal enhanced computed tomography (CT) showing marked ascites and gastro-esophageal varices with a dilated gastro-renal shunt (arrows); however, there were no findings suggestive of cirrhosis, such as splenomegaly, irregularity of the liver surface, or portal vein thrombus (a). In addition, there were multiple hypervascular hepatic nodules (b). These nodules showed hypoattenuation on CT during arterial portography (c), and hyperattenuation on CT during hepatic arteriography (d). The hepatobiliary phase of gadoxetate-enhanced T1-weighted magnetic resonance imaging showed doughnut-like enhancement with relative hypointensity in the central portion (e, f).**

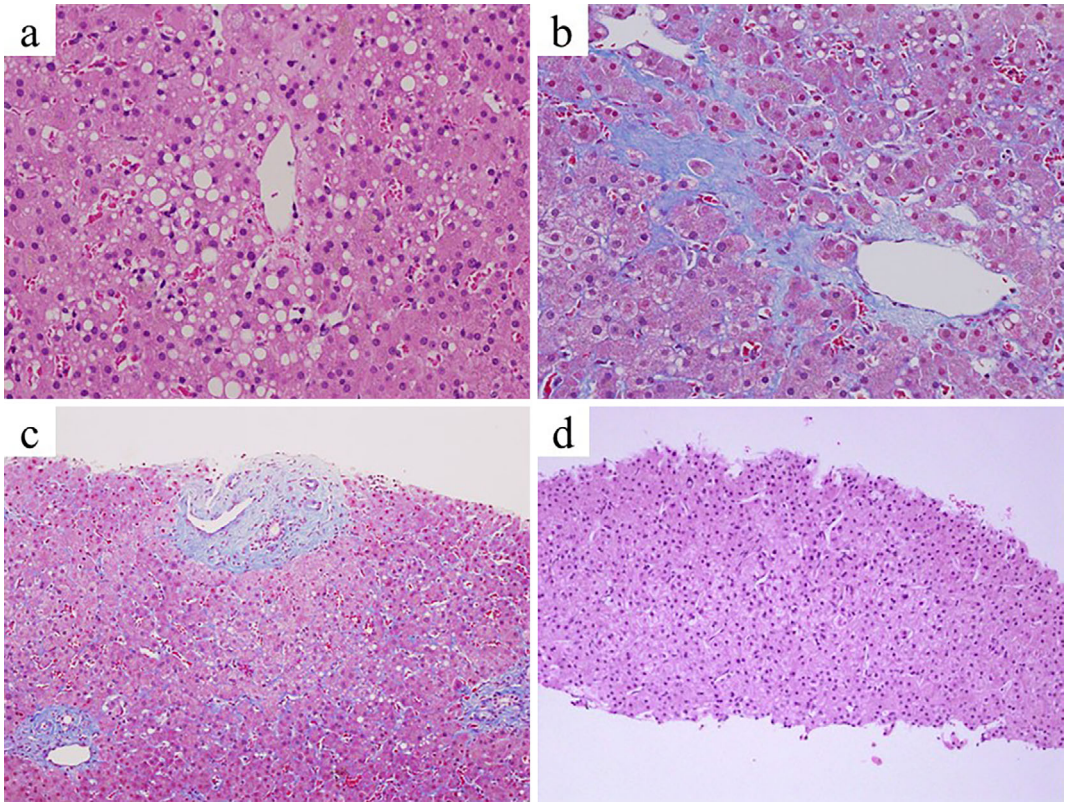

Figure 3. **The histological examination of a liver biopsy specimen. Mild steatosis was observed in zone 3 (a). Pericellular/perivenular fibrosis and fibrosis were observed in the expanded portal areas (b, c). The tissue obtained from the mass showed hyperplastic nodules (d) [a, magnification: ×400; Hematoxylin and Eosin (H&E) staining; b, magnification: ×600; Masson's trichrome staining; c, magnification: ×200; Masson's trichrome staining; d, magnification: ×40. H&E staining].**

present case developed GEV without frank cirrhosis; however, a histological examination revealed mild hepatic steatosis and fibrosis in the expanded portal areas with pericellular fibrosis, similar to the features of NAFLD (5-7).

As mentioned above, patients with AN may present with NAFLD-like histology. NAFLD is a hepatic manifestation of metabolic syndrome. Although it is known that numerous etiologies, such as the use of steatogenic medication, hereditary disorders, and starvation can cause pathological findings similar to NAFLD, these are excluded when diagnosing NAFLD under the current guidelines (14, 15). A mechanism for liver injury, steatohepatitis, and hepatic fibrosis in the setting of starvation has not been elucidated. However, several possibilities have been proposed, including the induction of autophagy due to starvation; mitochondrial injury and cytokine release caused by the oxidation of free fatty acids; an influx of endotoxins into the portal circulation caused by increased intestinal permeability in malnutrition; and circulatory disturbance of the liver due to dehydration (16-18).

To the best of our knowledge, there are five reported cases of portal hypertension in patients with AN. Of these, one was associated with Budd-Chiari syndrome (BCS) (19). All remaining patients had a ≥10-year medical history of AN, and one patient had ruptured varices (Table 2) (18-20). Similarly to our case, those four cases showed pericellular fibrosis in a liver specimen obtained by needle biopsy (18, 20). Furthermore, there are a few other reports showing pericellular fibrosis in patients with AN (5-7). However, it is difficult to evaluate liver fibrosis by needle biopsy because the specimen obtained by needle biopsy is only a small part of the entire liver. It is interesting to note that none of the previously reported cases, including our case, had obvious cirrhosis. It is also unclear whether the portal hypertension in patients with AN is due to liver fibrosis or non-cirrhotic factors. Typical causes of non-cirrhotic portal hypertension include schistosomiasis, idiopathic portal hypertension, BCS, extrahepatic portal vein obstruction, veno-occlusive disease, sinusoidal obstruction syndrome, portal or splenic vein thrombosis, and NRH. Our case did not have any of these factors, but both portal hypertension and multiple nodules, which differed from NRH in that the arterial blood flow was dominant in comparison to the portal blood flow (8), were still found in the liver.

These liver nodules are considered an important finding in explaining the pathophysiology of this case. On imaging, these nodules appear similar to benign liver nodules, such as FNH-like lesions and NRH; histopathologically, they appear as hyperplastic lesions. FNH-like lesions, NRH, and hepatocellular adenoma arise in similar patient populations and have overlapping imaging findings; therefore, in some cases, it is atypical and difficult to diagnose or classify (8, 21, 22).

Table 2. Previous Reports of Portal Hypertension in the Patients with Eating Disorder Including Our Cases.

Reference	Age	Sex	BMI (kg/m^2)	Eating disorder	duration (years)	Portal hypertension	Platelets ($10^3/\mu L$)	AST (IU/L)	ALT (IU/L)	Histology of the liver	Comorbidities
18	29	F	19.2	BN	9	superficial epigastric vein dilatation	116	25	23	N/A	Budd-Chiari syndrome
17	52	F	15.4	AN-BP	20	GR-shunt superficial epigastric vein dilatation	324	79	62	pericellular fibrosis (non-cirrhosis)	None
17	38	F	15.8	AN-BP	15	EV	320	70	59	pericellular fibrosis (non-cirrhosis)	None
17	29	F	14.8	AN-BP	10	GEV GR-shunt	269	41	34	pericellular fibrosis (non-cirrhosis)	None
19	34	F	14.3	AN-BP	12	GEV splenomegaly splenic vein tortuosity	322	69	36	pericellular fibrosis enlargement of the portal area (non-cirrhosis)	Tublointerstitial nephritis HFpEF
Present case	35	F	14.0	AN-BP	10	GEV GR-shunt elevated HVPG	140	48	32	pericellular/ perivenular fibrosis enlargement of the portal area (non-cirrhosis) hyperplastic nodules	None

BMI: body mass index, AST: aspartate aminotransferas, ALT: alanine aminotransferase, BN: bulimia nervosa, AN-BP: anorexia nervosa, binge-eating/purging type, GR-shunt: gastrorenal-shunt, EV: esophageal varices, GEV: gastroesophageal varices, HVPG: hepatic venous pressure gradient, HFpEF: heart failure with preserved ejection fraction

Instead, these nodules appear to be consistent with Kondo's concept of anomalous portal tract syndrome, which suggests a vascular anomaly as the origin of these benign nodular hepatocellular lesions (22). When an area in the liver receives higher blood flow from the combined arterial and portal flows, it can become hyperplastic. Simple occlusion of the portal vein and a compensatory increase in arterial blood flow are inadequate for nodule formation; however, many other factors have been suggested to be involved. Additional cases should be accumulated and further studied to clarify the cause of varices and portal hypertension in patients with AN.

In conclusion, patients with long-term AN may sometimes have concomitant varices, placing them at risk for bleeding. Both GEV and hyperplastic nodules in the liver are found in these cases, which may be due to the uneven distribution of portal blood flow. Therefore, clinicians should consider abdominal and esophageal imaging examinations for patients with long-term AN.

Written informed consent was given by the patient for the publication of this manuscript. Identifying information, aside from age and sex, was removed and the images provided were anonymized to protect patient confidentiality.

The authors state that they have no Conflict of Interest (COI).

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