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Case Report

A Probable Case of Burn-out NASH Caused by Panhypopituitarism Secondary to Craniopharyngioma

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Abstract

A 38-year-old man diagnosed with craniopharyngioma at 8 years old underwent repeated surgery and radiation therapy. Complications included panhypopituitarism including growth hormone deficiency and hypogonadism at 13 years old. At 26 years of age, a slight fatty liver was found, which finally developed into liver cirrhosis (LC) at 35 years old. Viral infection or other etiologies causing LC were negative on serum examinations. Liver biopsy suggested a possibility of burn-out non-alcoholic steatohepatitis. This case indicates that a long-standing growth hormone deficiency and hypogonadism may lead to LC as a type of burn-out non-alcoholic steatohepatitis.

Key words : Craniopharyngioma・Panhypopituitarism・Liver cirrhosis・Growth hormone deficiency・Non-alcoholic stetohepatitis・Non-alcoholic fatty liver disease

Introduction

Although pathologically benign, craniopharyngioma grows and progresses to adjacent tissues such as cerebral parenchyma, the pituitary gland, and others[1]. In addition, local inflammation via various inflammatory cytokines secreted by the craniopharyngioma causes strong adhesion to surrounding tissue, making it difficult to remove craniopharyngioma completely, thus leading to frequent recurrence of the tumor[2]. Consequently, patients with panhypopituitarism, because of repeated surgery and radiation therapy, are often encountered.

Non-alcoholic fatty liver disease (NAFLD) is a broad term encompassing a broad spectrum of abnormalities of the liver including the accumulation of lipids within hepatocytes (fatty liver or hepatic steatosis), inflammation of the liver (NASH), and finally liver cirrhosis (LC)[3]. NASH eventually develops into hepatocellular carcinoma[3]. The prevalence of NAFLD is thought to be rapidly increasing and associated strongly with the pandemic increase in obesity, type 2 diabetes mellitus, and insulin resistance[3][4]. Importantly, visceral adiposity is a significant risk factor for the development of fibrosis associated with NAFLD[5].

Laboratory data are insufficient to make a diagnosis of hepatic steatosis and NASH[6]. The gold standard for diagnosis is liver biopsy, and approximately 20-50% of healthy individuals assessed for partial liver donation have biopsy-proven hepatic steatosis[7][8]. While the pathogenesis of NAFLD is complex, a three-hit hypothesis has been proposed[4]. The accumulation of lipids, the initiation of an inflammatory response, and a defective repair and regenerative response are considered the three "hits". Specifi-

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cally, "the second hit", oxidative stress, inflammatory cytokines, iron overload and others have been thought to trigger or cause hepatic death (the third hit).

NAFLD is often seen in patients with endocrine disorders including growth hormone deficiency (GHD), hypogonadism, hypothyroidism, and hypercortisolemia[9~12], but has often been overlooked, even by endocrinologists. Indeed, in Japan, few reports are available on NAFLD/NASH and endocrine disorders, and only two research papers from one group demonstrated NASH in association with GHD[11)12)].

Here, we report the case of a 38-year-old man with LC and panhypopituitarism who had a history of repeated treatment for craniopharyngioma by surgery and radiation therapy. From this distinctive clinical course, long-standing GHD and hypogonadism were speculated to be the main cause of LC in this patient, likely via NASH.

Case Report

A 38-year-old man first visited our hospital at 8 years of age because of headache, vomiting, and anoxia. Examinations led to a diagnosis of craniopharyngioma. He underwent surgery and received radiation therapy. However, the tumor relapsed six times and he underwent surgery every time. At 13 years of age, he was diagnosed with panhypopituitarism and since then he has taken hydrocortisone and levothyroxin. Presently, he takes hydrocortisone 20 mg twice daily and levothyroxine 100μg once daily. At 26 years of age, his serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated, and he was subsequently diagnosed with a slight fatty liver by abdominal ultrasound. At 31 years of age, his maximum body weight was recorded (78.4 kg ; body mass index (BMI), 26.7 kg/m^2). At 33 years of age, he was diagnosed with diabetes and abdominal ultrasound again showed fatty liver. Currently, he takes once-daily sitagliptin 50 mg and gliclazide 20 mg. At 34 years of age, his serum sodium level was elevated, but he was asymptomatic. At 35 years of age, he was diagnosed with LC by abdominal ultrasound. At 38 years of age, his serum sodium level was 161 mEq/L and he was diagnosed with postoperative diabetes insipidus, administered desmopressin, and hospitalized to investigate endocrine function. The patient's physical examination revealed height, 171.4 cm ; weight, 59.6 kg ; BMI, 20.3 kg/m^2 ; blood pressure, 92/70 mmHg ; pulse, 65 bpm regular ; right complete blindness, and left temporal hemianopsia due to residual craniopharyngioma. He doesn't smoke and drink alcohol. The loss of pubic and axillary hair because of panhypopituitarism was also observed, but no Cushingoid feature was demonstrated. No abnormalities of the chest, abdomen, and nervous system were observed.

Endocrinological examination revealed complete panhypopituitarism including deficiencies of ACTH, TSH, PRL, GH, LH, and FSH. The secretion of these hormones was not stimulated by a combined test with CRH, TRH, GRH, and LH-RH. GH was not increased even after the GH-RP2 test and the peak value was less than 9 ng/mL, indicating a severe form of GHD (Table 2). The serum level of testosterone was also very low, indicating hypogonadotropic hypogonadism. Laboratory data and image analysis revealed thrombocytopenia, dull marginal liver and gastric varix was observed, suggesting the presence of LC (Fig. 1). During hospitalization, hypernatremia was improved by desmopressin. After hospitalization in our department, he was admitted to the Department of Gastroenterology to investigate the cause of LC and for treatment of esophageal varices (Fig. 2). Laboratory tests and past history indicated that LC was not caused by hepatitis B or C virus, alcohol, hemochromatosis, Wilson's disease, autoimmune hepatitis, or primary biliary cirrhosis (Table 1). His gastric varix was treated with sclerotherapy. Liver biopsy showed a mild inflammatory infiltrate and moderate fibrosis in the portal areas with Kupffer cell hyperplasia (Fig. 3).

Table 1 Laboratory data

〈Complete blood count〉			〈Blood chemistry〉					
WBC	5.6	$\times 10^3/\mu L$	TP	7.1	g/dL	BUN	11	mg/dL
Neutrophil	46.1	%	Alb	3.9	g/dL	Cr	0.9	mg/dL
Eosinophil	2.0	%	T-Bil	0.3	mg/dL	UA	5.7	mg/dL
Baso	0.4	%	AST	28	U/L	Na	152	mmol/L
Lymphocyte	47.0	%	ALT	29	U/L	K	3.5	mmol/L
Monocyte	4.5	%	LDH	216	U/L	Cl	113	mmol/L
RBC	4.87	$\times 10^6/\mu L$	ALP	267	U/L	Ca	9.7	mg/dL
Hb	12.6	g/dl	γ GTP	37	U/L	TC	214	mg/dL
Ht	41.1	%	ChE	480	U/L	TG	143	mg/dL
Plt	87	$\times 10^3/\mu L$	CK	48	U/L	HDL-C	44	mg/dL
						LDL-C	138	mg/dL

〈Endocrinology data〉			〈Diabetic data〉		
LH	<0.1	mIU/mL	HbA1c	7.5	%
FSH	<0.1	mIU/mL	BG	114	mg/dL
PRL	<1.0	ng/mL	insulin	12.9	μU/mL
GH	<0.03	ng/mL	CPR	2.75	ng/mL
IGF-1	10	ng/mL	Urine CPR	32.6	μg/day
(normal range 67-318 ng/mL)			24HCCr	88	mL/min
ACTH	<2.0	pg/mL	Anti-GAD	<0.3	U/mL
DHEA-S	<2	μg/dL	Antibody		
TSH	0.011	μIU/mL			
Total testosterone	8.0	ng/mL			

〈Laboratory data associated with hepatocyte〉					
HBs-Ag	(−)		Type Ⅳ		
HCV-Ab	(−)		Collagen 7S	5.9	ng/mL
PT	12.3s		(normal range ≦ 6.0ng/mL)		
PT-INR	1.10		IgG	1270	mg/dL
APTT	34.7s		IgM	86	mg/dL
Cu	122	μg/dL	Antinuclear		
Fe	91	μg/dL	antibody	7	Index
Ferrtin	24	ng/mL	Anti-mitochondrial		
Hyaluronic acid	121.9	ng/mL	antibody	(−)	
(normal range ≦50ng/mL)			AFP	6.6	ng/mL
ceruloplasmin	27.2	mg/dL	PIVKA-Ⅱ	17	mAU/mL

WBC, white blood cell ; RBC, red blood cell ; Hb, hemoglobin ; Ht, hematocrit ; Plt, platelet ; TP, total protein ; Alb, albumin ; T-Bill, total bilirubin ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; LDH, lactate dehydrogenase ; ALP, alkali phosphatase ; γGTP, γ-glutamyl transpeptidase ; ChE, cholinesterase ; CK, creatine kinase ; BUN, blood urea nitrogen ; Cr, creatine ; UA, uric acid ; Na, sodium ; TC, total cholesterol ; TG, triglyceride ; HDL-C, high density lipoprotein-cholesterol ; LDL-C, low density lipoprotein-cholesterol ; LH, luteinizing hormone ; FSH, follicle-stimulating hormone ; PRL, prolactin ; GH, growth hormone ; IGF-1, insulin-like growth factor 1 ; ACTH, adrenocorticotropic hormone ; DHEA-S, dehydroepiandrosterone sulfate ; TSH, thyrotropin-stimulating hormone ; BG, blood glucose ; CPR, C-peptide immunoreactivity ; CCr, creatine clearance ; HBs-Ag, hepatitis B surface antibody ; HCV, hepatitis C virus ; PT, prothrombin time ; APTT, activated partial thromboplastin time ; Cu, copper ; Fe, iron ; AFP, alpha-fetoprotein ; PIVKA-II, protein induced by vitamin K antagonist-II.

Table 2 A LH-RH, TRH, GRH and CRH stimulation test

	pre	15'	30'	60'	90'
ACTH (pg/mL)	< 2.0	×	2.3	< 2.0	< 2.0
PRL (ng/mL)	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
GH (ng/mL)	< 0.03	×	< 0.03	< 0.03	< 0.03
LH (mIU/mL)	< 0.1	×	< 0.1	< 0.1	< 0.1
FSH (mIU/mL)	< 0.1	×	< 0.1	< 0.1	< 0.1
TSH (μIU/mL)	0.011	0.013	0.012	0.018	0.021

Table 2 B GHRP2 stimulation test

	pre	15 分	30 分	60 分	90 分
GH (ng/mL)	< 0.03	0.03	0.03	< 0.03	< 0.03

Table 2 Endocrinological examinations
A. Provocation tests of GH, ACTH, LH, FSH, and TSH with growth hormone-releasing hormone (GRH), corticotropin-releasing hormone (CRH), luteinizing hormone-releasing hormone (LH-RH), and thyrotropin-releasing hormone (TRH).
B. Provocation test of GH secretion with growth hormone-releasing peptide 2 (GHRP2)

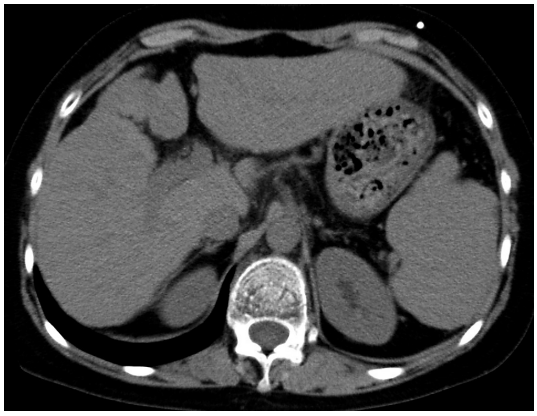

Fig. 1 Abdominal simple computed tomography showing dullness of the marginal liver, swelling of the left lobe, and splenomegaly.

Discussion

With regard to the cause of the patient's LC, laboratory tests and past medical history indicated that it was not caused by hepatitis B or C virus, alcohol, hemochromatosis, Wilson's disease, autoimmune hepatitis, or primary biliary cirrhosis. Thus, he was taken no drugs at diagnosed liver dysfunction, so it was not caused by drug hepatopathy. Based on the previous history of fatty liver, long history of panhypopituitarism as a result of repeated treatment for craniopharyngioma, and the current endocrinological findings of GHD, the main cause of the patient's LC was suspected to be NASH secondary to adult GHD (AGHD) and/or hypogonadotropic hypogonadism[9]. This patient's medication has included levothyroxine and hydrocortisone, thus ruling out the possibility of hypothyroidism as a cause of NASH by endocrinological disorders[13)14)]. In addition, hypercortisolemia as a cause of NASH[15)16)] can be ruled out from the absence of

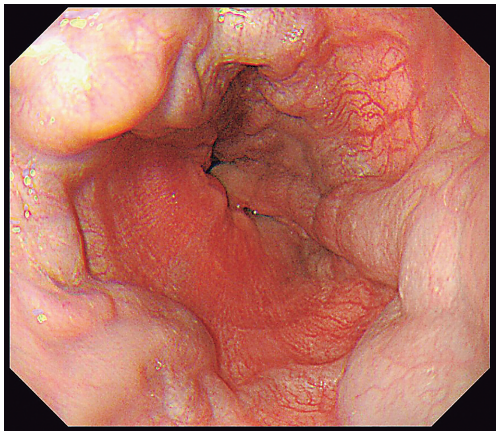

Fig. 2 Esophagogastroduodenoscopy showed esophageal varices in the lower esophagus without red color sign.

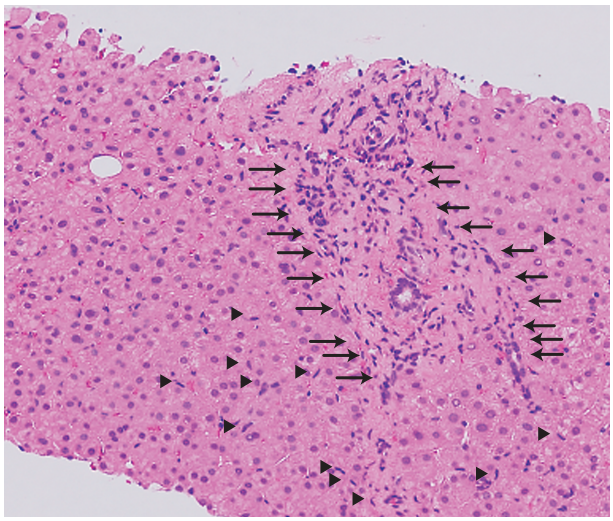

Fig. 3 Liver biopsy showing a mild inflammatory infiltrate and moderate fibrosis in the portal areas with Kupffer cell hyperplasia. No malignant changes were observed.
The black arrowheads indicate Kupffer cells. Surrounded the part by the black arrows suggests inflammatory cell infiltration.

Cushingoid features and no supporting biochemical data.

Pituitary hormone deficiencies occur most often in the following order ; growth hormone, gonadotropin, corticotropin, and thyrotropin. GHD occurs within 5 years after receiving external radiotherapy for pituitary tumors[17]. In our case, considering that the patient was operated on and received radiation therapy at 8 years of age, and he was already receiving adrenal hormone and thyroid hormone administrations at 13 years of age after 5 years, we suggest that the onset of GHD was around 13 years of age. Previous cohort studies have shown that 7-21 years after the onset of NASH, LC can develop. The prevalence of developing LC from NASH is around 5-8%[18)~20)], but little is known in the case of endocrinological etiologies. In our case, at least 25 years duration of panhypopituitarism seems to have been sufficient to lead to LC.

Because GH plays an important role in lipid metabolism, patients with AGHD are often

diagnosed with dyslipidemia[21]. GH inhibits lipoprotein lipase activity in human adipose tissue[22] and modulation of 11beta-hydroxysteroid dehydrogenase isozymes[23]. Nishizawa et al. reported that the prevalence of NAFLD in a GHD group significantly increased by 65% compared with healthy age-, sex-, and BMI-matched controls (77% vs. 12%, $p < 0.01$), and the prevalence of NASH was 21% in patients with NAFLD in the GHD group compared with the prevalence of NASH of 1-3% for the Japanese population[11]. The Janus kinabqse-2 (JAK2)/signal transducer and activator of transcription 5 (STAT5) pathway is the main pathway involved in GH activity. In previous studies, attenuation of GH secretion rescues fatty liver in mice with hepatocyte-specific deletion of JAK2[24], and loss of STAT5 leads to hepatosteatosis and impaired liver regeneration[25]. From these findings, the loss of the GH-JAK2-STAT5 pathway may partly contribute to the pathogenesis of NAFLD. In addition, GH-independent IGF-1 action was also shown to be essential for the prevention of NASH in a GH-deficient rat model[26].

In Japan, GH-replacement therapy is adapted for severe AGHD. In a previous study, GH-replacement therapy led to a dramatic improvement in NASH associated with AGHD[12], thus it is possible that GH-replacement therapy may lead to prevention of NAFLD/NASH. However, in cases with recurrence of tumor and diabetes mellitus, GH-replacement therapy may not always be viable. Our case with repeated recurrence of craniopharyngioma and diabetes illustrated such a standpoint, making it difficult to perform GH replacement.

As well as GHD, hypogonadotropic hypogonadism was also an important cause of NAFLD in our case. Male hypogonadism due to testosterone deficiency is associated with obesity, metabolic syndrome, and diabetes[9,27,28]. Mice specifically lacking the hepatic androgen receptor have been shown to have increased hepatic steatosis[29]. The pathophysiology of metabolic disorders in testosterone deficiency involves not only androgen activity, but also estrogen deficiency because testosterone is converted to estrogens in peripheral tissue by aromatase. Translational studies have demonstrated an association between hepatic steatosis and low serum testosterone levels[30,31]. Testosterone replacement in hypogonadal men causes a significant reduction in weight, BMI, waist circumference[32].

According to the two hit theory, the increase of inflammatory cytokines like Hs-CRP and interleukin 6 in AGHD[33] and tumor necrosis factor alpha in testosterone deficiency[34] may work as the second hit and may promote the development of NASH from simple steatosis.

The minimal criteria for the histological diagnosis of adult NASH include steatosis, hepatocyte injury, usually in the form of ballooning and apoptotic (acidophil) bodies, and lobular inflammation, typically localized in acinar zone 3. Fibrosis, as featured in other forms of chronic hepatitis, is not a required diagnostic feature of NASH[35]. However, liver biopsy in our case showed a mild inflammatory infiltrate and moderate fibrosis in the portal areas with Kupffer cell hyperplasia, but not the above typical features. However, the histopathology of advanced NASH is not always stereotypical. Advanced liver fibrosis in NASH is often accompanied by a reduction in hepatic fat to the point of complete fat loss[36]. The terminal pathology of NASH is called burn-out NASH in which a typical feature of NASH is not observed. Histopathology of our case was non-stereotypical, likely owing to burn-out NASH in which steatohepatitis may burn out leaving no evidence of NAFLD[36]. In addition, there is a possibility that we could not obtain the typical lesion of NASH by needle biopsy.

In conclusion, we presented a case of panhypopituitarism due to craniopharyngioma, accompanied by LC. The cause of the patient's LC was thought to be NASH likely caused by long-term GHD and/or hypogonadotropic hypogonadism, though liver biopsy suggested a possibility of

burn-out NASH. Because detailed case reports of NAFLD due to panhypopituitarism including a liver biopsy are very rare in Japan, our case adds important information to the understanding of the pathophysiology of NASH caused by panhypopituitarism.

The authors state that they have no conflict of interest.

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（和文抄録）

頭蓋咽頭腫の長期治療経過に伴う汎下垂体機能低下症により肝硬変症をきたしたと考えられる一例

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症例は 38 歳男性．8 歳時に頭蓋咽頭腫と診断され，手術及び放射線療法がおこなわれた．その後も再発を繰り返し，13 歳時には成長ホルモン分泌不全症及び性腺機能低下症を伴う汎下垂体機能低下症を認めた．26 歳時に軽度の脂肪肝を指摘され，35 歳時には肝硬変に至った．肝硬変を引き起こすようなウイルス性やその他の肝疾患は血液検査などから否定的であり，肝生検の結果は burn-out NASH が疑われた．本症例の長期経過から，汎下垂体機能低下症に伴う長期の GH 分泌不全症に起因する NASH がその原因と推定された．