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Case Report

Possible Development of Burn-Out Nonalcoholic Steatohepatitis under Long-Term Steroid Use

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Keywords
Nonalcoholic steatohepatitis · Steroid · Complication

Abstract
A 74-year-old man, who lived alone, was found in an unconscious state in his house by a neighbor after mail accumulated in his mailbox. He had asthma and nephrotic syndrome, which had been treated by prednisolone (10 mg) for more than 10 years, and steroid-induced DM. He had been obese since his 20s and had never drunk or smoked in his life. On arrival, he was obese and in a coma and shock state with respiratory failure. He therefore underwent rapid fluid resuscitation, tracheal intubation, mechanical ventilation, with cardiopressor treatment. Whole body computed tomography revealed atrophic liver and excess visceral fat. The clinical diagnosis was septic shock, acute respiratory failure, renal failure with hyperkalemia, cerebral ischemia, liver cirrhosis, rhabdomyolysis, DM, and upper gastrointestinal bleeding. On day 3, his circulation, respiratory function, and consciousness stabilized, and he was extubated. Further studies led to a diagnosis of burn-out nonalcoholic steatohepatitis (NASH). His condition was complicated by adrenal insufficiency, pulmonary embolism, lower extremity motor weakness, and left leg phlegmon during hospitalization. He was transferred to another hospital for rehabilitation on day 34 after the improvement of phlegmon. The present case showed the potential for NASH to develop in individuals with long-term steroid use. The further accumulation and analysis of cases is required to determine whether this possibility is correct or not.

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Case Rep Gastroenterol 2022;16:557–562
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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the industrialized world [1–4]. NAFLD encompasses a spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. NASH is notably characterized by steatosis as well as evidence of hepatocyte injury and inflammation, with or without fibrosis. NASH can lead to hepatocellular carcinoma and is the most rapidly increasing indication for liver transplantation in western countries and therefore represents a global health issue [4]. The pathophysiology of NASH is complex and includes multiple parallel hits [1–4]. In recent years, we have witnessed multiple genome-wide association and large candidate gene studies have been conducted, and the I148M PNPLA3 variant has been identified as the major common genetic determinant of NAFLD [5]. Variants with a moderate effect size in TM6SF2, MBOAT7, and GCKR have also been shown to have a significant contribution [5]. NASH is frequently associated with type 2 diabetes mellitus (DM) and conditions associated with insulin resistance [1–4]. Moreover, NASH may be found in many other endocrine diseases, such as polycystic ovary syndrome, hypothyroidism, male hypogonadism, growth hormone deficiency, or glucocorticoid excess [4]. We herein report a case of burn-out NASH that developed in association with long-term steroid use.

Case Report/Case Presentation

A 74-year-old man who lived alone was found in unconscious state in his house by a neighbor after mail accumulated in his mailbox. He was transported to our hospital by an ambulance. He had asthma and nephritic syndrome, which had been treated by prednisolone (10 mg) for more than 10 years, as well as steroid-induced DM. He had been obese since his 20s and had never drunk or smoked in his life. These facts were confirmed after he regained consciousness. On arrival, his vital signs were as follows: Glasgow Coma Scale, E2V1M4; blood pressure, no measurable but positive pulsation on carotid artery; heart rate, 110 beats per minute; respiratory rate, 24 breaths per minute; and body temperature, 35.2°C. His body mass index was 28. A physical examination revealed obesity, near obstruction of the airway, left conjugated deviated ocular position, right hemiparesis, hematemesis, double incontinence, and complete phimosis with hypogonadism. He underwent rapid fluid resuscitation, tracheal intubation, mechanical ventilation, and indwelling nasogastric tube placement, followed by infusion of noradrenaline and vasopressin. Electrocardiography showed sinus tachycardia with complete right bundle branch block. Whole body computed tomography (CT) showed an atrophic liver (Fig. 1), multiple pancreatic cysts, excess visceral fat, and his penis was

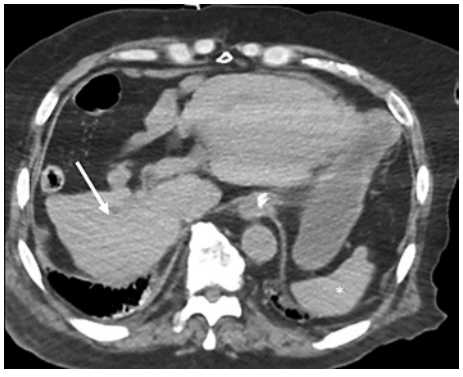

Fig. 1. Whole body computed tomography (CT) on arrival CT showed atrophic liver (arrow). The density of the liver was similar to that of the spleen (asterisk).

Case Reports in Gastroenterology

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Table 1. Results of blood test on arrival

Cell blood count			
White blood count	18,500/μL	Hemoglobin	10.5 g/dL
Platelet	14.0×10^4/μL		
Serum biochemical data			
Total protein	5.3 g/dL	Albumin	2.2 g/dL
Aspartate aminotransferase	117 IU/L	Alanine aminotransferase	44 U/L
γ-Glutamyl transpeptidase	50 IU/L	Alkaline phosphatase	83 IU/L
Amylase	111 IU/L	Choline esterase	114 U/L
Creatine phosphokinase	3,758 IU/L	Total bilirubin	2.2 mg/dL
Blood urea nitrogen	80.1 mg/dL	Creatinine	2.4 mg/dL
Glucose	237 mg/dL	HgA_1C	7.8%
Total cholesterol	113 mg/dL	Triglyceride	76 mg/dL
Sodium	142 mEq/L	Potassium	6.6 mEq/L
Chloride	106 mEq/L	C-reactive protein	14.6 mg/dL
Adrenocorticotropic hormone	14 (7–63) pg/mL	Cortisol	17.4 (7–19) μg/dL
Thyroid-stimulating hormone	1.8 (0.5–4) μIU/mL	Free T3	1.5 (2.4–4.5) pg/mL
Free T4	1.3 (1–1.7) ng/dL	Antidiuretic hormone	12.1 (0–4.1) pg/mL
Luteinizing hormone	8.4 (<7) mIU/mL	Testosterone	22.4 (142–923) pg/mL
Follicle-stimulating hormone	7.1 (2–8.3) mIU/mL	Estradiol	75 (19–51) pg/mL
Coagulation			
Fibrinogen	271 mg/dL	Fibrinogen degradation products	15.3 μg/mL
Prothrombin time			39%
Activated partial thromboplastin time 44.5 s			

Arterial blood gas under 10 L per minute of oxygen: pH, 7.158; PCO_2, 38.8 mm Hg; PO_2, 80.0 mm Hg; HCO^{3-}, 13.2 mmol/L; base excess, –14.4 mmol/L; lactate, 11.4 mmol/L.

buried under a layer of subcutaneous fat. His blood test results are shown in Table 1. The clinical diagnosis was septic shock of unknown focus, acute respiratory failure, renal failure with hyperkalemia, cerebral ischemia, liver cirrhosis, rhabdomyolysis, DM, and upper gastrointestinal bleeding. He underwent infusion of calcium chloride, insulin therapy and zirconium for hyperkalemia and hyperglycemia, and the administration of broad-spectrum antibiotics (2 g of meropenem 1 g + 1,200 mg of linezolid per day) after culture sampling and mineral corticoid for septic shock. As his external urethral orifice could not be identified, emergency circumcision was performed to insert a balloon catheter. He was admitted to the intensive care unit. On day 3, his circulation was stabilized without cardiopressor treatment, PaO_2/FiO_2 reached >300, and he could obey orders. He was therefore extubated. After communication with the patient, his past history was confirmed. Blood culturing revealed *Staphylococcus capitis*. When the steroid dose was rapidly decreased, his circulation became unstable; thus, the steroid dose was gradually tapered under the suspicion of adrenal insufficiency. A blood test revealed that his ACTH level was 5 pg/mL and his cortisol level was 7.0 μg/dL under unstable circulation; thus, adrenal insufficiency was confirmed. Due to liver cirrhosis, blood tests for hepatitis B, hepatitis C, and autoimmune antibodies were conducted; however, all

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were negative. His M2BPGI: Mac-2 binding protein (M2BP) value was 2+, his NAFLD fibrosis score was 2.0 points, and his FIB-4 index was 9.45, all of which were compatible with liver cirrhosis [6–8]. The patient's body mass index was 28, and he had history of obesity, DM, and long-term steroid use. However, abdominal CT did not show fatty liver because the density of the liver and spleen were similar. Accordingly, he was diagnosed with burn-out NASH [9]. On day 6, he had ascites, was newly observed on abdominal CT; however, there were no fresh ischemic lesions, and the pituitary gland had a normal appearance on cerebral magnetic resonance imaging. His initial neurological deficits were judged to be due to transient ischemic attack or Todd's paralysis. Regarding hypogonadism, his testosterone level was low but his estradiol level was high; thus, it was judged that hypogonadism was induced by NASH rather than hypothalamic obesity [4]. On day 7, he could feed himself but required assistance for transfer due to severe lower extremity muscle weakness due to disuse or critical illness myopathy. On day 15, his respiratory function temporally deteriorated, and enhanced CT showed thrombosis in the right pulmonary artery and right common iliac vein; thus he underwent heparinization. Blood tests revealed that his renal function had returned to the normal range and his rhabdomyolysis had resolved; however, liver dysfunction, coagulopathy, and anemia remained. On day 18, he had left leg phlegmon, which was treated by antibiotics. On day 27, esophagogastroscopy showed only atrophic gastritis. He was transferred to another hospital for rehabilitation on day 34 after the improvement of phlegmon.

Discussion

In the present case, long-term steroid use for asthma and nephrotic syndrome resulted in the development of DM, adrenal insufficiency, immune suppression, and burn-out NASH complicated by hypogonadism, sepsis with multiple organ failure, pulmonary embolism, gait disturbance due to disuse or critical illness myopathy, and leg phlegmon. To the best of our knowledge, this was the first report describing the development of burn-out NASH under long-term steroid use.

NAFLD is traditionally categorized as primary or secondary depending on the underlying etiology [10]. Primary NAFLD is closely associated with insulin resistance and metabolic syndrome. Currently, the term secondary NAFLD is discouraged, and the preferred nomenclature includes the known causative factor and the resultant pathology (e.g., total parenteral nutrition-induced, drug-induced steatosis/steatohepatitis). Drug-induced fatty liver disease is a relatively rare entity that is identified when steatohepatitis appears to result from a direct toxic effect of a drug on the liver [11]. It is most commonly associated with the prolonged intake of the offending medication. Approximately 2% of fatty liver disease cases are estimated to be drug induced; thus, fatty liver is a rare manifestation of drug toxicity [11]. Drug-induced fatty liver is strongly associated with the duration and dose of the medication. Some drugs induce an acute energy crisis by interrupting adenosine triphosphate synthesis by mitochondria, resulting in microvesicular steatosis [11]. Drugs can cause both microvesicular and macrovesicular steatosis, but it usually begins acutely with microvesicular lesions [12]. The major causative drugs of NAFLD and NASH include amiodarone, aspirin, ibuprofen, azidothymidine, nucleoside reverse transcriptase inhibitor, protease inhibitors, valproic acid, carbamazepine, perhexiline maleate, diethylaminoethoxyhexestrol, tamoxifen, methotrexate, 5-fluorouracil, irinotecan, and glucocorticoids [11].

In humans, glucocorticoids are widely prescribed for a variety of medical conditions. However, pharmacovigilance studies have shown their use to be associated with an adverse metabolic profile including NAFLD, obesity, hypertension, insulin resistance, proximal myopathy, an increased fracture risk, skin thinning, and bruising [13]. Biochemically, glucocorticoids

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drive the availability of glucose as a substrate for de novo lipogenesis by stimulating gluconeogenesis in the liver and promoting glycogenolysis [13]. Glucocorticoids were found to promote insulin-induced lipogenesis in rat hepatocytes. In hepatocytes, glucocorticoids are a potent regulator of key genes that drive lipogenesis including fatty acid synthase (FASN) and acetyl-CoA carboxylases 1 and 2, stimulating de novo lipogenesis and free fatty acid utilization and promoting hepatic steatosis. Glucocorticoid also regulates cholesterol and fatty acid synthesis and high-density lipoprotein processing in hepatocytes, which can significantly contribute to lipid accumulation and reduced very low-density lipoprotein secretion [13]. Rodents treated with corticosterone develop hepatic steatosis [13]. In combination with a high-fat diet, excess glucocorticoid was associated with increased fibrosis, although interestingly, the inflammatory response was relatively suppressed [14]. Clinically, patients with excess glucocorticoid (Cushing's syndrome) develop hepatic steatosis as well as obesity and insulin resistance in a significant proportion of cases [15]. In the present case, in addition to obesity and steroid-induced DM, long-term steroid use might have contributed to the development of NASH.

The first limitation of the present case was the focus on steroid use as a causative factor of NASH, given that the main pathophysiology of NASH is complex and includes multiple parallel hits in addition to multiple genome-wide associations. The second limitation was that it lacked a histological analysis of the liver, which is the gold standard for the diagnosis of NAFLD/NASH. As the present case showed the possibility that long-term steroid may be associated with the development of NASH, the accumulation and analysis of further cases is required to confirm whether or not long-term steroid use is associated with the development of NASH.

Statement of Ethics

This study protocol was reviewed and approved by Juntendo Shizuoka Hospital Review Board, approval number [298]. Written informed consent was obtained from the patient for publication of the details of his medical case and any accompanying images.

Conflict of Interest Statement

We have no conflicts of interest to declare.

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Author Contributions

Soichiro Ota, Michika Hamada, Ken-ichi Muramatsu, Ikuto Takeuchi, and Youichi Yanagawa collected data; Soichiro Ota drafted the manuscript; Michika Hamada, Ken-ichi Muramatsu, Ikuto Takeuchi, and Youichi Yanagawa aided in interpreting the results and worked on the

manuscript. Soichiro Ota, Michika Hamada, Ken-ichi Muramatsu, Ikuto Takeuchi, and Youichi Yanagawa discussed the results and commented on the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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