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【 CASE REPORT 】

The Efficacy of Corticosteroid Therapy in a Patient with Non-alcoholic Steatohepatitis Overlapping Autoimmune Hepatitis

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Abstract:
The overlap of multiple liver diseases can cause the disease activity and severity to worsen rapidly in some cases. We rarely see patients with non-alcoholic steatohepatitis (NASH) with overlapping autoimmune hepatitis (AIH). A 64-year-old woman who had been prescribed oral drugs to treat diabetes and hypertension (metformin 500 mg/day and voglibose 0.9 mg/day, and termisartan 40 mg/day and amlodipine 5 mg/day, respectively) was diagnosed with NASH with histological confirmation. At 68 years of age, her liver injury worsened with an IgG of 2,871 mg/dL and a high serum anti-nuclear antibody (ANA) level of 2,560. We repeated the liver biopsy, which revealed NASH and mild interface hepatitis with some lobular focal necrosis consisting of overlapping AIH. Therefore, she was treated with 30 mg of prednisolone daily. The treatment led to an improvement in her IgG levels and ANA in the serum and an improvement in the histology results.

Key words: non-alcoholic steatohepatitis, autoimmune hepatitis, overlap

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Introduction

The increasing prevalence of non-alcoholic steatohepatitis (NASH), a progressive form of nonalcoholic fatty liver disease (NAFLD), has recently become a major health concern worldwide (1). NAFLD/NASH is closely related to metabolic disorders such as hyperinsulinemia, diabetes, dyslipidemia, visceral adiposity, and hypertension, which are considered the hepatic phenotype of metabolic syndrome, with increased risks of morbidity and mortality related to cardiovascular diseases (2-4).

Chronic liver diseases are sometimes complicated with other liver diseases, such as hepatitis C overlapping NAFLD/NASH, which involves a more aggressive inflammatory condition and progressive stage (5). In addition, NAFLD/NASH can overlap autoimmune hepatitis (AIH) (6), and this has a reported worldwide prevalence of 1.8-3.6% (7) and a prevalence of 1.9% in Japan (8).

Anti-nuclear antibodies (ANAs), an essential diagnostic criterion for AIH, are positive in 20-33% of patients with NAFLD/NASH (7, 9). Consequently, ANA-positive women with NASH are sometimes misdiagnosed with AIH. Therefore, histological confirmation with a liver biopsy is critical for a definitive diagnosis of NASH overlapping AIH (10, 11). There are few reports on the role of a liver biopsy in developing a treatment strategy for NASH overlapping AIH. We herein report a case in which the histological confirmation of AIH led to remission with appropriate corticosteroid therapy in a deteriorating patient with NASH

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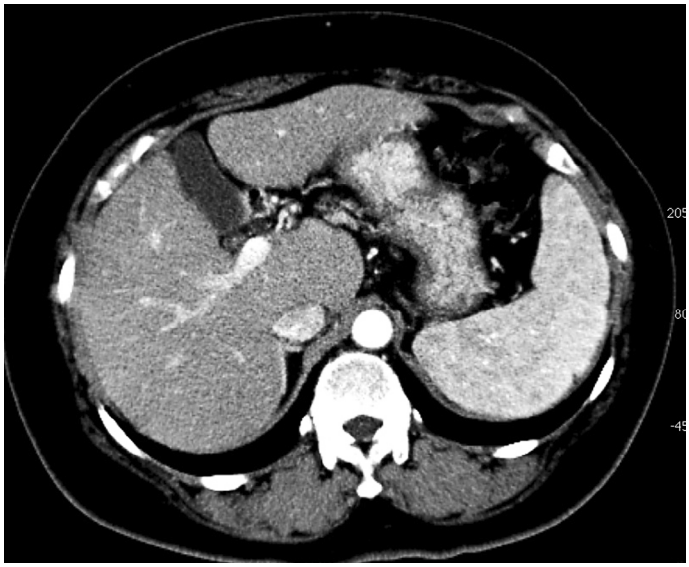

Figure 1. **Abdominal CT showing liver deformity and splenomegaly, indicating advanced chronic liver disease. No hepatocellular carcinoma or ascites was evident.**

Table 1. **Laboratory Data at the First Time of Liver Biopsy.**

WBC	6.9×10^3 /mm^3	T-Bil	0.5 mg/dL	IgG	1,608 mg/dL
Neu	55 %	D-Bil	0.3 mg/dL	IgA	479 mg/dL
Eos	6.0 %	ALP	428 IU/L	IgM	182 mg/dL
Baso	0 %	γ-GTP	68 IU/L	HA	92.4 ng/mL
Lym	34 %	AST	43 IU/L	AFP	4.3 ng/mL
Mono	5.0 %	ALT	32 IU/L	ANA	×40
RBC	4.1×10^6 /mm^3	LDH	227 IU/L	Anti-M2 Ab	(-)
Hb	12.1 g/dL	ZTT	12.1 U	HBs-Ag	(-)
Ht	37.1 %	TTT	7.3 U	HBs-Ab	(-)
Plt	12.4×10^4 /mm^3	TP	7.9 g/dL	HCV-Ab	(-)
PT-INR	1.13	Alb	4.2 g/dL	FBS	135 mg/dL
BUN	17.5 mg/dL	T-chol	191 mg/dL	HbA1c	6.0 %
Cre	0.63 mg/dL	HDL-C	50 mg/dL		
		LDL-C	112 mg/dL		
		TG	145 mg/dL		
		UA	4.8 mg/dL		

HA: hyaluronic acid, Ab: anti-body, ANA: anti-nuclear antibody, FBS: fasting blood sugar, TG: triglyceride, UA: Uric acid

overlapping AIH.

Case Report

A 64-year-old woman (height: 156 cm, body weight: 61.0 kg, body mass index: 25.1 kg/m^2), who had been taking oral drugs to treat type 2 diabetes and hypertension, was diagnosed with liver injury based on blood tests. She had no other remarkable medical history, and there was no evidence of endocrine disease. She had no history of any digestive or gynecological surgeries. There was also no drinking history. Abdominal ultrasonography and computed tomography (CT) revealed fatty changes and the appearance of chronic liver disease with splenomegaly, but no ascites (Fig. 1). Various viral hepatitis markers, ANA, and anti-mitochondrial antibody were negative, and the serum immunoglobulin fraction was normal (Table 1). The liver biopsy showed mild interface hepatitis in the mild inflamed portal tracts in addition to steatohepatitis, including moderate steatosis (20%), some focal necrosis (Fig. 2a), perivenular/pericellular fibrosis (Fig. 2b), ballooning hepatocytes (Fig. 2c), and Mallory-Denk bodies (Fig. 2d). She was classified as Matteoni classification type 4 and Brunt classification grade 1 stage 4. Her NAFLD activity score (NAS) was 4 (steatosis 1; lobular inflammation 1; and hepatocyte ballooning 2). Her international AIH score increased to 18 points.

Consequently, the patient was diagnosed with advanced chronic liver disease caused by mainly NASH. Her treatment involved improved control of her diabetes and lifestyle follow-up.

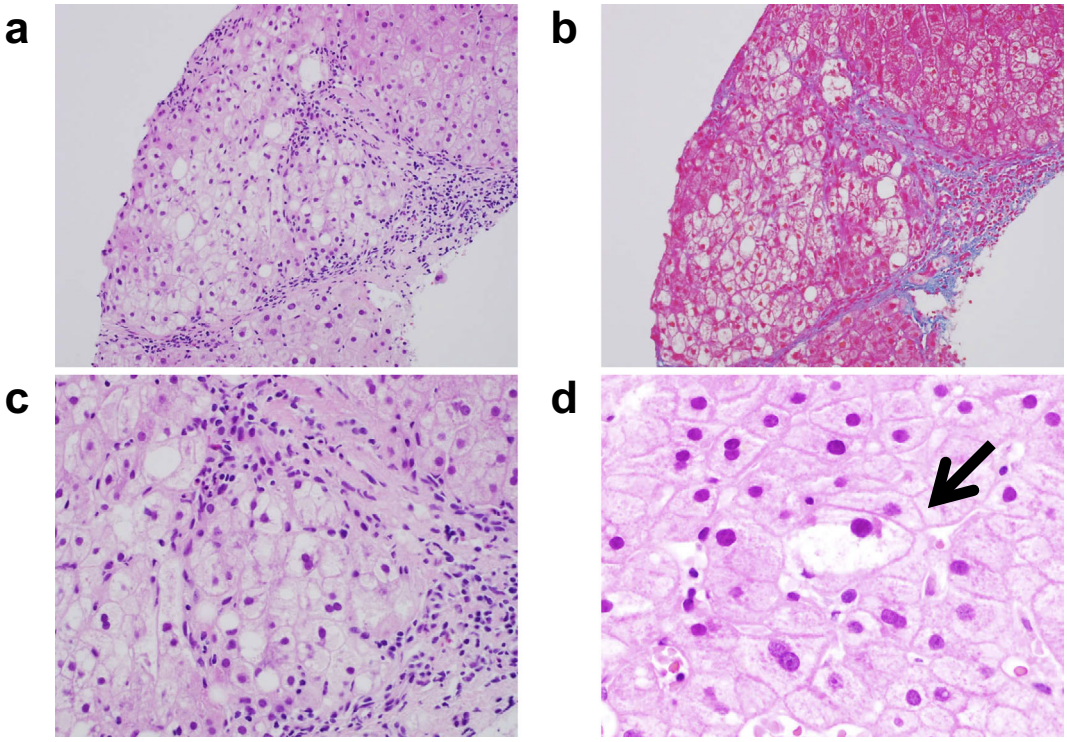

Figure 2. **Liver pathology at the time of the initial diagnosis (a). Hematoxylin and Eosin (H&E) staining shows mild interface hepatitis in the portal area. Focal necrosis of hepatocytes and steatosis are observed (b). Azan staining shows perivenular and pericellular fibrosis forming bridging (c). H&E staining shows ballooning hepatocytes and Mallory-Denk bodies (d).**

Table 2. **Laboratory Data at the Second Time of Liver Biopsy.**

WBC	4.0×10³ /mm³	T-Bil	1.0 mg/dL	IgG	2,871 mg/dL
Neu	59.1 %	D-Bil	0.5 mg/dL	IgA	524 mg/dL
Eos	3.5 %	ALP	302 IU/L	IgM	135 mg/dL
Baso	0.5 %	γ-GTP	99 IU/L	HA	735 ng/mL
Lym	28.8 %	AST	114 IU/L	AFP	6.8 ng/mL
Mono	8.1 %	ALT	58 IU/L	ANA	×>2,560 speckled pattern
RBC	4.0×10⁶ /mm³	LDH	270 IU/L		
Hb	12.2 g/dL	ZTT	16.0 U	Anti-M2 Ab	(-)
Ht	35.3 %	TTT	23.0 U	HBs-Ag	(-)
Plt	8.5×10⁴ /mm³	TP	7.8 g/dL	HBs-Ab	(-)
PT-INR	1.17	Alb	3.9 g/dL	HCV-Ab	(-)
BUN	16.1 mg/dL	T-Chol	125 mg/dL	FBS	111 mg/dL
Cre	0.64 mg/dL	HDL-C	50 mg/dL	HbA1c	5.9 %
		LDL-C	32 mg/dL		
		TG	114 mg/dL		
		UA	6.4 mg/dL		
		Ferritin	86.8 ng/dL		

HA: hyaluronic acid, Ab: anti-body, ANA: anti-nuclear antibody, FBS: fasting blood sugar, TG: triglyceride, UA: Uric acid

After about 4 years on this therapy, her liver function test results again worsened with an IgG of 2,871 mg/dL and a serum ANA titer of over 2,560 times the normal amount (Table 2). We repeated the liver biopsy, which revealed steatosis with moderate perivenular/pericellular fibrosis forming bridging (Fig. 3a, b), mild interface hepatitis (Fig. 3c) in the moderately inflamed portal tracts with several plasma cells (Fig. 3d), and hepatic rosettes (Fig. 3e) [Matteoni classification type 4; Brunt classification grade 2, stage 4; and NAS score of 4 (steatosis 1; lobular inflammation 1; and hepatocyte ballooning 2)]. Her international AIH score increased to 20 points. Since she was diagnosed with NASH overlapping AIH, oral corticosteroid therapy was initiated at 30 mg of prednisolone daily.

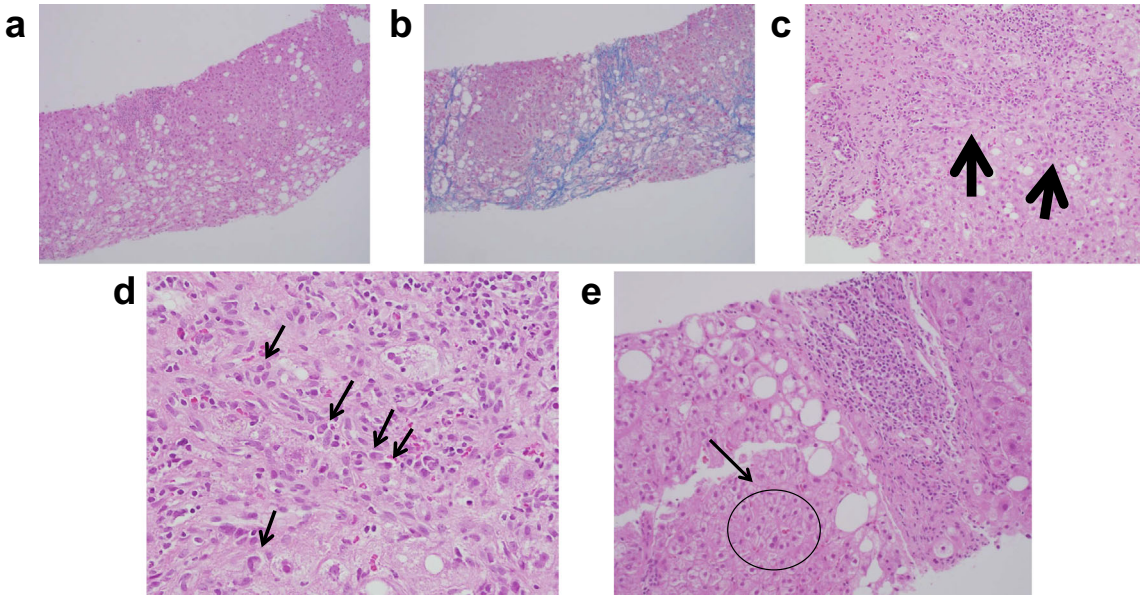

Figure 3. **Liver pathology showing worsening of AIH-like disease activity. Hematoxylin and Eosin (H&E) staining shows steatohepatitis with moderate focal necrosis of hepatocytes (a). Azan staining shows moderate perivenular and pericellular fibrosis forming bridging (b). H&E staining shows moderate portal inflammation with mild interface hepatitis (c) and several plasma cells (d). The arrow indicates hepatic rosettes (e). AIH: autoimmune hepatitis**

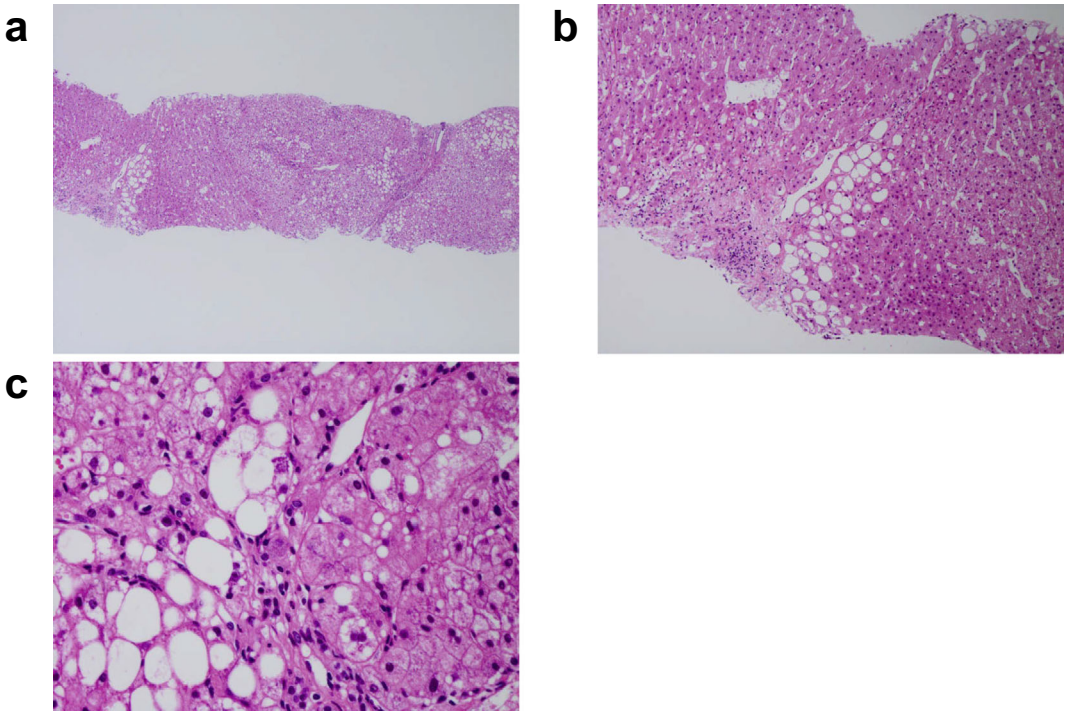

Figure 4. **Liver histology after steroid therapy. Hematoxylin and Eosin (H&E) staining shows an improvement in portal inflammation and interface hepatitis and the absence of plasma cell infiltration and hepatic rosettes (a, b). H&E staining shows that steatosis with ballooning hepatocytes is still present (c).**

Although the IgG level and ANA titer decreased, the liver function test results did not improve. Furthermore, we observed increases in her body weight and HbA1c level. We postulated that the NASH disease activity had worsened, while the AIH had improved. This was confirmed histologically with a liver biopsy after six months of corticosteroid therapy. The histology results showed an improvement in interface hepatitis and portal inflammation with several plasma

cells, but steatosis was still observed (Fig. 4) [Matteoni classification type 4; Brunt classification grade 2, stage 4; and NAS score of 5 (steatosis 1; lobular inflammation 2; and hepatocyte ballooning 2)]. The CT results did not show a change in the extent of her fatty liver, although her liver fibrosis had progressed (Fig. 5). Her international AIH score decreased to 15 points. Therefore, we focused on improving the control of her diabetes with insulin therapy (Insulin lispro 16 Units, 16 Units, 16 Units) and lifestyle changes. These treatments led to not only an improvement in her diabetes and body weight but also an improvement in her liver function test results (Fig. 6).

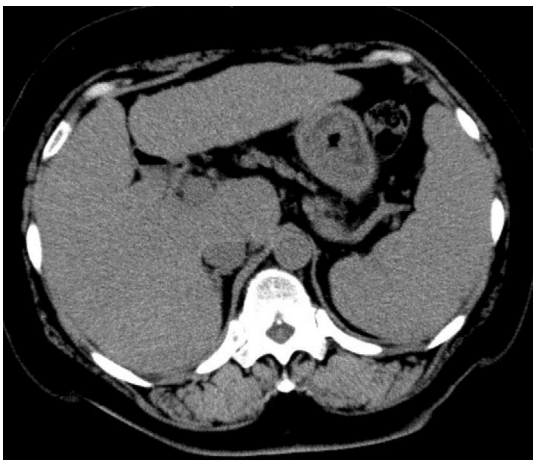

Figure 5. Abdominal plain CT shows no changes in the extent of fatty liver, although her liver fibrosis progressed.

Discussion

We reported a patient with NASH overlapping AIH with corticosteroid therapy, which led to improved focal necrosis and interface hepatitis confirmed histologically with an improvement in the serum IgG level and ANA titer, but the development of steatosis as the NASH worsened.

Although NASH occasionally overlaps AIH, it is difficult to diagnose the presence of overlapping AIH because the serum ANA titer is sometimes positive in NASH patients. It is very important to diagnose AIH because steroid therapy, which is the first-line therapy for AIH, often exacerbates NASH due to worsening of fatty liver and diabetes, as in our case. Although no criteria have been established for diagnosing NASH overlapping AIH, coexisting AIH has distinct histological features, such as interface hepatitis and rosette formation, in addition to the histological features of NASH (12). Our patient had more marked interface hepatitis in the portal area than is typical in NASH patients, with elevated serum IgG levels and ANA titer. The serum IgG concentration has been recognized as an essential marker for diagnosing and treating AIH. The improvement in the serum IgG concentration, interface hepatitis, and portal inflammation confirmed the presence of NASH overlapping AIH in our case. However, we can minimize the steroid-induced worsening of NASH by controlling patients' body weight and metabolic abnormalities, such as diabetes, that often coexist with NASH (13). If the NASH is not under control because of steroid therapy, azathioprine or ursodeoxycholic

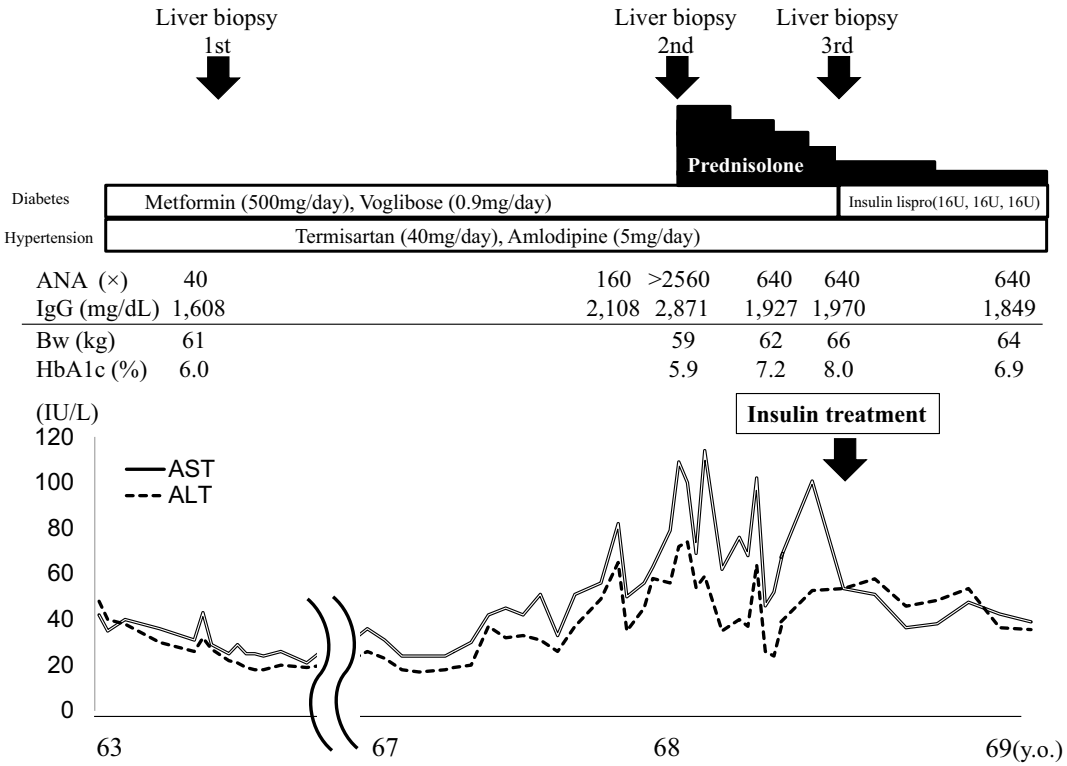

Figure 6. Summary of the clinical course.

acid is recommended to control NASH overlapping AIH (8).

The liver is a central immune organ with high exposure to circulating antigens and endotoxins via the gut microbiota. It contains many innate immune cells, such as macrophages and innate lymphoid cells (14), and Toll-like receptor signaling or inflammasome activation initiates inflammatory responses in the liver. Innate immune activation plays a crucial role in triggering and the progression of hepatic inflammation, injury, and fibrosis in NASH (15, 16), as in AIH (17). Therefore, further studies are needed to clarify the common points and differences in the host immune response in NASH overlapping AIH in order to establish a treatment strategy and elucidate the disease state.

In conclusion, histological confirmation is useful for determining the disease status and selecting a therapeutic strategy in patients with NASH overlapping with AIH. Steroid therapy is necessary to treat the condition when the presence of focal necrosis is confirmed through a liver biopsy. However, we must be careful, as steroid therapy can worsen NASH.

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

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