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Single Case

5-Aminosalicylic Acid-Induced Liver Injury in a Patient with Ulcerative Colitis: A Case Report

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Keywords

5-Aminosalicylic acid · Drug-induced liver injury · Ulcerative colitis · Liver biopsy · Interface hepatitis

Abstract

Introduction: Drug-induced liver injury (DILI) associated with 5-aminosalicylic acid (5-ASA) is a rare but potentially life-threatening adverse event. ***Case Presentation:*** We report the case of a 58-year-old woman with ulcerative colitis who developed DILI after initiating maintenance therapy with the multimatrix system 5-ASA. The patient presented with grade 4 liver enzyme elevation on day 98 after initiating 5-ASA and was admitted to the hospital. Blood tests revealed the mixed liver injury, and imaging studies showed no abnormalities except for mild lymph node enlargement. Liver biopsy revealed acute lobular hepatitis with interfacial activity. The patient's score on the International Autoimmune Hepatitis Group 1999 revised scoring system was a total score of 10, causing a suspicion for the diagnosis of autoimmune hepatitis. The DDW-J 2004 scale calculated a total score of six, indicating a high probability of DILI. We suspected DILI due to 5-ASA, and the 5-ASA formulations were discontinued. The patient was treated with ursodeoxycholic acid and neominophagen C, and her liver function gradually improved without steroid treatment. Finally, we definitively diagnosed DILI based on the pathological findings and clinical course after discontinuation of 5-ASA. ***Conclusion:*** This case highlights the importance of monitoring liver function in patients receiving 5-ASA therapy.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that can be present in variable degrees and can be present from the rectum to the proximal region in a continuous manner. The primary goal of treatment is to induce and maintain remission to prevent disease-related complications. 5-aminosalicylic acid (5-ASA), also known as mesalazine, is commonly used to treat UC. 5-ASA is a first-line treatment for mild to moderate UC and is generally considered a safe drug with few side effects. A systematic review showed that 5-ASA is relatively safe for treating patients with UC [1]. However, the incidence of adverse events (AEs) associated with 5-ASA use of patients with UC has been reported to range from 7% to 14% [2–4]. In our retrospective study, AE associated with 5-ASA use was observed in 12% (35/288) of patients [5]. The most common clinical phenotype was systemic lupus erythematosus-like clinical features [6], comprising 56% of cases, including symptoms such as polyarthritis, hair loss, neutropenia, and serositis. Blood test abnormalities were the second most prevalent phenotype (26%), manifesting as acute pancreatitis, interstitial nephritis [7], and hepatitis, as diagnosed by blood test abnormalities [8]. The third phenotype, accounting for 15% of cases, mimicked IBD exacerbation (15%) and presented with high fever, worsening diarrhea, abdominal pain, and bloody stools. Because of the wide range of clinical manifestations of these AEs of 5-ASA, they have not yet been established. Therefore, they are referred to by various names, such as mesalazine allergy [9], mesalazine-induced lupus [6, 10], 5-ASA intolerance [11, 12], or side effects.

Among AEs associated with 5-ASA, the mechanism by which 5-ASA causes liver injury is not completely understood. The liver injury caused by 5-ASA is usually mild and reversible but sometimes leads to severe disease. To date, there have been few reports on drug-induced liver injury (DILI) caused by 5-ASA and its underlying mechanisms. Herein, we report the case of a patient with UC who was treated with 5-ASA with a multimatrix system at a dose of 2,400 mg/body and developed DILI.

Case Report

A 58-year-old woman was diagnosed with proctitis due to UC and was referred to our department in December 2021. After induction therapy with topical budesonide for 5 months, she started additional maintenance therapy with 5-ASA, which is an multimatrix system, and due to a sufficient response, it was given at a daily dosage of 2,400 mg in May 2022. On day 35, following the commencement of the tablets, the patient developed Common Terminology Criteria for Adverse Events (CTCAE) [13] grade 2 neutropenia, which was closely monitored. Despite close monitoring, on day 98, the patient developed CTCAE grade 4 liver enzyme elevation. The patient was then hospitalized for further examination and treatment.

Physical examination did not reveal any abnormalities, and the liver and spleen were not palpable. Blood test results indicated grade 2 leukopenia without progression; however, mixed-type liver damage was diagnosed based on an AST 1,064 U/L, ALT 1,293 U/L, gamma GTP 567 U/L, and ALP 269 U/L. The patient tested negative for hepatitis A immunoglobulin M, hepatitis B surface antigen, hepatitis C virus (HCV) antibody, herpes simplex virus (HSV) immunoglobulin M, antinuclear, anti-LKM-1, and anti-mitochondrial M2 antibodies and had a history of cytomegalovirus and Epstein-Barr virus infection. Thyroid function was normal (Table 1). There was no family history of liver disease, alcohol abuse, or international travel. Computed tomography did not reveal any abnormalities in the biliary system or pancreas, and no gallstones were found (Fig. 1). Abdominal ultrasonography revealed a sharp hepatic margin, smooth surface, and normal internal echo without fatty liver changes. However, there

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Table 1. Laboratory data on admission

Complete blood count		
WBC	2,600	/μL
Neut	63.8	%
Eosi	0.4	%
Baso	0.4	%
Mono	8.1	%
Lymph	27.3	%
RBC	471 × 10^4	/μL
Hemoglobin	13.8	g/dL
Hematocrit	42.8	%
MCV	90.9	fL
MCH	29.3	pg
MCHC	32.2	g/dL
Platelets	22.3 × 10^4	/μL
ESR (1 h)	14	mm
ESR (2 h)	37	mm
Coagulation		
Prothrombin time-INR	0.85	
APTT	26	sec
D-dimer	<0.5	μg/mL
Viral markers		
Anti-HBs-Ag	<0.05	IU/mL
Anti-HBs-Ab	2.0	IU/L
Anti-HBcAb	0.3	COI
Anti-Hbe-Ag	0.1	COI
Anti-HCVAb	0.0	COI
Anti-HA-IgM	<0.40	S/CO
Anti-HSV-gM	0.13	
Anti-HSV-IgG	<2.0	
Anti-CMV-IgM	<0.10	
Anti-CMV IgG	≥250	AU/mL
Anti-EBV IgM	<10	
Anti-EBV IgG	320	
Anti-EBV nuclear Ag	40	
Blood chemistry		
AST	1064	U/L
ALT	1293	U/L
LDH	413	U/L
γGTP	567	U/L
ALP	269	U/L

(Continued on following page)

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Table 1 (continued)

Total protein	7.5	g/dL
Albumin	4.0	g/dL
Creatinine kinase	195	U/L
Total amylase	86	U/L
Total bilirubin	1.15	mg/dL
Direct bilirubin	0.72	mg/dL
BUN	12	mg/dL
Creatinine	0.62	mg/dL
Uric acid	4.3	mg/dL
Na	144	mEq/L
K	3.7	mEq/L
Cl	106	mEq/L
Ca	9.2	mg/dL
Fasting glucose	94	mg/dL
C-reactive protein	0.62	mg/dL
IgG	1857	mg/dL
IgA	211	mg/dL
IgM	76	mg/dL
Hormones		
TSH	2.98	μIU/mL
Free T4	1.38	ng/dL
Autoantibodies		
Anti-nuclear-Ab	40	
Anti-LKM--Ab	5	
Anti-mitochondrial M2-Ab	<1.5	

WBC, white blood cells; RBC, red blood cells; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; APTT, activated partial thromboplastin time; HBs, hepatitis B surface; Ag, antigen; Ab, antibody; HBc, hepatitis B core; HBe, hepatitis B envelope; CMV, cytomegalovirus; EBV, Epstein-Barr virus; Ig, immunoglobulin; TSH, thyroid stimulating hormone; LKM, liver kidney microsomal; HCV, hepatitis C virus; HSV, herpes simplex virus.

was slight swelling of the lymph nodes in the porta hepatis. However, mild liver stiffness presented on two-dimensional shear wave elastography (1.53 m/s, compatible with fibrosis score 2). The patient did not take any medication other than 5-ASA. Based on these findings and the consideration that she took no other oral medications other than 5-ASA, we suspected that she had DILI due to the 5-ASA, and the 5-ASA formulations and topical budesonide were discontinued. However, liver injury did not improve significantly. A liver biopsy performed on day 7 of hospitalization showed scattered small necrotic foci as well as a considerable number of Councilman's bodies in the lobule and interface activity with modest inflammatory infiltration, suggesting liver injury with an acute hepatitis pattern. The inflammatory infiltrates in the portal area were primarily composed of lymphocytes, although few plasma cells were

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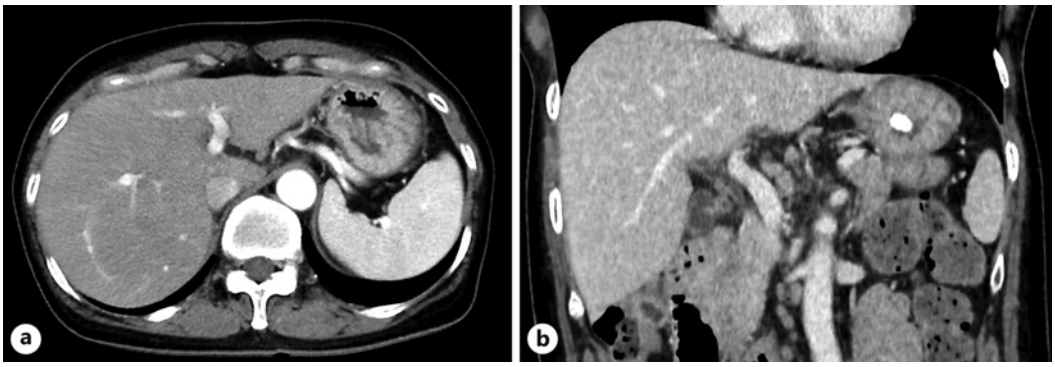

Fig. 1. Computed tomography did not reveal any abnormalities, hepatomegaly, or splenomegaly. No abnormalities in the hepatobiliary system were observed (**a**: horizontal view, **b**: coronal view).

observed (Fig. 2). The International Autoimmune Hepatitis Group (IAIHG) 1999 revised scoring system [14] calculated a total score of 10, causing a suspicion of AIH but not for a definitive diagnosis of AIH. A total score of 6 was calculated on the DDW-J 2004 scale [15], indicating a high probability of DILI. We initiated treatment with ursodeoxycholic acid at a daily dosage of 300 mg and subsequently increased it to 600 mg/day, and this was given together with a stronger neominophagen C at a daily dosage of 40 mL. Eventually, the patient's liver function improved without steroid therapy. After 24 days of hospitalization, the patient was discharged (AST, 49 U/L; ALT, 105 U/L; gamma GTP, 199 U/L; and ALP, 134 U/L). Finally, we made a definitive diagnosis of DILI due to the 5-ASA formulations based on the clinical course and liver biopsy results (Fig. 3).

On the eleventh day after discharge from the hospital, the patient's liver function tests showed improvement with AST levels of 21 U/L and ALT levels of 27 U/L. In addition, the white blood cell count improved to 5,400/μL. Since then, there has been no evidence of liver injury recurrence. However, despite restarting treatment with topical budesonide 11 days after discharge from the hospital, the patient's UC symptoms remained incomplete, with moderate symptoms persisting, as evidenced by a full Mayo score of approximately 6 points. Colonoscopy revealed rectal erosions. Consequently, vedolizumab was initiated 3 months after discharge, and the patient is currently being followed-up on an outpatient basis. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536097).

Discussion

DILI is a liver injury caused by drugs and other chemical compounds. Symptoms can range from elevated liver enzyme levels and inflammation to liver cell damage or death. DILI can be acute or chronic and can range in severity. DILI accounts for 10% of all hepatitis cases and is the leading cause of acute liver failure in the USA [16]. Recent studies have shown that certain drugs are associated with DILI [17]. 5-ASA is generally considered a safe drug with few side effects. The estimated annual incidence rate of DILI associated with 5-ASA is rare, reported to be 3.2 cases per million prescriptions [18]. However, the incidence of DILI related to 5-ASA formulations is reported to be relatively low at 0.3–1.0%, accounting for 3.2–11.1% of all 5-ASA AEs [5, 12, 19, 20] and may be underestimated.

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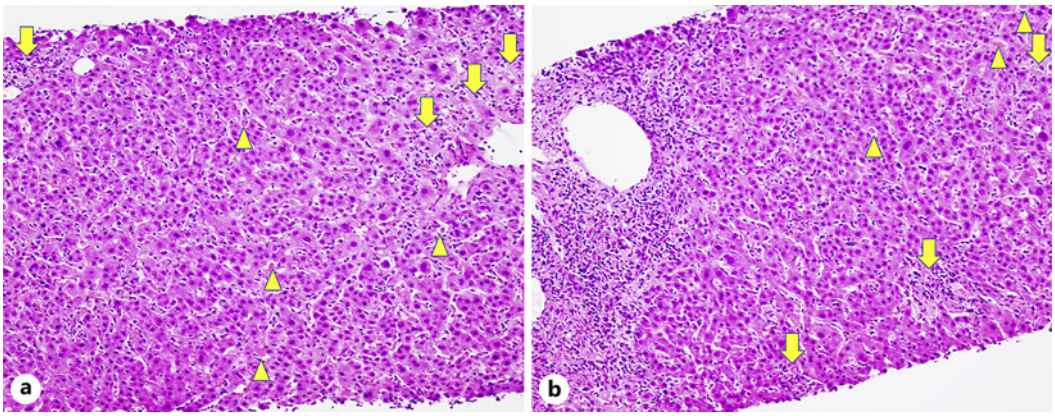

Fig. 2. Histology of the biopsy specimen. **a** The central vein in the upper right of the image is surrounded by a rim of loose connective tissue with loss of hepatocytes (arrows). Scattered Coundilman's bodies (arrowheads) are observed in the lobule. **b** Interface activity by lymphocytic infiltrates in the portal area. A few eosinophils, as well as lymphocytes, are also observed in the necrotic foci in the lobule (arrows).

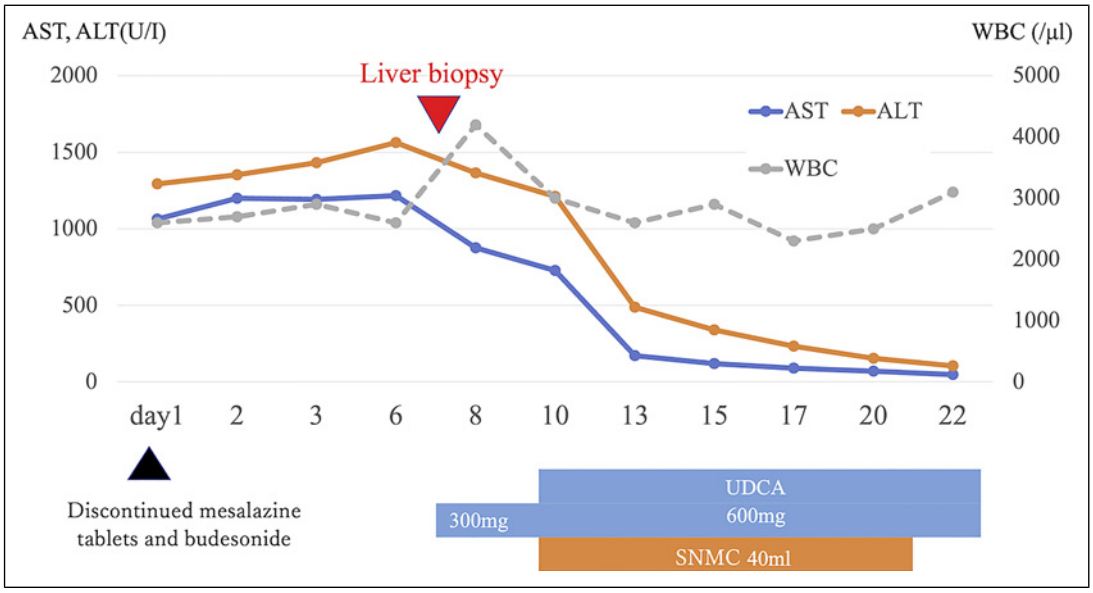

Fig. 3. Clinical course.

A recent review by Hoofnagle et al. [21] classified DILI as either direct or idiosyncratic, with a new classification of indirect injury as a third type. Direct DILI is caused by toxic agents and is predictable, dose dependent, and reproducible in animal studies. Idiosyncratic DILI is unpredictable and not reproducible in animal studies and is divided into allergic and metabolic types. Idiosyncratic DILI causes the majority of DILI cases. The clinical phenotype is categorized as hepatocellular, cholestatic, or mixed type using the R ratio, calculated by dividing the alanine aminotransferase level by the alkaline phosphatase level from the initial presentation [22]. The present case was classified as metabolic idiosyncratic DILI with mixed types according to the R-ratio. Indirect DILI is

Table 2. Case reports regarding DILI associated with 5-ASA

Reports	Year	Age	Sex	Disease	Mechanism of DILI type	5-ASA dose	Onset time after initiation of 5-ASA	CTCAE Grade	Treatment
Hautekeete et al. [26]	1992	21	F	Crohn disease	Idiosyncratic, allergic	800 mg/day	1 week	4	Withdrawal of 5-ASA, PSL40 mg/day
Braun et al. [27]	1999	42	F	UC	Idiosyncratic, metabolic	2,400 mg/day	2 weeks	3	Withdrawal of 5-ASA
Garrido et al. [28]	2021	51	F	UC	Idiosyncratic metabolic	3,000 mg/day	2 weeks	4	Withdrawal of 5-ASA
Stelzer, et al. [29]	2015	51	M	UC	Idiosyncratic metabolic	4,000 mg/day	2 months	3	Withdrawal of 5-ASA, PSL 40 mg/day
Our case	2022	58	F	UC	Idiosyncratic metabolic	2,400 mg/day	3 months	4	Withdrawal of 5-ASA, UDCA, SNMC
Stoschus et al. [30]	1997	30	M	Crohn disease	Idiosyncratic metabolic	4,000 mg/day	4 months	3	Withdrawal of 5-ASA
Ter Avest et al. [31]	2021	56	M	Crohn disease	Idiosyncratic metabolic	4,000 mg/day	5 months	4	Withdrawal of 5-ASA
Deltenre et al. [32]	1999	65	M	Suspected CD	Idiosyncratic metabolic	3,000 mg/day	8 months	3	Withdrawal of 5-ASA

5-ASA, 5-aminosalicylic acid; DILI, drug-induced liver injury; CTCAE, Common Toxicity Criteria for adverse event; M, male; F, female; UDCA, ursodeoxycholic acid; CD, Crohn's disease.

caused by the toxic or idiosyncratic properties of a drug and can lead to new liver conditions or the worsening of existing conditions. Examples of indirect DILI include drug-induced fatty liver disease, reactivation of the hepatitis B virus [23, 24], and liver injury caused by immune checkpoint inhibitors [25].

In our literature review in January 2023, we searched PubMed for case reports of liver dysfunction, hepatotoxicity, or liver injury caused by the use of 5-ASA or mesalazine. As a result, we excluded cases not associated with 5-ASA-induced liver injury and found 7 case reports with an onset time that was after the initiation of 5-ASA (Table 2 [26–32]). Given the frequency of liver injury caused by 5-ASA preparations, the number of reports was small, suggesting potential publication bias. Therefore, the pathogenesis and timing of 5-ASA-induced liver injury are not yet well understood. After evaluating eight case reports, including our case, one case was due to idiosyncratic DILI (allergic type), and the other cases were due to idiosyncratic DILI (metabolic type). Our review revealed that the timing of the onset of 5-ASA-related DILI varied widely, with some cases occurring as early as 1 week and others occurring as late as 8 months. The wide distribution of symptom onset and the rare incidence suggest that the occurrence of liver injury caused by 5-ASA is difficult to predict and that regular monitoring of liver function is necessary for patients taking this medication. The monitoring methods and intervals will be discussed in the

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future due to the cost-benefit issues, but it is important to recognize that a serious liver injury can occur when 5-ASA is prescribed, as in this case, although this is a rare occurrence.

Recently, we classified patients with 5-ASA-related AEs into four subgroups based on the most dominant adverse drug reactions: (1) lupus-like symptoms, (2) blood test abnormalities, (3) mimicking IBD exacerbations, and (4) others. Drug-induced liver injuries caused by 5-ASA are typically classified as blood test abnormalities, with a median onset of 55 days (approximately 2 months) [5]. However, this literature review suggests that, in liver dysfunction caused by 5-ASA, it may be challenging to identify the mechanism of DILI through simple blood tests, as liver dysfunction caused by 5-ASA can present in various ways, including mimicking IBD exacerbations or lupus-like symptoms. In conclusion, although mesalamine remains a safe and effective treatment, when prescribing 5-ASA, it is essential to be aware of the potential for liver injury and to monitor patients carefully for signs of liver damage as well as other IBD drugs.

Statement of Ethics

The patient's treatment was conducted in accordance with the Declaration of Helsinki and the ethical principles of Toyonaka Municipal Hospital. Ethical approval is not required for this case report in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Writing – original draft: Asuka Watanabe and Tsutomu Nishida, Supervision: Tsutomu Nishida, Shiro Adachi, and Koji Fukui. Data and image curation: Asuka Watanabe. Pathological support: Shiro Adachi. Naoto Osugi, Takao Kitanaka, Yutaro Minoura, Satoru Okabe, Naohiro Sakamoto, Yoshifumi Fujii, Aya Sugimoto, Dai Nakamatsu, Kengo Matsumoto, and Masashi Yamamoto reviewed the draft manuscript, revised it critically for intellectual content, and approved the final version of the manuscript for publication.

Data Availability Statement

Data supporting the findings of this study are available on request from the corresponding author, Nishida T. The data are not publicly available due to restrictions (e.g., they contain information that could compromise the privacy of the research participants).

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