Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2366-23
Intern Med 63: 1081-1085, 2024
http://internmed.jp

【 CASE REPORT 】

Drug-induced Interstitial Nephritis in a Patient with Ulcerative Colitis Treated with 5-Aminosalicylic Acid

Daichi Hayashi[1], Tsutomu Nishida[1], Naoto Osugi[1], Yasuo Kusunoki[2], Satoru Okabe[1], Yoshifumi Fujii[1], Dai Nakamatsu[1], Kengo Matsumoto[1], Masashi Yamamoto[1] and Koji Fukui[1]

Abstract:
This report describes the case of a 76-year-old man with ulcerative colitis who developed interstitial nephritis after starting 5-Aminosalicylic acid (5-ASA) therapy. The patient experienced an initial improvement in symptoms, but developed fatigue, anorexia, and severe renal dysfunction 2.5 months later. Renal biopsy confirmed drug-induced interstitial nephritis, and conservative treatment with fluid replacement and the discontinuation of 5-ASA improved the patient's condition. Clinicians should monitor patients receiving 5-ASA therapy for potential adverse effects, particularly renal injury, and promptly investigate symptoms of renal dysfunction. Early recognition and discontinuation of the offending agent may prevent further damage and improve patient outcomes.

Key words: 5-Aminosalicylic acid, drug-induced renal injury, acute renal failure

(Intern Med 63: 1081-1085, 2024)
(DOI: 10.2169/internalmedicine.2366-23)

Introduction

5-Aminosalicylic acid (5-ASA) is commonly used as the first-line treatment for inflammatory bowel disease (IBD). Although it is generally considered safe with minimal side effects, recent attention has focused on adverse events associated with 5-ASA, which have been reported to be more prevalent than previously recognized (1). The clinical presentation of these adverse events is diverse and the time of onset varies widely, making it difficult to predict. Adverse events occur in 7-14% of ulcerative colitis (UC) patients treated with 5-ASA and may include high fever, worsening diarrhea, abdominal pain, and bloody stools, which can mimic a disease exacerbation (2-4). Owing to the varied clinical manifestations of 5-ASA-induced adverse events, they have been described by different names, including mesalazine allergy (5), mesalazine-induced lupus (6, 7), 5-ASA intolerance (8, 9), or side effects. Among these adverse events, renal damage has been reported but is relatively rare (10, 11). Often, it is not considered a significant risk in routine practice. Renal damage can lead to interstitial nephritis, which can have severe health consequences if left untreated.

We report a case of drug-induced interstitial nephritis caused by 5-ASA, which was diagnosed by renal biopsy after renal failure 2.5 months after the initiation of 5-ASA treatment. This case highlights the importance of monitoring the renal function for several months after the initiation of 5-ASA treatment. Recovery may not be possible once kidney damage occurs and the timing of 5-ASA-induced kidney injury development varies widely.

Case Report

A 76-year-old man with a history of irritable bowel syndrome presented to his doctor with persistent bloody stool and diarrhea that had persisted for several weeks since May 2021. Colonoscopy revealed a diffuse coarse mucosa, loss of vascular permeability, mucosal fragility with a tendency to bleed easily, erosions, and purulent mucus in the rectum and sigmoid colon (Fig. 1). The patient was diagnosed with UC on the left side (Mayo Clinic Endoscopic Subscore: 2). Following the diagnosis, 2,000 mg of mesalazine was pre-

[1]Department of Gastroenterology, Toyonaka Municipal Hospital, Japan and [2]Division of Nephrology, Department of Internal Medicine, Toyonaka Municipal Hospital, Japan
Received: May 29, 2023; Accepted: July 21, 2023; Advance Publication by J-STAGE: September 1, 2023
Correspondence to Dr. Tsutomu Nishida, tnishida.gastro@gmail.com

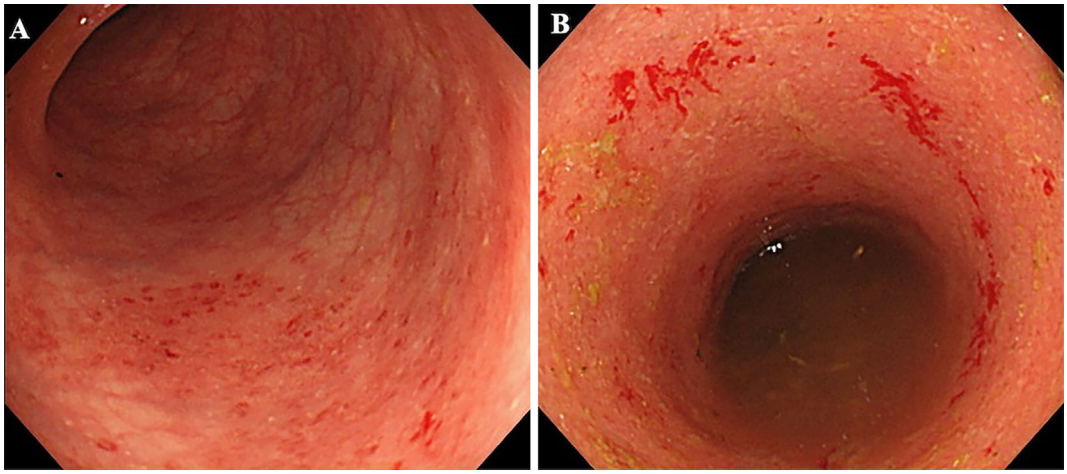

Figure 1. Colonoscopy without bowel preparation at the previous clinic revealed a diffuse coarse mucosa, loss of vascular permeability, fragility with a tendency to bleed easily, erosions and purulent mucus (A, B). He had a history of radiation therapy for prostate cancer but no findings of radiation proctitis.

scribed (Pentasa Granule, KYORIN Holdings, Tokyo, Japan) twice daily from approximately one month after the onset of the initial symptoms, resulting in an improvement in symptoms within two weeks. However, approximately 2.5 months after starting 5-ASA, he developed generalized fatigue and anorexia, and blood tests revealed mild liver dysfunction and severe kidney dysfunction with a creatinine level of 3.42 mg/dL. An adverse reaction to 5-ASA was suspected, and it was discontinued 87 days after the initiation of 5-ASA treatment. Despite discontinuation for seven days, the patient continued to experience fatigue and anorexia, prompting his admission to our department for further evaluation and treatment.

On admission, the patient exhibited renal dysfunction with a creatinine level of 2.06 mg/dL, elevated urinary β2-microglobulin without significant protein urine, and mild liver dysfunction [aspartate aminotransferase (AST), 45 U/L; alanin aminotransferase (ALT), 53 U/L] (Table). His relevant history included radiotherapy for prostate and lung cancers, neither of which had recurred. One month before admission, he underwent a blood test for cancer surveillance, and his renal and liver function levels were within normal limits. In addition to renal dysfunction, liver injury is considered an adverse event of 5-ASA. The patient reported a comorbidity of dyslipidemia, but not hypertension or diabetes mellitus. The patient had no history of alcohol consumption, smoking, or use of medications that cause interstitial nephritis. The results of a physical examination on admission were unremarkable. No exacerbation of abdominal symptoms was observed. Colonoscopy at admission showed no significant improvement in comparison to the findings before the initiation of treatment with 5-ASA, and no progression to the oral side (Fig. 2). Abdominal ultrasonography revealed no stenosis of the renal artery. Doppler echography showed that the renal parenchymal blood flow was preserved. There were also no abnormalities in kidney size or morphology. Therefore, fluid replacement was initiated. The patient's liver function completely improved, but his kidney function did not. Thus, the patient underwent further evaluation via a renal biopsy. The kidney biopsy revealed the infiltration of lymphocyte-based inflammatory cells in the renal interstitium (Fig. 2). Ultimately, the patient was diagnosed with drug-induced interstitial nephritis. Corticosteroid treatment was not administered because the degree of inflammation was mild (12), and discontinuation of the suspected drug (mesalazine) and continued fluid replacement treatment eventually improved the renal function to a creatinine level of 1.1 mg/dL [estimated glomerular filtration rate (eGFR), 50.4] (Fig. 3). The patient was discharged from the hospital after 20 days. During his first outpatient visit, in the second week after discharge, the patient's diarrhea symptoms flared up again, and topical budesonide was started. The UC symptoms improved and did not worsen without the reintroduction of mesalazine. At six months after discharge from the hospital, the patient's UC symptoms remained in remission on colonoscopy, and he is currently being followed (Fig. 4).

Discussion

Acute interstitial nephritis (AIN) accounts for 15-27% of kidney biopsies performed to investigate unexplained kidney injury in adults (13, 14). AIN can result from medications, infections, systemic inflammatory conditions, or idiopathic causes (14). Renal dysfunction has been reported to occur in approximately 1% of patients with inflammatory bowel disease (IBD) treated with 5-ASA, and interstitial nephritis occurs in approximately 0.2% of patients (10, 15). The onset of 5-ASA-induced AIN may be immediate or delayed, ranging from months to years after the initiation of treatment (16). Therefore, monitoring during the first year is recommended (16). However, the duration of monitoring of the renal function after the initiation of 5-ASA treatment and

Table. Laboratory Data on Admission.

Complete blood count		***Blood chemistry***	
WBC	4,800 /μL	AST	45 U/L
Neutrophil	76.9 %	ALT	53 U/L
Eosinophil	0.0 %	LDH	204 U/L
Basophil	0.6 %	γ-GT	102 U/L
Monocyte	7.8 %	Total protein	7.6 g/dL
Lymphcyte	14.7 %	Albumin	3.9 g/dL
RBC	383×10^4 /μL	Creatinine kinase	71 U/L
Hemoglobin	12.0 g/dL	Total amylase	105 U/L
Hematocrit	34.2 %	T-bilirubin	0.44 mg/dL
MCV	89.3 fl	BUN	56 mg/dL
MCH	31.3 pg	Creatinine	2.06 mg/dL
MCHC	35.1 g/dL	Uric acid	6.4 mg/dL
Platelet	22.9×10^4 /μL	Na	135 mEq/L
ESR (1 h)	76 mm	K	3.6 mEq/L
ESR (2 h)	116 mm	Cl	100 mEq/L
Urinalysis		Ca	9.7 mg/dL
Specific gravity	1.017	Fasting glucose	122 mg/dL
pH	6.0	C-reactive protein	0.19 mg/dL
Protein	(±)	***Coagulation***	
Sugar	(-)	Prothrombin time	0.92
Ketone body	(-)	APTT	25 s
Occult blood	(1+)	***Viral marker***	
Bilirubin	Normal	HBs-Ag	<0.05 IU/mL
Nitrite	(-)	HBs-Ab	2.0 IU/L
Urine sediment		HBc-Ab	0.1 COI
RBC	1-4 /HPF	HCV-Ab	0.0 COI
WBC	10-19 /HPF	***Thyroid marker***	
Hyaline casts	2+	TSH	1.03 IU/mL
Urine protein assay*	12 mg/dL	fT4	1.74 ng/dL
Protein/Creatinine*	0.11 g/gCr	Thyroglobulin	25.1 ng/mL
β2-microglobulin*	1,671 μg/L	Anti-thyroglobulin-Ab	13 IU/mL
NAG*	11.2 U/L	Anti-TPO-Ab	<9 IU/mL
FENa*	0.49 %	TSH receptor-Ab	<0.8 IU/L

*These values were measured on day 13 of admission.

WBC: white blood cells, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, ESR: erythrocyte sedimentation rate, NAG: N-acetyl-beta-D-glycosaminidase activity, FENa: fractional excretion of sodium, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GT: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, APTT: activated partial thromboplastin time, HB: hepatitis B, Ag: antigen, Ab: antibody, HCV: hepatitis C virus, TSH: thyroid stimulating hormone, fT4: free thyroxine 4, TPO-Ab: thyroid peroxidase antibody

the intervals at which it should be performed remain to be established. The degree of renal dysfunction is not necessarily correlated with the duration or dosage of 5-ASA. Approximately 40% of patients completely recover from AIN with 5-ASA preparations, but 9-13% do not (16). Furthermore, the adverse events associated with 5-ASA, including renal dysfunction, are still not well understood. Thus, many cases of 5-ASA-induced renal dysfunction may be overlooked because of the lack of regular monitoring of the renal function (16).

Monitoring of the renal function, including the serum creatinine level, estimated glomerular filtration rate, and 24-hour proteinuria, is recommended for patients taking 5-ASA (17). AIN is often associated with mild proteinuria and elevated serum creatinine. Because 24-hour urine collection is relatively complicated, routine blood tests to measure creatinine levels are preferable. In the present case, the patient had no history of chronic kidney disease and was not under active surveillance. In addition, the patient had no obvious proteinuria, suggesting that a urinalysis may not always be effective in monitoring for 5-ASA-induced kidney injury. 5-ASA is generally considered to have few side effects, especially delayed adverse events; thus, blood tests are often not performed once the symptoms of enteritis have resolved. During mesalazine treatment, it is important to closely monitor patients for signs and symptoms of interstitial nephritis and to take appropriate action as soon as possible in order to prevent further damage.

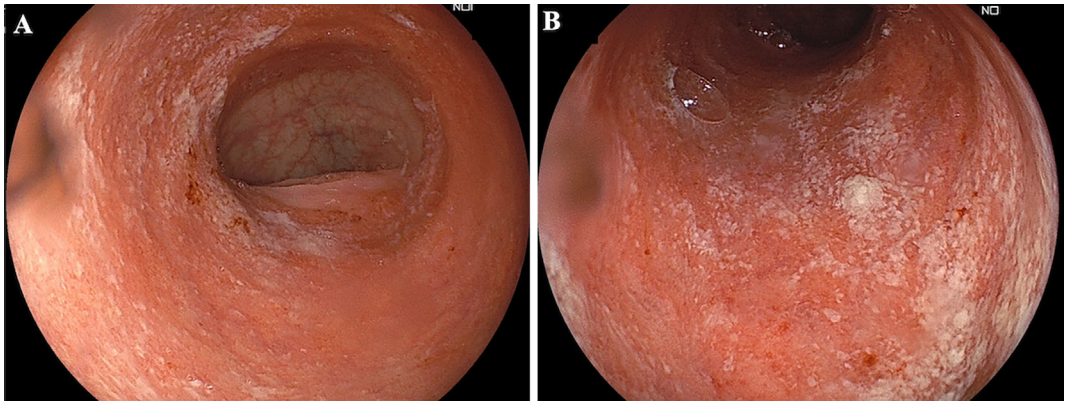

Figure 2. **Colonoscopy at admission revealed mucosal erythema, loss of vascular permeability, a granular mucosa, and the adhesion of purulent mucus to the rectum and sigmoid colon (A, B). Vascular permeability is seen in the proximal sigmoid colon (A).**

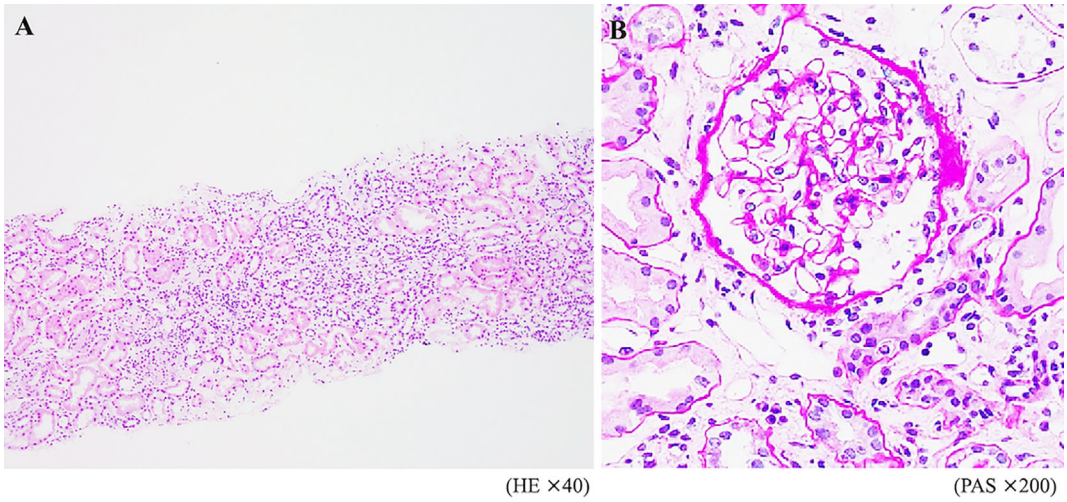

Figure 3. **The kidney biopsy revealed the infiltration of lymphocyte-based inflammatory cells in the renal interstitium. Hematoxylin and Eosin staining; original magnification 40× (A). Periodic acid-Schiff staining; original magnification 200× (B).**

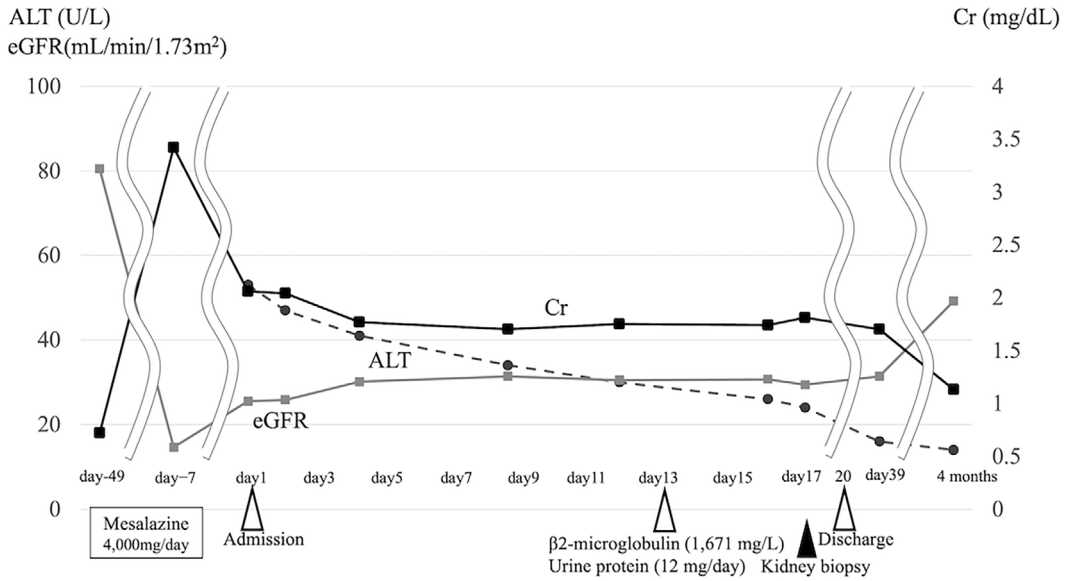

Figure 4. **The clinical course.**

Although no definition of 5-ASA intolerance has been established, the term is commonly used to describe allergic intolerance, which manifests as an immune response, and intolerance, which occurs as a side effect without an immune response. Symptoms of 5-ASA intolerance include a sudden onset of fever and worsening of abdominal symptoms, such as abdominal pain or diarrhea, arthralgia, headache, and renal dysfunction, as occurred in this case. Recently, to facilitate early detection, we classified 5-ASA-induced adverse events into four subgroups based on the symptoms and the timing of the onset of adverse drug reactions, as follows:1) lupus-like symptoms, 2) blood test abnormalities, 3) mimicking IBD exacerbations, and 4) others (1). 5-ASA-induced AIN is classified as either lupus-like or blood test abnormalities. Our previous study showed that the onset of lupus-like symptoms and blood test abnormalities occurs at three weeks and two months, respectively (1). In addition, symptoms of 5-ASA intolerance can sometimes present with multiple overlapping symptoms (1). In the present case, liver injury was observed in addition to renal impairment; however, there was no deposition of immune complexes, as observed in lupus nephritis. Therefore, we believe that the AIN and liver injury caused by 5-ASA in this case should be classified as blood test abnormalities.

A drug-induced lymphocyte stimulation test (DLST) can be used to assess drug allergies or intolerance, including those associated with 5-ASA. A positive DLST result indicates the possibility of a drug allergy or intolerance. However, DLSTs are limited, and may not always be reliable. One report found that the sensitivity and specificity of a DLST for 5-ASA intolerance were 0.24 and 0.81, respectively. In addition, the false-positive and false-negative rates were 0.195 and 0.76, respectively (18). A positive DLST result is likely to indicate an acute intolerance to 5-ASA, whereas a negative result does not completely exclude this possibility. If renal dysfunction due to 5-ASA intolerance is suspected, oral 5-ASA should be discontinued without waiting for the DLST results. Instead, monitoring of the renal function using blood samples, including creatinine, is critical.

In conclusion, we encountered a patient with UC who developed interstitial nephritis during 5-ASA treatment. Although interstitial nephritis rarely occurs in association with the use of this drug, there have been a few clinical reports. It is important to monitor patients with UC who are started on 5-ASA preparations using blood tests, including measurement of creatinine, and to consider acute interstitial nephritis as a possible side effect.

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

Acknowledgement

We would like to express our deepest appreciation to Dr. Yasuo Sakamoto for his invaluable contributions to our case report.

References

1. Tsujii Y, Nishida T, Osugi N, et al. Classification and clinical features of adverse drug reactions in patients with ulcerative colitis treated with 5-aminosalicylate acid: a single-center, observational study. Scand J Gastroenterol **57**: 190-196, 2022.
2. Nakase H, Uchino M, Shinzaki S, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol **56**: 489-526, 2021.
3. Goldstein F, DiMarino AJ Jr. Diarrhea as a side effect of mesalamine treatment for inflammatory bowel disease. J Clin Gastroenterol **31**: 60-62, 2000.
4. Shimodate Y, Takanashi K, Waga E, Fujita T, Katsuki S, Nomura M. Exacerbation of bloody diarrhea as a side effect of mesalamine treatment of active ulcerative colitis. Case Rep Gastroenterol **5**: 159-165, 2011.
5. Matsumoto S, Mashima H. Mesalazine allergy and an attempt at desensitization therapy in patients with inflammatory bowel disease. Sci Rep **10**: 22176, 2020.
6. Timsit MA, Anglicheau D, Lioté F, Marteau P, Dryll A. Mesalazine-induced lupus. Rev Rhum Engl Ed **64**: 586-588, 1997.
7. Kirkpatrick AW, Bookman AA, Habal F. Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease. Can J Gastroenterol **13**: 159-162, 1999.
8. Mizuno S, Ono K, Mikami Y, et al. 5-aminosalicylic acid intolerance is associated with a risk of adverse clinical outcomes and dysbiosis in patients with ulcerative colitis. Intest Res **18**: 69-78, 2020.
9. Hiraoka S, Fujiwara A, Toyokawa T, et al. Multicenter survey on mesalamine intolerance in patients with ulcerative colitis. J Gastroenterol Hepatol **36**: 137-143, 2021.
10. Patel H, Barr A, Jeejeebhoy KN. Renal effects of long-term treatment with 5-aminosalicylic acid. Can J Gastroenterol **23**: 170-176, 2009.
11. Zallot C, Billioud V, Frimat L, Faure P, Peyrin-Biroulet L; CREGG (Club de Reflexion des Cabinets et Groupes d'Hépato-Gastroentérologie). 5-aminosalicylates and renal function monitoring in inflammatory bowel disease: a nationwide survey. J Crohns Colitis **7**: 551-555, 2013.
12. Moledina DG, Perazella MA. Drug-Induced Acute Interstitial Nephritis. Clin J Am Soc Nephrol **12**: 2046-2049, 2017.
13. Farrington K, Levison DA, Greenwood RN, Cattell WR, Baker LR. Renal biopsy in patients with unexplained renal impairment and normal kidney size. Q J Med **70**: 221-233, 1989.
14. Praga M, Gonzalez E. Acute interstitial nephritis. Kidney Int **77**: 956-961, 2010.
15. Gisbert JP, Luna M, Gonzalez-Lama Y, et al. Effect of 5-aminosalicylates on renal function in patients with inflammatory bowel disease: 4-year follow-up study. Gastroenterol Hepatol **31**: 477-484, 2008.
16. Moss JG, Parry CM, Holt RCL, McWilliam SJ. 5-ASA induced interstitial nephritis in patients with inflammatory bowel disease: a systematic review. Eur J Med Res **27**: 61, 2022.
17. Guillo L, D'Amico F, Achit H, et al. Kidney function monitoring to prevent 5-aminosalicylic acid nephrotoxicity: what the gastroenterologist should know. Dig Liver Dis **53**: 691-696, 2021.
18. Saito D, Hayashida M, Sato T, et al. Evaluation of the drug-induced lymphocyte stimulation test for diagnosing mesalazine allergy. Intest Res **16**: 273-281, 2018.