CASE REPORT

Ulcerative Colitis Preceding Asymptomatic Wilson's Disease: A Case Report and Literature Review

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An 11-year-old girl with quiescent ulcerative colitis had sustained elevation of liver enzymes. Although she had no clinical symptoms suggestive of Wilson's disease, such as Kayser–Fleischer rings, laboratory data showed decreased serum copper and ceruloplasmin levels and increased urinary copper excretion. Genetic testing showed pathogenic variants in *ATP7B* allele 1: c.2004_2006delGAT (p. Met668del) and allele 2: c.1708-5T>G. After starting copper chelators, her liver function normalized, and she maintained clinical and endoscopic remission of ulcerative colitis. Mutations or defective functions of *ATP7B* lead to hepatic dysfunction and intestinal inflammation.

Keywords: Ulcerative Colitis; Wilson's Disease; Copper Metabolism; Liver Dysfunction

Introduction

Inflammatory bowel disease (IBD) is a chronic intestinal disorder that includes ulcerative colitis (UC) and Crohn's disease.[1] Several factors are involved in the pathogenesis of IBD, including immune disorders, genetic and environmental factors, and the intestinal microbiome.[2] IBD is associated with extraintestinal complications such as autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC).[3] Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism that occurs in children, adolescents, and young adults[4]; however, it is rarely associated with IBD.[5] Herein, we report a patient with UC who developed sustained liver dysfunction following treatment with biologics and was later diagnosed with WD.

Case Report

An 11-year-old girl presented with abdominal pain and loose stools and was diagnosed with UC following colonoscopy and histological examination in September 2016. Her blood tests showed no liver damage (Table 1). The treatment course for UC remission is shown in Figure 1.

Laboratory data from October 2016 showed abnormal liver function with a predominance of alanine aminotransferase. Therefore, she was admitted to our hospital for further evaluation. No gait disturbances, Kayser–Fleischer rings, or neurological symptoms were noted at the time of admission. Serological tests for hepatitis B and C viruses, Epstein–Barr virus, and cytomegalovirus were negative. IgG4 levels were not elevated, and tests for autoantibodies were negative.

Liver biopsy showed chronic hepatitis with moderate to severe lymphocyte-dominant inflammation in the portal tracts, interface hepatitis, mild bridging fibrosis, and mild fatty changes in 20% of the hepatocytes. Owing to the clinical suspicion of AIH or drug-induced hepatitis, budesonide treatment was initiated; however, mildly increased levels of liver enzymes persisted. The patient underwent magnetic resonance cholangiopancreatography in January 2020, which revealed a slight caliber irregularity and beaded intrahepatic bile ducts. PSC was suspected and she was treated with ursodeoxycholic acid. However, liver enzyme levels did not normalize. Considering drug-induced liver dysfunction, we switched from golimumab to vedolizumab (VED). However, no improvement in hepatic function occurred.

The patient was admitted for a second liver biopsy in April 2020. The patient did not show any symptoms suggestive of WD. The laboratory data from April 2020 are shown in Table 2. The laboratory data did not show any significant changes compared with those from August 2018 (Table 1). Upon admission, we performed blood and urine tests for copper metabolism, which showed decreased platelet counts, decreased serum copper and ceruloplasmin,

2772-5723
https://doi.org/10.1016/j.gastha.2024.09.003

Table 1. Laboratory results during the patient's clinical course

	At diagnosis in September 2016	During tapering off prednisolone in October 2016	At first liver biopsy in August 2018	At second liver biopsy in April 2020	At remission in January 2024	Reference values
AST	16	26	150	96	16	11–39 U/L
ALT	8	51	215	124	17	5–40 U/L
ALP	214	452	580	572	85	110–370 U/L
GGT	28	176	102	103	19	6–35 U/L
Platelet count				11.5×10^3		13.2–36.8 $\times 10^3/\mu$L
Copper	-	76	-	75	47	78–131 μg/dL
Ceruloplasmin	-	-	-	12.6	13.0	21–37 μg/dL
Urinary copper	-	-	-	243	-	40 μg/day

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

and elevated urinary copper excretion (Table 1). The second liver biopsy showed portal fibrosis and inflammation, interface hepatitis, lobular necrosis, and rosettes (Figure 2A). No findings of PSC, such as intrahepatic cholangiectasis, gross fibrous thickening of the duct wall, or onion skin appearance, were observed. Based on the international diagnostic criteria for AIH, a diagnosis of "probable" AIH was suggested. However, the patient did not respond to high-dose methylprednisolone pulse therapy. In addition, rubeanic acid staining of hepatocytes revealed black granules in some hepatocytes (Figure 2B), suggesting copper deposition. Given abnormal copper metabolism-related parameters, genetic testing was performed. Genetic testing revealed a compound heterozygous variant in *ATP7B* allele 1: c.2004_2006delGAT (p. Met668del) and allele 2: c.1708-5T>G. Consequently, she was diagnosed with UC accompanied by WD. The liver function of the patient normalized after treatment with copper chelators (Table 1). Four years after VED treatment and administration of copper chelators, the patient has maintained clinical and endoscopic remission of UC and normal liver function.

Discussion

We report a sporadic case of WD in a young patient with UC in remission during treatment with biologics. The absence of clinical symptoms and physical findings characteristic of WD made the diagnosis difficult. In cases of liver dysfunction in young patients with IBD, distinguishing hereditary liver disorders from autoimmune-related disorders such as PSC is necessary.

WD is an autosomal recessive disorder of copper metabolism.[6] Mutations in *ATP7B* on chromosome 13 result in insufficient excretion of absorbed dietary copper via the bile, leading to the accumulation of toxic amounts of copper in the liver and other organs. Copper is an essential enzyme cofactor that catalyzes biochemical reactions that are important for cellular homeostasis.[7] However, cellular copper accumulation causes a form of cell death known as cuproptosis that depends on mitochondrial respiration. WD models, such as *Atp7b*$^{-/-}$ knockout mice and zebrafish, show neutrophil infiltration into the liver due to the high expression of transforming growth factor in hepatocytes, which can lead to the progression of liver disease and cirrhosis.[8]

The protein encoded by *ATP7B* is expressed in the intestine and regulates copper levels in enterocytes and chylomicron metabolism.[9] Previous reports have suggested that abnormalities in copper metabolism are present in patients with UC and are associated with the development of UC.[10] In patients with UC, the expression level of *ATP7B* is lower in inflamed intestinal mucosa than in noninflamed

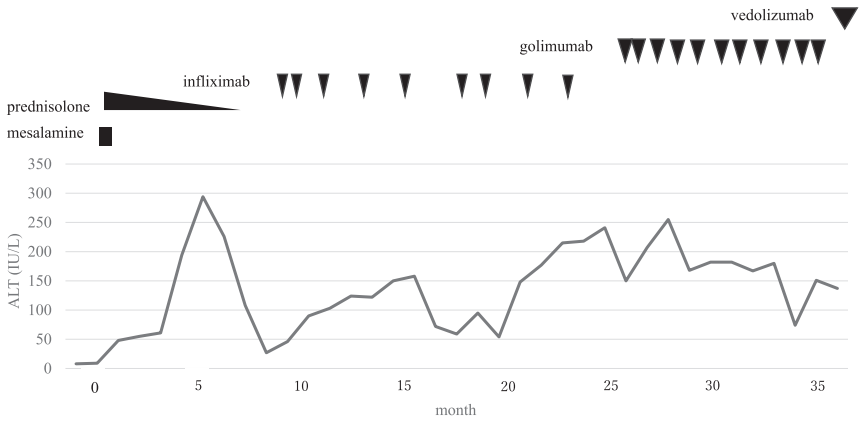

Figure 1. Changes in liver enzymes during the patient's clinical course of UC from September 2016 to September 2019.

Table 2. Laboratory data in April 2020

Biochemistry		Blood count		Other	
TP	6.7 g/dL	WBC	3500 μL	IgG	1190 mg/dL
Alb	3.4 g/dL	Neut	49.0%	IgA	162 mg/dL
AST	96 U/L	Hb	12.7 g/dL	IgM	202 mg/dL
ALT	124 U/L	Platelet	11.5 $\times$ $10^3/\mu$L	IgG4	8.1 mg/dL
LDH	262 U/L			Antinuclear antibodies	<40$\times$
ALP	603 U/L	Virus marker		Antiliver kidney microsomal-1	Negative
T.Bil	0.7 mg/dL	EBV VCA IgM	Negative	Antimitochondrial	Negative
BUN	9 mg/dL	EBV VCA IgG	Negative	Perinuclear antineutrophil cytoplasmic antibody	Negative
Cre	0.46 mg/dL	EBV EBNA IgG	Negative	Myeloperoxidase antineutrophil cytoplasmic antibody	Negative
Na	141 mEq/L	CMV IgM	Negative		
K	3.7 mEq/L	CMV IgG	Negative		

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CMV, cytomegalovirus; Cre, creatinine; EBNA, Epstein–Barr virus nuclear antigen; EBV, Epstein–Barr virus; Hb, hemoglobin; LDH, lactate dehydrogenase; TP, total protein; VCA, virus capsid antigen; WBC, white blood count.

mucosa.[11] In addition, a negative relationship exists between *ATP7B* expression and immune cell infiltration in UC.[11,12] Therefore, *ATP7B* is considered a cuproptosis-related hub gene during active UC. Several cases have been reported regarding an association between WD and IBD, including some cases of WD followed by IBD[13,14] and others of IBD followed by WD.[5] Although the common mechanisms in the onset of WD and IBD remain unclear, Zou et al. reported that VED improves impaired cuproptosis of the intestinal mucosa in patients with active UC by regulating a cuproptosis-related hub gene,[11] which may suggest a correlation between the expression of *ATP7B* and onset of remission in our patient.

In the present case, the concerned patient was diagnosed with WD due to liver dysfunction after the onset of UC. The patient had no clinical manifestations characteristic of WD, suggesting a very early stage of WD status. The clinical spectrum of WD is very broad[6] so that differences in the severity of clinical symptoms[15] and timing of onset[16] are evident, even in patients with identical genetic mutations.[17] This suggests that other factors such as the intestinal microflora[18] and reactive oxygen species[19,20] may play a role in the development of WD.

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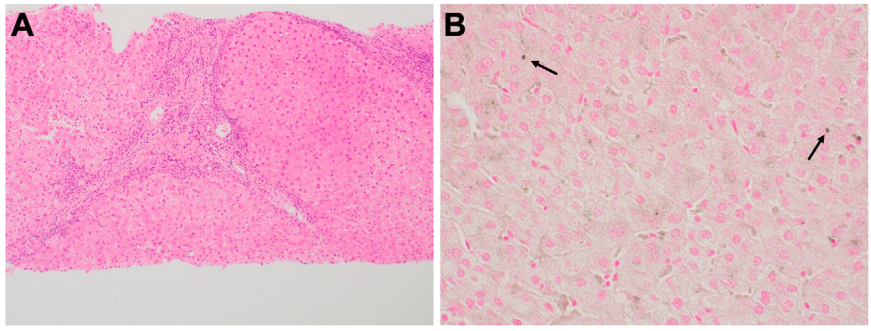

Figure 2. Histology of the second liver biopsy. (A) Histology reveals portal fibrosis and inflammation, interface hepatitis, necrotic changes in the lobules, and rosettes (hematoxylin and eosin staining, 100$\times$). (B) Black granules are evident in some hepatocytes (black arrows) (rubeanic acid staining, 400$\times$).

Received August 19, 2024. Accepted September 6, 2024.

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Acknowledgments:
The authors are grateful for the work of past and present staff of the Department of Pediatrics and Gastroenterology and Hepatology at Sapporo Medical University School of Medicine. They would like to thank Editage (www.editage.jp) for English language editing.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
The authors report no funding.

Ethical Statement:
The participants were informed both verbally and in writing about the protection of personal information and the dissemination of the results, and their consent was obtained. Appropriate ethical measures were strictly implemented to ensure that individuals could not be identified.

Reporting Guidelines:
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