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Case Report

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Asymptomatic Wilson's Disease Diagnosed during the Course of Ulcerative Colitis: A Case Report and Review

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Keywords
Wilson's disease · ATP7B · Ulcerative colitis · Inflammatory bowel disease · Liver damage

Abstract
Introduction: While previous reports have suggested an association between Wilson's disease (WD) and ulcerative colitis (UC), we present the first case of asymptomatic WD diagnosed during the treatment course of UC. ***Case Presentation:*** A 14-year-old male receiving treatment for UC developed elevated liver enzymes without any related symptoms. After ruling out drug-induced liver toxicity and other possible causes of hepatitis, further investigation was initiated due to his sister's subsequent diagnosis of WD. Tests revealed low serum ceruloplasmin and ATP7B gene variants, confirming WD. Following zinc therapy, liver enzymes have been normalized, and his previously refractory UC became under control. ***Conclusion:*** This case raises important questions about potential pathophysiological interactions between the two diseases.

Introduction

Wilson's disease (WD) is a genetic disorder of copper metabolism. The autosomal recessive pattern of mutation within the ATP7B gene leads to impaired function of the copper transporter ATP7B, leading to reduced biliary copper excretion and excessive copper accumulation in the liver and other tissues throughout the body [1]. The patterns of clinical presentation vary, but most include (1) liver-related issues, such as jaundice and ascites; (2) neurological symptoms, like dysarthria and cerebellar ataxia; or (3) psychiatric symptoms, including mood disorders, psychosis, and sleep disturbances [1]. Symptoms commonly manifest between the ages of 3 and 55 [1].

There have been several reports of WD coexisting with ulcerative colitis (UC), raising discussions about a potential association between the two diseases [2, 3]. While most cases of WD in these reports were diagnosed based on clinical symptoms, we present the first documented case of asymptomatic WD discovered during the treatment course of UC.

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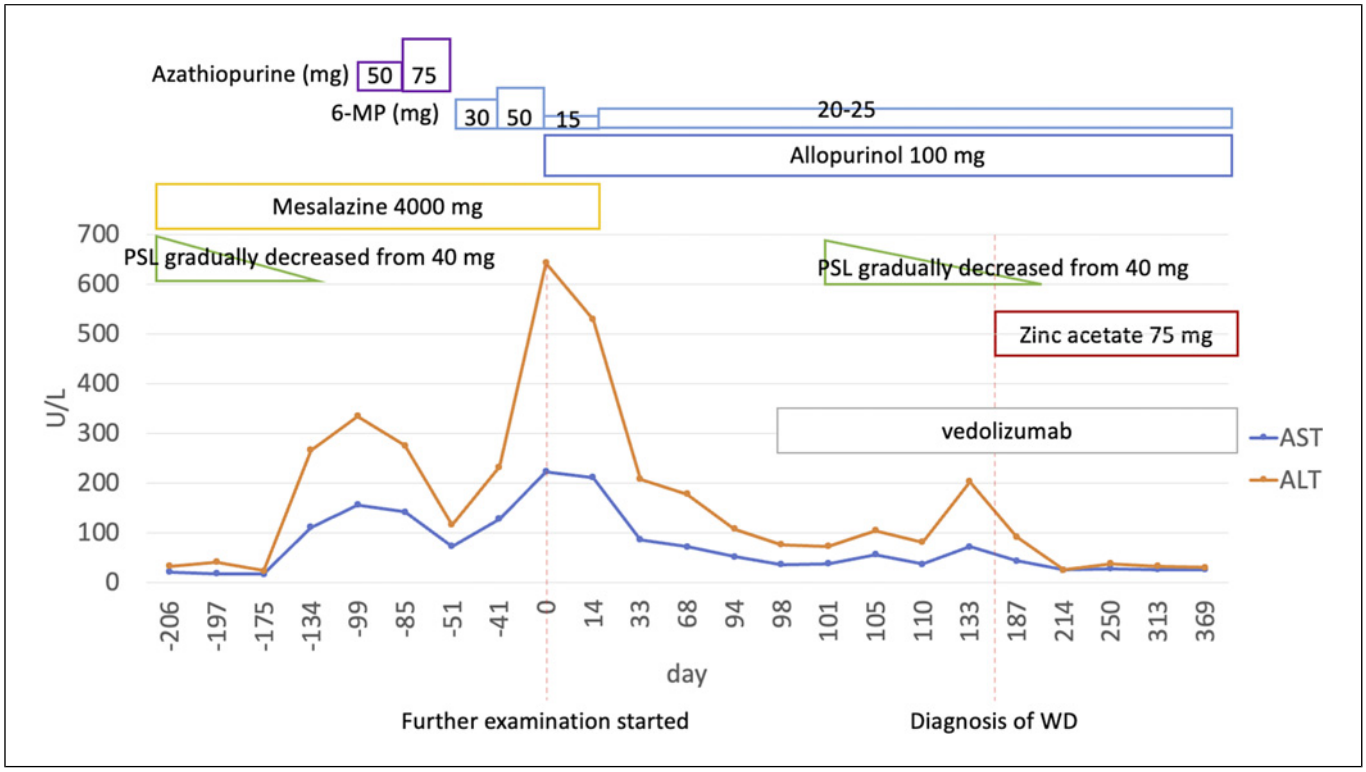

Fig. 1. Treatment course and trends in hepatic enzymes. AST, aspartate aminotransferase; ALT, alanine aminotransferase; 6-MP, 6-mercaptopurine; PSL, prednisolone; WD, Wilson's disease.

Case Report

The trends in hepatic enzymes and medications are summarized in Figure 1. A 14-year-old male with no other comorbidities initially presented to a previous clinic with hematochezia, leading to a diagnosis of UC. Due to poor disease control, the patient was referred to our center. At the first visit, laboratory tests showed normal liver enzyme levels, including an aspartate aminotransferase (AST) of 21 IU/L and an alanine aminotransferase (ALT) of 33 IU/L.

In addition to mesalazine 4 g/day, prednisolone was initiated from 40 mg/day with gradual tapering. Two months after starting steroids, AST and ALT levels increased, despite an improvement in UC symptoms (AST/ALT: 111/266 IU/L). This elevation in liver enzymes was initially considered transient, potentially due to prednisolone or refeeding syndrome. Azathioprine was started following steroid induction but was later switched to 6-mercaptopurine (6-MP) 50 mg/day due to epigastric pain. However, AST and ALT levels remained elevated. Seven months after the initial visit, liver enzymes worsened (AST/ALT: 223/642 IU/L), prompting further investigation.

Laboratory results showed elevated liver function tests, with normal gamma-glutamyl transpeptidase levels. Other tests, including serologies for hepatitis, thyroid function, and autoantibodies, were normal. Abdominal ultrasound revealed mild fatty changes in the liver and splenomegaly. Physical examination was unremarkable, with no evidence of Kayser-Fleischer rings or neurological symptoms, such as cogwheel rigidity in the limbs, and the patient remained asymptomatic. Additionally, the patient did not complain any psychiatric symptoms.

Initially, drug-induced liver injury was suspected, and the dosage of 6-MP was reduced in combination with allopurinol. However, 2 weeks later, AST and ALT levels remained elevated. Mesalazine was then discontinued, and a subsequent decline in AST and ALT levels was observed, though they remain above the normal range.

Three months after the initial detection of elevated liver enzymes, the patient developed abdominal pain and bloody stools, prompting a diagnosis of UC relapse. His condition gradually worsened, with bloody stools exceeding 10 episodes per day, leading him to revisit our clinic, where he initiated vedolizumab. Three days after starting vedolizumab, the patient was emergently admitted

Table 1. Previous reports of the cases with coexistence of IBD and WD

Author (year)	Sex	Age at diagnosis of WD, y/o	Symptoms of WD at diagnosis	Liver enzymes at diagnosis of WD	UC/CD	Age at diagnosis of IBD, y/o	Need for corticosteroid for IBD
Torisu et al. [2] (2002)	M	12	Disorientation, jaundice, Kayser-Fleischer ring	?	UC	24	–
Wörns et al. [5] (2006)	F	? (<16)	Kayser-Fleischer ring	?	UC	16 or 17	–
Jang et al. [6] (2010)	F	10 months	None	Elevated	UC	8	– (Enema)
Nery et al. [3] (2010)	F	20	Nausea, jaundice, abdominal pain	?	UC	17	–
Chen et al. [7] (2023)	M	5	None	Elevated	CD	16	– (Biologic was used)
This case	M	15	None	Elevated	UC	14	–

CD, Crohn disease.

due to persistent hematochezia with slightly improved CRP. Short-term steroid (prednisolone 40 mg) was added given his exacerbating symptoms and slow-acting nature of vedolizumab. After 2 days, both bloody stools and abdominal pain resolved, resulting in clinical remission; nevertheless, AST and ALT levels remained elevated (Fig. 1).

A more detailed family history revealed that the patient's older sister had just been diagnosed with WD after his diagnosis with UC. Given this new information, additional testing was performed, showing low serum ceruloplasmin (3 mg/dL) and ATP7B gene mutations on both chromosomes. Based on these findings, the patient was diagnosed with WD, scoring 6 points on the diagnostic criteria (serum ceruloplasmin <10 mg/dL: 2 points; mutations on both chromosomes: 4 points) [1].

After initiating treatment with zinc acetate hydrate (75 mg/day), AST and ALT levels returned to normal. Interestingly, although UC had been refractory, requiring intravenous corticosteroids and vedolizumab prior to the WD diagnosis, UC symptoms came under control once zinc acetate therapy was initiated. Six months after starting zinc acetate and 9 months after initiating vedolizumab, endoscopic findings showed remission with a Mayo endoscopic subscore of 0 [4].

Discussion

We report the first case of asymptomatic WD diagnosed during the treatment for UC. Table 1 shows the list of previous case reports of co-existing WD and inflammatory bowel disease (IBD), identified through a literature search on PubMed and Embase (until July 2024). These reports have suggested that WD might worsen IBD by allowing copper to accumulate in the intestinal epithelial cells, disrupting tight junctions and triggering an inflammatory response [2]. Specifically, oxidative stress from copper ions and a copper-dependent cell death process called cuproptosis are believed to contribute to the inflammation [2]. In fact, Nery et al. [3] reported a case where the diagnosis of UC preceded the development of WD symptoms, and her UC, initially unresponsive to systemic corticosteroids, became easier to manage, leading to long-term remission for over 3 years after treatment with trientine. Similarly, our patient required corticosteroids and vedolizumab during the first year of UC treatment. However, after starting zinc acetate therapy for WD, there have been no further symptom flare-ups. These cases support the hypothesis that WD may exacerbate IBD, although the follow-up periods in these cases were relatively short. Furthermore, considering the epithelial injury caused by copper accumulation, WD may increase the risk of IBD onset. At this point, however, ATP7B is not identified as a disease susceptibility gene of UC or Crohn disease. Nonetheless, there is still potential that ATP7B is actually the IBD susceptibility gene but has not been confirmed yet because the prevalence of WD variant in ATP7B gene is very low. Moreover, since WD tends to precede the onset of IBD, the copper level would be controlled before the symptom of colitis begins, reducing the risk of IBD development.

On the other hand, IBD could have influenced the progression of WD in this case. While WD is primarily caused by mutations in the ATP7B gene, secondary factors can influence the disease's progression and symptom severity. There

are several potential mechanisms by which IBD might accelerate WD. For example, Liao et al. [8] found that inflammatory cytokines can increase cellular copper uptake. Copper is absorbed in tissues as cuprous (Cu I) copper, requiring a metalloreductase to convert cupric (Cu II) copper to the cuprous form [8]. Their study on IL-17-primed mouse colon organoids showed increased levels of the copper metalloreductase and higher cellular copper content [8]. Given that inflammatory chemokines and cytokines are elevated in IBD [9], increased copper uptake and storage might trigger WD onset in patients with ATP7B gene variants.

Another possible link between IBD and WD could involve liver dysfunction unrelated to copper metabolism. It is reported that approximately 30% of patients with IBD have abnormal liver function tests [10]. The potential causes could be (1) IBD-related liver conditions, such as malabsorption, portal vein thrombosis, or autoimmune liver diseases, or (2) drug-induced liver injury [10]. For patients with ATP7B gene variants, existing liver dysfunction from IBD could be worsened by copper toxicity, leading to faster progression of WD. Our patient also showed signs of mild fatty liver, though it was unclear whether this was due to the course of UC, mesalazine-induced liver injury, or the effects of WD. Temporary improvement in liver function was observed after discontinuing mesalazine. However, AST and ALT levels remained elevated until treatment for WD was initiated, which ultimately resolved the abnormalities. These findings suggest that while mesalazine may have partially contributed to the liver injury, it was not the primary cause. Further research is needed to investigate the impact of IBD on liver function and WD progression.

In conclusion, this is the first reported case of asymptomatic WD diagnosed during the course of UC. While WD may have influenced UC relapse, it is also possible that UC contributed to the progression of WD. Although more studies are needed to explore the mechanisms involved, this case highlights the potential interplay between these two conditions and opens the door for further discussion on their natural course and mutual effects. This report complies with the CARE guidelines, and the CARE Checklist is attached as an online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545142).

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Shintaro Sagami has served as a speaker for AbbVie, Eli Lilly, Janssen Pharmaceutical, Gilead Sciences, Inc., JIMRO Co., Ltd., KISSEI Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, EA Pharma Co., Takeda, Nippon Kayaku, and Zeria. He has also held endowed chairs sponsored by AbbVie, JIMRO Co., Ltd., Zeria Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., and EA Pharma Co., Ltd., and has received research grants from Bristol-Myers Squibb, EA Pharma Co., AbbVie GK, Gilead Sciences, Inc., and Ferring Pharmaceuticals. Kunio Asonuma received lecture fees from Mitsubishi Tanabe, Takeda, KISSEI Pharmaceutical Co., AbbVie GK, and Mochida. Toshifumi Hibi has received lecture fees from AbbVie GK, EA Pharma, JIMRO, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Pfizer, and Takeda Pharmaceutical and received advisory/consultancy fees from AbbVie, Celltrion, EA Pharma, Eli Lilly, Gilead Sciences, Janssen, Mitsubishi Tanabe, Takeda, Zeria, MSD, and Pfizer. Taku Kobayashi received the research grant from AbbVie GK, Activaid, Alfresa Pharma, JMDC, Gilead Sciences, Nippon Kayaku, Eli Lilly, Japan, Mochida, Janssen Pharmaceutical, Pfizer, Japan, Takeda, Bristol-Myers Squibb, Google Asia Pacific Pte. Ltd., received the scholarship grant from Mitsubishi Tanabe, Zeria, Nippon Kayaku, and EA Pharma, and received per diem or honorariums from AbbVie, Janssen Pharma, Takeda, Mitsubishi Tanabe Pharma, and Pfizer and was endowed the chair from Otsuka Holdings, EA Pharma, JIMRO, AbbVie GK, Zeria, Kyorin, Mochida, and Miyarisan. Dr. Toshifumi Hibi and Dr. Taku Kobayashi were both a member of the journal's Editorial Board at the time of submission. The other authors have no conflicts of interest to declare.

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Author Contributions

Megumi Kinjo: conceptualization, investigation, and writing – original draft. Shintaro Sagami: investigation, writing – review and editing, and supervision. Akira Nogami, Kanade Serizawa, Shunsuke Shibui, Satoko Umeda, Kunio Asonuma, Hidetsugu Saito, Masaru Nakano, and Toshifumi Hibi: investigation and writing – review and editing. Taku Kobayashi: conceptualization, investigation, writing – review and editing, and supervision.

Data Availability Statement

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

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