

A rare case of DIC in a patient with Wilson's disease: D-penicillamine

Yavuz Emre Parlar¹, Hatice Yasemin Balaban¹, Umit Yavuz Malkan², Erdogan Deniz³, Fatma Rukiye Uysal³

¹Department of Gastroenterology, Hacettepe University School of Medicine, Ankara, Turkey; ²Department of Haematology, Hacettepe University School of Medicine, Ankara, Turkey; ³Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey

Abstract

D-penicillamine therapy is considered an effective and safe treatment for Wilson's disease. Except for one experimental study, there has been no report in the literature about the development of disseminated intravascular coagulation (DIC) with the use of the drug. A 24-year-old female patient with Wilson's disease, followed up with zinc and D-penicillamine treatment, was admitted to the emergency service because of oral mucosal bleeding and lethargy. Initial laboratory tests showed hemoglobin 7.1 g/dL (11.7-15.5), platelet $24 \times 10^3 \mu\text{L}^{-1}$ (159-388), total bilirubin 18 mg/dL (0.3-1.2), direct bilirubin 9.8 mg/dL (0.0-0.2), INR >10 (0.8-1.2), aPTT 64.5 s (22.5-32), fibrinogen 23 mg/dL (180-350), and factor 8 26.4% (70-150). Melena, hematemesis, and hematochezia were not present, and no active bleeding focus was detected on endoscopic evaluation. Upon meeting the DIC criteria, the patient underwent plasma exchange four times for the treatment of acute-on-chronic liver failure. Haemocomplettan-P, cryoprecipitate replacements were made as a supportive treatment for DIC. As the clinical bleeding continued despite plasma exchanges and factor replacement treatment, D-penicillamine was switched to trientine (1250 mg/day). After this change, the mucosal bleeding stopped, and DIC parameters improved. We suggest that if hemorrhagic complications develop on D-penicillamine treatment, the possibility of DIC induced by D-penicillamine activating the fibrinolysis should also be considered.

Keywords: Wilson's disease; disseminated intravascular coagulation; D-penicillamine.

Introduction

Wilson's disease is an autosomal recessive copper metabolism disorder caused by mutations in the ATP7B gene that cause dysfunction. The ATP7B gene encodes an enzyme involved in the metabolism of ceruloplasmin and copper. Its mutation causes the deterioration of bile

copper excretion, causing the accumulation of copper in many organs.^[1] Although hepatic findings are the most common abnormalities in Wilson's disease, hemolytic anemia, neurologic and psychiatric symptoms, renal abnormalities, and endocrine abnormalities are not uncommon. D-penicillamine therapy is considered an effective and safe treatment for Wilson's disease. However, side effects such as thrombocytopenia, hemolytic anemia, and thrombotic thrombocytopenic purpura may occur during D-penicillamine treatment.

Disseminated intravascular coagulation (DIC) is a systemic disorder characterized by procoagulator cascade activation, fibrinolysis, and the development of consumptive coagulopathy. Fibrin formation and accumulation due to the activation of the coagulation system causes microvascular thrombus, leading to multiorgan dysfunction.^[2] DIC has often been associated with malignancy, sepsis, and trauma. Other causes include liver diseases, pancreatitis, transfusion reactions, obstetric conditions, and surgery.^[3] Here, for the first time in the literature, a case of DIC developing as a complication of D-penicillamine use in a patient with Wilson's disease is presented.

Case Report

A 24-year-old female patient is admitted to the emergency department with bleeding from her mouth and being lethargic. She was diagnosed with Wilson's disease when she was being investigated for swelling in her feet and jaundice at the age of 9 for the first time. She was followed up with zinc (3×50 mg) and D-penicillamine (2×600 mg). In the examination of the patient who had intraoral bleeding in his emergency admission, it was determined that the bleeding originated from the gingiva; she had no complaints of hematemesis, hematochezia, melena, abdominal pain, fever, diarrhea, nausea, or vomiting. Brain tomography was performed to exclude neurological events due to lethargy. The patient was diagnosed with stage 2 hepatic encephalopathy, and hepatic encephalopathy treatment was started. In the first laboratory examination, hemoglobin was 7.1 g/dL (11.7-15.5), platelets $24 \times 10^3 \mu\text{L}^{-1}$ (159-388), INR >10 (0.8-1.2), aPTT 64.5 s (22.5-32.0), and fibrinogen was 23 mg/dL (180-350). In tests for hemolysis, reticulocyte 1.8% (0.2%-2.0%), haptoglobin <5.8 mg/dL (40-240 mg/dL), total bilirubin 18 mg/dL (0.3-1.2), direct bilirubin 9.8 mg/dL (0.0-0.2), and antiglobulin antibody tests were negative. The hemoglobin value was similar to previous controls and was measured at 7 mg/dL. The patient had no history of hepatotoxic drug or alcohol intake. Viral hepatitis markers were negative. No active bleeding foci were detected in the endoscopic examination of the patient with a history of esophageal varices. In her peripheral smear, marked hypochromia, occasional schistocytes, and giant platelets were detected. The patient was started on daily fresh frozen plasma and cryoprecipitate

How to cite this article: Parlar YE, Balaban HY, Malkan UY, Deniz E, Uysal FR. A rare case of DIC in a patient with Wilson's disease: D-penicillamine. Hepatology Forum 2022; 3(2):61-63.

Received: February 01, 2022; **Accepted:** February 28, 2022; **Available online:** April 26, 2022

Corresponding author: Yavuz Emre Parlar; Hacettepe Universitesi Tip Fakultesi, Gastroenteroloji Anabilim Dalı, Ankara, Turkey

Phone: +90 312 305 17 12 - 13; **e-mail:** yavuzemreparlar@gmail.com



OPEN ACCESS
This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Hepatology Forum - Available online at www.hepatologyforum.org



treatments. Haemocomplettan-P was planned as a supportive treatment for the patient who met the criteria for DIC. In the follow-up, plasmapheresis was applied four times in total because acute-on-chronic liver failure could not be excluded in the patient whose bilirubin levels increased. In the factor levels of the patient whose coagulation parameters continued to prolong, the factor 8 level was found to be 26.4% (70-150), and the factor 8 inhibitor level was negative. A low factor 8 level was considered secondary to active mucosal bleeding. As clinical bleeding continued despite plasma exchange and factor replacement, D-penicillamine was replaced with trientine (1250 mg/day). After this change, the active mucosal bleeding of the patient stopped in the following period, and DIC parameters improved (Table 1). After this change, the patient did not need factor replacement within 4 months of follow-up.

Discussion

This is the first report showing DIC in a patient who received D-penicillamine treatment for Wilson's disease. Wilson's disease is caused by a mutation in the ATP7B gene, which encodes the ATPase protein involved in the transport of copper from hepatocytes. Due to the disruption of copper excretion from hepatocytes, copper accumulates in the brain, kidney, and cornea. It is a rare autosomal recessive disease.^[4] Patients with Wilson's disease may present with a broad spectrum clinical picture, predominantly hepatic, neurological, and psychiatric symptoms. However, admission with DIC clinical and laboratory findings is rare in these patients.

The most feared clinical picture in the follow-up of patients with Wilson's disease is the development of acute liver failure (ALF). ALF is associated with hemolysis in Wilson's crisis and has a progressive clinical course, and its mortality is high in the absence of liver transplantation.^[5] In our case, the patient presented with mucosal bleeding and stage 2 hepatic encephalopathy. In the laboratory values, coagulopathy, increased bilirubin, and abnormality in DIC parameters were detected. Laboratory values of the patient did not support hemolytic crisis. Acute-on-chronic liver failure could not be excluded in the patient with DIC, elevated bilirubin levels, and HES, and the CLIF-ACLF score was calculated as grade 2. Plasmapheresis was applied to the patient four times in total. In studies conducted in the literature regarding the application of plasmapheresis to patients with Wilson's disease who were thought to have ACLF, patients who recovered clinically without the need for liver transplant with plasmapheresis treatment were defined.^[6] In our patient, although hepatic encephalopathy and bilirubin levels were regressed with plasmapheresis treatment, it was observed that coagulopathy and mucosal bleeding did not regress, and the need for factor replacement continued.

Factor 8 deficiency was detected in the tests sent for factor deficiencies from the patient whose clinical mucosal bleeding continued with INR and aPTT elevation. Factor 8 deficiency is an inherited bleeding disorder that is inherited on the X chromosome (X). Hereditary factor 8 deficiency was excluded as factor 8 deficiency usually shows clinical findings in the first year of life, and the patient did not have a history of bleeding. Considering that acquired factor 8 inhibitors may have occurred due to the use of D-penicillamine, the factor 8 inhibitor level was sent, but it was found to be negative. It was thought that the patient had a factor deficiency secondary to consumption due to continued active bleeding.

D-penicillamine is a copper chelating agent that has long been used safely in the treatment of Wilson's disease.^[7] D-penicillamine is also used in cystinuria and lead poisoning. Among the known hematological side effects of D-penicillamine are thrombocytopenia, leukopenia,

Table 1. Laboratory findings

	At the time of emergency	In the 4 th month follow-up
aPTT	64.5 s	39 s
INR	>10	1.86
Platelet	24X10 ³ μ L ⁻¹	81X10 ³ μ L ⁻¹
Total bilirubin	18 mg/dL	8.2 mg/dL
Direct bilirubin	9.8 mg/dL	4.5 mg/dL
Factor 8	26.4%	71.2%
Fibrinogen	23 mg/dL	130 mg/dL

aPTT: Activated partial thromboplastin time; INR: International normalized ratio.

thrombotic thrombocytopenic purpura, and hemolytic anemia.^[8] In our case, DIC parameters did not improve after plasmapheresis was applied to the patient, and D-penicillamine was changed with trientine treatment when the bleeding continued. After the chelator drug change, the patient's bleeding stopped in the following period, and it was observed that the need for factor replacement disappeared to improve the coagulopathy of the patient with DIC. Except for an animal study, there has been no study in the literature regarding the possibility of DIC development with long-term use of D-penicillamine.^[9] In this study, it was observed that rats given D-penicillamine died of DIC. Several hypotheses have been proposed for the pathogenesis of DIC development with the use of D-penicillamine. First, D-penicillamine causes endothelial damage, causes subendothelial collagen to appear, and causes intravascular coagulation in collagen-reactive platelets.^[10] Second, endothelial damage may trigger the release of platelet-activating factor, thromboxane A₂, or other prostaglandin-like substances, resulting in DIC.^[10]

This case report has one limitation. The patient's time to stop bleeding and the improvement of DIC laboratory values with the change of medication may have been completely incidental. However, the facts that the patient did not have mucosal bleeding again in the 4 months following the start of trientine treatment and that there was no need for factor replacement to improve her coagulopathy suggest that the development is secondary to the drug rather than an insignificant relationship.

Conclusion

In summary, we present a patient who used D-penicillamine for Wilson's disease and presented with DIC during treatment. In our recommendation, it should be kept in mind that in case of hemorrhagic complications in patients with Wilson's disease, after excluding other common causes, D-penicillamine may cause endothelial damage and cause DIC by activating intravascular coagulation, apart from causing platelet damage.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – YEP, HYB, UYM, ED, FRU; Design – YEP, HYB, UYM, ED, FRU; Supervision – YEP, HYB, UYM, ED, FRU; Data Collection and/or Processing – YEP, HYB; Analysis and/or Interpretation – YEP, HYB; Literature Search – YEP; Writing – YEP, HYB; Critical Reviews – YEP, HYB.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Członkowska A, Litwin T, Dusek P, Ferenci P, Lutsenko S, Medici V, et al. Wilson disease. *Nat Rev Dis Primers* 2018;4(1):21. [\[CrossRef\]](#)
2. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;86(5):1327-1330. [\[CrossRef\]](#)
3. Levi M. Disseminated intravascular coagulation. *Crit Care Med* 2007;35(9):2191-2195. [\[CrossRef\]](#)
4. Holtzman NA, Gaumnitz BM. Studies on the rate of release and turnover of ceruloplasmin and apoceruloplasmin in rat plasma. *J Biol Chem* 1970;245(9):2354-2358. [\[CrossRef\]](#)
5. Gow PJ, Smallwood RA, Angus PW, Smith AL, Wall AJ, Sewell RB. Diagnosis of Wilson's disease: an experience over three decades. *Gut* 2000;46(3):415-419. [\[CrossRef\]](#)
6. Asfaha S, Almansori M, Qarni U, Gutfreund KS. Plasmapheresis for hemolytic crisis and impending acute liver failure in Wilson disease. *J Clin Apher* 2007;22(5):295-298. [\[CrossRef\]](#)
7. Członkowska A, Litwin T, Karliński M, Dziezyc K, Chabik G, Czerska M. D-penicillamine versus zinc sulfate as first-line therapy for Wilson's disease. *Eur J Neurol* 2014;21(4):599-606. [\[CrossRef\]](#)
8. Hennemann HH, Hubertus H, Stocker WG. Schwere Nebenwirkungen bei der Therapie mit D-Penicillamin [Severe side-effects of treatment with D-penicillamine (author's transl)]. *Dtsch Med Wochenschr* 1975;100(32):1634-1638. [German] [\[CrossRef\]](#)
9. Donker AJ, Venuto RC, Vladutiu AO, Brentjens JR, Andres GA. Effects of prolonged administration of D-penicillamine or captopril in various strains of rats. Brown Norway rats treated with D-penicillamine develop autoantibodies, circulating immune complexes, and disseminated intravascular coagulation. *Clin Immunol Immunopathol* 1984;30(1):142-155. [\[CrossRef\]](#)
10. Santoro SA, Cunningham LW. Collagen-mediated platelet aggregation. Evidence for multivalent interactions of intermediate specificity between collagen and platelets. *J Clin Invest* 1977;60(5):1054-1060. [\[CrossRef\]](#)