Ann Vasc Dis Vol. 16, No. 2; 2023; pp 146–149

Online June 14, 2023
doi: 10.3400/avd.cr.22-00130

Case Report

Improvement in Quality of Life Following Celiprolol Hydrochloride Administration in a Patient with Vascular Ehlers–Danlos Syndrome: A Case Report

Kanichiro Shimizu, MD, PhD,[1] Yoshihiko Kameoka, MD,[1] Kenji Motohashi, MD,[1] Yohei Munetomo, MD,[1] Naoki Kurata, MD,[1] and Shunichi Sadaoka, MD, PhD[2]

A 40-year-old female, who underwent transcatheter arterial embolization due to acute bleeding from an iliolumbar artery, was subsequently genetically diagnosed with vascular Ehlers–Danlos syndrome. She experienced chronic anemia for many years due to the easy bruising of her whole body. The bruising improved with oral administration of celiprolol hydrochloride. There were no cardiac or vascular events during the 7 years following the transcatheter arterial embolization. Vascular Ehlers–Danlos syndrome requires specialized treatment that is scientifically proven to prevent a major vascular event. Proactive genetic diagnosis is recommended in patients suspected of having vascular Ehlers–Danlos syndrome after careful patient interview.

Keywords: vascular Ehlers–Danlos syndrome, transcatheter arterial embolization, celiprolol hydrochloride

Introduction

Although the clinical diagnosis of vascular Ehlers–Danlos syndrome (vEDS) is difficult due to its varied symptoms, genetic diagnosis is important for selecting a specialized treatment option.[1)]

Any surgical intervention is difficult and had high mortality in case of emergent complication such as acute bleeding, uterine rupture, and gastrointestinal perforation.[1)] Celiprolol hydrochloride administration is required for the long-term management of vEDS, as it reduces the risk of vascular events and is recognized as the only drug effective against vEDS.[2)]

We herein present a case of vEDS caused by bleeding from a ruptured aneurysm arising from a branch of the iliolumbar artery. Although the patient's symptoms and family history were unclear, the patient underwent genetic testing, which accurately diagnosed vEDS. Oral administration of celiprolol hydrochloride improved her symptoms of chronic anemia and, as a result, her quality of life.

Case Report

A 40-year-old woman was admitted to our institution with a complaint of sudden right lower quadrant abdominal pain. On physical examination, the right lower abdomen was swollen with elastic hardness, and the right femoral artery was poorly palpable compared with the opposite side. Her blood pressure was within the normal range (118/64 mmHg), and tachycardia (103 beats/min) was observed. The serum hemoglobin level was 14.1 g/dL and mildly decreased to 10.8 g/dL after 10 days. Contrast-enhanced computed tomography revealed a right retroperitoneal hematoma and an aneurysm arising from the branch of the right iliolumbar artery, which was suspected to be the cause of bleeding (**Figs. 1A** and **1B**), as well as the dissection of the right external iliac artery (**Fig. 1C**).

At the age of 24, she developed internal carotid artery stenosis and experienced spontaneous bruising or bruising from only minor trauma. Therefore, she was prescribed iron pills for iron deficiency anemia for several years. Nevertheless, her two pregnancies were uneventful. Physical

[1] *Department of Radiology, Kashiwa Hospital, The Jikei University School of Medicine, Kashiwa, Chiba, Japan*
[2] *Department of Radiology, Kyoundo Hospital of the Sasaki Institute, Tokyo, Japan*

Received: December 12, 2022; Accepted: April 18, 2023
Corresponding author: Kanichiro Shimizu, MD, PhD. Department of Radiology, Kashiwa Hospital, The Jikei University School of Medicine, 163-1 Kashiwashita, Kashiwa, Chiba 277-8567, Japan
Tel: +81-4-7164-1111, Fax: +81-4-7166-9374
E-mail: shimikan@jikei.ac.jp

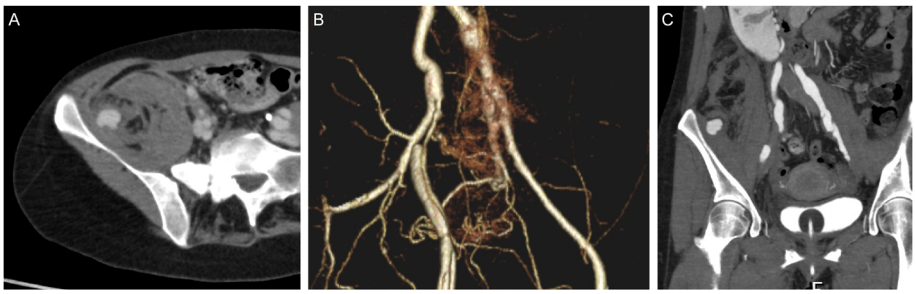

Fig. 1 Contrast-enhanced computed tomography shows the retroperitoneal hematoma and aneurysm arising from the branch of the right iliolumbar artery. (**A**) Axial image. (**B**) Coronal image. (**C**) Three dimensional reconstruction image shows stenosis due to the dissection of the right external iliac artery.

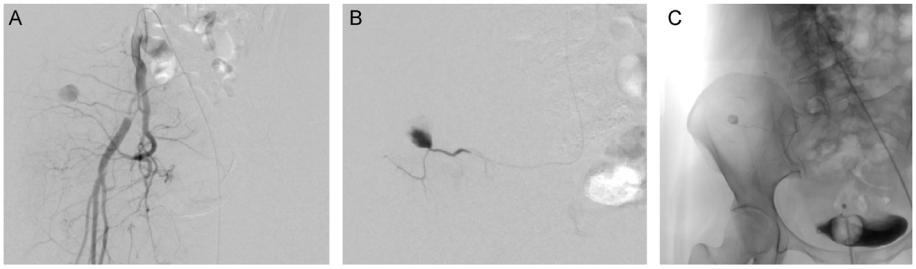

Fig. 2 (**A**) Right common iliac angiography shows an aneurysm arising from the right iliolumbar artery. (**B**) Microcatheter is selectively inserted in the affected artery and 0.7 mL of 1 : 2 mixture of n-butyl-2-cyanoacrylate (NBCA) and iodized oil is injected. (**C**) Disappearance of the aneurysm is confirmed by the right common iliac angiogram. A cast of the NBCA was formed in the aneurysm.

examination revealed scoliosis and clubfoot. Her family history included carotid cavernous fistula in her mother in her 50s, myocardial infarction in her maternal uncle in his 40s, and aortic dissection in her maternal aunt in her 60s.

Given her medical history, we suspected that the patient might have vEDS. Emergent transcatheter arterial embolization (TAE) for retroperitoneal hemorrhage was planned with a cardiovascular surgeon on standby. TAE was performed under local anesthesia with the left femoral artery approach, considering the right external iliac artery stenosis due to dissection. The anterior wall of the femoral artery was punctured under ultrasonographic guidance to prevent injury to the vessel. A right common iliac angiogram using a 5Fr-RIM catheter (Cook, Bloomington, IN, USA) via a 5Fr-25 cm sheath introducer revealed an aneurysm arising from the branch of the right iliolumbar artery and right external iliac artery stenosis (**Fig. 2A**). A 2.5-Fr Renegade (Boston Scientific, Natick, MA, USA) was inserted near the aneurysm (**Fig. 2B**). Disappearance of the aneurysm was confirmed by injecting 0.7 mL of 1 : 2 mixture of n-butyl-2-cyanoacrylate (NBCA) and iodized oil from the microcatheter (**Fig. 2C**). She was discharged on the 8th day of hospitalization without complications. vEDS was genetically diagnosed based on a heterozygous mutation in the *COL3A1* gene. Thus, administration of 400 mg celiprolol hydrochloride commenced, which improved bruising symptoms and resolved the iron deficiency anemia. The iron prescription was then discontinued. Serum hemoglobin, iron, and ferritin levels improved with celiprolol hydrochloride than that with iron administration (**Fig. 3**). There were no cardiac or vascular events during the 7 years following the TAE. She underwent contrast-enhanced computed tomography of the entire body every year to evaluate the internal carotid artery and the dissection of the right external iliac artery. The ankle-brachial index was measured every year to evaluate lower extremity ischemia by the dissection of the right external iliac artery. There were no changes in the morphology of the main arteries, including the internal carotid artery and external iliac artery, during the follow-up period (**Fig. 4**). The ankle-brachial index also remained in the normal range.

The study participant provided informed consent for participation in this case study and for its publication. This study was carried out in accordance with the principles embodied in the Declaration of Helsinki, its revisions, and any guidelines approved by the institutional review board. Our institutional review board approved this study (34-324).

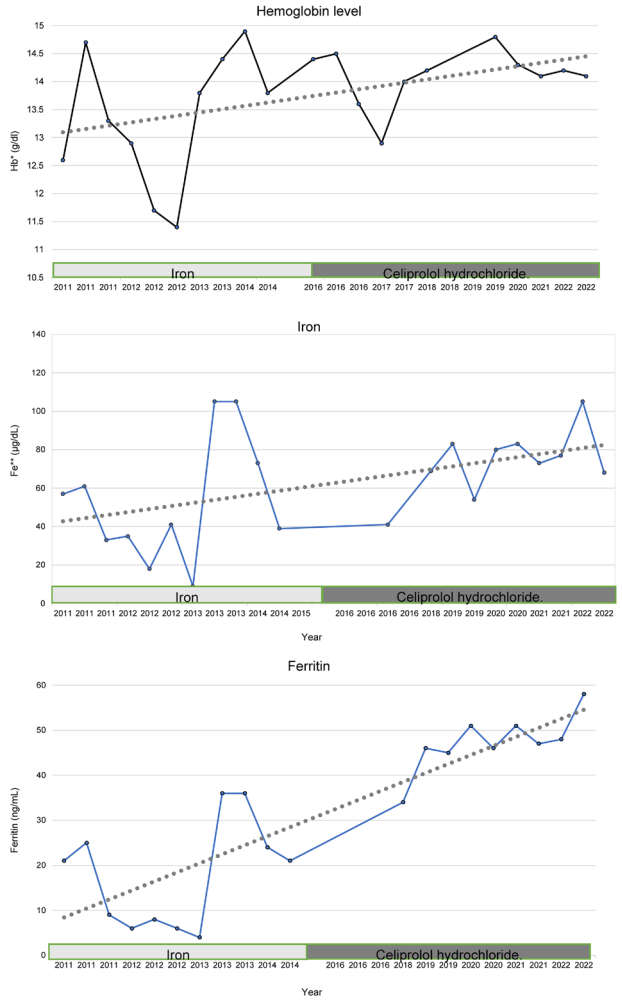

Fig. 3 The graphs show the changes in (**A**) serum hemoglobin level, (**B**) iron level, (**C**) ferritin level after taking celiprolol hydrochloride instead of iron. The approximate line (dotted line) shows an upward trend with the celiprolol hydrochloride intake.
*Hb: hemoglobin; **Fe: iron.

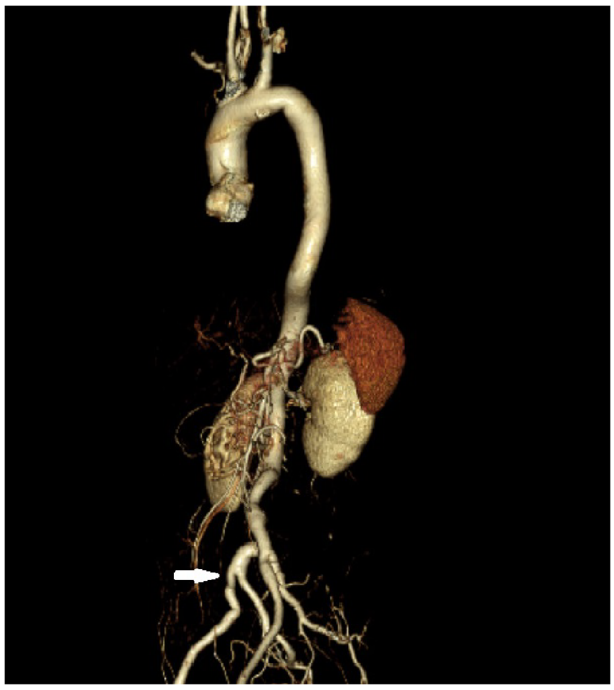

Fig. 4 Contrast-enhanced computed tomography of the entire body 7 years after transcatheter arterial embolization shows no change in the morphology of the main artery. Although the cast of the n-butyl-2-cyanoacrylate in the right iliolumbar artery has disappeared, there is no evidence of recurrence of the aneurysm. Stenosis of the right external iliac artery due to the dissection has remained (arrow).

Discussion

vEDS is a dominant genetic disorder that is characterized by the rupture of aneurysms, arterial dissection, digestive rupture, and pregnancy-related complications, such as uterine rupture and bleeding at a young age.[1] Mutation of the *COL3A1* gene, which encodes type III collagen, the major protein forming the walls of the vessels and digestive tract, is the cause of such complications.[3,4] The *COL3A1* mutation should be proven for the diagnosis of vEDS because the clinical symptoms are often similar to those of Loeys–Dietz syndrome, Marfan syndrome, and other familial diseases. Mutations in *COL3A1* are currently the only explanation of the vEDS phenotypic spectrum.[5] The 2017 international guidelines for vEDS recommended genetic testing for patients who met the major criteria such as the rupture of aneurysms, arterial dissection, and family history and minor criteria such as facial, dermatological, and osteoarticular abnormalities.[4] The major diagnostic criteria for our patient were external iliac artery dissection and rupture of the iliolumbar artery aneurysm. However, her two pregnancies had normal courses. On physical examination, clubfoot and scoliosis were expected, but the typical symptoms were unclear. Although aortic dissection and myocardial infarction were observed in her family at a young age, no family members were diagnosed with vEDS. All findings were minor and nonspecific, except for arterial dissection and ruptured aneurysms. Therefore, careful examination and proper interviews for gaining insight into the family history were important.

The patient underwent TAE for retroperitoneal hemorrhage. Several authors have reported successful TAE treatment for vascular events.[6,7] Byers et al.[5] recommended minimally invasive treatment whenever possible. Surgical intervention should be avoided as much as possible due to the fragility of the vessels, which can be difficult to repair.[8] Liquid embolic material was used for embolization in our case. Unlike coils, liquid embolic material did not generate radial force and was believed to reduce vascular

aggression.[9] Although it is reported that embolization using NBCA causes reflux, which causes adhesion to the microcatheter and non-target embolization, the risk of organ infarction by the reflux of NBCA was estimated to be minimum because the affected artery was distal to the internal iliac artery.[10]

Even in these undiagnosed cases, it is important to suspect vEDS to determine the appropriate treatment strategy in an emergency.

Celiprolol hydrochloride, a mixed β1 antagonist and β2 agonist, is the only drug with a proven efficacy in vEDS.[2] This study suggested that the time to vascular events was prolonged by the administration of celiprolol hydrochloride. Moreover, Baderkhan et al.[11] reported the effectiveness of celiprolol for fetal vascular events in patients with vEDS. A dose of 400 mg/day of celiprolol hydrochloride was recommended in these reports.[2,11] Our patient experienced improvement regarding easy bruising. In addition, serum iron and ferritin levels improved despite the discontinuation of iron supplementation. Although there have been several reports regarding the efficacy of celiprolol for major vascular events, to our knowledge, this is the first report to show the efficacy of celiprolol for minor symptoms that worsen the patient's quality of life. The diagnosis of vEDS is important for determining the most effective treatment strategies for both the emergent complication and the long-term follow-up. Proactive genetic diagnosis is recommended in patients suspected of having vEDS after careful patient interview.

Conclusion

The first step toward appropriate treatment is to consider vEDS as a possible diagnosis after careful patient interview and examination. The variety of symptoms and diagnostic methods for this disease should be understood.

Acknowledgments

We would like to thank Editage for the English editing of the manuscript. No funding was provided for this study.

Disclosure Statement

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: KS
Interventions: KS, YK
Data collection: YM, KM
Data analysis and investigation: NK
Writing-original draft preparation: KS
Writing-review and editing: SS
Resources: KS
Supervision: SS
Critical review and revision: all authors
Final approval of the article: all authors
Accountability of all aspects of the work: all authors

References

1) Byers PH. Vascular Ehlers-Danlos Syndrome. GeneReviews®[Internet], 2019. Retrieved May 22, 2023, from https://www.ncbi.nlm.nih.gov/sites/books/NBK1494/
2) Ong KT, Perdu J, De Backer J, et al. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial. Lancet 2010; **376**: 1476-84.
3) Pepin MG, Schwarze U, Rice KM, et al. Survival is affected by mutation type and molecular mechanism in vascular Ehlers–Danlos syndrome (EDS type IV). Genet Med 2014; **16**: 881-8.
4) Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017; **175**: 8-26.
5) Byers PH, Belmont J, Black J, et al. Diagnosis, natural history, and management in vascular Ehlers–Danlos syndrome. Am J Med Genet C Semin Med Genet 2017; **175**: 40-7.
6) Sugawara Y, Ban K, Imai K, et al. Successful coil embolization for spontaneous arterial rupture in association with Ehlers-Danlos syndrome type IV: report of a case. Surg Today 2004; **34**: 94-6.
7) Kamalanathan KC, Barnacle AM, Holbrook C, et al. Splenic rupture secondary to vascular Ehlers–Danlos syndrome managed by coil embolization of the splenic artery. European J Pediatr Surg Rep 2019; **7**: e83-5.
8) Malz SB, Fantus RJ, Mellett MM, et al. Surgical complication of Ehlers-Danlos syndrome type IV: case report and review of the literature. J Trauma 2001; **51**: 387-90.
9) Xiao N, Lewandowski RJ. Embolic agents: coils. In: Ray CE Jr ed. Seminars in Interventional Radiology. New York: Thieme Medical Publishers, Inc, 2022: 113-8.
10) Hill H, Chick JFB, Hage A, et al. N-butyl cyanoacrylate embolotherapy: technique, complications, and management. Diagn Interv Radiol 2018; **24**: 98-103.
11) Baderkhan H, Wanhainen A, Stenborg A, et al. Celiprolol treatment in patients with vascular Ehlers-Danlos Syndrome. Eur J Vasc Endovasc Surg 2021; **61**: 326-31.