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Vascular Ehlers-Danlos Syndrome Diagnosed in a Patient Initiating Hemodialysis

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Received 2 June 2019; revised 30 July 2019; accepted 31 July 2019; published online 8 August 2019

Kidney Int Rep (2019) **4,** 1646–1648; https://doi.org/10.1016/j.ekir.2019.07.020

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disorder that is caused by defects in collagen, other extracellular matrix proteins, or associated enzymes. As of 2017, the syndrome comprises 13 subtypes with a significant overlap in features.[1] Among them, vascular EDS (vEDS), the most severe subtype in terms of clinical manifestation and mortality, is caused by a mutation of the *COL3A1* gene encoding collagen type III alpha 1 chain. With regard to signs and symptoms, in contrast to classical EDS involving flexible joint structures and stretchy cutaneous tissue, vEDS is characterized by translucent skin; fragile arteries, muscles, and internal organs; and sometimes a characteristic facial appearance. We recently encountered a young male patient with advanced chronic kidney disease who needed to start hemodialysis (HD). During his surgeries to form vascular access, his brachial artery (BA) and its branch arteries were unusually friable, which led us to believe that he had profound vascular fragility due to some congenital disorder. Here, we describe a clinical history ending with a vEDS diagnosis and a practical approach to vEDS complicated by end-stage kidney disease (ESKD).

CASE PRSENTATION

A 25-year-old man was referred with ESKD of unknown etiology (renal biopsy was not performed) with a serum creatinine level of 5.6 mg/dl (estimated glomerular filtration rate of 11.7 ml/min per 1.73 m^2), requiring initiating of renal replacement therapy. The patient chose to undergo HD. His past medical history was significant for diabetes, dyslipidemia, hypersensitivity pneumonitis, a benign skull base tumor, and congestive heart failure for which he was hospitalized twice in the past year. His left ventricular function was markedly reduced, although the cause was unable to be defined. He also had paresis of his left arm caused by a brachial plexus injury at birth.

To initiate HD, vascular access surgery was scheduled. An arteriovenous fistula is known to sometimes exacerbate heart failure due to the marked hemodynamic changes related to a large increase in blood flow, although its impact on cardiovascular mortality remains unknown.[2] The risk is considered higher particularly in those with preexisting cardiac dysfunction. Superficialization of the BA is an established method and is often used in Japan as an alternative vascular access technique in patients for whom an arteriovenous fistula cannot be created.[3] Because the patient had had repeated episodes of decompensated heart failure and showed an ejection fraction less than 30%, we decided to perform a right-sided BA superficialization to form a vascular access. However, in spite of the experienced vascular surgeon's best efforts, a gentle traction of silicone vessel loop completely transected the BA, which was immediately repaired by a primary end-to-end anastomosis (Figure 1). Although the blood flow was successfully maintained, this event forced abandonment of the BA superficialization of this side. A month later, a contralateral, left-sided BA superficialization was successfully

completed in a second surgery, although the branch artery was also easily lacerated. We suspected that he was suffering from a connective tissue disorder, particularly vEDS, although he did not have other typical features, such as thin, translucent skin, hypermobility of small joints, or characteristic facial appearance, but his father had a history of subarachnoid hemorrhage in his thirties. We performed genetic analysis of hereditary thoracic aortic aneurysm and dissection using thoracic aortic aneurysm and dissection multigene panel testing for 14 genes (Kazusa DNA Research Institute, Chiba, Japan), which was approved by the University of Tokyo Hospital ethics committee (G-1538). We concluded that the p.Gly801Asp (c.2402G>A) variant within exon 36 of *COL3A1* gene (NM_00090.3) was likely to have been responsible for causing his deleterious arterial phenotypes. We could not examine the cosegregation with vascular phenotypes in his family members. However, the variant disrupts an amino acid glycine in the $[Gly\text{-}Xaa\text{-}Yaa]_{343}$ repeats of the triple helical region of the type III pro-collagen molecule, and has been reported to induce vEDS.[4] The patient was finally diagnosed with vEDS, based on a constellation of his friable arteries and the result of genetic analysis.

Three months later when his renal function had further deteriorated, HD had to be initiated. To avoid the potential risk of mechanically damaging the elevated left-sided BA with repeated needle punctures during HD sessions, we decided to implant a tunneled cuffed catheter to his right jugular vein. Using this vascular access, we then successfully conducted HD.

DISCUSSION

In this case, unexpected BA injuries during the patient's surgeries to establish a vascular access enabled us to consider the possibility of a congenital vascular fragility including vEDS. vEDS should be suspected in individuals, particularly those younger than 40, with any one of the major diagnostic criteria, including arterial aneurysms/dissection/rupture, intestinal rupture, uterine rupture during pregnancy, or a family history of vEDS. There are also several minor diagnostic criteria: thin, translucent skin (especially noticeable on the chest/abdomen), and a characteristic facial appearance (thin vermilion lips, micrognathia, narrow nose, prominent eyes).[1] The criteria listed do not include vascular injuries during gentle surgical manipulation (as seen in our patient), which we considered equivalent to arterial aneurysms/dissection/rupture, one of the major criteria of vEDS.

vEDS in ESKD has not been widely reported.[5] When it comes to renal replacement therapy modality choices, HD may be the only option, as both kidney transplantation and peritoneal dialysis may lead to hemorrhagic complications during surgery.[6] When HD is to be initiated, the current case suggests that vascular access surgery should be avoided or conducted with caution and a tunneled cuffed catheter could be placed without the complications seen with arterial surgery.

Past studies on vEDS genetics analyzed the relationship of the *COL3A1* genotype to the vascular phenotype.[4,7,8] We revealed that the current case had a heterozygous and likely pathogenic variant of *COL3A1* (c.2402G>A;p.Gly801Asp)[4] within the triple helical tripeptide Gly-Xaa-Yaa repeat region, based on the American College of Medical Genomics–Association for Molecular Pathology classification guideline.[9] The substitution of glycine by aspartic acid is known to result in increased risk of overall survival in patients with vEDS. Mutated residues other than Asp were mostly either Val or Glu, and this selection bias is positively correlated to the triple helix destabilizing effects.[S1] Most of the remaining pathogenic variants are located within potential splice sites leading to an in-frame exon skipping and generation of a shortened translated product. These 2 genotypes lead to arterial complications and early mortality.[8]

Given the patient's past medical history of ESKD, diabetes, benign brain tumor, and dyslipidemia all in his 20s, some other genetic disorder may be undiagnosed because one genetic disease or disorder is unlikely to cause all the problems. We do not exclude the possibility that the current case is a newly reported vEDS subtype with a concurrently developing metabolic and tumorigenesis phenotype as above, but future case reports with the same *COL3A1* mutation should be collected before making such a determination.

In summary, we reported a vEDS case with ESKD. A genetic disease was suspected when the patient underwent vascular access surgery, and the definitive diagnosis was established by subsequent multigene panel

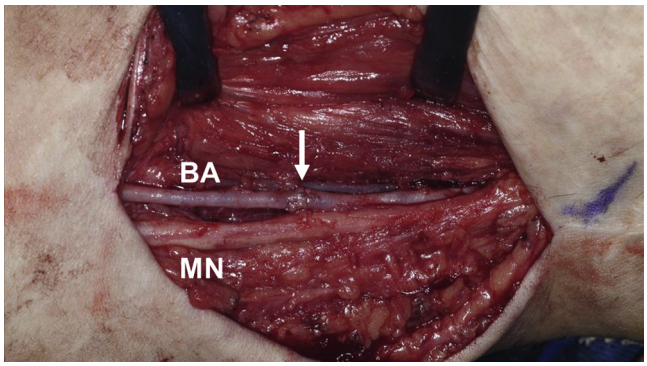

Figure 1. The right-sided brachial artery (BA) superficialization was performed to create a vascular access necessary for maintenance hemodialysis. Arrow denotes a lacerated site of the brachial vessel that was sutured with 7–0 Prolene. MN, median nerve.

Table 1. Teaching points

1. Unexpected arterial injury, such as laceration and transection, during a surgery to establish VA indicates the presence of congenital vascular fragility.
2. A multigene panel testing designated for hereditary aortic aneurysm and dissection may help secure the diagnosis.
3. For a patient with vascular Ehlers-Danlos syndrome with end-stage kidney disease, VA surgery should be avoided or conducted with caution and a tunneled cuffed catheter may be preferred.

VA, vascular access.

testing (Table 1). In cases requiring renal replacement therapy, HD with installment of a tunneled cuffed catheter is considered one of the best solutions from the viewpoint of medical safety (Table 1).

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Reference.

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