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Case Report

Ballooning and Bursting of Barrels and Pipes: A Rare Case of Suspected Vascular Ehlers–Danlos Disease

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Abstract: Vascular Ehler–Danlos disease (vEDS), a rare subtype of a rare disease, is a life-threatening disease, with an increased risk for spontaneous vascular or visceral rupture. These patients have fatal complications ranging from vascular aneurysms, dissection, and rupture of systemic vessels to frequent thromboembolic events, the common causes of death in these individuals with a shortened life span. In the present case, a 28-year-old male with history of shoulder dislocations and spontaneous colon perforation presented to the primary care clinic with right lower extremity swelling and pain. His history includes presentation to the emergency department with left lower leg swelling with compartment syndrome one year prior. A CT angiogram of lower extremities and abdomen revealed acute arterial extravasation of the left posterior tibial artery, indicating a ruptured aneurysm along with aneurysms of the splenic artery and left common iliac artery. He was treated with a saphenous vein graft, but was associated with post-operative complications that necessitated below-knee amputation. CT angiogram of his right leg revealed occlusion of the anterior tibial and peroneal arteries with aneurysms, and, ultimately, he was referred to a tertiary care center for aneurysm embolization. This case report emphasizes the frequent vascular complications encountered in vascular EDS patients, and thus advocates for close and regular monitoring for early referral and surgical management of their vascular anomalies. Finally, genetic counseling and screening of asymptomatic family members should be routinely implemented in these patients.

Keywords: Ehler–Danlos syndrome; collagen; fibrosis; vascular Ehler–Danlos syndrome; aneurysm and arterial rupture

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1. Background

Ehler–Danlos syndrome is the term used for a group of relatively rare genetic disorders of connective tissue that are characterized by several features, including skin hyperextensibility, joint hypermobility, and tissue fragility. The overall frequency of EDS is 1 in 5000, with EDS hypermobility type (hEDS) being by far the most common subtype [1]. The prevalence of the vascular form of EDS (vEDS) is not well studied. Nevertheless, estimates based on the currently available data suggest a frequency of at least 1 in 100,000–250,000 population, thereby accounting for approximately 4% of all EDS cases [2]. In total, 80% of the patients with vEDS experience a major vascular event or rupture of an internal organ by age 40 due to vascular fragility [2]. As a result of these ripple effects, there is a shortened lifespan with a median age of death of 48 years in this subset of patients [2].

COL3A1 encodes a type III collagen, which forms the foundational and paramount protein in the wall of systemic blood vessels and hollow organs [3,4]. Any stumbling blocks impeding the synthesis of this vital protein can derail the integrity of the vascular wall, thus

instigating deleterious ramifications. Therefore, vascular EDS (vEDS) typically manifests as fragility of the vascular, urinary, intestinal, and reproductive systems [3].

We present a case where a patient with a past history of recurrent shoulder dislocations, spontaneous colon rupture, and vascular aneurysm presented with right lower limb swelling and discoloration. A CT angiogram revealed occlusion of the popliteal and peritoneal arteries, and thus the patient was referred to the tertiary care center for aneurysm embolization. His previous ruptured aneurysm of the left posterior tibial artery was repaired with a saphenous vein graft, but, unfortunately, the post-operative course was confronted with complications, thence necessitating a below-knee amputation. This case emphasizes the underlying proclivity of vEDS patients to repeated aneurysms and hollow organ rupture due to defective synthesis of type III collagens. The cardinal function of collagens in maintaining the integrity of vessel wall and systemic organs is curtailed, thus affecting their physiological properties including elasticity, resilience, contraction, and dilation.

2. Case Presentation

Patient is a 28-year-old male with past medical history of tobacco/marijuana abuse, multiple spontaneous shoulder joint dislocations, and a history of spontaneous colon perforation (s/p colon resection 1 year ago). He noticed bruises and pain around his left ankle initially, before presenting with right lower extremity pain/swelling since 1 day. Eventually, pain and swelling gradually progressed, necessitating his ED visit. Pain was described as a muscle cramp in his calf, constant, non-radiating, with associated numbness, and worsening difficulty moving his left toes present for several days.

Initial vitals were mildly elevated blood pressure (142/74), tachycardia (HR: 91 bpm), normal body temperature, and oxygen saturation of 98%. On physical examination, erythematous skin discoloration is present on the medial aspect of the right calf, along with purplish skin discoloration at the right medial malleolus. The right leg was swollen, tense, warm, and tender to touch. Right calf pain with plantar and passive flexion of the right foot was present. Dorsalis pedis and posterior tibial pulsations were only palpable with a Doppler. A below-knee amputation of left leg is present. His fingers, wrists, and knees were hypermobile bilaterally. Cardiovascular and other system examinations were otherwise normal.

Imaging evaluation with Vascular Doppler Ultrasonography was suggestive of peripheral arterial disease in the peroneal and posterior tibial arteries. CT angiogram of abdomen and pelvis with runoff revealed vascular changes and aneurysms in the superior mesenteric artery, splenic artery, left iliac artery, and with distal occlusion of the anterior tibial and peroneal arteries on the right. There was occlusion of the popliteal artery on the left with no flow distally and a below-the-knee amputation on the left. He was transferred to a tertiary specialized center to undergo aneurysmal embolization.

Of note, this patient presented one year ago with worsening left leg swelling for one day with associated pain worse with movement and palpation. He was found to have diffuse swelling of the left posterior leg, indicating compartment syndrome (Figure 1) extending below the knee to the ankle with bruising, numbness, paresthesia, and decreased movement at the toes. Radiological evaluation with CT Angio Abdomen and bilateral lower extremity (Figures 2 and 3) revealed an active arterial extravasation from the left posterior tibial artery just distal to its origin from the tibioperoneal trunk, reflecting a ruptured aneurysm given his history.

The patient underwent repair of the ruptured left posterior tibial artery aneurysm with a reverse saphenous vein interposition graft. Unfortunately, the intra-operative and post-operative course was associated with complications that ultimately resulted in left below-the-knee amputation. Biopsy and histopathological examination of the left posterior tibial artery showed thickening of the muscularis propria with fibrosis consistent with Ehlers–Danlos disease. Furthermore, an immunology evaluation at previous presentation showed negative ANA titer, ANCA proteinase 3 negative, negative CCP antibody, negative anti-

DNA antibody, negative DS antibody, rheumatoid factor negative, and myeloperoxidase antibody negative. The rheumatologist made the diagnosis of vascular EDS and referred the patient to be followed up at a specialist center and for genetic counseling. He was referred to volunteer home health physical therapy. Moreover, pertinent clinical studies, clinical assays, proteomics, and metabolomics to confirm the diagnosis of vEDS were not performed as the patient was lost to follow up.

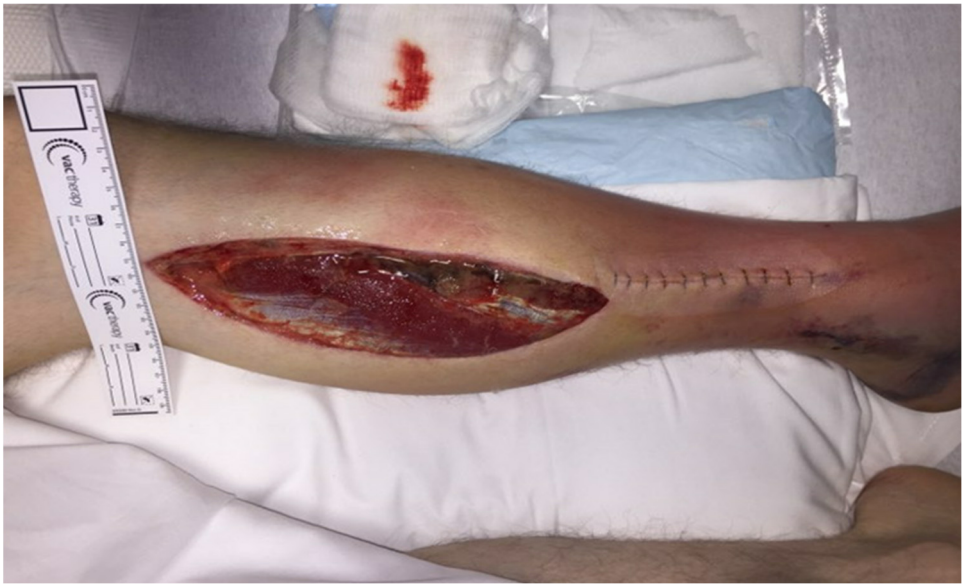

Figure 1. Fasciotomy following complication of acute compartment syndrome.

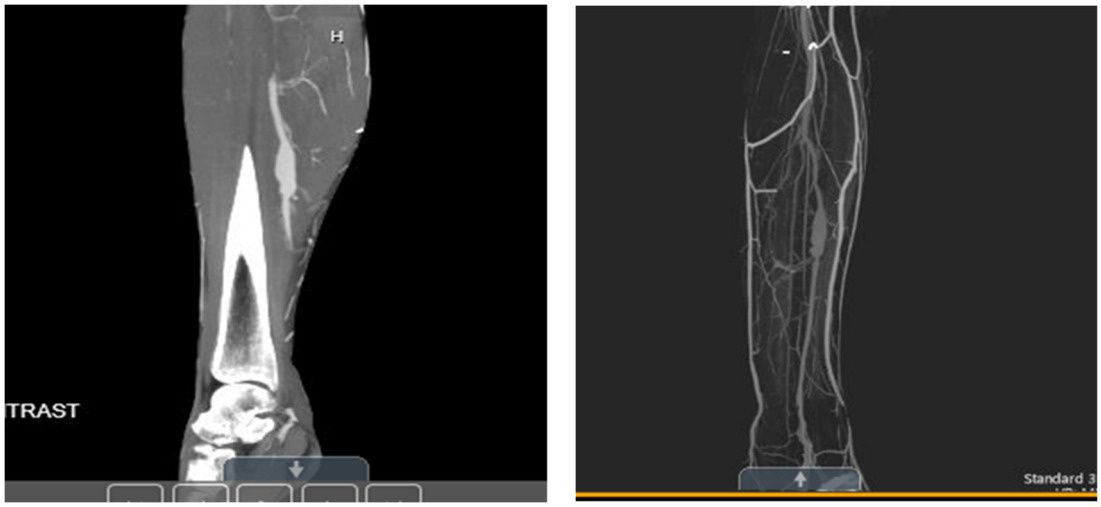

Figure 2. CT angiogram of the left lower extremity: Above shows a partial thrombosed 1.1 cm aneurysm of the left posterior tibial artery, which is otherwise patent to the left leg. A 1.8 cm left common iliac artery aneurysm. A 1.2 cm aneurysm with probable dissection of the left external iliac artery extending to the common femoral artery. Recommend correlation for underlying connective tissue disorder or vasculopathy. Additionally, it showed interval increase in size of previously identified mixed morphology saccular and fusiform aneurysmal segment of the proximal posterior tibial artery from comparison. Given a slight interval increase in size, this may reflect a pseudoaneurysm, although an aneurysm is favored. Correlation with clinical history may be beneficial to determine if infectious etiology for aneurysm is a possibility.

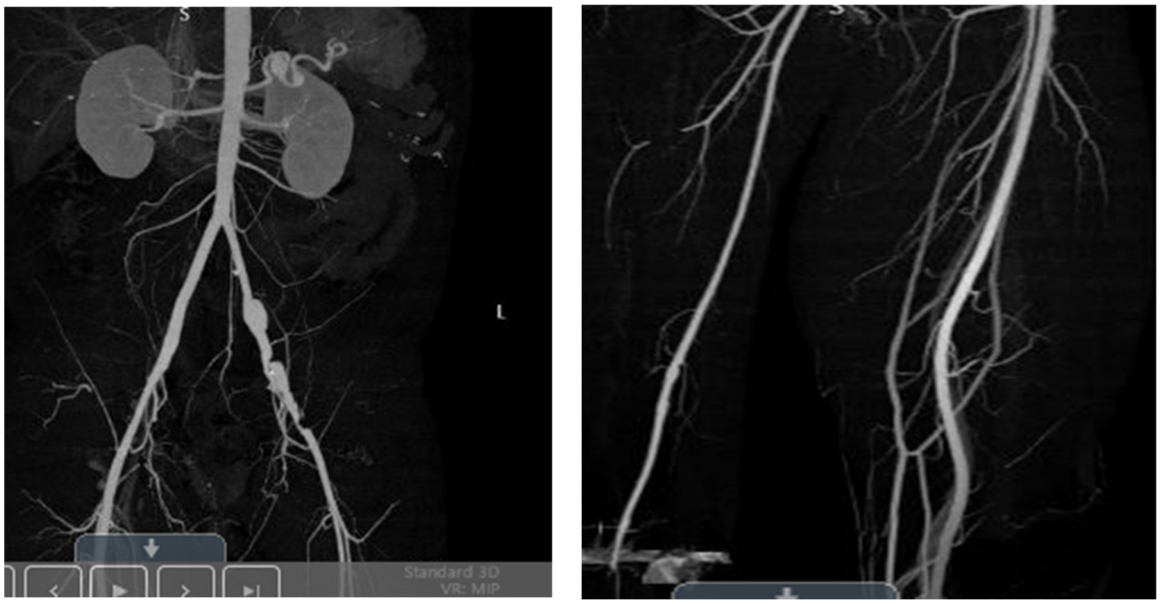

Figure 3. Images from CT angiogram abdomen and pelvis with B/L runoff, showing multiple arterial aneurysms and thrombotic occlusion. Active arterial extravasation from the L. posterior tibial artery just distal to its origin from the tibioperoneal trunk w/surrounding facial and subcutaneous edema. May reflect a ruptured aneurysm, given patient's history. Splenic artery and left common iliac artery aneurysms. Diffuse dilatation of the left external iliac artery 10 mm in diameter with an intimal dissection flap.

3. Discussion

Ehler–Danlos syndrome (EDS) is an inherited disorder characterized by skin, vascular, dental, and joint symptoms [5]. It was initially described by Edvard Ehlers and Henri-Alexandre Danlos, where they discovered patients presenting with excessive elasticity and easy bruising of the skin (1901) and fibrous pseudo tumors (1908), respectively [5–7]. Consequently, the term Ehlers–Danlos syndrome is coined by Pommeau-Delille and Soussie in 1984 [7]. It was classified into I–VIII subtypes, with each subtype varying in clinical presentation and severity [5]. The overall prevalence of EDS is estimated to be around 1 in 5000–100,000 [8]. Our present case is suspected vascular EDS. Vascular EDS accounts for approximately 10–20% of all EDS cases reported. Our patient was presented to the emergency department with vascular complications at 28 years. Although 60% of vEDS cases are diagnosed before the age 18 due to their positive family history, their clinical presentation is delayed until their end-organ complications crystalize and unfold [9]. Rupturing of arterial vessels and hollow digestive organs are the most common complications in vEDS, because of which, these patients end up presenting to the emergency department [10]. Apparently, it is reported that vascular complications surface in 25% of the vEDS patients before 20 years, whereas in 80% of these patients, vascular sequelae come to light around the age of 40 years [10].

In EDS, a defect in collagen synthesis and processing is present in varying proportions in all of the sub-types. In vascular EDS, the underlying defect is due to diminution in the percentage of type III collagen secondary to variants in gene COL3A1 [4,8,11]. Due to this defective collagen synthesis, the vessel wall becomes fragile and becomes prone to rupture, occlusions, severe stenosis, aneurysms, bleeding, and dissections in the aorta, extremities, uterus, and bowel wall.

Vascular EDS is characterized by major criteria including arterial dissection [aneurysm, arteriovenous fistula, and arteriovenous fistula], gastrointestinal rupture [sigmoid colon, small bowel, and stomach], uterine perforation, and family history of EDS [9]. Some of the minor criteria included in the diagnosis include increased skin fragility, typical facial features (micrognathia, thin vermilion of lips, narrow lips, and prominent eyes), acrogeria

(wrinkled appearance of the extremities), hypermobility of joints, joint dislocations, tendon rupture, early onset varicose veins, club foot, and pneumothorax [9]. However, the typical presentation of adults with vascular EDS can range from retroperitoneal bleeding and uterine bleeding to shock. Uncommonly, patients with vascular EDS can present with muscle pain, muscle cramps, tendon contractures, seizures, and ischemic stroke [12]. Once the diagnosis of vascular EDS is suspected based on the clinical spectrum and family history, targeted gene testing and comprehensive genetic testing are necessary for confirmation of diagnosis [9]. A CT angiograph is more preferrable than MRI angiography because it is widely available, has less chance of radiation exposure, and is a better choice in unstable patients [13].

Management of patients with vascular EDS requires teamwork involving close coordination between primary care physicians, surgeons, gynecologists, intervention radiologists and psychologists, and physical therapists [11]. Vascular complications including dissection, rupture, occlusion, and aneurysms are managed with open surgery or endovascular techniques including coils, rings, plugs, glue, and shunts [14–16]. Due the vascular vulnerability associated in this disorder, surgical interventions are associated with a high risk of complications and mortality [17–20]. Post-operative bleeding (37%), graft-related issues (40%), procedure related morbidity (46%), and overall mortality (35–68%) in vEDS are relatively high, and efforts should be made to identify them at earlier stages [21]. Keeping in mind the vulnerability of patients with vascular EDS to develop vascular anomalies, these patients should be monitored for the occurrence of aneurysms, dissections, and rupturing of the vasculature of the abdomen, uterus, and extremities. In this regard, conventional arterial angiography is not routinely recommended because, given the vascular tissue fragility due to defective collagen, they might be at increased proclivity of developing procedure induced arterial tears, dissections, and aneurysms [22]. Vascular complications, including bleeding at the site of arterial injury and death, are reported between at least 25% and 5.6% of the vascular EDS patients undergoing angiography [23,24]. To avert these complications from happening, non-invasive monitoring strategies such as Doppler ultrasound, CT angiogram, and MRI angiogram are more preferrable for surveillance in these patients [25]. Studies indicate that these patients should be monitored for every 18 months even in the presence of normal vascular morphology [9]. Celiprolol is a partial β1-andrenoceptor antagonist with partial β2 agonist activity and has been shown to increase collagen synthesis via acting through transforming growth factor β, thus being associated with a three-fold reduction in arterial events as compared to controls in vEDS patients [26,27]. Genetic counseling, lifestyle modification, and regular low-intensity exercise should be advocated in these patients [28].

4. Research and Future Directions

Since there is no specific therapy to manage vascular EDS, manipulating the gene expression of collagen gene through RNA-interfering technology to countervail the COL3A1 variant should be explored as a therapeutic option [11]. The role of the angiotensin receptor II blockade has been tested, and currently clinical trials are underway to assess their clinical efficacy in reducing the vascular complications in vEDS [29]. Lastly, favorable prognosis in these groups of patients is dependent on early recognition of vascular complications, usage of non-invasive imaging for modalities, surgical interventions to restore tissue circulation, and regular monitoring for recurrent vascular complications.

5. Conclusions

Vascular EDS should be recognized by positive family history, vascular complications (arterial aneurysm, stroke, intestinal rupture, and uterine rupture), characteristic facial appearance, fragile skin, and aged skin of extremities. Histopathology of vascular tissues shows a thickening of the muscularis propria with fibrosis consistent with Ehlers–Danlos disease, not vasculitis, as there was no intimal inflammation or destruction consistent with vasculitis. Vascular complications such as aneurysm and rupture are managed with

endovascular interventions. Endovascular procedures in patients with vascular EDS have an increased risk profile due to the delicate vasculature. Close surveillance of these patients by primary care physicians and early referral to surgery will prevent complications, and this will result in favorable prognosis with reduced morbidity and mortality.

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