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CHALLENGES IN THE MANAGEMENT OF PATIENTS WITH VASCULAR EHLERS-DANLOS SYNDROME: LESSONS FROM THREE CLINICAL CASES

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ABSTRACT

Vascular Ehlers-Danlos syndrome (vEDS) is one of the most severe heritable connective tissue disorders, caused by pathogenic variants in *COL3A1* and characterized by arterial fragility, premature mortality, and a high burden of vascular events. Management remains particularly challenging, requiring careful balance between the risks of intervention and the prevention of catastrophic complications. We present three cases of genetically confirmed vEDS that exemplify the complexity of patient care in this setting. These cases underline the importance of early referral to expert centers, where multidisciplinary care, genetic counseling, and structured follow-up can be guaranteed. They also highlight the central role of therapeutic adherence and long-term surveillance, as interruption of validated medical therapy may lead to life-threatening vascular events. Pharmacological treatment with celiprolol remains the first strategy supported by randomized trial evidence, while recent data suggest that the addition of angiotensin receptor blockers may further reduce vascular risk. Nevertheless, outcomes remain poor, and the prognosis of vEDS continues to be dominated by recurrent arterial complications despite optimal management. Conservative strategies are generally preferred, with invasive interventions reserved for life-threatening circumstances and best performed in specialized centers. These cases underscore both the progress made and the unmet need for novel therapeutic options to improve outcomes in this high-risk population.

KEYWORDS

Vascular Ehlers-Danlos syndrome, multidisciplinary management, therapeutic adherence, celiprolol, long-term surveillance

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LEARNING POINTS

- Vascular Ehlers-Danlos syndrome (vEDS) is a rare inherited connective tissue disorder marked by extreme arterial fragility, requiring high clinical suspicion to avoid misdiagnosis and inappropriate interventions.
- Strict adherence to evidence-based pharmacological therapy and structured long-term follow-up are crucial, as treatment discontinuation may lead to rapid and life-threatening vascular events.
- Management should be centralized in expert centres with a multidisciplinary approach, where individualized and predominantly conservative strategies can optimize outcomes in this high-risk population.

INTRODUCTION

Vascular Ehlers-Danlos syndrome (vEDS) is a rare autosomal dominant connective tissue disorder caused by pathogenic variants in the *COL3A1* gene, which encodes the pro-α1 chain of type III collagen, a major structural component of blood vessels and hollow organs. The resulting tissue fragility predisposes affected individuals to life-threatening complications, including spontaneous arterial dissections, aneurysms, ruptures, and visceral perforations[1]. Median life expectancy of individuals with vEDS remains shorter than that of the general population, with arterial events representing the leading cause of morbidity and mortality[2].

Diagnosis is often challenging, as clinical manifestations may mimic more common vascular conditions such as vasculitis, fibromuscular dysplasia, or even venous thrombosis. Early recognition and referral to specialized centres are therefore essential to avoid inappropriate interventions and to optimize patient management. Genetic testing represents the gold standard for confirming the diagnosis and allows appropriate familial screening[2].

Therapeutic management of vEDS is particularly complex. Surgical and endovascular interventions are associated with high perioperative risks due to the extreme fragility of connective tissue and are generally reserved for life-threatening emergencies. For this reason, pharmacological treatment and structured surveillance are the mainstays of care. Among pharmacological strategies, celiprolol, a cardioselective β-blocker with β2-agonist activity, has demonstrated efficacy in reducing vascular events in the BBEST trial[3]. More recently, the ARCADE study provided additional evidence suggesting that angiotensin receptor blockers in combination with celiprolol may further improve vascular outcomes[4]. Nevertheless, despite these advances, evidence remains scarce and clinical decisions are often guided by expert consensus and real-world clinical experience[5].

We present here three cases of genetically confirmed vEDS, illustrating key aspects of patient care, including diagnostic pitfalls, the impact of therapeutic discontinuation, and the importance of a multidisciplinary and individualized approach. These cases also underscore the remarkable clinical complexity and management challenges posed by vEDS, where each presentation requires tailored decision-making in high-risk and often unpredictable scenarios.

CASE DESCRIPTION

Case 1: A 53-year-old woman with genetically confirmed vEDS (*COL3A1* c.1347+1 G>A mutation) experienced sudden pain and swelling in the volar surface of her forearms, followed by paraesthesia in the fourth and fifth fingers of both hands. An initial evaluation at another centre misdiagnosed the condition as bilateral thrombosis of the ulnar veins. Re-evaluation at our centre confirmed a partially thrombosed aneurysm of the ulnar artery in the mid-forearm on both sides. Conservative management was chosen due to the high surgical risk.

Two weeks later, the patient developed a "hand of benediction" posture with sensory and motor deficits in the

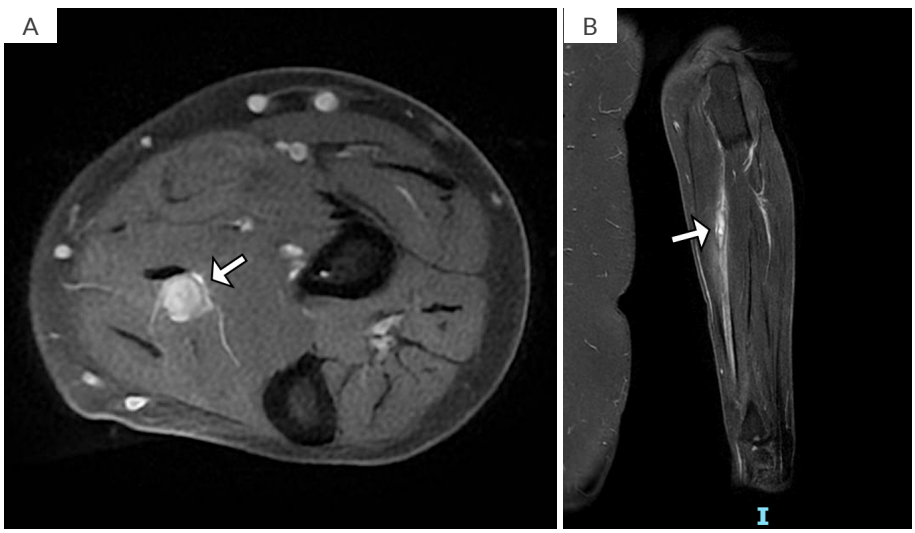


Figure 1. Case 1. Partially thrombosed aneurysm of the left ulnar artery in the mid-forearm on magnetic resonance imaging (white arrow): A) axial T1-weighted fat-saturated sequence and B) coronal proton density fast spin-echo with fat saturation.



Figure 2. Case 2. A) left renal artery dissection with kidney infarction (asterisk) and B) left external iliac artery dissection (white arrow).

fourth and fifth fingers of her left hand. Magnetic resonance imaging (MRI) revealed compression of the ulnar nerve caused by the aneurysm in the proximal third of the left ulnar artery *(Fig. 1)*. Electromyography confirmed denervation in the left ulnar territory. Following multidisciplinary discussion, surgical intervention was performed with resection of the aneurysm and decompression of the ulnar nerve. The patient subsequently underwent physiotherapy, with progressive neurological improvement. A follow-up electromyography showed partial functional recovery. She remains under close clinical surveillance.

Case 2: A 32-year-old woman with genetically confirmed vEDS (*COL3A1* c.1662+1G>C mutation), followed at our Centre for a history of multiple arterial dissections and aneurysms, expressed her firm intention to discontinue drug therapy consisting of celiprolol 400 mg and losartan 50 mg daily. This decision was motivated by a refusal to continue lifelong medications and concern about potential adverse effects. Despite being adequately informed of the risks, she remained determined. After involving her family in the discussion, she eventually agreed to maintain losartan once daily while discontinuing celiprolol. We suggested a gradual tapering of the drug and scheduled a follow-up visit at six months.

After three months, the patient presented to the Emergency Department of another hospital with acute left flank pain and new onset left lower limb claudication after a few meters. The symptoms were initially misinterpreted as lumbar radiculopathy, and she was discharged with nonsteroidal anti-inflammatory drugs. At our insistence, she underwent vascular imaging with computed tomography angiography (CTA), which revealed dissections of the left renal artery with kidney infarction and left external iliac artery *(Fig. 2)*. The left ankle-brachial index (ABI) was reduced to 0.56.

She was subsequently admitted to our hospital, where a multidisciplinary discussion recommended close clinical surveillance. Celiprolol was reintroduced, and antiplatelet therapy with aspirin was initiated. Renal function remained stable, while pain-free and maximal walking distance progressively improved after mobilization was resumed. At one month, all symptoms had resolved completely, and the ABI had normalized bilaterally (1.01). A follow-up vascular ultrasound demonstrated good collateralization without residual symptoms.

Case 3: A 45-year-old male with genetically confirmed vEDS (*COL3A1* c.1195G>C mutation) was initially misdiagnosed with vasculitis after presenting with epigastric pain and imaging findings of superior mesenteric artery (SMA) wall

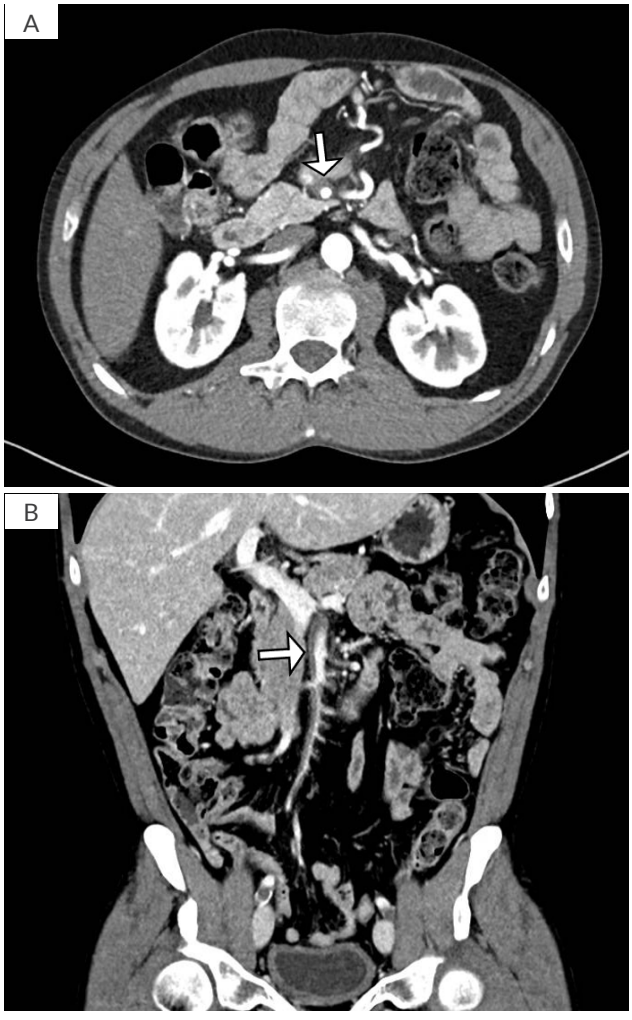


Figure 3. Case 3. Superior mesenteric artery dissection with circumferential mural hematoma (white arrow): A) axial view and B) coronal view.

thickening and a saccular aneurysm *(Fig. 3)*. Laboratory tests, however, did not reveal elevations in inflammatory markers. Following a multidisciplinary re-evaluation at our centre and reassessment of imaging studies, the diagnosis was revised to SMA dissection with circumferential mural hematoma, prompting a change in management.

The patient had an extensive history of vascular complications, including spontaneous arterial dissections, splenic rupture, and iliac artery involvement requiring multiple surgical and endovascular interventions. In light of his clinical course, therapy was optimized with irbesartan and celiprolol, in accordance with evidence from the BBEST and ARCADE studies, which resulted in improved vascular stability during follow-up. A control imaging study demonstrated complete regression of the mural hematoma with good arterial perfusion and no recurrence of symptoms.

DISCUSSION

The cases described highlight the clinical complexity of vEDS, one of the most severe heritable connective tissue disorders, characterized by extreme vascular fragility and a high risk of premature mortality. Management requires balancing the risks of intervention against the need to prevent catastrophic complications. Despite advances in understanding its molecular basis, treatment remains largely empirical, and outcomes hinge on early recognition, judicious therapeutic strategies, and coordinated multidisciplinary follow-up. Several key lessons can be drawn.

Therapeutic adherence, long-term surveillance, and structured follow-up are pivotal. Case 2 illustrates how discontinuation of celiprolol precipitated multiple life-threatening arterial dissections within a short period. The importance of sustained pharmacological therapy and regular imaging has been confirmed in observational cohorts, which report improved survival and reduced vascular events among patients enrolled in structured follow-up programs[6,7]. The VASCERN initiative similarly emphasizes the need for lifelong monitoring, with tailored imaging schedules adapted to patient history and local expertise[8]. Importantly, diagnostic pitfalls remain a major concern. Although challenging in the emergency setting, cases 1 and 2 show that arterial complications should be ruled out in case of a suggestive clinical presentation, especially in patients not on optimal medical therapy. In all our cases, misdiagnosis at first presentation delayed appropriate recognition, potentially exposing patients to inappropriate treatments and avoidable risks. Timely referral to specialized centres with expertise in vEDS is therefore essential to ensure accurate diagnostic reassessment, access to genetic counselling, and multidisciplinary care[7].

Management often requires individualized and predominantly conservative strategies, supported by validated pharmacological agents. Celiprolol is the first drug with randomized trial evidence showing a significant reduction in arterial morbidity and mortality[3]. Registry data and real-world cohorts have confirmed its benefit, although limitations persist due to small sample sizes and heterogeneous patient populations[6,9]. More recently, the ARCADE trial demonstrated that adding irbesartan to background celiprolol therapy further reduced vascular events compared with placebo[4], supporting β-blockade combined with angiotensin receptor blockade as the current evidence-based standard. Conservative treatment remains the preferred approach given the high surgical risk, yet intervention becomes unavoidable in the presence of severe complications, such as neurological compression in Case 1. Even then, outcomes are optimized when procedures are performed in high-volume referral centres with expertise in connective tissue fragility[7].

Despite these strategies, prognosis remains poor, although survival has improved over recent decades. Early studies reported a median survival of 48 years, with most patients experiencing at least one complication before the age of 40[1]. Recent data are more encouraging. Frank et al. reported a 5-year survival of 71.6% and over 80% survival at 50 years in a French referral cohort, while a UK multicentre study estimated 5-year survival at approximately 90%[6,7]. Nonetheless, event rates remain excessive. In our previous cohort, the annual risk of symptomatic life-threatening vascular events was 6.4%, similar to treated patients in the BBEST trial (5%) and in a Swedish registry (4.7%)[10] but substantially lower than untreated controls (12%)[3]. When asymptomatic events were included, rates approached 14.4%, despite a high proportion of patients receiving celiprolol at maximal recommended doses. This indicates that much remains to be done to further improve outcomes in this population. Novel therapeutic targets, including agents modulating extracellular matrix organization and TGF-β signalling, are under investigation and may expand available options in the future[5].

In summary, optimal care for vEDS hinges on three pillars: early referral to expert centres and multidisciplinary care, strict adherence to validated long-term pharmacological therapy with structured surveillance, and a conservative, individualized approach to intervention. Ongoing collaborative research efforts and prospective registries remain crucial to refine management strategies and to develop novel therapeutic options for this high-risk population.

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