Received: 25 October 2023 | Revised: 23 January 2024 | Accepted: 25 January 2024

DOI: 10.1002/ccr3.8517

CASE REPORT

Clinical Case Reports Open Access WILEY

Vascular Ehlers-Danlos syndrome: A null COL3A1 variant found in a patient with loin pain without marked cutaneous features (case report)

Shreenidhi Ranganatha Subramaniam[1,2] | **Lam Fung Yeung**[3] | **L. Y. Lois Choy**[1,2] | **Jeffrey Sung Shing Kwok**[1,2]

[1]Department of Chemical Pathology, Prince of Wales Hospital, Hospital Authority, Hong Kong, China

[2]Department of Chemical Pathology, The Chinese University of Hong Kong, Hong Kong, China

[3]Department of Medicine & Geriatrics, Tai Po Hospital, Hospital Authority, Hong Kong, China

Correspondence
Jeffrey Sung Shing Kwok, Department of Chemical Pathology, Prince of Wales Hospital, Hospital Authority, Hong Kong, China.
Email: jeffreykwok@cuhk.edu.hk

Key Clinical Message

Patients with null variants may have milder vascular Ehlers-Danlos syndrome, presenting with seemingly non-specific complaints and subtle cutaneous features that may be missed. A high index of suspicion and early genetic testing (aided by next-generation sequencing) were crucial for prevention of life-threatening complications in the patient and family members.

KEYWORDS

arterial dissection, case report, *COL3A1*, Ehlers-Danlos syndrome, vascular Ehlers-Danlos syndrome

1 | INTRODUCTION

Ehlers-Danlos syndrome describes a group of heritable connective tissue disorders which are characterized by features such as joint hypermobility, skin hyperextensibility and tissue fragility.[1] Vascular Ehlers-Danlos syndrome (vEDS) is the most severe form. Patients may demonstrate fragility of arteries, gastrointestinal tract and uterus and may have other features such as thin and translucent skin, easy bruising and characteristic facies.[2] It is mostly inherited in an autosomal dominant manner but there have been rare cases with biallelic inheritance reported.[2] vEDS is caused by *COL3A1* mutations that lead to type III collagen molecule abnormalities. We describe a Chinese male proband who presented with acute complications from vEDS, in whom we detected a null variant.

2 | CASE HISTORY/EXAMINATION

A 27-year-old man presented with acute-onset severe left-sided loin pain for 1 day. He also had similar pain 2.5 years ago with computed tomography (CT) at the time suggestive of either pyelonephritis or renal infarct; this was ultimately treated as pyelonephritis. One year before the current episode, he also suffered from bilateral lower limb weakness, however CT brain and spine magnetic resonance imaging were unrevealing. The weakness subsequently self-resolved. The patient also complained of groin and lower limb pain previously.

For the present episode, the patient had no fever, no significant urinary or bowel symptoms, and no history of trauma or easy bruising. He denied smoking and substance abuse. Relevant family history included a paternal

aunt who died of suspected acute coronary syndrome in her 50s.

Physical examination was rather unremarkable. On admission, his blood pressure was normal, however, it rose to 159/74 mmHg over the next 3 days (likely due to activation of the renin-angiotensin-aldosterone system). There was no notable syndromic facies, disproportionate limbs or joint laxity. There were no obvious clinical features of vasculitis or rheumatological diseases. However, the skin of his posterior calves was slightly lax, thin and translucent with reference to his age and body build (Figure 1). No skin laxity was noted at other sites.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT)

Blood tests, including complete blood count, clotting profile, liver and renal function tests and rheumatological investigations were unremarkable, except an elevated creatinine of 131 μmol/L. Chest X-ray and X-ray of kidneys, ureters, bladder were also unrevealing.

Contrast CT of the abdomen, pelvis and subsequently aortogram were arranged (Figure 2) and showed a left renal infarct with a total left main renal artery occlusion (1.5 cm from origin). There was contour irregularity and a suspicious intimal flap along the right main renal artery and dissection flaps along the left common and left external iliac arteries. A non-calcified thrombus was noted with a short segment of stenosis along the right external iliac artery and focal high-grade stenosis along the proximal celiac trunk. There was no vessel wall enhancement or peri-vascular stranding. The patient was treated with enoxaparin and antihypertensive therapy. The urologist and vascular surgeon did not recommend surgical intervention.

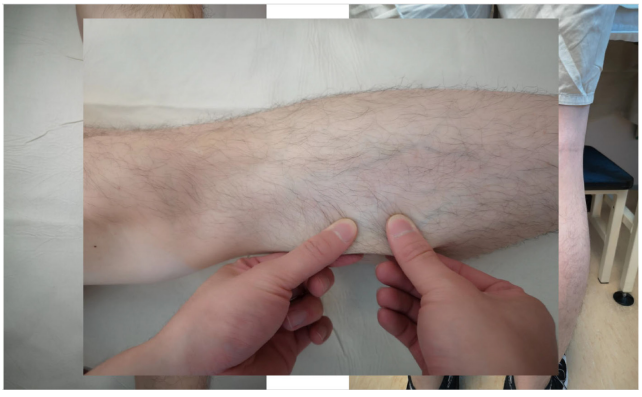

FIGURE 1 Demonstration of patient's subtle skin laxity.

vEDS was deemed the most probable diagnosis given the subtle skin laxity and translucence and the absence of typical clinical and radiological features of other connective tissue diseases such as Marfan's syndrome, fibromuscular dysplasia, active vasculitis, and other rheumatological diseases.

Genetic testing was thus requested and performed using gene panel testing by Next-Generation Sequencing (TruSight Cardio Sequencing Kit, MiSeq, Illumina). A heterozygous *COL3A1* variant NM_000090.4:c.712C>T p.(Arg238Ter) was detected. This was further confirmed with Sanger sequencing (Figure 3). This is a null variant which is absent from gnomAD exomes and genomes databases (v.2.1). It is classified by ClinVar as pathogenic/likely pathogenic and is also listed as a disease-causing mutation in HGMD Professional 2022.3. It has previously been reported in a patient with spontaneous coronary artery dissection but without other typical characteristics of vEDS.[3] Multiple in-silico algorithms (e.g., DANN, EIGEN, MutationTaster) consistently predict this variant to be pathogenic. Thus, with reference to the Standards and Guidelines for the Interpretation of Sequence Variants by the American College of Medical Genetics and Genomics,[4] the variant was classified as pathogenic and vEDS was confirmed. Genetic counseling was provided and subsequent cascade family screening revealed the same mutation in the patient's father, paternal uncle, and his younger brother and sister. However, the family members were followed up and clinically managed at a different centre.

In terms of medical therapy, the patient received subcutaneous Enoxaparin 60 mg every 12 h (1 mg/kg every 12 h) for 2 weeks and was further switched to Dabigatran 150 mg twice daily for a further 6 months. He requires multiple antihypertensive agents for optimal blood pressure control and is currently on Amlodipine 5 mg twice daily, Carvedilol 25 mg twice daily, Hydralazine 75 mg twice daily and Terazosin 4 mg twice daily.

4 | CONCLUSION AND RESULTS (OUTCOME AND FOLLOW-UP)

The patient's clinical condition and follow-up imaging have been relatively static.

5 | DISCUSSION

vEDS is a potentially life-threatening condition, with an estimated prevalence of up to 1 per 50,000,[5] caused by heterozygous pathogenic variants in *COL3A1* that result in problems in type III collagen synthesis. This can

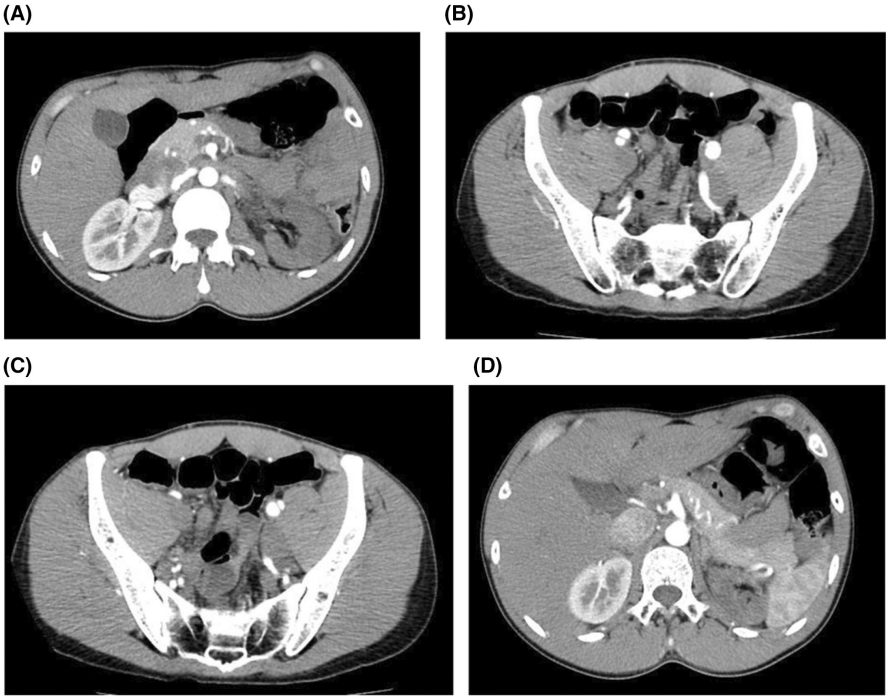

FIGURE 2 Computed tomography of abdomen and pelvis with contrast.

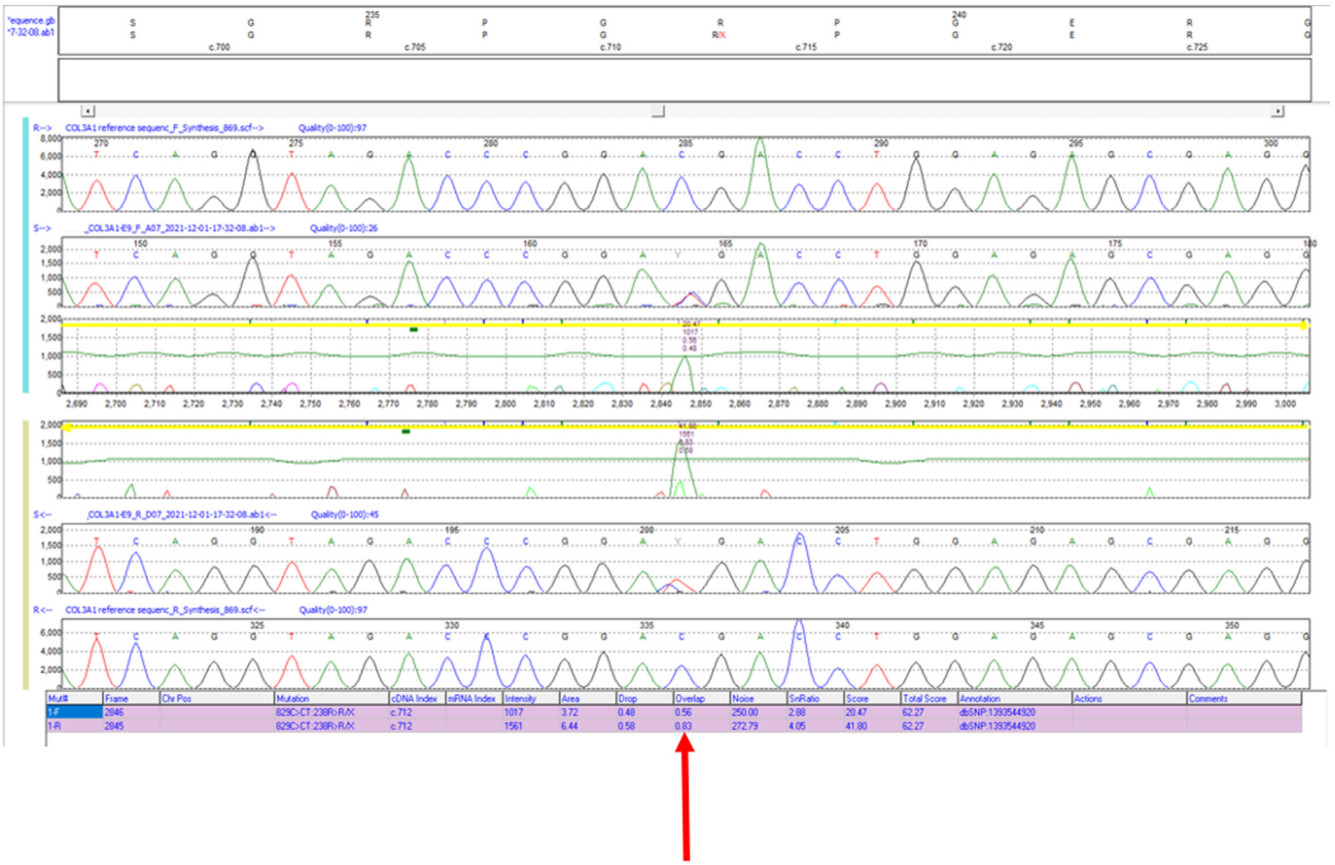

FIGURE 3 Electropherogram produced by Sanger sequencing showing pathogenic variant (indicated by arrow).

lead to fragility of the arteries and hollow organs such as the intestines and the uterus.[2] Malfait et al. defined criteria for this condition.[6] However, diagnosis remains challenging because not all of the criteria may be easily identified. Additionally, around 50% of affected individuals have a de novo pathogenic variant and thus family

history may be absent.[2] Early diagnosis may also be hindered by overlapping features with other conditions for example, Loeys-Dietz, Marfan, and familial arterial aneurysm and dissection syndromes.[5] Thus, due to difficulties in early diagnosis, patients often present with severe complications including vascular dissection/rupture, perforation of the gastrointestinal tract or organ rupture. We presented the case of a 27-year-old male patient who presented with severe loin pain, which was initially treated as pyelonephritis but was genetically confirmed to be vEDS 2 years later.

In retrospect, many of the patient's seemingly nonspecific clinical symptoms could be explained by his diagnosis. His groin pain might be explained by the iliac arteries dissection. Regarding his lower limb weakness, the radiologist retrospectively commented that the original MRI spine in fact did show evidence of spinal artery dissection. Ultimately, his first episode of loin pain, which had been treated as pyelonephritis turned out to be due to segmental renal infarction. Such features may easily be missed in patients with vEDS, due to lack of awareness of this rare disease. The detection of a null variant, a relatively rare form of mutation of *COL3A1*, may explain his lack of marked cutaneous features that may be seen in other forms of genetic variant of vEDS. This led to delays in diagnosis and the development of further vascular and end organ complications. Thus, a high index of suspicion is necessary in patients with unexplained vascular dissection even without marked cutaneous features of vEDS.

Molecular testing plays a significant role in the diagnosis of vEDS. Apart from providing definitive diagnosis in this otherwise diagnostically challenging condition, it also enables family screening, which allows for earlier diagnosis in asymptomatic relatives prior to the development of life-threatening complications. For instance, our patient's father, paternal uncle and siblings were asymptomatic, and may not have been identified without molecular testing. Such asymptomatic individuals may benefit from earlier lifestyle modifications. In our case, molecular testing was performed by next-generation sequencing; this technique proved to be particularly advantageous given the large size of the *COL3A1* gene. It has previously been suggested that null variants (~5%) in *COL3A1* are associated with milder phenotypes.[2] The null mutation has lower penetrance, better survival and later onset (15 years later).[2] Additionally, the phenotype tends to be mainly limited to vascular complications, with a lower risk of gastrointestinal and obstetric complications, as seen in our patient.[2] This milder phenotype is thought to be due to haploinsufficiency, in which there is a quantitative defect, which lead to a simple 50% reduction of type III collagen amount. This contrasts with the structural problems seen in some other variants, in which there are qualitative defects affecting triple helix folding, causing a dominant negative effect on the normal type III collagen as well.[7] On the other hand, patients with milder phenotypes may be more challenging to diagnose, thus necessitating a high index of suspicion. Additional research on differences between null variants and other types of *COL3A1* variants may provide invaluable information on pathogenesis, as well as allowing more accurate genotype-driven prognostication and improved management.

Management of these patients involves a combination of surveillance, complication prevention and treatment under the care of a multidisciplinary team. Lifestyle modifications, including the avoidance of collision sports, are an important aspect of prevention. Indeed, in our patient, prior to diagnosis, he was in the habit of intensifying gym training in response to the development of weakness. However, heavy weight training might increase development of complications and so proper education on lifestyle measures is essential, to avoid adverse outcomes once a diagnosis is made or suspected.

In conclusion, vEDS, and particularly null *COL3A1* variants, present a diagnostically challenging condition in which maintaining a high index of clinical suspicion, followed by early molecular diagnosis with cascade family screening may allow earlier diagnosis and management, thereby reducing the development of life-threatening complications. Patients with null variants may have a milder form of disease with subtle cutaneous features that could be easily missed. Compared with other forms of mutation in general, the life expectancy for patients with null variants may approach normal, and thus an earlier diagnosis in our patient may have allowed earlier multidisciplinary management, which may have further improved his prognosis. Further data on the management of patients with different genotypes may be helpful to allow personalized treatment that maximizes treatment benefits while minimizing risks.

AUTHOR CONTRIBUTIONS

Shreenidhi Ranganatha Subramaniam: Conceptualization; writing – original draft; writing – review and editing. **Lam Fung Yeung:** Conceptualization; writing – original draft; writing – review and editing. **L. Y. Lois Choy:** Conceptualization; writing – review and editing. **Jeffrey Sung Shing Kwok:** Conceptualization; supervision; writing – review and editing.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

CONSENT

Written informed consent was obtained from the patient and the patient consented to publication of his clinical data.

ORCID

Shreenidhi Ranganatha Subramaniam https://orcid.org/0000-0002-4085-2529

REFERENCES

1. Parapia LA, Jackson C. Ehlers-Danlos syndrome—a historical review. *Br. J. Haematol.* 2008;141(1):32-35. doi:10.1111/j.1365-2141.2008.06994.x
2. Byers PH. Vascular Ehlers-Danlos Syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. University of Washington, Seattle. *GeneReviews((R))*; 1993.
3. Carss KJ, Baranowska AA, Armisen J, et al. Spontaneous coronary artery dissection: insights on rare genetic variation from genome sequencing. *Circ Genom Precis Med*. 2020;13(6):e003030. doi:10.1161/CIRCGEN.120.003030
4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 2015;17(5):405-424. doi:10.1038/gim.2015.30
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(1):40-47. doi:10.1002/ajmg.c.31553
6. 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(1):8-26. doi:10.1002/ajmg.c.31552
7. Solyst S, Oksjoki R, Farholt S, et al. Carriers of COL3A1 pathogenic variants in Denmark: interfamilial variability in severity and outcome of elective surgical procedures. *Clin. Genet.* 2022;102(3):191-200. doi:10.1111/cge.14176

How to cite this article: Subramaniam SR, Yeung LF, Choy LYL, Kwok JSS. Vascular Ehlers-Danlos syndrome: A null COL3A1 variant found in a patient with loin pain without marked cutaneous features (case report). *Clin Case Rep*. 2024;12:e8517. doi:10.1002/ccr3.8517