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COEXISTENCE OF VASCULAR EHLERS-DANLOS SYNDROME AND STICKY PLATELET SYNDROME: A LETHAL COMBINATION IN A YOUNG PATIENT WITH THROMBOPHILIA AND HAEMORRHAGIC DIATHESIS

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ABSTRACT

Background: The coexistence of hypercoagulability and bleeding diathesis in the same patient represents a potentially lethal combination due to its complex management. Vascular Ehlers-Danlos syndrome (vEDS) and sticky platelet syndrome (SPS) are classified as rare diseases due to their low prevalence. vEDS is associated with bleeding tendencies caused by vascular wall fragility, while SPS is characterized by atypical arterial and venous thrombosis.

Case Report: We report a 27-year-old woman, smoker and regular consumer of energy drinks, with a medical history of subclinical hypothyroidism, minor thalassemia, recurrent joint sprains, high myopia, and anterior mitral valve prolapse, who was diagnosed with both vEDS and SPS type I. The patient experienced a catastrophic progression over a short time period, marked by numerous thrombotic and bleeding episodes, ultimately leading to a fatal outcome.

Conclusions: This report documents the first known case of concurrent vEDS and SPS, highlighting the complexity and challenges in the management of these two rare conditions together. The interplay between these syndromes necessitates careful clinical consideration and the development of tailored management strategies to mitigate associated risks. This underscores the crucial role of the internist in overseeing such cases. Further studies are needed to explore new therapeutic strategies aimed at improving survival rates and outcomes for patients with this unique combination of disorders.

KEYWORDS

Elhers-Danlos syndrome, sticky platelet syndrome, coagulopathy, bleeding diathesis, hypercoagulability

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LEARNING POINTS

- The coexistence of vascular Ehlers-Danlos syndrome (vEDS) and sticky platelet syndrome (SPS) creates a unique clinical scenario where the underlying connective tissue weakness and platelet hyperaggregability synergistically increase the risk of both thrombotic and haemorrhagic events, complicating management strategies.
- Internists must assume a pivotal role in the integrated management of patients with vEDS and SPS, facilitating a multidisciplinary strategy that not only addresses the dual risk of thromboembolic and haemorrhagic complications but also emphasizes the importance of personalized treatment algorithms and ongoing surveillance to optimize long-term outcomes.

INTRODUCTION

Ehlers-Danlos syndrome (EDS) encompasses a group of rare genetic collagen disorders, with vascular EDS (vEDS) being a particularly severe subtype due to its association with arterial fragility and risk of spontaneous rupture. This condition, caused by pathogenic mutations in the *COL3A1* gene, presents unique diagnostic and management challenges, particularly in young patients with unexplained vascular events. Sticky platelet syndrome (SPS), an autosomal dominant disorder characterized by platelet hyperaggregability, further complicates management due to its propensity for thrombotic events. We report the case of a 27-year-old woman who developed multiple episodes of thrombosis and haemorrhages as a consequence of the coexistence of these two rare diseases, resulting in a fatal outcome. To the best of our knowledge, this association has not been previously reported in the scientific literature.

CASE DESCRIPTION

A 27-year-old woman, with a smoking habit of 10 cigarettes per day and regular energy drink consumption, presented with a medical history including subclinical hypothyroidism, minor thalassemia, recurrent joint sprains, high myopia, and anterior mitral valve prolapse incidentally detected during an echocardiographic study following recurrent vasovagal syncope. Her family history was notable for her father's sudden death at age 35 from an undetermined abdominal cause. She presented to the emergency department with acute, severe left renal fossa pain unresponsive to standard analgesic treatments. An abdominal computed tomography (CT) scan revealed an extensive left renal infarction secondary to thrombosis in a left renal artery (LRA) aneurysm, along with multiple ectatic and irregular vessels *(Fig. 1)*. Given the established infarction, urgent surgical intervention was deemed unnecessary. She was discharged without anticoagulation due to the aneurysmal bleeding risk, with negative coagulopathy study results. One week later, the patient returned with right renal fossa pain, due to a right renal infarction and evidence of progression of the LRA aneurysm. Aneurysmal embolization was performed via arteriography. An exhaustive examination revealed hyperlaxity and joint hypermobility. After ophthalmologic assessment lens subluxation was excluded but angioid streaks were identified. Suspecting hereditary

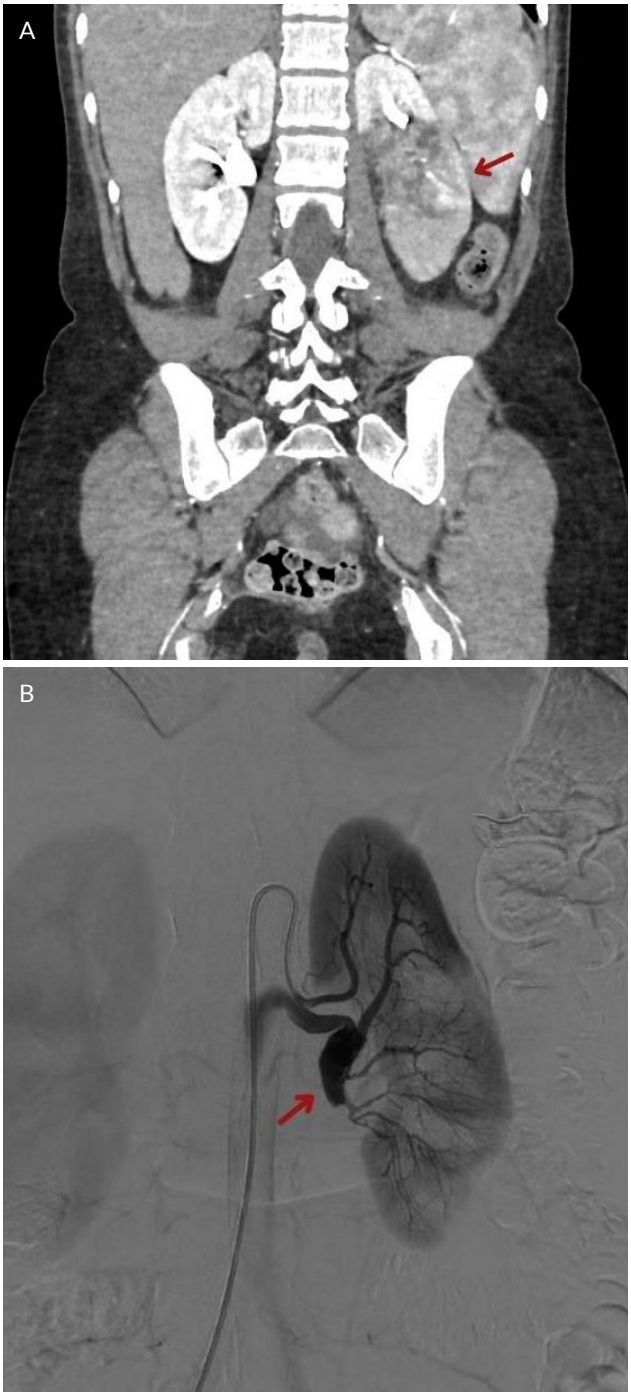


Figure 1. A) Abdominal computed tomography angiography showing an extensive left renal infarction (red arrow); B) Selective left renal arteriography displaying a fusiform aneurysm (red arrow), affecting the posterior branch of the left renal artery.

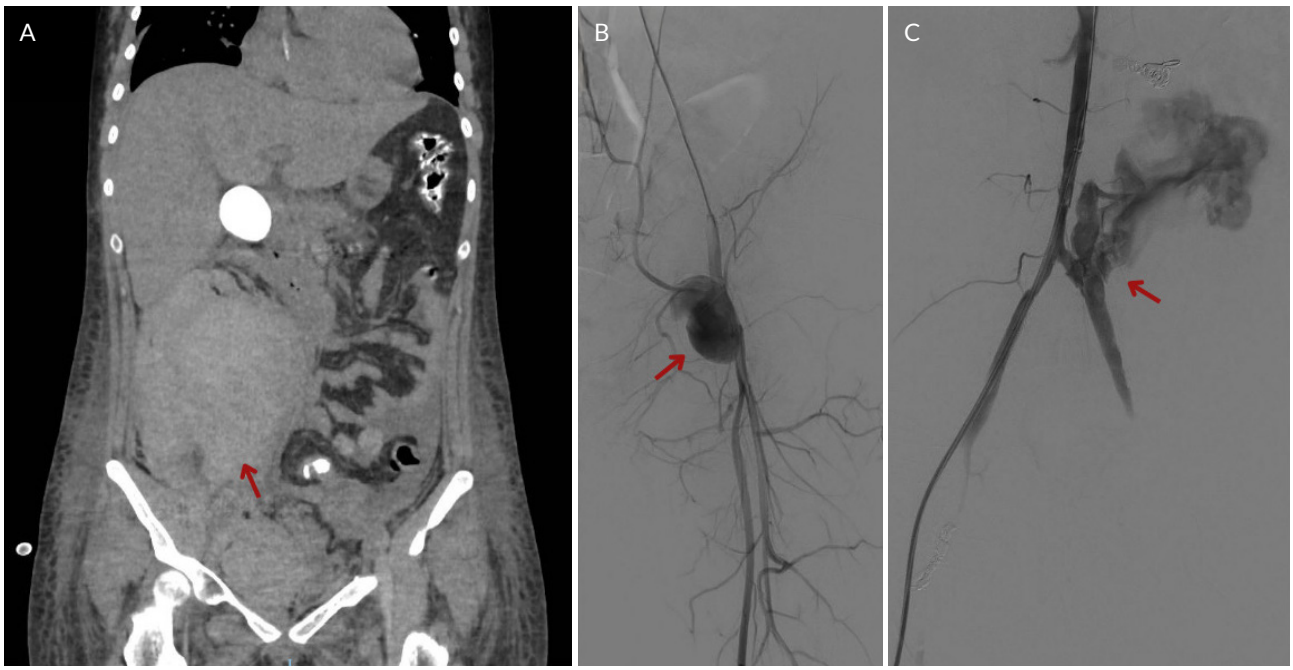


Figure 2. A) Abdominal computed tomography scan: extensive retroperitoneal hematoma (red arrow) resulting from spontaneous rupture of a branch of the left gluteal artery; B) Arteriography: pseudoaneurysm of the left femoral artery (red arrow) during embolization; C) Dissection and rupture of the aorta at the aortoiliac junction (red arrow), with evident bleeding due to contrast leakage.

collagenopathy, a genetic study confirmed a pathogenic mutation in the *COL3A1* gene, consistent with a diagnosis of vEDS. At discharge, considering her repeated thrombotic episodes, anticoagulation with low molecular weight heparin (LMWH) was recommended despite bleeding risk.

Two months later, she was admitted to the intensive care unit in haemorrhagic shock due to spontaneous bleeding from the left gluteal artery caused by an aneurysmal rupture, resulting in a significant retroperitoneal hematoma *(Fig. 2)*. Anticoagulation was suspended, and aneurysmal embolization was successfully performed. Following initial improvement, the patient developed massive venous thrombosis extending from the right popliteal vein to the infrarenal vena cava. After multidisciplinary consultation, a trans jugular vena cava filter was placed due to her previous haemorrhagic complications with anticoagulation. Given her recurrent arterial and venous thrombotic episodes, a hypercoagulable state was suspected. Despite prior negative coagulopathy studies, alternative diagnoses explaining the simultaneous predisposition to haemorrhage and thrombosis, even with anticoagulation, were reconsidered. A hyperaggregability study confirmed SPS type I *(Fig. 3)*, prompting treatment initiation with ticagrelor and therapeutic-dose LMWH. One month after discharge, she experienced new spontaneous bleeding from a pseudoaneurysm of the left femoral artery. During attempted embolization and stent placement, the patient suffered an irreparable dissection and rupture of the aortoiliac junction *(Fig. 2)*, ultimately resulting in her death.

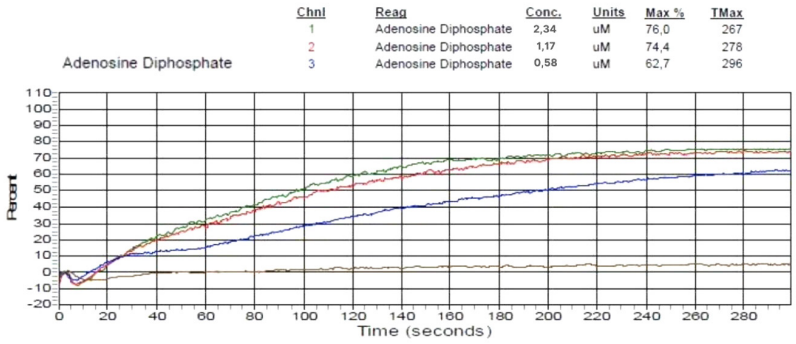
DISCUSSION

EDS encompasses a rare group of syndromic collagen disorders, classified under non-fibrillinopathies[1,2]. Within EDS, subtypes are defined by specific organ involvement[3]. Our patient exhibited vEDS (type IV), attributed to heterozygous pathogenic mutations in the *COL3A1* gene, encoding type III collagen, with an estimated prevalence of 1 in 50,000[4]. This group of disorders should be considered in differential diagnoses for young patients presenting with vascular phenomena (e.g., spontaneous arterial dissections, intestinal ruptures) and compatible family history, as they are integral diagnostic criteria for vEDS, confirmed via genetic testing.

Conversely, SPS is an autosomal dominant disorder marked by an abnormal platelet response to low concentrations of adenosine diphosphate (ADP) and/or epinephrine (EPI). SPS can be classified as type I, II, or III, depending on whether hyperaggregability occurs with EPI and ADP, with EPI alone, or with ADP alone, respectively. Haematological studies confirmed that our patient had SPS type I. This syndrome manifests through venous and/or arterial thromboembolic events associated with platelet hyperaggregability. The diagnosis was suspected due to thrombotic events in atypical locations and the patient's young age[5].

SPS often remains subclinical until a vascular event elevates ADP and EPI levels, with EDS type IV possibly acting as a precipitating factor in this case. To our knowledge, no previous cases document both conditions concurrently. The diagnostic challenge lies in the symptom heterogeneity across both syndromes, often leading to delays with detrimental impacts on prognosis. This case underscores the lack of evidence regarding treatment for type IV EDS. While celiprolol is the only agent proven to reduce vascular events, the role of angiotensin II receptor antagonists remains uncertain[6]. Emerging therapies targeting the PLC/IP3/PKC/ERK signalling pathway[7] and epigenomic

A



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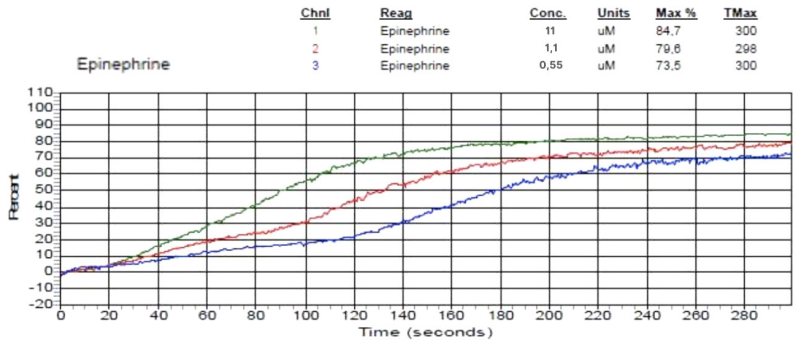

C

	ADP			EPI		
Conc (µM)	0.58	1.17	2.34	0.55	1.1	11
N range (%)*	0-12	2-36	7.5-55	9-20	15-27	39-80

Figure 3. A) Abdominal computed tomography scan: extensive retroperitoneal hematoma (red arrow) resulting from spontaneous rupture of a branch of the left gluteal artery; B) Arteriography: pseudoaneurysm of the left femoral artery (red arrow) during embolization; C) Dissection and rupture of the aorta at the aortoiliac junction (red arrow), with evident bleeding due to contrast leakage. Abbreviations: Chnl, chanel; Reag, reagent; Conc, concentration; TMax, maximum time; ADP, adenosine diphosphate; EPI, epinephrine; Conc, concentration; N range, normal range.

approaches to modulate non-coding ribonucleic acid expression in cardiovascular diseases[8] may offer new therapeutic avenues. Rigorous management of vascular risk factors and regular imaging follow-ups are essential. While percutaneous surgical interventions are options for acute complications, concerns persist regarding adverse effects in vEDS patients[9]. Their utility in preventing complications from associated comorbidities remains unclear. Additionally, the patient's hypercoagulable state, attributed to SPS, presented complex treatment challenges due to limited evidence. Current literature suggests antiplatelet agents, particularly acetylsalicylic acid, as first-line prophylaxis for thromboembolic events[10]. However, the complex decision-making and management in our patient was heightened by the lack of evidence specific to her underlying conditions.

Platelet aggregability abnormalities have been documented in patients with vEDS, revealing significant variability in platelet function among patients, particularly subgroups with prolonged bleeding times and reduced aggregation responses in platelet function tests[11]. Our case, however, demonstrates platelet hyperfunction consistent with a type I SPS diagnosis. Further studies are needed to clarify the role of this disease in platelet aggregability and to delineate the range of potential abnormalities associated with it.

CONCLUSION

This case illustrates the significant diagnostic challenges posed by vEDS and SPS, both independently and, more notably, in combination. Early, accurate diagnosis and comprehensive management are critical to prevent complications in these pathologies, highlighting the pivotal role of internists in coordinating care. The absence of established treatment protocols for these coexisting conditions emphasizes an urgent need for further research into effective management and treatments in light of improve patient outcomes.

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