CASE REPORT

Recurrent venous thrombosis in Ehlers-Danlos syndrome type III: an atypical manifestation

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SUMMARY

Ehlers-Danlos syndrome (EDS) comprises a group of hereditary connective tissue disorders in which collagen synthesis and fibrogenesis are impaired. Patients with EDS type III have a bleeding tendency manifested by ecchymoses and haematomas. However, thrombotic events are rare in this entity. Herein, we present a 48-year-old Hispanic man with EDS type III who had recurrent cephalic vein thrombophlebitis and thrombosis, and brachial vein thrombosis. Tests for hypercoagulable disorders including antithrombin III activity, protein C activity, protein S activity, anticardiolipin antibodies, homocysteine levels, factor V Leiden mutation and prothrombin gene mutation were negative. The patient required long-term anticoagulation with warfarin. After 3 years follow-up, he did not present further thrombotic events. Clinicians should be aware that patients with EDS might be at risk for hypercoagulable disorders.

BACKGROUND

Ehlers-Danlos syndrome (EDS) comprises a group of hereditary connective tissue disorders first described by McKusick *et al.*^{1–2} It is an autosomal dominant disorder in which the genetic defect impairs collagen synthesis and fibrogenesis. The prevalence of EDS varies between 1:10 000 and 1:150 000.^{1–3} The diagnosis depends primarily on clinical findings and family history. The classic clinical manifestations of EDS type III are joint hypermobility, skin hyperelasticity, dystrophic scars and bleeding tendency manifested by ecchymoses and haematomas.⁴ Conversely, thrombotic disorders are rare in this type of EDS. Herein, we present a 48-year-old Hispanic man with EDS type III with recurrent cephalic vein thrombophlebitis and thrombosis, and brachial vein thrombosis.

CASE PRESENTATION

A 48-year-old Hispanic man with EDS type III presented with right forearm pain in January 2009. He had no history of systemic illnesses or cigarette smoking, and was not using any medications. He had no recent trauma, surgical procedures, hospitalisations or immobilisation. He was retired from military service and spent a sedentary life at home. He had no family history of hypercoagulable disorders. His daughter had EDS. Physical examination was remarkable for hypermobility of joints (figure 1A), hyperextensibility of skin (figure 1B), as well as dystrophic scars indicative of skin fragility. Erythema, pitting oedema and induration of the right upper extremity were observed. A palpable, tender, red, rope-like structure was present from

the medial aspect of the forearm up to the elbow. Duplex/Doppler ultrasonography revealed a lack of flow, no compressibility and an intramural hypoechoic thrombus in the cephalic vein below the elbow level (figure 2A). No extension into the deep venous system was identified. He was started on full anticoagulation with low-molecular weight heparin followed by warfarin with a target international normalised ratio (INR) of 2–3.

Three months later, the patient presented to the emergency room with swelling, pain and erythema of the contralateral forearm. He had no history of trauma, insect bite or recent venipuncture. He was treated for skin infection with amoxicillin/clavulanate 875/125 mg twice daily for 7 days. Two weeks later, he had worsening of forearm oedema and erythema. Duplex/Doppler ultrasonography revealed intramural echoes involving portions of the cephalic vein approximately 3 inches above the wrist level, with patent deep vein system (figure 2B). INR was subtherapeutic at 1.01. Studies for hypercoagulable disorders including tests for antithrombin III activity, protein C activity, protein S activity, anticardiolipin antibodies, homocysteine levels, factor V Leiden mutation and prothrombin gene mutation were negative. Prostatic specific antigen levels were normal. Colonoscopy did not reveal any abnormalities. The patient was treated with low-molecular weight heparin and warfarin. He was discharged home on warfarin, but he was not adherent to this therapy and INR failed to reach target levels.

One month later, the patient presented to the emergency room again for left forearm pain, this time associated with limited motion on pronation and supination. He had induration of the vein at the wrist level, which was very tender to palpation. Duplex/Doppler ultrasonography revealed acute deep vein thrombosis (DVT) involving the brachial vein. He was started on full anticoagulation with fondaparinux and warfarin. After the initiation of treatment, therapeutic INR was achieved and his symptoms resolved. The patient required long-term anticoagulation with warfarin. After 3 years follow-up, he did not present further thrombotic events.

OUTCOME AND FOLLOW-UP

The patient required long-term anticoagulation with warfarin. After 3 years follow-up, he did not present further thrombotic events.

DISCUSSION

We present a case of a patient with EDS type III who had recurrent venous thrombosis in the upper extremities. EDS type III or hypermobility type is

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Figure 1 (A) Hyperextension of metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints of the fifth digit, and (B) hyperelastic skin of the neck.

generally considered to be the least severe type of EDS, although significant complications, primarily musculoskeletal, may occur.^{1–3} Also, easy bruising is quite common, frequently occurring without obvious cause.⁴ Mild bleeding, gingival haemorrhages and menometrorrhagia may also occur.⁴ In contrast to other types of EDS, vascular manifestations such as artery dissection, rupture and aneurysm are rarely seen in EDS type III.⁵

Even though EDS is usually associated with bleeding tendency, there are some reports of thrombotic events occurring in these patients. Venous thromboembolism and pulmonary

embolism have been reported after a caesarean section in women with EDS, but in the presence of positive antiphospholipid antibodies.⁶ Furthermore, EDS has been associated with transient antiphospholipid antibodies elevations.⁷ In contrast, our patient had negative antiphospholipid antibodies. The thrombotic events in our patient occurred at a late stage of his life; thus, it could be argued that these were attributed to other factors instead of EDS. However, we performed an extensive work-up for hypercoagulable disorders which was negative. Also, our patient had no history of potential precipitating conditions prior to the time of thrombosis.

Figure 2 (A) Right arm venous duplex/Doppler showing intramural hypoechoic thrombus in the cephalic vein below the elbow level. (B) Left arm venous duplex/Doppler showing intramural echoes involving portions of the cephalic vein approximately 3 inches above the wrist level.

It is not surprising that patients with EDS type III may develop thrombotic events. In all types of EDS, the collagen that supports blood vessels is unusually weak and elastic, making blood vessels more prone to injury. Subsequently, damage to endothelial cells exposes extracellular matrix leading to the engagement of the haemostatic system including platelet adhesion and activation. Therefore, a thrombotic event may occur as a result of this damage.

Our patient presented with recurrent spontaneous superficial venous thrombophlebitis (SVTP), which has been identified as a risk factor for the development of deep vein thrombosis. Furthermore, SVTP confers a 10-fold risk of developing DVT within 6 months for which treatment should be aimed at preventing venous thromboembolism.⁸ Primary or idiopathic upper extremity DVT (UEDVT), especially forearm DVT, is a rare disorder occurring in 2/100 000 persons/year.⁹ UEDVT is an important clinical entity with a potential for considerable mortality, especially for fatal pulmonary embolism.⁹ Although many risk factors have been described for the development of UEDVT, EDS type III has not been previously recognised as a risk factor.

In summary, clinicians should be aware that patients with EDS type III might be at risk for hypercoagulable disorders. Moreover, this case highlights the importance to make an early diagnosis and initiate prompt therapy in this potentially life-threatening condition.

Learning points

- Fragility of blood vessels caused by a defect in collagen synthesis in patients with Ehlers-Danlos syndrome (EDS) might prone to injury and endothelial cell damage.
- We report a 48-year-old Hispanic man with EDS type III who presented with recurrent cephalic vein thrombophlebitis and thrombosis, and brachial vein thrombosis.
- Clinicians should be aware that patients with EDS type III might be at risk for hypercoagulable disorders.

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Competing interests None.

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